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Synthesiology

English edition

Synthesiology editorial board

MESSAGES FROM THE EDITORIAL BOARD

There has been a wide gap between science and society. The last three hundred years of the history of modern science indicates to us that many research results disappeared or took a long time to become useful to society. Due to the difficulties of bridging this gap, it has been recently called the valley of death or the nightmare stage (Note 1). Rather than passively waiting, therefore, researchers and engineers who understand the potential of the research should be active.

To bridge the gap, technology integration (i.e. *Type 2 Basic Research* – Note 2) of scientific findings for utilizing them in society, in addition to analytical research, has been one of the wheels of progress (i.e. *Full Research* – Note 3). Traditional journals, have been collecting much analytical type knowledge that is factual knowledge and establishing many scientific disciplines (i.e. *Type 1 Basic Research* – Note 4). Technology integration research activities, on the other hand, have been kept as personal know-how. They have not been formalized as universal knowledge of what ought to be done.

As there must be common theories, principles, and practices in the methodologies of technology integration, we regard it as basic research. This is the reason why we have decided to publish "*Synthesiology*", a new academic journal. *Synthesiology* is a coined word combining "synthesis" and "ology". Synthesis which has its origin in Greek means integration. Ology is a suffix attached to scientific disciplines.

Each paper in this journal will present scenarios selected for their societal value, identify elemental knowledge and/or technologies to be integrated, and describe the procedures and processes to achieve this goal. Through the publishing of papers in this journal, researchers and engineers can enhance the transformation of scientific outputs into the societal prosperity and make technical contributions to sustainable development. Efforts such as this will serve to increase the significance of research activities to society.

We look forward to your active contributions of papers on technology integration to the journal.

Addendum to Synthesiology-English edition,

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Synthesiology Editorial Board

Note 1 : The period was named "nightmare stage" by Hiroyuki Yoshikawa, President of AIST, and historical scientist Joseph Hatvany. The "valley of death" was by Vernon Ehlers in 1998 when he was Vice Chairman of US Congress, Science and Technology Committee. Lewis Branscomb, Professor emeritus of Harvard University, called this gap as "Darwinian sea" where natural selection takes place.

Note 2 : *Type 2 Basic Research*
This is a research type where various known and new knowledge is combined and integrated in order to achieve the specific goal that has social value. It also includes research activities that develop common theories or principles in technology integration.

Note 3 : *Full Research*
This is a research type where the theme is placed within the scenario toward the future society, and where framework is developed in which researchers from wide range of research fields can participate in studying actual issues. This research is done continuously and concurrently from *Type 1 Basic Research* (Note 4) to *Product Realization Research* (Note 5), centered by *Type 2 Basic Research* (Note 2).

Note 4 : *Type 1 Basic Research*
This is an analytical research type where unknown phenomena are analyzed, by observation, experimentation, and theoretical calculation, to establish universal principles and theories.

Note 5 : *Product Realization Research*
This is a research where the results and knowledge from *Type 1 Basic Research* and *Type 2 Basic Research* are applied to embody use of a new technology in the society.

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Contents

A bioinformatics strategy to produce a cyclically developing project structure

— Comprehensive functional analysis of the drug design target genes —

Makiko Suwa * and Yukiteru Ono

[Translation from *Synthesiology*, Vol.2, No.4, p.299-309 (2009)]

In the midst of the information flood of biological data, the role of the bioinformatics technology rises. This technology is expected to provide information to reduce the risk in the experiments and to help the designing of the experimental protocol. For this purpose, we mainly targeted a G protein coupling receptor (GPCR) and developed a computational pipeline which identifies these genes from genome sequences and performs their functional analyses. The applied results have been worked out into an integrated comprehensive functional analysis database (SEVENS).
This core technology has become the trigger of collaborative researches, which continues today in a spiral evolutionary form. This flow is the dynamic form that continues advancing by the interaction between the research direction determined by three elements as a driving force and the direction of the life science fields progressing rapidly. The three elements are the core technique matured for a long term, the close cooperation with the experiment researcher, and the environment producing technical incubation.

Keywords : G-protein coupled receptor, genome, gene finding, G protein coupling selectivity prediction, a spiral development, SEVENS, GRIFFIN

1 Introduction

Ever since the draft sequence of human genome was published in 2001[1], massive volume of bioinformation began to flood the scene. In about ten years, genome sequence for over 1,000 species of organisms had been decoded. Moreover, with the recent advent of the next-generation sequencer that can decode at a speed that is approximately 1,000 times that of the devices in 2000, there is now a flood of bioinformation. It is certain that an enormous amount of industrially applicable targets (information for genes, RNAs, proteins, etc.) can be obtained in the future, and a highly efficient biochemical experimental technology that can analyze functions will be in demand. However, such analyses require incredible amount of cost and time, and therefore are not feasible at this point.

In this situation, the expectation for bioinformatics technology is increasing. Bioinformatics is a discipline formed by the fusion of biology, information science, and other borderline disciplines. It is a study where large amount of data is processed using a computer, the biological information (code) is digitized and organized as database, the new biological findings are obtained while developing and applying the decoding technology, and the biological phenomena are modeled and described in terms of informatics and physics. It has the advantage of being able to predict and control the behavior of genes that carry biological information. There is the potential that the answer for an analysis that cannot be carried out as a biochemical experiment can be given by the computer at lower cost and higher speed. If this can be accomplished, it may become a navigator that dramatically raises the efficiency of functional analysis experiments.

Among the several industrial application targets, the main biological molecule is the G protein coupled receptor (GPCR)[2]. It exists in the cell membrane, and forms a tubular structure with seven spirals that penetrate the membrane (transmembrane helix). By binding with various ligands, such as neurotransmitters, peptides, odor molecules, and others, from outside the cell, the G protein coupling in the cytoplasm is activated, and the route of information transmission into the cell is determined according to the type (Fig. 1). In many cases, the abnormality of the information transmission system causes severe diseases such as hypertension, cardiac disease, and cancer, and nearly 30 % of the drugs shipped in the world today attempt to control this receptor system. If a drug that can selectively control the activation of G protein is identified, the impact on the market is extremely great. For example, the peptide that controls the expression mechanism of obesity through GPCR is expected to have an enormous market (tens of billions of yen annually) as health food and a useful seed of drugs.

However, biochemical experiments for drug discovery involve extremely high risks and are likened to throwing millions of yen into the sea. For example, the isolation of active peptide with bioactivity is not guaranteed even after years and years of research. Or, in case of searching for the ligand of an orphan receptor whose bonding ligand is unknown, it is necessary to set up a cell environment where

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the GPCR is expressed and can function upon bonding with the G protein. However, since the type of coupled G protein is unknown to the GPCR, it is necessary to set up the experimental systems for all the cell environments where the GPCR is combined with several major types of G proteins. Even if one is capable of reaching this phase, it is difficult to achieve further high efficiency.

In the following chapters, we shall present an approach from the standpoint of bioinformatics to reduce the above-mentioned risks as much as possible, using the GPCR research (hereinafter, referred to as “the Project”) that we have been doing as a model case.

2 Objective of research and research scenario to achieve the objectives

The initial objective of the Project that was started in 2000 was “to present information that contributes to the experimental design by predicting the experimental result with bioinformatics technology, to minimize the risk of biochemical experiment for GPCR drug discovery.”

Specific objectives were: (1) to comprehensively identify and retain the human GPCR genes including the new genes from the genome sequence and to create a database (DB), and to add functional and structural information to these genes in highly efficient manner using the computational method. If the foundation were laid for this DB, it would become easy to find the new GPCRs that may be difficult to isolate or to be expressed by the biochemical experiment.

The other objective was: (2) to develop a program to predict the activation of G protein by entering the ligand and

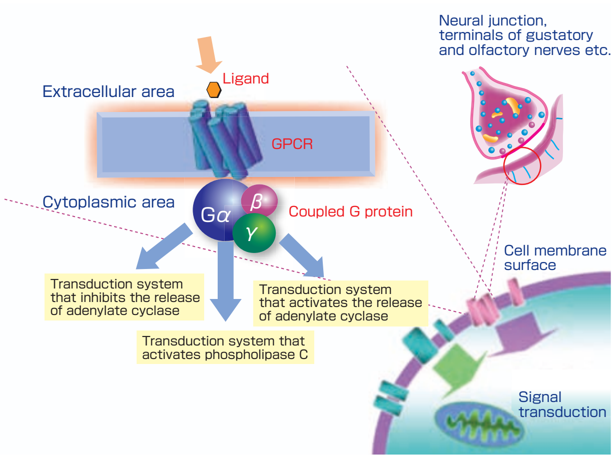

Fig. 1 Conceptual diagram for G protein coupled receptors (GPCR).
The GPCRs are present in the cell membrane at places such as the neural junction (right). Various types of molecules (ligands) from extracellular area bond to the structure that is composed by seven transmembrane helices, whereby activating the coupled G proteins, and the signaling pathway to the cell are determined by the G protein type (roughly 3 types) (left).

GPCR sequence information and to apply this to orphan receptors whose bonding ligands are unknown. By doing so, the combination of the GPCR and the regulatory drug could be investigated comprehensively, and the design of ligand screening experiment for the orphan receptor would be possible. This would then accelerate the pharmaceutical researches.

Above two were the main objectives considered at the start of the Project. The research cycle of bioinformatics, which ranges from basic research to application, is short and as such, the results will instantly become “products” in the form of DB and programs. As the cycle of a typical *Full Research* could be completed in a visible manner, we thought this would be a milestone.

In fact, this would not be the end of the cycle, but it was impossible to correctly draft any future research scenario since the advancement of the life science field was extremely fast. However, we did have some expectations that we would be dealing with a larger flow based on our “product.” Right from the beginning, we could predict that the Project would take several years to be accomplished.

3 First cycle of *Full Research*

Following is a description of the first cycle of the research since the Project was started. It started from identifying the genes from the human genome sequence.

3.1 Gene identification from the genome sequence

The genome is the blueprint of life written on the chromosomes in the cell nucleus. Identifying genes using the computer is like finding a region that has the characteristics of the gene from the DNA (deoxyribonucleic acid) sequence recorded as a long text file. [According to recent understanding, “gene region” has a wide meaning, as it includes the region that codes the functional RNA (ribonucleic acid) as well as the region that codes protein. In this paper, for the sake of discussion, we limit the “gene region” to mean the code region of protein only.]

In most eukaryotes, the genes are separated by several regions called the intron on the genome DNA sequence (Fig. 2). Before this information finally becomes the protein, it is transcribed to mRNA, the introns are cut off, mature mRNA that is bonded only to the exon region of the separated side is formed, and this is then translated into an amino acid sequence. The sequence of three sets of bases that correspond to one code of amino acid during translation is called the codon.

When the DNA sequence is read in order in units of codon, there will be a codon sequence for the starting point. There can be six different codon sequences, including those where one or two bases are shifted from the starting point or where it is read from the opposite end (reading frame). To capture the gene region by the computational method, a model is created by learning the codon at the place where the translation of the protein to amino acid sequence starts (start codon or initiation codon), the codon where it stops (stop codon or termination codon), and the sequence information of the characteristic region such as the boundary between the exon and intron for each reading frame. Then, the regions that match these are extracted.

If the target of search is GPCR, in addition to the general characteristic of the gene, the characteristic region common to protein GPCR is included into the model. These characteristics of the region include the seven transmembrane helixes, as well as the glycosylation site on the NH_2 terminal side of the amino acid sequence, fatty acid binding site of the COOH terminal side, short common functional sequence (functional motif) such as the three amino acids (sequence of Asp, Arg, Tyr (DRY sequence)), and also domains that are globally common over several residues.

The elemental technologies for informatics used in gene identification are groups of programs that capture the above-mentioned characteristics of the gene. An experimental researcher who spends all his/her effort to find new genes without error may be reluctant to use such a program even if the prediction is possible with a certain rate of success. The researcher's demand is that the prediction must be almost entirely correct. Therefore, to allow predictions at extremely high accuracy, we selected a group of appropriate programs from abroad and in Japan, and evaluated their performances.

First we evaluated the program where a known gene sequence is pasted onto the genome by modeling the exon-intron boundaries (ALN[3]), and a program where the expression and transition probability model of nucleic acid base (hidden Markov model) is applied to gene structure (Gene Decoder[4]). We confirmed the maximum length of the gene region from the learned data for nucleic acid sequence region for which

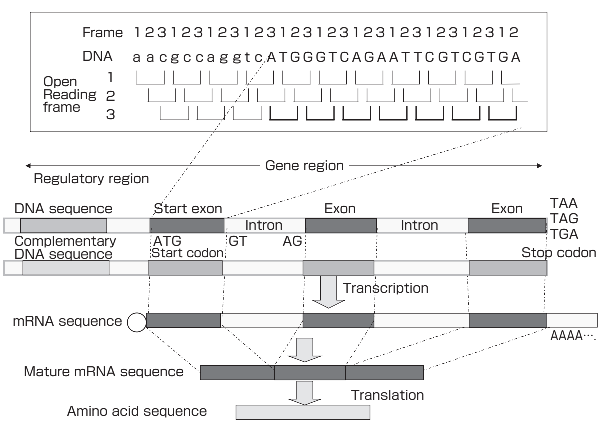

Fig. 2 Conceptual diagram of gene region on the DNA sequence.

the exon-intron structure is decoded in a known gene, and evaluated the ability of the programs to clarify how much upstream and downstream extension from arbitrary exon (additional extension) is needed to cover the entire region of the gene, and studied the sequence resemblance score for identifying the exon most accurately.

Next, as a tool to see whether the gene sequence candidate is actually GPCR or not, the program for sequence investigation (blastp), the program to check the motif characteristic to GPCR (HMMER[5]), and the program to predict the transmembrane helix region (SOSUI[6]) were evaluated. The parameters for selecting GPCR were: resemblance expectation score (E-value) when searching the protein sequence with blastp; E-value for searching the functional motif (Pfam) expressed in the hidden Malkov mode in the HMMER; and the number of predicted helixes in SOSUI. From the learning set including the known GPCR sequence and the non-GPCR sequences in the protein sequence DB (such as UniProt and GPCRDB), the thresholds of the parameters for determining the correct GPCR sequence were set while evaluating sensitivity (percentage of correct predictions among correct sequences) and selectivity (percentage of correct sequences among the predictions). The threshold where almost 100 % selectivity could be achieved while false-negative results (where correct sequence cannot be predicted) were kept to a minimum was defined as "maximum selectivity threshold," while the threshold where nearly 100 % sensitivity could be achieved while false-positive results (where sequence different from GPCR is predicted) were held to the minimum was defined as "maximum sensitivity threshold."

Since the objective was to "understand" the properties of elemental programs that were necessary basic knowledge for solving the issues of the research, this phase could be considered as *Type 1 Basic Research*.

3.2 Gene identification and function analysis pipeline

Based on the research of section 3.1, we developed a system for comprehensively identifying the GPCR gene from the genome sequence. Each elemental program was considered to be a pipe with input and resultant output, and these pipes were joined together step-by-step in optimal order and threshold (SEVENS pipeline, Fig. 3). It is composed of phases for extracting the protein code region from the genome sequence (gene discovery phase), determining the GPCR gene candidate (GPCR gene refinement phase), and adding the function and structure information (functional analysis phase).

This part takes the stance of systematizing by combining the elemental programs and then controlling them as a result and, therefore, may be considered as *Type 2 Basic Research*.

1) Gene discovery phase

The DNA sequence of the genome is scanned for every 6 reading frames, and the corresponding codons are translated to the amino acid sequence, and the fragmented region (corresponding to the exon region) that matches by certain level of resemblance score with the known GPCR amino acid sequence are completely listed (tblasn program). This will narrow down the region where the genes are present, and by using ALN[3], the whole length of the gene corresponding to the known sequence is composed by extending the search region to 1,000 bases upstream and downstream. Also, at the same time, a sequence is obtained by the Gene Decoder[4], which is a probability model of the gene region. Some regions overlap as several sequences match completely or partially, and the parts with significant overlaps are joined to determine the longest amino acid sequence.

2) GPCR gene refinement phase

The determined amino acid sequence is sent to the sequence search program (blastp), the functional motif identification program (HMMER[5]), and the transmembrane helix prediction program (SOSUI[6]) (Fig. 3). By combining the maximum selectivity thresholds and maximum sensitivity thresholds determined for each program in section 3.1, data sets are created from various detection selectivities and sensitivities. While allowing some false-positives (error-in-prediction), if one wished to extract all GPCR, the union of output obtained from the maximum sensitivity threshold for blastp, HMMER, and SOSUI (E-value < 10^{-30}, E-value < 10^{-1}, and predicted number 6~8, respectively) is calculated. This presents 100 % sensitivity at 20.4 % selectivity (level D) for the learning set. On the other hand, the most accurate data set (level A) is the union of output of maximum selectivity threshold of blast and HMMER (E-value < 10^{-80}, E-value < 10^{-10}, respectively). This shows 99.4 % sensitivity and 96.6 % selectivity for the learning set. Also, we created level B (sensitivity 99.8 %, selectivity 70 %) and level C (sensitivity 99.9 %, selectivity 48.4 %) data sets as intermediates between the two levels. Finally the dataset is matched with sequence data for non-GPCR genes, and the wrongly predicted sequences are eliminated.

3) Functional analysis phase

Using the identified GPCR sequence, the sequences related to E-value < 10^{-30} are grouped together, and added to the known family. The sequences that show resemblance of 96 % or over at 100 residues or more for the known GPCR sequence are considered the same as the known sequence, and any other sequences are considered new sequences. If stop-start codons are found in the exon region, it is considered a pseudo-gene. Based on the analysis conducted in the GPCR gene refinement phase, the functional and structural information such as the coordinates on the chromosome, the number of exons, the length of sequence, the sequence search information, the transmembrane helix region, the functional motif region, and the domain region are added to each sequence.

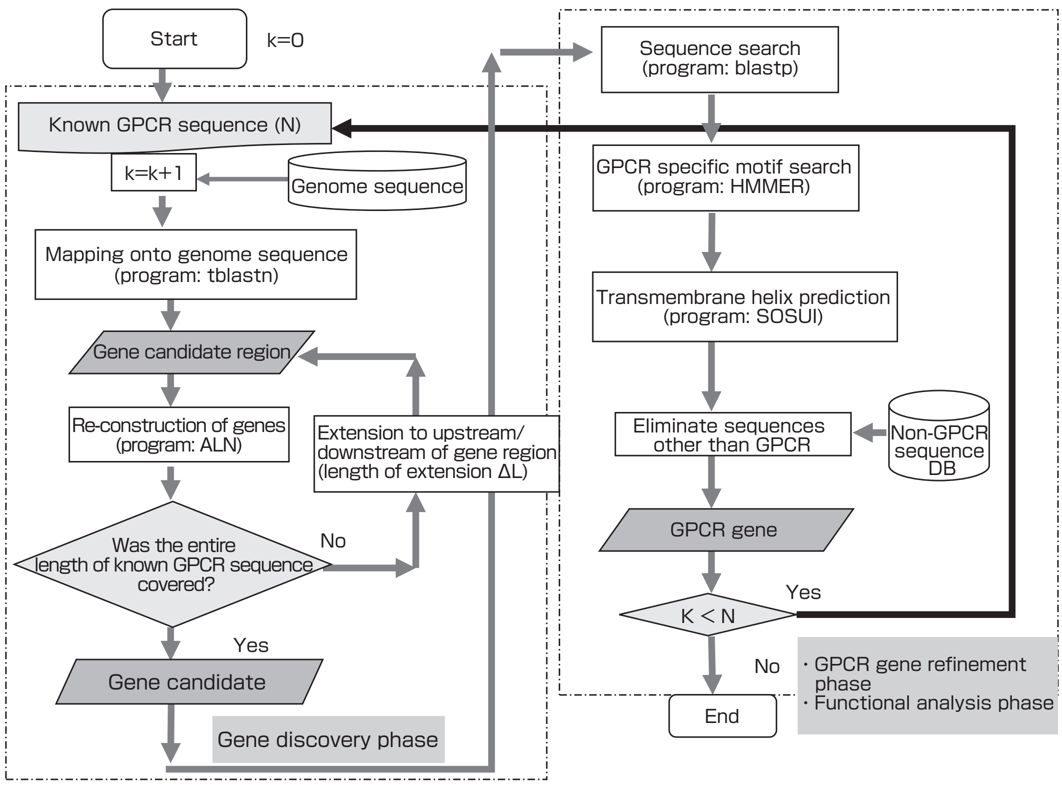

Fig. 3 SEVENS pipeline.

This is an analysis pipeline where various tools are combined sequentially at optimal threshold and order, to comprehensively identify the GPCR genes from the genome sequence.

3.3 Output of the Project

When all GPCRs were identified from the human genome, we obtained 827 level A, 1300 level B, 1517 level C, and 2109 level D sequences. While there were higher possibilities of false-positives (where wrong sequences may be predicted) in sets with higher numbers, they also had higher chances of including new GPCRs. Interestingly, it was found that the majority of the GPCRs were concentrated on chromosome 11, they were dominated by olfactory receptors, and the chemokine receptors were concentrated on chromosome 3. This finding was possible for the first time through this comprehensive gene identification. We applied for patent in 2002 for several hundred sequences that were determined to be new sequences. A certain pharmaceutical company requested disclosure and we received income from this disclosure. Hence, we were able to produce results of the *Product Realization Research*.

The GPCR sequence with additional structural and functional information using the computational method was organized as a database and publicized in 2003 (SEVENS[7] http://sevens.cbrc.jp/1.20/, the very first version). At this point, the core technology was completed to a point, and the first cycle of the Project that started from scratch came to a milestone.

4 Project that undergoes cyclic development

4.1 Hop: Core technology development of the whole Project

The Project that started in 2000 completed one cycle consisting of analysis of elemental technology, systemization, and product realization, and still continues after publication on the website. If the "first cycle of *Full Research*" as described in the previous section was the "hop" of the triple jump, the leap continued in "step" and "jump." Following is the description of the development into joint research, and further technological development through joint research.

4.2 Step: Feedback to core technology through collaboration with industry and academia

In 2002, we experimentally confirmed the expression of several sequences in human tissue for the new GPCR in SEVENS jointly with companies, and applied for patent for particularly important sequences. The fact that the expressions were confirmed for genes predicted by the computational method demonstrated the adequacy of our policy.

However, we also had issues. As a method for confirming the gene expression, we used the polymerase chain reaction (PCR) where minute nucleic acid sequence samples could be rapidly multiplied in a short time. However, it is desirable that the sequence used in PCR analysis have full length with the correct terminals on both ends. However, we found that there were many cases where the terminals were lacking as a result of failure of start (or stop) exon identification in the predicted genes. Most of these were long genes composed of several exons, and since they extended into a wide region, the parameter set in section 3.1 (1,000 bases) was not sufficient as the parameter for the extension of the gene region. Therefore, we investigated the gene existence region to cover a wider area than the commonly assumed area, and it was surprisingly found that it was necessary to extend an arbitrary exon upstream and downstream to 140,000 bases.

Although the subject of SEVENS pipeline was GPCR, it is applicable to other types of protein if the parameters at each phase are changed. We attempted this in the joint research with a venture research center of the University of Tokyo in 2002. In chronic inflammatory diseases, such as rheumatoid arthritis and multiple sclerosis, the immunocytes aggregate excessively at the site of the chronic inflammation and destroy the tissue. This is because the migration of the immunocytes is triggered when the protein called chemokine binds with its GPCR (CCR2). There was a competition for the search of a molecule that inhibits the binding of chemokine (antagonist). However, to avoid the side effects that were expected to occur when the antagonist intercepted the chemokine receptors of different subtypes with structures similar to CCR2 that may be active during organ formation, cell multiplication and differentiation, there was demand to look for a molecule that controlled CCR2 through a different route from the antagonist.

The experimental research showed that a new gene that gathered specifically at the C-terminal of the CCR2 (FROUNT) could be the candidate. We found that this was a long protein composed of 600 residues, where multiple helixes appeared repeatedly. Also, as a result of searching the genome for the characteristic of having several short and weak motifs, we found that there were only two regions that completely matched the new gene, but there were several that showed matches at a weak score. This study was published in *Nature Immunology*[8]. The technologies that were re-investigated in the two joint researches were reflected in the SEVENS pipeline.

4.3 Jump: The development of the new function prediction program

Joint research with a pharmaceutical company started in 2004. Here, a computation system to efficiently and comprehensively screen the ligands that regulate the activation of G protein selectively was build, and we applied this to the ligand screening of the orphan receptors whose binding ligands were unknown.

First, we selected 108 novel human GPCRs from the level A data set of SEVENS. These were orphan receptors. Next, the ligands to be used in screening were comprehensively identified from the human genome based on known peptide ligands after optimizing the gene identification pipeline for peptide ligand search.

On the other hand, we developed a program to monitor the G protein activation. First, using the sequence with known coupled G protein and binding ligand ($G_{i/o}$ type: 61, $G_{q/11}$ type: 47, G_s type: 23), we determined the parameter effective for determining and categorizing the types of coupled G protein and the optimal determination plane from the physicochemical parameters of various sites of the ligand, GPCR, and G protein using the support vector machine (SVM) method that is thought to have the highest identification performance. Using the optimized parameter[9] and determination plane, we created a hierarchical determination program (GRIFFIN) that conducted binary determination of $G_{i/o}$ or $G_{q/11}$ from the remnant after selecting the G_s bonding type upon entering the ligand molecular weight and GPCR. The prediction could be conducted at sensitivity and selectivity of 85 % or higher[10].

Using the above, it is possible to predict the G protein type that is activated in the downstream of signal transmission by the receptor to which certain peptide ligand bonded, based on the database of the ligand that bonds with GPCR, and this will be useful in designing the evaluation system for the expression of the receptor. GRIFFIN would be used for predicting the GPCR with unknown functions in the functional analysis phase of SEVENS.

4.4 Hop again: Type 1 Basic Research to up-scale the research

Up to this point, the research handled human genome only, but this research, in principle, is applicable to genomes of other species. From 2005, we participated in the Scientific Research on Priority Area of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and started comparative genome research in earnest. It was necessary to alter the SEVENS pipeline for other organisms. Based on the genome sequences of about dozen eukaryotes and over 200 prokaryotes that were available at the time, we studied the resemblance expectation score (E-value) when mapping the known gene onto the genome sequence, and the additional extension upstream and downstream to the gene candidate regions. Using the improved pipeline, while GPCR could not be identified from prokaryotes, in eukaryotes, we found some GPCR in yeasts, a dozen in plants, about 200 in insects, several hundreds in fish and birds, and several hundreds to thousands in mammals. Among insects, nematodes, and vertebrates, the minimal number of receptors necessary for life activities such as neurotransmission and intercellular interaction were retained in all organisms, and the types of receptors for complex functions increased dramatically in vertebrates. The receptors for chemical substances in the environment were distributed uniquely in different organisms according to atmospheric or aqueous environments. For example, mammals had high percentage of olfactory receptors in the GPCR genes, and they dominated about 70 %. This indicates that they increased rapidly with repeated high-density gene duplication[11]. The SEVENS pipeline for multiple organisms was almost completely automated at this point, and it became possible to continue analysis even with increased number of organisms.

4.5 Step again: use of pipeline with new protocol

We received high acclaim for identifying and publicizing the GPCRs of various organisms, and from 2007, participated in the Silkworm Genome Project, a joint research of China and Japan. The silkworm genome was the first sequence to be completed for the lepidopterans. By accelerating the production technology development of medical proteins and silk with new functions through analysis, it may contribute to developments of new agrichemicals and insect industry.

We collaborated with the groups from the University of Tokyo and the Kyoto Institute of Technology, and identified the seven transmembrane helix receptors from the silkworm genome and clarified the family distribution. Particularly, we found several characteristics unique to silkworms compared to other insects (drosophila, anopheles, and honeybee) concerning olfactory and gustatory receptors[12].

For this project also, it was necessary to modify the SEVENS pipeline for insects. We conducted studies of sequence resemblance score when pasting the known gene onto the genome, survey of additional extension for upstream and downstream, and the hidden Malkov modeling for common sequences seen only in the insect olfactory receptor. Also, we introduced a new protocol since the aim was to maximize the number of identified genes. In ordinary pipelines, when the known genes are used as seeds, a greater number of gene candidates emerge including new genes. Therefore, by using theses new genes as initial seeds of the pipeline, the number of new genes will increase. This is repeated sequentially until the number of predicted genes settles out (recursive computation). We identified 66 olfactory receptors. Among these, we identified 18 expressions of new receptors, and the odorous material (cis-Jasmone) that attracts the silkworm to mulberry leaves and its receptor were identified for the first time in the world. This became a world-class result in the field of biology, and was published in *Current Biology*[13].

The pipeline for insects and recursive computation protocol are reflected in the current SEVENS.

4.6 Current results, SEVENS and GRIFFIN

As of 2009, SEVENS stores 24,545 genes for 43 eukaryotes, under the support of Grant-in-Aid for Scientific Research (Grant-in-Aid for Publication of Scientific Research Results). It is an integrated DB where various kinds of functional and structural information are visually presented and organized in hierarchical manner. The technologies improved in the joint researches are fed back, and the current information volume is abundant. Figure 4 shows the web page (http://sevens.cbrc.jp) of the current SEVENS.

The top page shows the list of the eukaryotes, and when an organism type is selected, the search page is shown. One can jump to the GPCR detailed analysis page from the chromosome map, the phylogenetic icon, or the search condition entry form. From the detailed analysis page, such information as the coordinates of selected GPCR, exon sequence, sequence resemblance search, gene expression pattern, ligand binding, G protein binding, composition of amino acid sequence, predicted transmembrane helix region, functional motif region, domain region, region predicted to be indeterminate structure (disorder region), exon-intron boundary, pseudo-gene, new gene, and 3D structure modeling can be viewed.

GRIFFIN that was developed for functional prediction can be used on the web (http://griffin.cbrc.jp/). When the molecular weight of the ligand and GPCR sequence are entered, the bonding G protein is predicted. The ligand molecular weight can be set in arbitrary steps for a certain value. The step-by-step ligand molecular weight setting is useful for the prediction of bonding G protein with an orphan receptor whose ligand is unknown.

5 Jump again: future research development

5.1 Understanding high-order biological phenomena

Up to this point, we placed weight on the functional analysis of individual genes from a comprehensive perspective, but in the future, research to understand high-order biological phenomena based on the entire gene network is necessary.

From this perspective, we started working on the system that involves the olfactory receptors that dominate the majority of the mammalian GPCR. The olfactory system induces memories and emotions through multitudinous combination of odor molecule types. Therefore, if this system can be understood systematically, it may lead to research for producing an environment that makes people feel pleasure by blending certain odor molecules.

The electric activation signals from all of the several hundred olfactory receptors that respond to diverse odor molecules are integrated to form 2D patterns (odor map) on the olfactory epithelium. We would like to understand the spatiotemporal cause-and-effect relationships among odor molecules, receptors, cells, and the odor map. Specifically, we are planning to develop a program to predict the activation of all olfactory receptors against odor molecules (activation array), and apply this to all olfactory receptors of humans and mice.

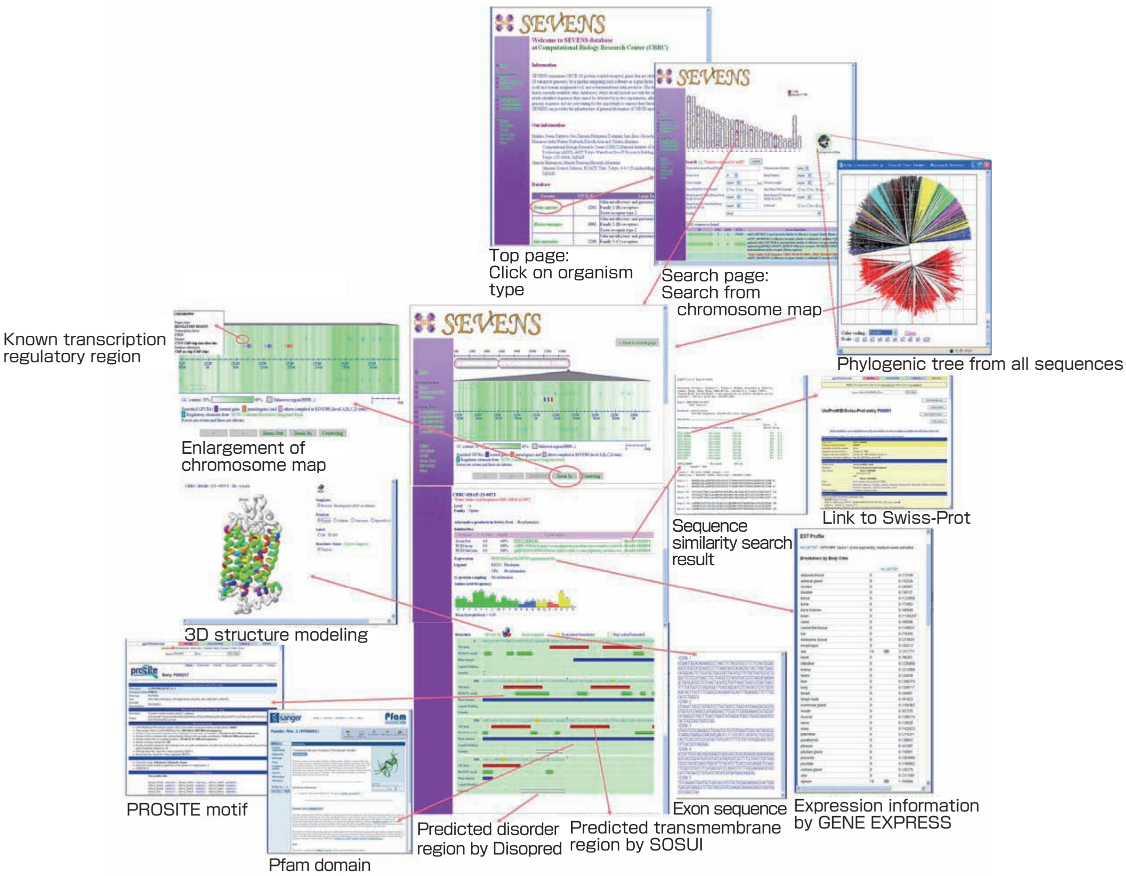

Fig. 4 Current SEVENS database (http://sevens.cbrc.jp).

We already possess all olfactory receptors in SEVENS. We believe we can conduct a response simulation of all olfactory receptors against odor molecules by modifying GRIFFIN.

5.2 New research phase of GPCR

It is necessary to consider the recent rapid advancement in the research on the 3D structure of GPCR. For a long time, the only protein to have its 3D structure deciphered was bovine rhodopsin, and this was used as a mold of the model structure to be analyzed, as a matter of fact, in drug discovery research. However, in 2007 to 2008, the GPCR structures of different families[14][15] were determined one after another, and the conventional research method is expected to change rapidly.

From the new 3D structure, it was found that the differences in the structures of the ligand binding site and the G protein binding site were spread out and could not be ignored between families. It was indicated that it is necessary to determine the 3D structures of all major GPCR families as molds. However, such immediate structure determination is quite difficult as both expression and crystallization have become bottlenecks. Therefore, structural information must be obtained through a different approach from the 3D structure determination. It is important to extract and overview the information that reflects the 3D structure for each family at sequence level, and SEVENS can be used for this very purpose.

5.3 Development of an integrated database

Although the databases containing bioinformation are the foundation of the life science research, their utility is low since they are scattered around in various research institutions. Therefore, the government is working on a system for integrating and managing the various DBs (for example, the Integrated DB Project of MECSST and Ministry of Economy, Trade and Industry). In the future, SEVENS must be designed for such integrations. It is necessary to take measures to completely automate updates for permanent maintenance and management, and yet maintain high data reliability.

6 Discussion

6.1 Research scenario: Cyclically developing Project structure

The results accomplished and the future developments of the Project were presented in the above chapters. It was stated earlier that it is difficult to write a “correct” research scenario into the far future since the advancement of research in the life science field is quick. Yet in retrospect, I think the research developed extremely efficiently. The Project started in 2000, and the first phase of *Full Research* was from the development and publication of the comprehensive DB of GPCR. However, this phase was the “hop” (*Type 1 Basic Research*) of the larger research development phase, and this was followed by the cyclic development of joint research in the manner of *Type 2 Basic Research*, joint research in the manner of *Product Realization Research*, and continues to the present (Fig. 5(a)).

Why did it take such a development form rather than being linear? One could think of the following reasons. First, as described in chapter 2, the time needed for results is short in the bioinformatics fields, and each research phase of Fig. 5(a) tends to be small projects that are resolved in 1~2 years. Considering such small-scale research directions as small vectors, the vector that is synthesized from those small vectors and the direction of life science in its entirety determines the direction of the whole project. The determination of the direction is accomplished at each phase. Next, since the direction of the life science field moves in cyclically developing manner together with dramatic technological development, it will continue to develop under such influence.

What was the driving force that propelled these small vectors without interruption to the present? Following is a list of the factors, and I think these worked as shown in Fig. 5(b) to determine the direction of research.

1) Core technology matured over a long-term

Over 8 years were spent on the Project. Normally, a project spans over about 5 years, and orders to stop the research could have been given at any time. However, in our case, the stage of research continued to rise through the long-term maturation of the core technology. The essential factor that prevented the interruption of the cyclically developing structure is the fact that SEVENS itself won trust by diligently building up improvements in gene identification pipeline, DB, and program. While there are many DBs that are completed, written up in a paper, and are never maintained afterwards, the fact that SEVENS is updated in accordance to the demand of the moment has become a brand power, and I think this is the reason we are getting offers for joint researches.

2) Close collaboration with experimental researchers

The bioinformatics technology is able to process large amounts of data in a short period and produce results. However, whether the results are meaningful or not must be demonstrated in experimental research. By obtaining feedback of the demonstrated results, the parameters set in elemental technology can be modified to move in a better direction. On the other hand, the experimental researchers can use the predictions to modify their experimental system to one with lower risk and cost. In our Project, we discussed extensively with experimental researchers through various joint researches. Feedback in both directions occurred several times, and the improvements of analysis and prediction technologies were accelerated. Our research center does not conduct experiments, but we feel it is necessary to collaborate with experimental researchers at all times in all researches in the future.

3) Place of incubation

The Project started in 2000, around the time of the establishment of the Computational Biology Research Center. It was not necessarily a good start. It was totally new without any model, and we tried to figure out how to start things and groped along the way. Of course, we did have some idea of how the Project should progress. While I had an image of "this can be done by doing this" as a researcher who has been studying the cell membrane protein for a long time, I could have never come up with a method toward specific realization on my own. Working with Dr. Akiyama, a specialist in parallel computing environment, and Dr. Asai, an expert in mathematical models, a powerful analysis could be done using a parallel supercomputer environment and advanced mathematical methods. To this day, discussions with other researchers are inspirational in various scenes. This could not have been possible if it were not done at the Computational Biology Research Center where researchers of various backgrounds are gathered in one place, and I am grateful for this opportunity.

6.2 Achievement of the research objectives

The objective of the Project at its start was to present information that may contribute to the design of experiments by predicting the experimental result to reduce major experimental risks using the bioinformatics technology in GPCR research. Compared to 2000, proteins other than GPCR such as Kinase and protein complex formation inhibitors dominate the higher percentage as drug discovery targets. However, the importance of GPCR has not faded, and the number of academic papers on GPCR is increasing with the increase of bioinformation. Did we achieve our objective in all this?

SEVENS has already analyzed genes that show potential expression in the body as well as GPCRs whose expressions have been confirmed by experiments. Therefore, it is unique since it is capable of a truly comprehensive analysis. We are certain that it can contribute greatly to the general understanding of GPCR and the related drug discovery. Whether it does contribute or not can be indicated by how often the developed tools were used and how much feedback was received. Currently, it is linked to the portal sites of international journals and Integrated DB Organization of MEXT and METI. There are on average about 1,000 serious accesses per month from companies and government organizations in Japan and other countries (such as United States, Germany, France, Brazil, Spain, Italy, and Taiwan). It is also reviewed in international literatures[16][17] as one of the major web DB for drug discovery. GRIFFIN is competing for the top position as a web tool for predicting the G protein

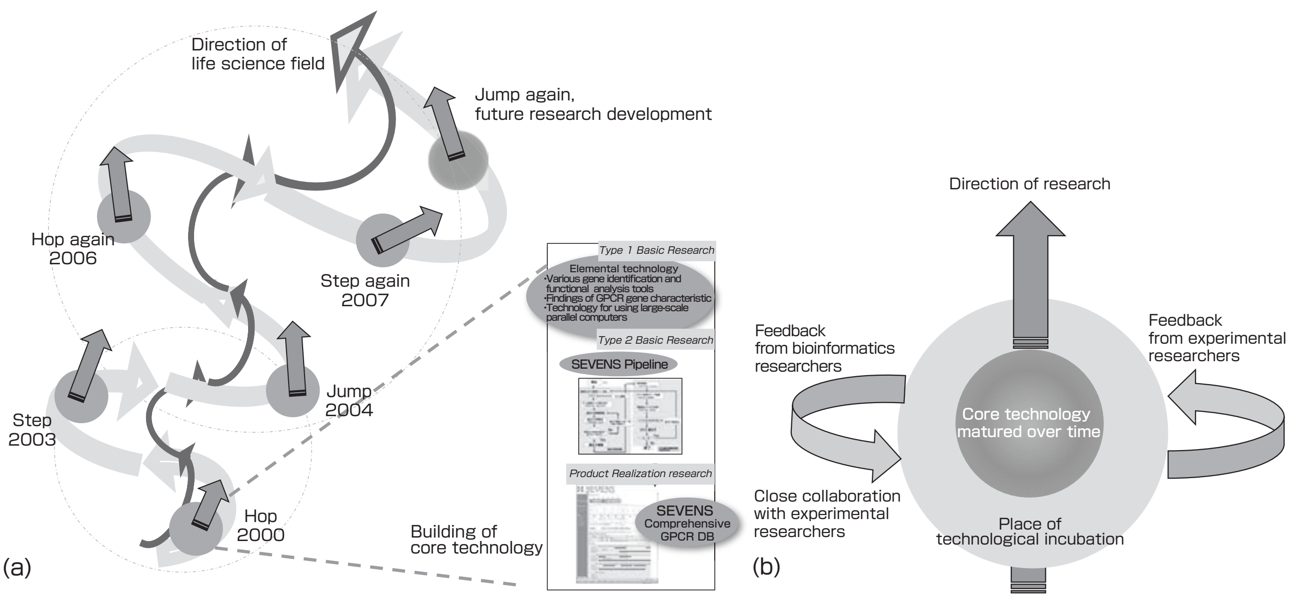

Fig. 5 Conceptual diagram of the research project structure that undergoes cyclical development.

(a) The process from the development to publication of the comprehensive DB for GPCR at the beginning of the Project was *Full Research* in a small scale. This phase was incorporated into the *Type 1 Basic Research*-like phase (hop, hop again) of the greater research development phases, followed by the cyclical development of *Type 2 Basic Research*-like joint research (step, step again) and *Product Realization Research*-like joint research (jump, jump again). This is a form that continues to develop through the interaction of directions of joint researches at each step and the direction of the life science fields that continue to advance rapidly.

(b) Relationship of the three factors that serve as the driving force of the joint research at each step. (1) The core technology that matured over a long period continues to grow and mature further in (2) the research environment that nurtured technological incubation. The cyclic movement (3)with feedback from the close collaboration between bioinformatics researchers and experimental researchers, based on (1) and (2), determines the direction of the vector of joint research. This is much like the determination of the axis direction by the rotation of a gyro.

bond, and this is also reviewed in international literature[18].

As described in chapter 4, various joint researches by collaboration among industry, academia, and government were conducted under cyclic development, and yielded important results. Although this was inconceivable initially, I am surprised that the research developed extremely efficiently in retrospect. At the beginning of the Project, there were mainly joint researches with companies, but joint researches with academia increased in the past 3 years. This shows that the users of SEVENS are increasing and covering wider areas. It is a joy to hear from many experimental researchers of pharmaceutical companies and universities that I meet for the first time at scientific conferences that they use SEVENS or GRIFFIN and that it is very useful in analyzing new genes. Looking back, the initial objectives were achieved to some degree, and I shall give a self-evaluation as being satisfactory.

The SEVENS project will continue to develop in the future. Based on the functional data accumulated over a long time, we wish to produce results that lead to the clarification of high-order biological phenomena in which GPCR is involved through advanced collaboration with experimental researchers.

Acknowledgements

This Project is a joint research with many people. Yutaka Akiyama (Tokyo Institute of Technology; former Director of CBRC), Kiyoshi Asai (The University of Tokyo; Director of CBRC), Masanori Arita (The University of Tokyo), Professor Hiroyuki Aburatani (The University of Tokyo), Tomoyuki Sato (Mizuho Information and Research Institute), and Ikuo Ohkochi (Mizuho Information and Research Institute) helped us incorporate the GPCR gene identification technology. Takatsugu Hirokawa (research team leader, CBRC) and Yukimitsu Yabuki (Information and Mathematical Science Laboratory, Inc.) helped us with the development of GRIFFIN. Wataru Fujibuchi (research team leader, CBRC), Tatsuya Nishizawa (Information and Mathematical Science Laboratory, Inc.), and the students of Nara Institute of Science and Technology helped us in the comparative genome analysis for GPCR. We are truly grateful to the above-mentioned collaborators.

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Authors

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Principle Research Scientist of Computational Biology Research Center, AIST. Completed studies at the Graduate School of Science and Engineering, Aoyama Gakuin University in 1986. Doctor (Science). Worked as technical official, associate researcher of education, Faculty of Technology, Tokyo University of Agriculture and Technology; senior investigator, Helix Research Institute Inc.: chief researcher, Electrotechnical Laboratory, Agency of Industrial Science and Technology; and research team leader and deputy director, Computational Biology Research Center, AIST. Assumed the current position in 2007. Specialties are bioinformatics and biophysics. In charge of the overall coordination for the Project described in this paper.

Yukiteru Ono

Manager of 8th Business Group, Biolife Science System Enterprise Division, Information and Mathematical Science Laboratory, Inc. Completed the master's course in biology at the Graduate School of Science, Nagoya University in 1994. Worked at JASTEC Co., Ltd. and assumed current position in 2001. Specialty is bioinformatics. For this paper, worked mainly on the web interface development for SEVENS and on the implementation of improvements resulting from the joint researches.

Discussions with Reviewers

1 Emphasis points on how the research was carried out

Comment (Motoyuki Akamatsu, Human Technology Research Institute, AIST)

As a *Synthesiology* paper, it is expected that the content will be about "bioinformatics strategy" as mentioned in the title. "Strategic" means that the research was carried out by setting a goal and laying out the research scenario (process) beforehand. If the authors intentionally set up ways to conduct cyclical research, please describe them. If the authors did not intend to do so but things developed spontaneously, I think you should describe what were the conditions necessary for such cyclical development of the DB to occur. Also, I think the main point of this paper is the description of the cyclical development process of the DB, so I think the point will be easier to be understood if you include a diagram of this development process.

Comment (Hideyuki Nakashima, Future University Hakodate)

I think it better to stress the points on your research method for the sake of general readers (researchers of other fields).

Answer (Makiko Suwa)

The bioinformatics strategy described in the text was not necessarily conducted by setting up a research scenario beforehand and then following the road map. Rather, in retrospect, I feel the research developed extremely efficiently regardless of my intent, and therefore I focused on the driving forces that are unique to bioinformatics and that enabled such development.

I think the overall flow of the development of the research project has a dynamic form where there is an upward spiral of the interactions of the direction of individual research that progresses with multiple factors (core technology that matured over time, close collaboration with experimental researcher, environment that nurtures technological incubation, etc.) as driving forces, and the direction of the life science field that evolves extremely quickly. (This development process is shown in Fig. 5(a) and (b)).

I think this form is the result of the characteristics of bioinformatics: it can set diverse directions depending on the situation since it is not strongly limited by research targets; and the individual researches are resolved in 1~2 years since the period required from basic research to application and realization is short.

2 Title

Comment (Motoyuki Akamatsu)

Please consider a title that represents the content from the synthesiological perspective. It must show that this is a paper that discusses research progress where the DB moved in an upward spiral through joint research.

Answer (Makiko Suwa)

The first title "Search and functional analysis of drug discovery target GPCR - Bioinformatics strategy" represented the content of the research, but as you indicated, it did not explain how the bioinformatics strategy is related to the entire Project when seen from a synthesiological perspective. Therefore, to clarify that point, I changed the title to "A bioinformatics strategy to produce a cyclically developing project structure - Comprehensive functional analysis of the drug design target genes."

3 *Type 2 Basic Research*

Comment (Motoyuki Akamatsu)

At the end of paragraph 1 of section 3.2 "Gene identification and functional analysis pipeline," it says that these combined researches can truly be called *Type 2 Basic Research*. If possible, can you explain what points you consider to be *Type 2 Basic Research*?

Answer (Makiko Suwa)

The description you indicate is the part about the development of gene identification and functional analysis pipeline. This can be called *Type 2 Basic Research* because the work is done from the perspective where the elemental programs that are established after accumulation of basic research are combined and systematized, and these are controlled and applied to the subject. I added this explanation.

4 Bioinformatics

Comment (Hideyuki Nakashima)

The explanation of "bioinformatics" on the first page emphasizes the aspect of information technology as a tool for biology. Certainly, that aspect is strong in this paper, but CBRC has emphasized that IT is not merely a tool I think it is better to add the points that the way of thinking and the approach of the information science are also important.

Answer (Makiko Suwa)

I agree that the description you indicate gives the impression that bioinformatics is "merely a tool". It is because we intend to emphasize the advantages of bioinformatics technology, when looking at it from the perspective of reducing the difficulty in experimental research approach. Therefore, I modified the description so that it indicates first the general definition of bioinformatics and after, the above advantage as one part of the whole picture.

Bioinformatics is a wide-ranging discipline with a collection of researchers of varying backgrounds. I feel that the understanding of the definition and the aspect one handles are diverse as they depend widely on the background of the researcher. In my case, I place emphasis on biological findings because I have a biophysics background.

Therefore the trial-and-error process tends to be unrefined work, depending heavily on the research subject. The ideations for “using a tool” such as in which order and how to combine the programs for a particular subject are essential, and that aspect became apparent in the text.

Our approach is different from the information science approach where a beautiful system is applied to whatever subject, but our unrefined approach is also accepted. I believe such diversity gives breadth of expanse in the field of bioinformatics.

The advanced geological researches and fundamental national land information

— Development process of the Geological Map of Japan 1:50,000 —

Makoto Saito

[Translation from *Synthesiology*, Vol.2, No.4, p.321-331 (2009)]

The Geological Map of Japan 1:50,000 shows fundamental national land information of the subsurface materials of the district, and is multifariously used for resources development, disaster prevention, siting of industrial activities, environment protection, and as the geological standard of the district. It is important basic information for understanding natural environments scientifically and is essential information for the sustainable development of Japan. While geological maps mostly made by universities or companies are for understanding specifically interesting strata or rocks, the 1:50,000 geological maps made by GSJ, AIST comprehensively integrate research results of all strata and rocks in the district and explain the geological evolution of the district. There has never been any paper describing the process in developing the 1:50,000 geological map, which integrates geological research for the district. The author shows his own development process with the 1:50,000 geological maps as examples.

Keywords : Geological map, 1:50,000, integration, geology, process, Tomochi

1 Introduction

Geological maps provide fundamental information about the Earth. They show the type, age of formation, configuration, and interrelationships of the rocks beneath vegetation and surface soil. In Japan, the Geographical Survey Institute (Ministry of Land, Infrastructure, Traffic and Tourism) is responsible for topographic mapping of the onshore land surface and landlocked bays and publishes topographic contour maps. The Hydrographic and Oceanographic Department of the Japan Coast Guard is responsible for mapping the ocean floor and publishes bathymetric charts. The Geological Survey of Japan (GSJ) looks beneath the surface of the Earth and gathers information to publish geological maps. These geological maps provide fundamental data for many uses in Japan, including resource exploration, disaster prevention, civil engineering, environmental protection, and academic research.

The basic geological maps published by GSJ are rectangular Geological Map of Japan (GMJ) sheets, which are defined by a grid of longitude and latitude, and are mostly at scales of 1:50,000 or 1:200,000. Maps at 1:50,000 scale are prepared from original geological survey data, whereas those at 1:200,000 scale cover a wider area and are created by sorting, selecting, and integrating (the process of compilation) the geological information from GMJ 1:50,000 sheets and other sources.

There is a variety of strata and rocks within most rectangular map sheet areas. In the past, one geologist could complete the survey for a GMJ 1:50,000 sheet. However, recent advances in the field of geology and geological mapping mean that the cooperation of several geologists with specialized knowledge is needed. Further, greater geological accuracy and professional result of research of individual rocks and strata are demanded than was the cases in the past. All strata and rocks must be unambiguously integrated to provide a plausible geological evolution of the area mapped.

In this paper, I discuss the synthesis and production of a GMJ 1:50,000 sheet from original geological survey data using as an example the Tomochi 1:50,000 sheet in central Kyushu (Figs. 1 and 6), the most geologically complicated GMJ 1:50,000 sheet that has been published recently. I also discuss how GMJ sheets are used for the benefit of Japanese society.

2 Our research objectives

The overall objective for our geological mapping of the GMJ 1:50,000 sheet was to apply state-of-the-art geological concepts to new field survey data. Other objectives were to clarify the relationship of the rocks of each GSJ 1:50,000 sheet to the wider regional geology and to create a new standard for production of 1:50,000 geological maps in each region.

Production of the Tomochi sheet is also part of a plan to methodically increase the GMJ 1:50,000 scale coverage to eventually cover the whole of the Japanese Archipelago. Even if new 1:50,000 mapping does not produce dramatically different conclusions to past mapping, integration of new survey data clarifies the broad regional geology and is an important result of the GMJ program, which also has considerable significance for Japanese society.

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2.1 Previously known geology of the area

The Tomochi 1:50,000 sheet includes the mountainous region of Gokanosho in Izumi-mura village (currently Yashiro-shi) said to have been the new home of fleeing warriors of the Heike clan. The sheet is also upstream of the Itsukimura area in the Kumamoto Prefecture of central Kyushu, which is known for the “Itsuki No Komori Uta” (Itsuki Lullaby). It is characterized by a complicated distribution of diverse strata and rocks in an area of steep mountain terrain that makes field survey work difficult (Fig. 1). The sheet area (23.5 km east–west, 18.5 km north–south, surface area approximately 435 km^2) contains the following geological elements:

1) accretionary complexes in which the rocks of a subducting oceanic plates have been accreted onto continental margins;
2) serpentinite including Paleozoic rocks;
3) metamorphic rocks that have been subjected to high temperatures or pressures;
4) granitic rocks that represent solidified felsic magma rich in SiO_2;
5) continental shelf deposits;
6) pyroclastic flow deposits erupted from volcanoes (Mt. Aso and others).

Almost all of the rock types known to exist in the Japanese Archipelago are found in the Tomochi sheet area. Because we expected the geology to be extremely complicated, we used four researchers with specific but different areas of expertise for our field survey, and we aimed at new results for each rock and strata. No previous geological mapping of the area incorporated the principles of plate tectonics, so the creation of a geological map based on plate tectonics (e.g., one that identifies the rocks of the accretionary complexes) was an important objective.

2.2 Regional geology and previous geological interpretation

The area that lies on the Pacific Ocean side of the Japanese Archipelago from Kyushu to the Kanto Mountains is known as the Outer Zone of Southwest Japan. Within this zone there is a complicated distribution of accretionary complexes formed by subduction of oceanic crust during the Jurassic (200 million to 145 million years ago), strata of Silurian to Devonian age (440 million to 360 million years ago), Permian to Cretaceous (300 million to 65 million years ago) shallow-marine deposits (and some terrestrial deposits), and serpentinites and other metamorphic and plutonic rocks.

2.3 Previous geological interpretations

The classification of the rock formations of the Jurassic accretionary complex and their relationship with other formations is confused. Individual researchers have developed different classification systems. For example, rock

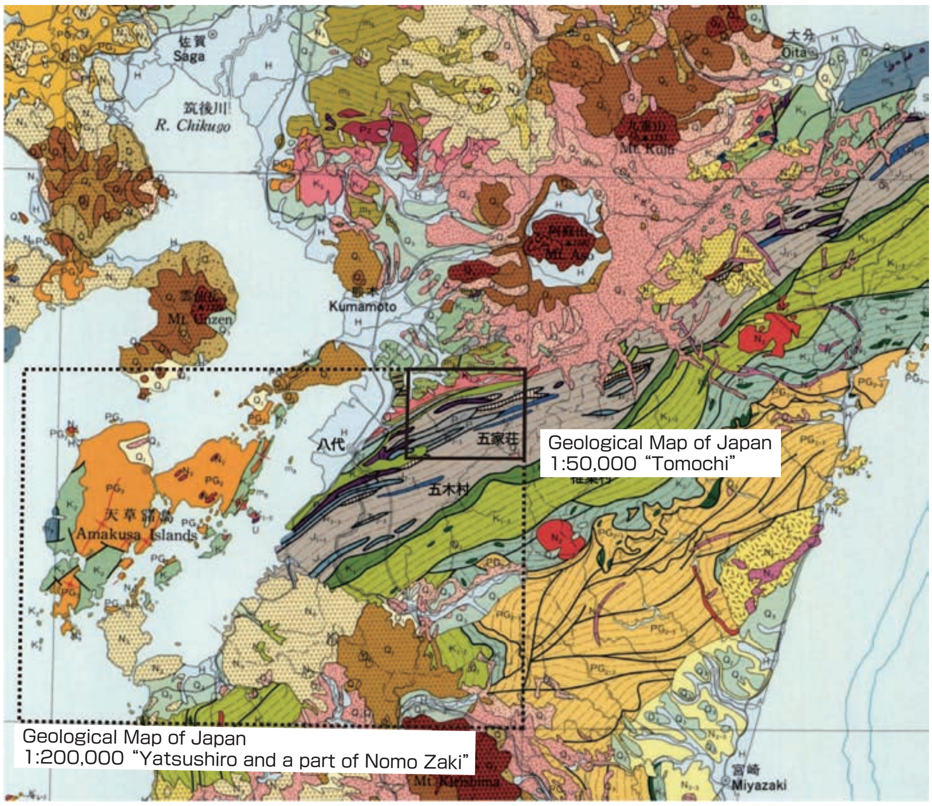

Fig. 1 Location of GMJ 1:50,000 Tomochi sheet (solid rectangle) in relation to the GMJ Yatsushiro and part of the Nomo Zaki 1:200,000 sheet (dashed rectangle)
The base map is the Geological Map of Japan 1:1,000,000 3rd Edition[1].

formations other than the Jurassic accretionary complex have in some cases been called the Kurosegawa Tectonic Zone. Other rock formations have been divided into three belts: the Southern and Northern Chichibu Belts, composed of Jurassic accretionary complexes, and the Central Chichibu Belt including other rock formations. Moreover, in the early 1990s, it was believed that the rocks on Shikoku composed of serpentinite and other metamorphic rocks (components of the so-called Kurosegawa Belt) overlie the Jurassic accretionary complex above a low-angle thrust fault[2][3].

2.4 Our specific geological objectives

In the Tomochi district, in addition to the Jurassic accretionary complex, serpentinites and other metamorphic rocks, Silurian to Devonian sedimentary rocks, and Permian to Cretaceous shallow-marine sediments are widely distributed. Investigation of the regional relationships of the previously identified geological entities was a specific objective of our mapping, with the aim of clarifying the classification of the rocks of the Jurassic accretionary complex and other formations, thus resolving the major contentious issues of previous interpretations of the geological evolution of the Japanese Archipelago.

There were many other interesting issues to investigate, such as the geological structure of Cretaceous shallow-marine deposits, the relationship of Cretaceous metamorphic rocks to the surrounding rocks, and the evolutionary history of Cretaceous high-temperature metamorphic rocks. Another specific objective was to clarify these issues so that our mapping of the Tomochi sheet would create a standard to be used in further investigations of the regional geology over a wide area surrounding the Tomochi sheet.

3 Societal value of the GMJ program

A discussion of the societal value of geological maps such as the GMJ 1:50,000 series has been published by AIST[4], and that of geological maps in general has been considered by the United States Geological Survey[5][6].

Products of the GMJ 1:50,000 series have many uses. Some of these are:

1) civil engineering and construction (e.g., construction of roads, dams, power stations, bridges, and commercial and residential buildings);
2) disaster prevention (e.g., information on active faults, volcanic eruptions, flooding of rivers, ground subsidence, landslides, unstable ground);
3) resource development (e.g., information about oil, natural gas, coal, geothermal energy, hot springs, groundwater, minerals such as metals and clay, dimension stone and aggregate);

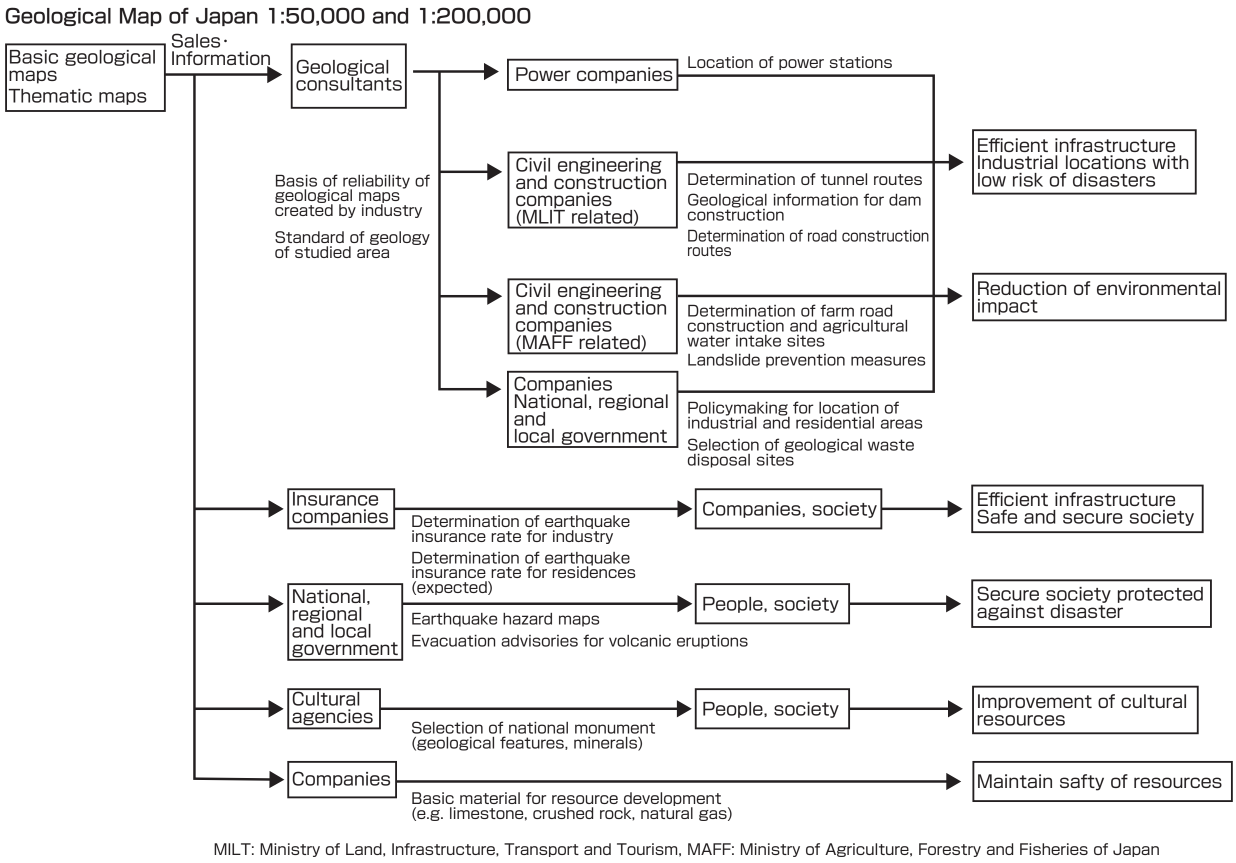

Fig. 2 Uses of GMJ products and outcomes[4].

4) environmental matters (e.g., groundwater flow, underground disposal of radioactive and hazardous waste);
5) academic information for investigation of regional geological evolution (e.g., the process of formation of the Japanese Archipelago, changes in the environment, compilation of seamless geological maps);
6) provision of a standard for investigating the detailed geology of Japan at the district level.

In Japan, geological maps have been produced since the mid-1800s. Initially, the main objective was the development of domestic resources. During the period of rapid Japanese economic growth in the 1950s and 1960s, identification of limestone resources suitable for use in cement was given high priority. Today, although one of the major emphases is on defining resources such as stone for use as aggregate and identifying hot springs, geological maps are used to satisfy other basic and diverse societal needs. They provide information that can be used to mitigate damage caused by earthquakes and volcanic eruptions. They can be used to identify unstable ground conditions, to determine safe locations for industry (e.g., nuclear power stations), and to select disposal sites for waste materials. They are important tools for geological consultants who need to understand the local geology in the areas of their projects. Recently, geological information has been used as a resource for tourism. Geoparks have been established throughout Japan where people can visit interesting geological formations. Geological maps also provide companies with basic information for use in business continuity plans that can minimize disruptions to their business activities following natural disasters. The effects of the use of geological maps described above can be divided into two categories: those that add to the economy (e.g., identification of resources), and those that reduce costs within the economy (e.g., reduction of the costs of disaster recovery).

Each GMJ 1:50,000 sheet is not initiated with any one of the above specific uses in mind. The decision to survey the Tomochi 1:50,000 sheet was made with the primary objective of developing a comprehensive and accurate representation of the geology of the entire district. However, the knowledge and information gained from the survey are used directly by society or through specific-purpose geological maps developed from the survey data (Fig. 2). The former Technology Information Department at AIST stated that the characteristic outcome of geological maps "fans out widely from the Geological Survey of Japan"[7].

4 Methodology for creating the GMJ

The development of a geological map is not a deductive research project. No experiment is performed to confirm a hypothesis. It uses an inductive method, where truth is determined from observations of strata and rocks exposed in a particular area. During a geological survey, a geological model of the area is created in the researcher's mind on the

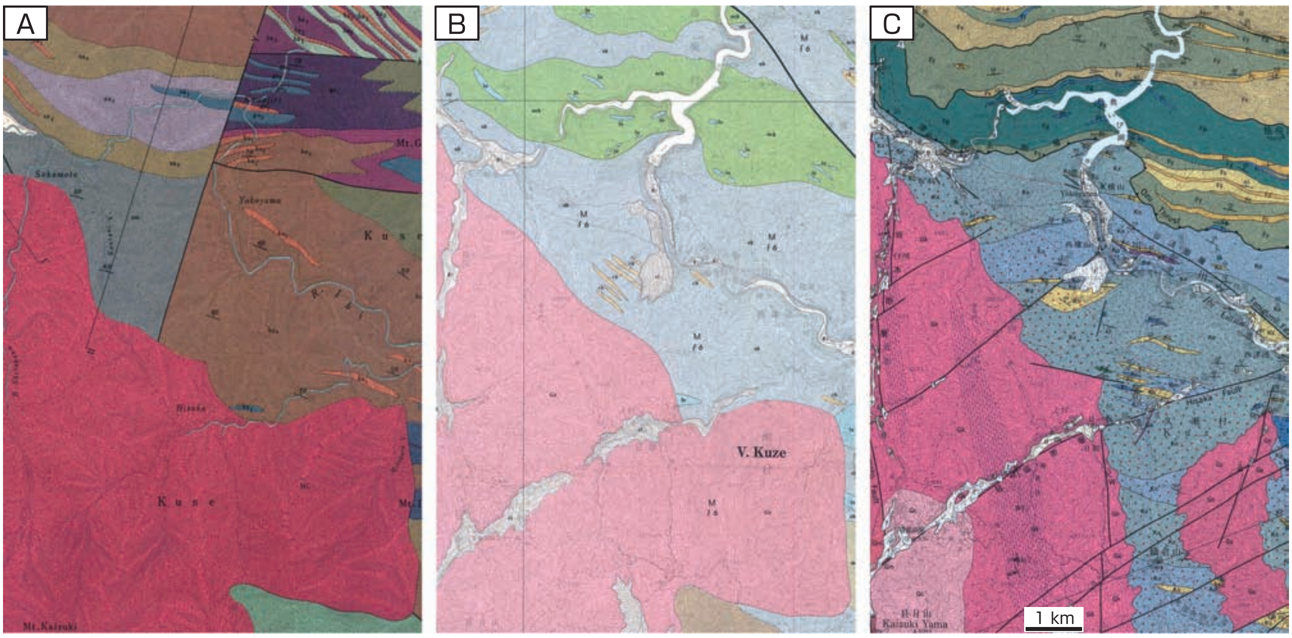

Fig. 3 Example of the changes in the geological map.
Example of GMJ 1:50,000 "Yokoyama" district [revised from Reference 8].
A: Geological map created in the 1960s[9]
The concept of an accretionary complex was not incorporated.
B: Surface geological map created in the 1990s[10]
This map was created without sufficient time for an adequate survey.
C: GMJ Yokoyama 1:50,000 sheet published in 2000[11]

basis of observations, and the model is progressively updated as the survey proceeds. The accuracy of the information gathered in the field is heavily dependent on the skills and knowledge of the researcher conducting the survey. Careful and knowledgeable observation in the field is the most important process in the creation of a geological map, and also can yield new discoveries.

New maps produced using more advanced methods to resurvey previously mapped areas may produce considerable changes. Improved accuracy may be the result of finding new areas of outcrop (places where rocks are exposed at the surface), or because observation methods have improved and geological theory has advanced since the original survey. It is similar to the case where noise may be reduced due to the advancement of the measuring technology and therefore precise measurement becomes possible. This is clearly shown by comparison of previous geological maps of a particular area with a current geological map (Fig. 3).

Therefore, the GMJ 1:50,000 “Tomochi” was expected to become the standard for determining the strata and rocks based on the latest geological knowledge of this district. Also, we employed the following three research methods to obtain advancements in this field as indicated in the research objective.

1) The researchers in charge collected the geological information based on the latest geological findings, and completed the geological map of the district in charge. Taking the example of the strata and rocks of the accretionary complex that the author was in charge, it is currently accepted that structures within an accretionary complex are nearly horizontal and are controlled largely by thrust faults. Within the complex, the rocks above thrust faults are older than those underlying the faults (Fig. 4). We used age data from abundant microfossils (plankton) to establish that the sediments above the thrust faults were older than those below it. Current geological theory also suggests that an accretionary complex in this district should be overlain by a rock sequence that includes serpentinite. During our field survey, we identified the rocks overlying the accretionary complex and noted their structural relationship with the accretionary complex (Fig. 5).

2) Older strata and rocks in their present position have been affected by repeated later episodes of folding and faulting. Therefore, for example, if the deformation that occurred after the formation of an accretionary complex is recognized, by comparing the structure within the complex with the present geological structure it is possible to understand the deformation that occurred both before and during the formation of the accretionary complex. We shared the geological survey data collected by the four researchers at the

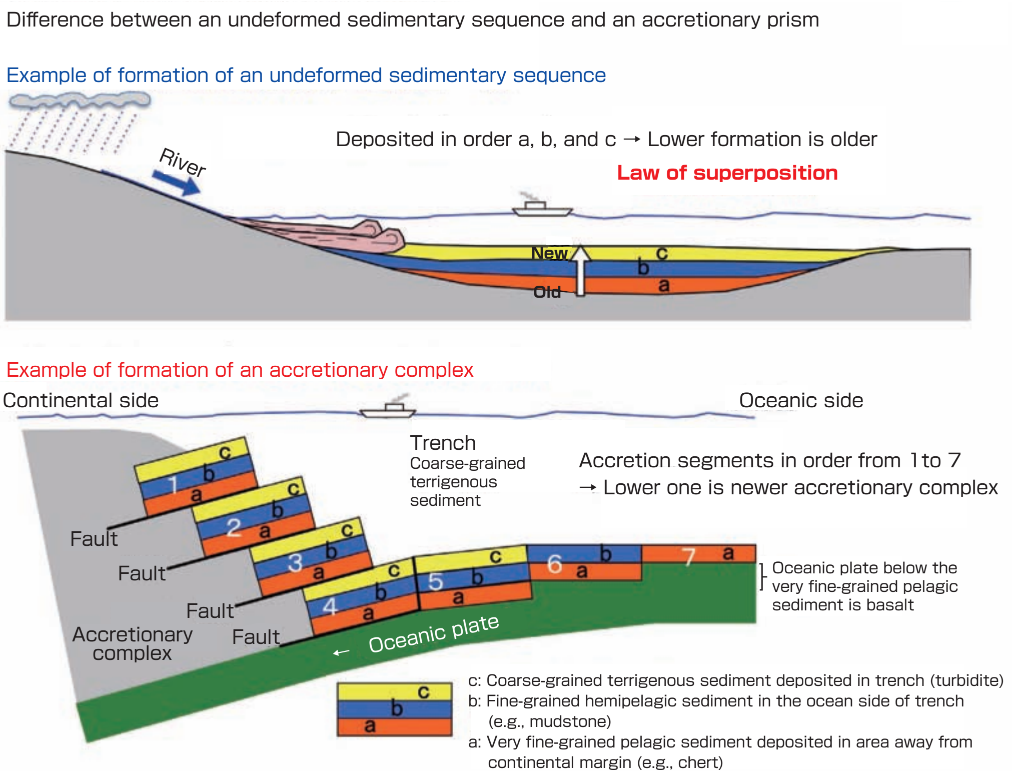

Fig. 4 Difference between an undeformed sedimentary sequence and an accretionary complex.
In an undeformed sedimentary sequence, the age of layers increases with depth (c to a). In an accretionary complex, there is an a-b-c sequence separated by low-angle faults. In each sequence, the age of layers increases in order of c to a, and sequence 1 (uppermost) is the oldest a–b–c sequence, and sequences 2 to 4 are successively younger. The stratification of the accretionary complex cannot be understood if considered in terms of an undeformed sedimentary sequence.

boundaries of their individual survey areas to ensure that the data at these boundaries was seamless.

3) An important aspect of a geological map is that the geological evolution of the rocks of the area being studied (the history of deposition and subsequent deformation of the rocks) is consistent with the present-day distribution and relationships of the rocks in the survey area. The original state of each of the rock unit identified in the survey can be determined (theoretically) by sequentially removing progressively older rock units and the effects of the deformations they have undergone. The principle of uniformitarianism states that the present-day geological processes are the same as those of the past. That is, “the present is the key to the past”. Thus, the structure and relationships of the rock units as they are today must not contradict the relationships of those rock units at their time of formation. The final Tomochi geological map produced from our research was the result of many discussions among four researchers, each of whom had different areas of expertise. In comparison, a geological map created by a single university researcher often reflects the specialized interests and expertise of that researcher. Without the opportunity for discussion among researchers in other fields, it is difficult to create a highly accurate geological map.

In addition to the three points discussed above, the GSJ (the main publisher of geological maps in Japan) must ensure the accuracy of the GMJ, and its reproducibility. That is, the geological maps produced by GSJ in a particular area must not contradict maps of the area produced by others. To ensure the accuracy of their geological maps, GSJ uses an internal multistep peer-review system. GSJ mapping is also subject

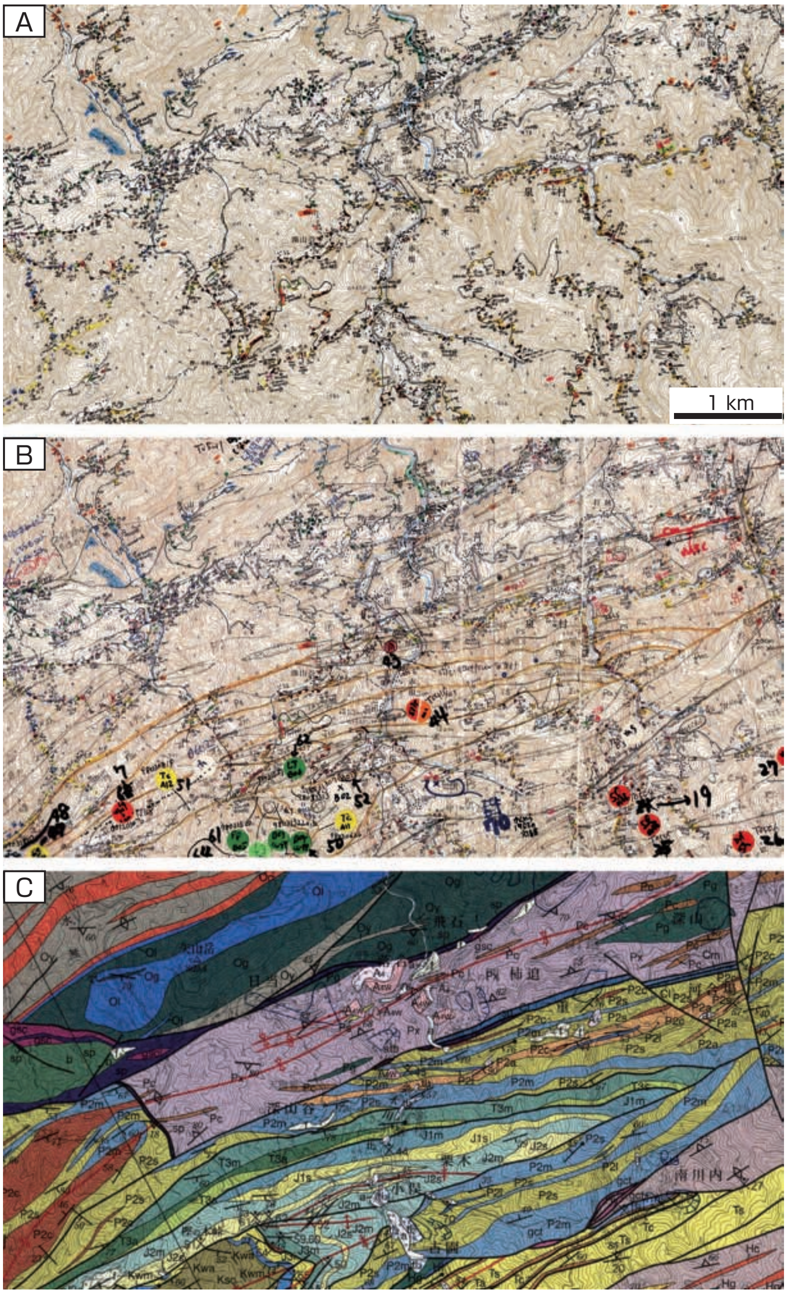

Fig. 5 From traverse map to geological map. Example of southwest area of the GMJ Tomochi 1:50,000 sheet[12].
A: Traverse map
B: Working version of the map with fossil data, formation boundaries, and faults annotated on the traverse map. Microfossil localities are shown as colored circles.
C: Part of the final GMJ Tomochi 1:50,000 sheet[12].
Base map for A and B is the Topographical Map Kakizako 1:25,000 sheet, published by the Geographical Survey Institute of Japan.

to external evaluation by the Geological Society of Japan and others. To allow confirmation of reproducibility, raw data (such as traverse maps and borehole data) are published by GSJ as research reports, and the fossils and rock samples used are registered and stored at the AIST Geological Museum so they can later be validated by other researchers. Future development of a database to catalogue these raw data would facilitate this validation.

5 Research elements in compilation of the GMJ Tomochi sheet

Integration of the research elements used in the creation of a GMJ 1:50,000 sheet is generally preceded by the following sequence of steps.

1) Before the field survey, researchers conduct a literature search and use existing aerial photos and satellite images to identify surface geological and geomorphological features, such as active faults and terraces. Before our mapping of the Tomochi sheet started in 1995, we obtained and interpreted aerial photos published by the Geographical Survey Institute and satellite images recorded by the Japanese Earth Resource Satellite 1 (JERS-1).

2) The field survey provides the basic data required for compilation of a geological map. To complete a field survey, geologists traverse the sheet area (usually on foot) looking for exposed rocks (outcrops) and record detailed observations of them. This field survey technique is most needed for the surveyor, but the know-hows are not available since it is difficult to describe them with words. The field survey approach used is of fundamental importance to the process, and varies greatly depending on the amount and type of exposed rock and the complexity of the geological structure. If the survey is in mountainous or hilly areas, the data is collected largely from outcrops near existing roads and paths, on ridges or valley floors (Fig. 5A). If the survey area is in flat country where there are few outcrops, borehole data acquired by government organizations becomes an important source of information.

The first step of the geological field survey is to determine from the available outcrops the types of strata and rocks in the area. The relationships among these are then investigated. Understanding these relationships is a particularly important part of the process. The characteristics of individual rock units can be obtained from only small areas of outcrops, but it is essential to find the boundaries between rock units to determine the relationships among them. This is achieved by developing a geological model that takes into account the scientific literature, and landforms observed from aerial photos and satellite images. The geological model indicates where there may be geological boundaries, allowing the survey to focus on those areas and thus be conducted efficiently. Because a geological survey is an observation of nature, the observations often do not exactly match the model. Therefore, as new outcrop information is gathered, the geological model is revised in the mind of the researcher to fit the new data, and the survey continues with, if necessary, a shift in emphasis influenced by the changing model.

Most of the Tomochi sheet area is mountainous, so the survey was conducted along roads, valley floors, and mountain ridges (see the traverse map of Fig. 5A). Although we expected the geology to be complex and the field survey to be time consuming, it was even more complex than we anticipated and required more time than was scheduled.

3) In addition to field observations, rock samples and fossils are collected during field work. The subsequent analyses and interpretations of these are reflected in the final geological map. The rock samples are cut into thin sections (0.02−0.03 mm thick) for microscopic examination to identify the rocks from their constituent minerals and to extract evidence of deformation and metamorphism. Samples expected to contain microfossils are chemically treated to extract the microfossils which are then examined under the microscope. Other laboratory work includes separation and identification of heavy minerals and dating of the rocks by radio-isotope methods. Together, these data can reveal properties of the rocks such as their age and the environment in which they were formed, which cannot be obtained by field observations alone. The results are fed back to the actual field survey. These contributions to the production of a geological map correspond to the academic research (*Type 1 Basic Research*) conducted by universities, and if significant results are obtained, they are published as individual papers.

The following subjects with relevance to the Tomochi sheet area were addressed by academic papers published before the creation of the GMJ.

(1) Clarification of the stratigraphy and structure of the Lower Cretaceous Tomochi Formation[13]
(2) Identification of the basement of the Lower Cretaceous Tomochi Formation as the Permian accretionary complex[14]
(3) Identification of Devonian strata from the discovery of *Leptophloeum*, a Late Devonian fern[15]
(4) Clarification of low-pressure high-temperature metamorphism of the Higo Metamorphic Complex in the northern part of the Tomochi sheet[16]
(5) Discovery and description of megacrystalline clinopyroxenite[17]
(6) Discovery of jadeite and its relationship with surrounding rocks[18]

Oral presentations to earth science and academic societies were also made on these and other related topics.

Fig. 6 Published GMJ Tomochi 1:50,000 sheet and accompanying report.
(A4 size, more than 200 pages[12])

6 Creation of the GMJ by integration of research elements

The GMJ Tomochi 1:50,000 sheet (Fig. 6) was finally compiled from the individual research elements described above. We found that the rocks exposed on the Tomochi sheet area ranged in age from the late Cambrian Period (at the beginning of the Paleozoic Era about 500 million years ago) to the present day. Classifying all of the geological features shown on the final map required 149 entries in the map legend. This is the largest number of legend entries to date for a published GMJ 1:50,000 sheet. Our map incorporated the concept of an accretionary complex and took into account the latest available information from the research papers listed in the previous section, as well as other research in the district (e.g., reports of large fossils in the area). The integration of all these sources of information produced a very detailed geological map. A report containing the data and analyses that support the final map was also published (Fig. 6). This report includes the route maps that provided the basis of the classification of the rocks and strata and the microfossil data used to determine the age of the rocks of the accretionary complex. The research that led to the final Tomochi 1:50,000 sheet provided the basic information and analysis that were used to create the regional GMJ Yatsushiro and a part of Nomo Zaki 1:200,000 sheet [19].

As previously mentioned, in creating a geological map it is important that the evolutionary model of the area is consistent with the distribution and relationships of the present-day rock units. The four researchers involved in mapping the Tomochi sheet engaged in long discussions to ensure this was the case. For example, we discussed the relationships of the Jurassic accretionary complex with serpentinite and other metamorphic rocks, with the shallow-marine deposits covered by low-angle thrust faults, and the overall geological evolution of the area.

Through these discussions we identified positive evidence that the rocks of the previously identified “Kurosegawa Belt” overlie Jurassic rocks above a low-angle thrust fault. This important finding established the existence of the Jurassic accretionary complex and is an important finding in the context of understanding the geological structure and evolution of southwestern Japan. We created a cross sectional diagram to illustrate this (Fig. 7). Moreover, through our discussions we were better able to understand the spatial and temporal relationships of the rocks of the “Kurosegawa Belt”, and also able to obtain results on the evolutionary history of the geological structure from the time it overlapped onto the Jurassic accretionary complex as a low-angle fault to present.

We also presented details of the evidence for faults in outcrops in the report that accompanies the published Tomochi sheet. This information can be used to verify our interpretation of the position, extent, and continuity of the faults. During our discussions of the faults, we were able to confirm the position of the concealed fault (i.e., where it is buried by younger sediments) and identify the faults that we could not confirm as active faults but which could be geologically recognized as active faults.

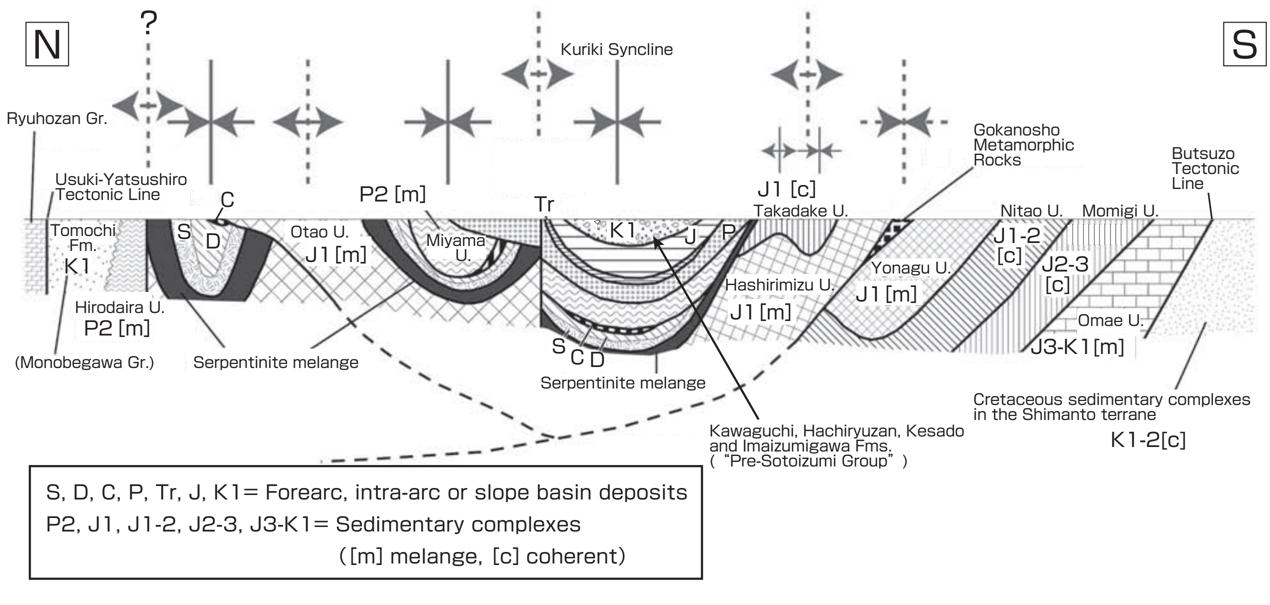

Fig. 7 Schematic cross section for the south to central area of the GMJ Tomochi 1:50,000 sheet area.

Serpentinite (serpentinite melange in the diagram), normal sediments, and the Permian accretionary complex (P2) overlie the Jurassic accretionary complexes (J1, J1-2, J2-3, J3-K1). The boundary between the Jurassic accretionary complexes and overlying rocks and strata was originally an almost horizontal fault, but was subsequently folded. This diagram summarizes the geological theory and evolution of the Tomochi district.

7 Value and uses of the GMJ Tomochi 1:50,000 sheet

The published GMJ Tomochi 1:50,000 sheet provides geological research results for an area that is geographically difficult to survey and geologically complex. We created an accurate geological map based on up-to-date geological theory and other current published information. This map will set the standard for determining the geology of this area and the surrounding region. On the basis of our work on the Tomochi sheet, we are now creating a regional-scale GMJ 1:200,000 map covering the Yatsushiro and a part of the Nomo Zaki sheet[19]. Our evidence-based interpretation of the geological structure and evolution of southwestern Japan advances the broader understanding of Japanese geology.

The published Tomochi sheet is not simply the result of basic research on individual rock units. It represents the synthesis of information from several geoscientific disciplines to create a geological map. Further, it is one individual published map of many that constitute the entire GMJ, for which there are many important uses in Japanese society.

The Tomochi 1:50,000 sheet, and the GMJ as a whole, are used not only immediately after publication. They will be valid for several decades and will continue to be used to satisfy basic societal information needs. Thus, the GMJ provides research results with a longer lifespan than, for instance, engineering research. However, some uses are expected at this point as follows.

7.1 The Tomochi sheet as a mapping standard

An example of the use of the Tomochi sheet as a standard is provided by the 1:200,000 GMJ of the Yatsushiro and part of the Nomo Zaki sheets[19]. In compilation of this map, the rock classifications of the Tomochi[12] and the GMJ Shiibamura 1:50,000 sheets[20] were used. Within this 1:200,000 sheet area, the geological classification of the Tomochi sheet was the most complex, and its completion was a prerequisite for compilation of the entire 1:200,000 sheet, which filled the last blank area of the GMJ 1:200,000 series in Kyushu.

7.2 Industrial locations

The Tomochi sheet clarified the relationship of the Jurassic accretionary complex with the rocks of the “Kurosegawa Belt” (that the “Kurosegawa Belt” rocks overlie the Jurassic accretionary complex above a low-angle thrust fault) (Fig. 7).This understanding can be transferred to improve understanding of industrial locations in areas of similar geology (e.g., the location of the Sendai Nuclear Power Station in Kagoshima Prefecture).

7.3 Disaster prevention

We believe the Tomochi sheet can contribute to the prediction of landslides, because it has clarified the structural relationships in areas of serpentinite rocks, where landslides are known to occur. Further, there are frequent failures of road embankments in the Tomochi area, for roads ranging from National highways to forest roads. These failures are commonly related to the local geology. Thus, the Tomochi map can provide basic information that can be used to develop measures to prevent these failures.

In the report that accompanies the Tomochi sheet, we have described both faults that have been repeatedly active since the late Pleistocene (125,000 years ago), and which are expected to cause future earthquakes, and faults that were not identified as active because there were no formations younger than the late Pleistocene to provide evidence of their activity. The map and report can therefore be used for investigation of regional crustal movement during the period from the late Pleistocene to the present.

7.4 Mining resources

Mapping of the Tomochi sheet indicated that the prospects for metal resources in the area are poor. It showed that limestone rocks are abundant in the mountainous regions, but that further development of these resources is unlikely, except in the northern area where there is current mining and transport infrastructure available. The prospects for other mineral resources and crushed stone are also poor. On the other hand, a hot spring developer indicated that the Tomochi sheet will be used extensively for hot spring development projects in the area.

7.5 Tourism

New uses of the Tomochi sheet include regional promotional activities and tourism. The research report that accompanies the map describes previously known sites of general interest, such as stalactite caves, and a natural stone bridge formed by welded pyroclastic rocks deposited about 90,000 years ago. There are natural features within the Tomochi sheet area that are potential national monuments, and others suitable for geo-sites or geoparks. These include previously known Cretaceous ammonite fossils, recently discovered Devonian fern fossils[15], megacrystalline clinopyroxenite[17], and deposits of jadeite[18]. These are described in the accompanying report.

Also, the geology of the mountains used for the mountain events of the National Athletic Meet as well as the mountains that comprise the unique landscape of the region are clarified, and this can be used as material to explain the natural environment of the district.

7.6 Utility value of the GMJ

The GMJ Tomochi 1:50,000 sheet will have many uses for decades after its publication. In addition to conventional uses of geological maps, new uses may arise in response to changes in society, or to the occurrence of natural disasters.

For society to continue sustainable development, human beings must have a scientifically based understanding of the natural environment. The GMJ Tomochi sheet and the GMJ in general are expected to play a crucial role in providing this understanding.

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Discussions with Reviewer

1 Use of geological data collected by other institutions

Question and comment (Akira Ono, AIST)

This article allows readers from other fields to understand that the GMJ 1:50,000 is created, and reviewed from various viewpoints based on the latest geological findings and with consideration of how it will be used by society. It is also an excellent paper of *Type 2 Basic Research* in its structure and content.

I got the impression that the creation of a geological map, as described in this paper, is an ambitious work that predicts the three-dimensional structure of a vast subsurface space from geological data obtained from sparse outcrops on the surface. Perhaps there is not much borehole data in the region mapped, but how would available borehole data be used? Would they be used as basic data for creating the geological map, or would they be used to validate the accuracy of the created geological map? Also, local governments and private companies in that area may conduct geological surveys for their own purposes. Does AIST use such data to make its own geological maps?

Answer (Makoto Saito)

1) The reviewer is under the impression that we make our predictions from the sparse outcrops on the surface, but it is possible to obtain sufficient data even if outcrop areas are small, particularly if we walk along a traverse that allows us to observe the overall picture of the strata and rocks. When creating the GMJ, in some places the geological map can be created from traverses at wide intervals, whereas in other places it cannot be made without a very detailed grid of traverses. We devise ways to undertake our surveys so we can collect sufficient data for mapping while also keeping the cost of the survey in mind.

2) As written in the paper, if there is local government borehole data that can be disclosed, of course, we use it in the compilation of the geological map. There are not many outcrops on the plains, but there is a lot of borehole data available from local governments in these areas, and we collect and analyze them carefully to create the GMJ. This is because the underground geology is particularly important on a plain. For the Tomochi sheet, we were allowed to view some commercial borehole data (not usually disclosed) obtained by hot spring explorers.

3) We also collect and use other geological maps. These include geological maps made for the public works of local governments and the national government. If these geological maps are based on data interpretation, we consider whether the interpretations are valid from the traverse maps and reports from which the interpretations were made. We also collect sketches from dam sites and tunnel walls. For our mapping of the Tomochi sheet, we looked at the geological maps from hot spring survey reports compiled by local governments, and used them to validate our geological map (in reality, the only useful things were the traverse maps in a few small areas).

2 Expansion of coverage and update cycle of the GMJ 1:50,000

Question (Akira Ono)

I understand that the GMJ 1:50,000 series is based on the latest geological findings. What is the cycle for re-survey and revision of the GMJ 1:50,000 series? Specifically, when was the last map before the current Tomochi sheet created? I imagine a survey requires a lot of labor and time. At this point, does the GMJ 1:50,000 entirely cover Japan? Please tell us about the basic thinking concerning the expansion of the area mapped.

Answer (Makoto Saito)

1) Re-surveying for the GMJ 1:50,000 series is not planned at present because we have not yet covered all of Japan. However, we finished the first phase of the GMJ 1:200,000 in FY 2009 and some of these sheets will be replaced with new ones that incorporate the latest findings. For revision of the GMJ 1:200,000 series, the GMJ 1:50,000 sheets provide the standard for geological classification. They also provide new geological information in areas that were previously poorly understood during 1:200,000 sheet compilation. Therefore, although, in principle, priority is given to areas not yet mapped at 1:50,000 scale, a few areas essential for revision of the GMJ 1:200,000 series are also given priority.

2) The GMJ Tomochi 1:50,000 sheet had not previously been created. Surface geology maps of doubtful accuracy were produced during a Fundamental Land Classification Survey undertaken originally by the Economic Planning Agency, later by the National Land Agency, and now by the prefectures under the current Ministry of Land, Infrastructure, Transport and Tourism.

3) It will be difficult to expand the GMJ 1:50,000 series to cover all of Japan with the current number of researchers at AIST. Future expansion will be primarily into important areas such as (1) densely populated cities and surrounds, (2) areas important in terms of disaster prevention, including those subject to earthquakes and volcanic eruptions, (3) areas with high social importance such as geoparks, and (4) areas that are essential for the understanding of Japanese geology (for example, areas required for revision of the GMJ 1:200,000 series).

3 Is creation of the GMJ *Type 2 Basic Research*?

Question and comment (Akira Ono)

There is a geological research paper entitled "Creation of seamless geological map of Japan at the scale of 1:200,000 and its distribution on the web" in *Synthesiology* Vol. 1, No. 2. Referring to the "Discussion with Reviewers" at the end of the paper, "5. Researches on geological maps" contains a discussion of whether the creation of the GMJ should be considered *Type 2 Basic Research* or *Type 1 Basic Research*. What does the author of this paper think about this?

Even if the geological data of the original outcrop may be the same, the geological maps may be created quite differently, depending on the knowledge and understanding of individual geologists. If the content of the geological map depends greatly on these attributes of individual researchers, this may have a negative influence on the reliability of the map. Reliability may be improved by introducing some standard procedures for geological map creation, including a reviewing process by third parties. What is the current status for this? Please tell us if the author has any insight on this matter.

Answer (Makoto Saito)

1) In *Synthesiology* Vol. 1, No. 2, the authors state in their "Introduction" that the GMJ represents *Type 1 Basic Research* and production of a seamless geological map represents *Type 2 Basic Research*. They also suggest that the valley of death represents a "situation when the data become hard to use because they are drawn based on an old geological model." In the final paragraph of the "Introduction," they state that although the compilation of geological maps has aspects of *Type 2 Basic Research*, it tends to represent basic research that incorporates advanced research results and, therefore, aspects of *Type 1 Basic Research* are more prominent. On the other hand, in "Discussion with Reviewers," a reviewer states that "there is inconsistency in the logical development to say all geological surveys up to now are *Type 1*" and "it has elements of both *Type 1* and *Type 2* … and it is grounded in *Type 2*." However, the lead author denies that it is grounded in *Type 2 Basic Research*. To support his argument, he states that the essence of "*Type 2 Basic Research*" is to extract a generalized methodology to realize a social value, and this was not carried out in the production of their geological map.

I think the different perspectives of the head author and the reviewer depend on their different research careers. The lead author was involved in the creation of the GMJ and the reviewer was a user of geological maps. I do not agree with the reviewer's view that GMJ is grounded in *Type 2 Basic Research*, but, unlike the lead author, I do not think it is essential that a geological map extracts a generalized methodology to realize a social value for it to be considered *Type 2 Basic Research*. I think the important element of *Type 2 Basic Research* is that the knowledge is presented in a form that can be directly used by society.

The outcome report (Reference 7) shows that there are several ways in which the GMJ is used. These include cases where particular content of the GMJ, or the entire GMJ, is used directly by an end user, and other cases where, for example, a consultant company extracts information from the GMJ directly but then provides that information to a client. In this case, the information may be provided to the client as another special geological map created from the GMJ for a specific purpose or a seamless geological map created from the GMJ. Because the GMJ can be used either directly or indirectly through a derivative map, I cannot draw a clear line between *Type 1* and *Type 2* research, but I do say that it satisfies some of the criteria for both *Type 1* and *Type 2* research. The GMJ Tomochi 1:50,000 sheet is *Type 1 Basic Research* in the minds of we who created it, but we did draw this geological map with accurate lithofacies distributions to be useful directly.

2) The several procedures applied to guarantee the reliability of the GMJ are described in the text. One of these is a multistep GSJ internal peer review system. The GMJ is published by GSJ, AIST, and is checked more thoroughly before publication than academic research papers. These checks include an internal review by geoscience specialists, by the manager of the GMJ team, and by the GSJ publication department. In fact, some completed maps have failed to pass successfully through internal checks and have never been published. After publication, we actively seek further evaluation of GMJ products by academic societies. The Tomochi sheet was reviewed in an article of the *News of the Geological Society of Japan*. Uniform notations are used in the geological maps according to Japanese Industrial Standards regulations. Because the GMJ is a product of research, it is undeniable that its quality depends on the ability of authors. However, authorship is annotated on the published GMJ; a specialist can recognize the authors and know their areas of specialization and their research skills. The display of authors' names is the driving force that an author keeps and improves accuracy.

I think the measures described above provide an appropriate guarantee of the validity of interpretation of the data and the accuracy of the published GMJ products.

Improving the reliability of temperature measurements up to 1550 °C

— Establishing the temperature standards and calibration system for thermocouples —

Masaru Arai *, **Hideki Ogura and Masaya Izuchi**

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Since late 1990's, the reliability of temperature measurements at high temperatures was remarkably upgraded by establishing the national measurement standards for calibration of thermocouples up to 1550 °C, and by implementing the traceability system. The traceability system, structured as a hierarchical link of calibrations between the national measurement standards and practical measurements, was designed in consideration of various elements such as availability of the measurement standards and sharing the responsibility with accredited calibration laboratories. The optimized scheme for industries in Japan was established by promoting a balanced combination of conventional techniques held by accredited calibration laboratories and progressive technology, taking into account the spread of the progressive technology.

Keywords : Thermocouple, measurement standard, calibration, temperature fixed point, eutectic point

1 Introduction

This paper describes in the framework of "synthesiology" about the development of the national measurement standard for a temperature range of 1000 °C to 1550 °C, and the establishment of a system that disseminates these temperature standards to the users in the field via the calibration laboratories, as a response to the rising demand from industry for the improvement of reliability of temperature measurement. Measurement standards will never find its importance until it is widely used in society. To implement a system that enables every on-site measurement to be traceable to the national standard, a system design that combines both the technologies that are currently available and those newly developed should be desirable. In this paper, the construction of a high-temperature standard system is discussed in detail, by focusing on the technological background of a newly developed transfer standards. We present the process of designing and forming such a standard system, by selecting the optimum among various scenarios upon the background, choosing the essential elements for ensuring high reliability of temperature measurement, and actually integrating these elements to accomplish our objective.

2 Social demands for high temperature measurement

The temperature range from 1000 °C to 1550 °C is important for the material (iron, steel, etc.) industries, the heat-treating process in the parts manufacturing industries and the semiconductor process industries. Considering the fact that thermocouples[Term 1] are the most commonly used thermometers for this temperature range, it is necessary to build a temperature standard traceability system for thermocouple calibration.

In Japanese industry, the standardization of the calibration and the testing method on thermocouples has been started in a relatively early times, leading back to the 1960s, when numerous investigative researches and joint experiments were performed by academic societies and industrial associations to ensure the reliability of temperature measurements One of the achievements was a method for calibrating the noble metal thermocouples using the melting point of palladium (1553.5 °C). The driving force of this development was the iron and steel industry that required measurements of the molten steel temperature at around 1500 °C with a precision of approximately 2 °C. Another achievement was a joint research for establishing a calibration method for the noble metal thermocouples based on the temperature fixed point [Term 2] up to 1100 °C. This joint research was motivated by an increased demand in the semiconductor-process industry in the 1980s, for fulfilling the technical requirements for the Class 1 thermocouple[1], the highest precision standard as designated by the International Electrotechnical Commission (IEC) for the temperature range up to around 1100 °C.

While, on one hand, such efforts were made in industry, it had been regrettable on the other hand that the national measurement standards that should be the reference were not sufficiently prepared at the time. There was, therefore, no way to verify either the calibration methods developed by industry or the reliability of thermometers calibrated

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by them. To solve this issue, the national measurement standards are developed and the temperature standard system is constructed. The aim is that the developed national measurement standards are transferred to the user's thermometers, and further, the calibration values declared by the calibration laboratories or thermometer manufacturers become verifiable, so that the reliability of thermometers widely used in society can be ensured.

3 Selection of scenario for the thermocouple traceability

In this chapter, the framework of the traceability system of thermocouples will first be described. It is followed by the description of the selection of scenarios that leads to the most-fit system design and the consideration on elements essential for implementing the selected scenario.

3.1 The framework of the thermocouple traceability system

Figure 1 shows the basic framework of the national measurement standards for temperatures in the range between 1000 °C and 1550 °C, and the traceability system for the thermocouples that uses these standards.

AIST maintains a series of temperature fixed points as national measurement standards. The freezing point of pure copper (1084.62 °C) and the freezing point of pure silver (961.78 °C) are temperature fixed points used conventionally by many metrology institutes around the world, including Japan. The temperature values at the freezing points are defined by an international agreement. The melting point of pure palladium (1553.5 °C) is also occasionally used as the high temperature fixed point in several countries.

The metal-carbon eutectic points are the newly proposed fixed points by AIST. There is a wide temperature range of about 500 °C between the copper point and palladium point, and from the perspective of disseminating temperature standards, finding applicable fixed points along that

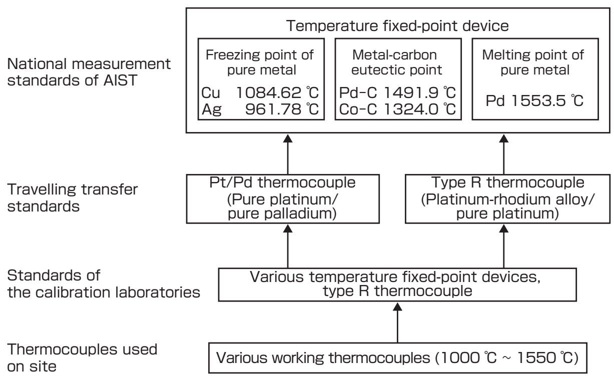

Fig. 1 Basic framework of the high-temperature traceability for thermocouples.

temperature range has a great significance. To this concern, therefore, AIST initiated research at the earliest time on finding possibilities of metal-carbon eutectic points to be used as the national measurement standards.

For transferring the national measurement standards from AIST to the thermocouple calibration laboratories, a transfer standard, which carries the temperature standard, is necessary. The transfer standard must possess high reliability to reproduce the standard accurately, and must be sufficiently robust to maintain the standard accurate during transportation. In practice, it must also be light-weight and low-cost. To these conditions, we considered two types of thermocouples as candidates. The first was the thermocouple that uses platinum-rhodium alloy with 13 % rhodium content and pure platinum as wires (type R thermocouple), and the other was the one that uses pure platinum and pure palladium as wires (platinum/palladium or Pt/Pd thermocouple). Both types are applicable for high temperature measurement. Although the type R thermocouple has already been used widely, there are some problems in stability at high temperatures. The Pt/Pd thermocouple was newly developed, and while a better stability was expected than the type R thermocouple, the related case studies were not significantly available, and the properties such as stability were not sufficiently understood.

After receiving the transfer standard already calibrated at AIST, the calibration laboratories transfer the temperature standards to the working standard they are maintaining. In Japan, most of the calibration laboratories use temperature fixed-point device as their own working standard. In this case, the calibration laboratories can calibrate the field users' thermocouples using their own temperature fixed-point device.

3.2 Scenario selection

AIST considered the scenarios from two perspectives: (a) what artifact is to be selected as the transfer standard, (b) what temperature fixed points are to be used for disseminating the calibration service. The national metrology institutes worldwide are always in competition in research and development for setting the measurement standards, where some new methods are proposed or conventional methods are improved upon further evaluation. For a national metrology institute, it is ideal to start by integrating those achievements, setting measurement standards of top level quality, and creating a traceability system based on them. On the other hand, for a calibration laboratory, it is more convenient to employ conventional methods already adopted, because the equipments already owned can be operated as they used to be, along with the accustomed calibration procedures Four scenarios below were considered from these two opposing standing points, as shown in Fig. 2.

• In the case where only type R thermocouple is the transfer standard

Scenario (1): AIST calibrates one type R thermocouple at the three temperature fixed points (Ag, Cu, and Pd fixed points), and expresses the relationship of temperature and thermal electromotive force (emf) between 960 °C and 1550 °C as a function based on the emf values (calibration values) at each point. This function is provided to the calibration laboratory as the standard.

Scenario (2): AIST either calibrates one type R thermocouple at the three temperature fixed points (Ag, Cu, and Pd fixed points) or, otherwise, calibrates three separate type R thermocouples, one at each of the three temperature fixed points (Ag, Cu, and Pd fixed points), and provides the emf values (calibration values) as the standards to the calibration laboratory.

• In the case where both Pt/Pd thermocouple and type R thermocouple are the transfer standards

Scenario (3): AIST calibrates two Pt/Pd thermocouples, one at each of the two fixed points (Ag and Cu fixed points), calibrates the type R thermocouple at one temperature fixed point (Pd fixed point), and provides the emf values (calibration values) as the standards to the calibration laboratory.

• In the case where Pt/Pd thermocouples are the transfer standards

Scenario (4): AIST calibrates four separate Pt/Pd thermocouples, one at each of the four temperature fixed points (Ag fixed point, Cu fixed point, Co-C eutectic point[Term 3], and Pd-C eutectic point), and provides the emf values (calibration values) as the standards to the calibration laboratory.

The important considerations for the above four scenarios are (a) what is to be selected as the transfer standard, and (b) what temperature fixed points are to be selected as the calibration temperature. The technical difficulties increase in the order from the Scenario (1) to the Scenario (4).

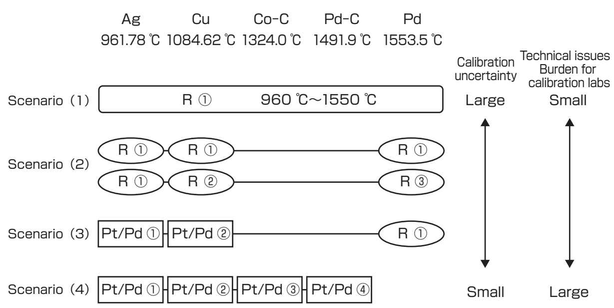

Fig. 2 Comparison of the scenarios for thermocouple traceability.

"R" and "Pt/Pd" represent the type R thermocouple and the Pt/Pd thermocouple that are used as transfer standards, and the circled numbers are for individual identification.

In the Scenario (1), it is more efficient to provide the calibration service from AIST directly to the thermometer users without intermediation by any calibration laboratory. This scenario is occasionally selected by the metrology institutes in the developing nations. The calibration uncertainty is the largest among the four scenarios.

Scenario (2) is convenient for the calibration laboratories that would be receiving the transfer standard because they can use the devices they already operate. However, for example, if the uncertainty of calibration service of the type R thermocouple at 1000 °C is set to be 0.3 °C, the uncertainly of the working standard of the calibration laboratory should be within 0.1 °C, which is approximately one-third the value. This figure is not easy to achieve in this scenario. As will be explained in chapter 4, there is a limit in the stability of the type R thermocouple when being used as the transfer standard.

Scenario (4) places the metal-carbon eutectic point, which is a recent research product, as the national measurement standard. It is an excellent method that can incorporate the findings of upcoming future research. However, the dissemination of the standard under this scenario involves the vast investment to introduce new facilities and the learning of new skills by the calibration laboratories, and their workload will increase. Although AIST positions Scenario (4) as an optimum solution for the future, Scenarios (2) and (3) that use the temperature fixed points are the practical solutions that could be readily adopted by the thermometer manufacturers and the calibration laboratories. Thus we have initially selected Scenarios (2) and (3) for the time being, and the preparations toward Scenario (4) has also been started.

AIST has been disclosing and updating the Measurement Standards Development Program for various quantities including temperature since 2001. Since this program clearly states when and which national measurement standards will be prepared, it is possible for the industry to prepare the necessary facilities and personnel for providing the calibration service, and to start the calibration service according to the release for the dissemination of the national measurement standards. AIST announced the commencement of the calibration service for thermocouples using the Ag and Cu fixed points as 2002 in this the Measurement Standards Development Program, and conducted research on the transfer standards using the available interval. The study sessions of the temperature-related academic societies and industrial associations were held almost every month. There, the status of standard development at AIST was reported, the thermometer calibration by the thermometer manufacturers and calibration laboratories were discussed, and the technical data obtained by AIST for the calibration of the transfer standard using the Ag and Cu fixed points were presented.

After numerous sessions of such information and opinion exchanges, the following agreement was reached between AIST and industry. While using the type R thermocouple as the transfer standard might be an easy solution, the uncertainty due to the inhomogeneity of the thermocouple will increase (explained in section 4.2.1). The demand from the thermometer manufacturers was to achieve a sufficiently small uncertainty that matches the quality of Class 1 thermocouple as designated by the IEC standards. It was recognized that the development of the transfer standards with small uncertainty and their dissemination in synch with the establishment of the national measurement standards would be a great advantage. The details of this R&D will be explained in section 4.2. Since there was a technical prospect for achieving small uncertainty of approximately 0.1 °C, we decided to select Scenario (3) that employed the Pt/Pd thermocouples as the transfer standards for the Ag and Cu fixed points.

3.3 Elements for the implementation of the scenario

The policy taken was to first quickly employ Scenario (3) to provide the advanced standard to industry, and then move toward Scenario (4) for further advancement. Elements ① to ⑥ were selected as the elements necessary for AIST to implement these scenarios.

① Fabrication of temperature fixed-point devices that would serve as the national measurement standards for high temperatures and the evaluation of their uncertainty
② Development of the stabilization technique of Pt/Pd thermocouples as transfer standards
③ Technique to calibrate transfer standards at temperature fixed points and the evaluation of their uncertainly
④ Confirmation of equivalence of the national measurement standards by international comparison
⑤ Building and operation of a quality management system to ensure regular and accurate provision of the calibration service
⑥ Designing a practical traceability system and drafting of the technical documents

The traceability system for high temperatures was attempted to be built by integrating and synthesizing the above elements.

Element ① involved the setting of the temperature fixed points as the national measurement standards. To realize Scenario (3), the freezing point of silver (961.78 °C), the freezing point of copper (1084.62 °C), and the melting point of palladium (1553.5 °C) were developed as the national measurement standards. Also, to progress to Scenario (4) in the future, Co-C eutectic point (1324.0 °C) and Pd-C eutectic point (1491.9 °C) were selected as new national measurement standards, and their researches were started. To provide the emf of thermocouples at each temperature fixed point as standards to the calibration laboratories, the type R thermocouple was selected as the transfer standard for the palladium melting point. For temperatures below 1500 °C, Pt/Pd thermocouple was selected as the transfer standard. Element ② was the development of this Pt/Pd thermocouple.

Element ③ was the technique to calibrate the transfer standard using the prepared fixed-point device, and the evaluation of the calibration uncertainly. Element ④ involved the comparison of the standards with the other competitive national standard institutes. This was carried out to confirm the international equivalence of the national measurement standards and the calibration technique. The method for conducting the international comparison was determined internationally, and 12 metrology institutes under the international organization called the Asia Pacific Metrology Programme (APMP) that was established for the Asia Pacific region participated.

Element ⑤ concerned the development of the system to ensure that AIST could conduct regular and accurate provision of the calibration service using the established national measurement standards. Element ⑥ was the traceability system of the temperature standards where the calibration laboratories would use the prepared measurement standards to calibrate the thermometers that would be used by industry. The drafting of the technical document that served as the basis for the third party to check the technical level of the calibration laboratory was also an important element. This document confirmed the calibration capability of the calibration laboratories.

The details of Elements ① to ⑤ will be explained in sections 4.1 to 4.5. Element ⑥ is discussed in chapter 5.

4 Preparation of the national measurement standards and development of the transfer standards

4.1 Element 1: Fabrication and evaluation of the fixed-point device

To realize the temperature fixed points for thermocouple calibration, it is known that there are two methods. One is the method using a crucible (crucible method) where the temperature fixed point is realized by melting or freezing of the metal founded in a crucible, and the other is the wire-bridge method where the temperature fixed point is realized by melting of metal directly attached at the measuring junction of the thermocouple for calibration. Since the crucible method indicates excellent reproducibility of the fixed-point temperature, and maintains the melting or freezing state over a long period, this method is generally used to realize the many temperature fixed points accurately. On the other hand, the wire-bridge method does not require a crucible to realize the temperature fixed point, and accordingly, it is simple and the calibration can be conducted with only a small amount of the fixed-point material of 0.1 g or less. The wire-bridge method is generally used in cases where the crucible material may contaminate the fixed-point material, or metals indicating high melting point, such as noble metals, is used as the fixed-point material. In order to start the calibration service of the thermocouples, AIST employed the crucible method for realizing the Ag fixed point, the Cu fixed point, and the Co-C eutectic point because of good reproducibility of the freezing and melting points. The wire-bridge method was used for realizing the Pd fixed point.

4.1.1 Ag fixed-point device

Figure 3 shows the schematic cross section of the Ag fixed-point device. The fixed-point device was mainly composed of the “fixed-point furnace” consisting of a heater and a control system, and the “fixed-point cell” that held the silver ingot as fixed-point material. A vertical electric furnace containing a sealed sodium heat pipe was used as the fixed-point furnace which indicated the high temperature stability within ±25 mK for 9 hours around 960 °C, and excellent temperature uniformity within ±6 mK over 14 cm height. The silver ingot with nominal purity 99.9999 % was 1390 g in weight and founded in a graphite crucible which was sealed in the fixed-point cell. This cell was an open type that allowed monitoring of gas pressure on the ingot. The freezing point temperature could be maintained for 5 hours within ±10 mK, and the standard deviation of reproducibility in 14 measurements was 3.8 mK[2]. By using this device, it was evaluated that thermocouples could be calibrated with the expanded uncertainty of 0.09 °C at the Ag fixed point (level of confidence of approximately 95 %).

4.1.2 Cu fixed-point device

Figure 4 shows the schematic cross section of the Cu fixed-point device. As in the aforementioned Ag fixed-point device, this device consisted of the “fixed-point furnace” composed of the heating element, control system and the “fixed-point cell” that held the fixed-point material. The fixed-point furnace was a vertical electric furnace with three-zone heater in a vertical direction for temperature control. Kanthal wires were wound noninductively as heaters, and type R thermocouples were installed in the center of each zone as the controlling thermocouple. The design characteristics of this fixed-point furnace compared with the conventional 3-zone electric furnace were the improvement of the heat contact between controlling thermocouples and heaters, and the improvement of heat-retention of the furnace by thickening insulation material. The quick response of the controlling thermocouple was realized by attaching them to the alumina tube on the heater, to improve the temperature control of the furnace. The high-temperature refractory fiber (ceramic fiber) was used as insulation around the heating elements, the thickness of which was over 150 mm to increase the heat-retention of the furnace. Due to these improvements, the electric power consumption was reduced below 1 kW. The fixed-point cell was the open type as shown in the Ag fixed-point, and 1450 g copper with nominal purity 99.9999 % was founded in a graphite crucible. Figure 5 shows the temperature inside the fixed-point cell during the freezing of the copper. The temperature at the freezing point was maintained for 8 hours within ±2 mK. The standard deviation of reproducibility of the freezing point measured by repeating the melting and freezing 26 times was 11.7 mK[3], and it was evaluated that by using this device, thermocouples could be calibrated with expanded uncertainly of 0.11 °C at the Cu fixed point (level of confidence of approximately 95 %).

4.1.3 Co-C eutectic-point device

When a pure metal was founded in the graphite crucible for realizing its melting and freezing points above 1100 °C , the carbon that is the component of the crucible dissolved into

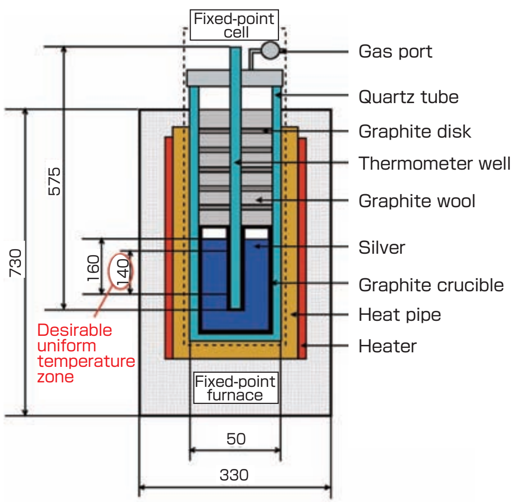

Fig. 3 Schematic diagram of the Ag fixed-point device.

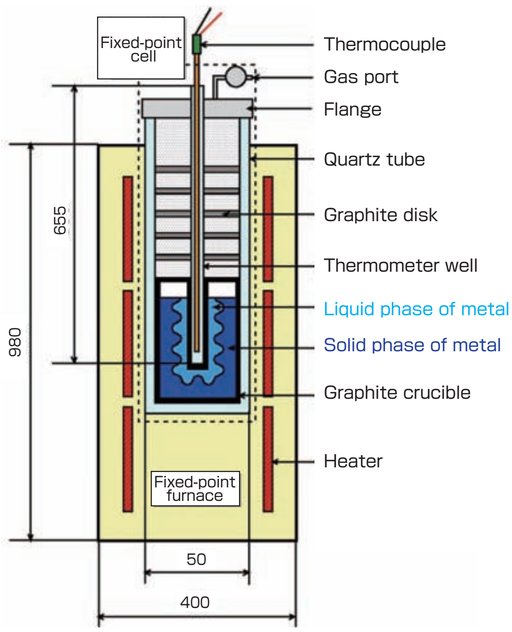

Fig. 4 Schematic diagram of the Cu fixed-point device.

the pure metal under high temperature, contaminated the pure metal, and decreased the melting and freezing points. This is the major reason that the temperature fixed point above 1100 °C could not be realized by using the pure metal with the graphite crucible. To solve this issue, it was proposed to mix the metal and carbon according to the ratio of the composition of eutectic alloy and then founding this mixture in the graphite crucible[4]. This enabled the realization of a melting temperature with good reproducibility in the crucible and could be used as the temperature fixed point. The metal-carbon eutectic points are currently studied in the advanced national metrology institutes around the world as new fixed points for the high temperature range. Using this technique, the Co-C eutectic point device for the thermocouple calibration was developed. We succeeded in fabricating a large-sized Co-C eutectic point cell for the first time in the world, and demonstrated that it can be used for accurate thermocouple calibrations[5]. In designing the device, the technique for the Cu fixed-point device was applied. Although a quartz tube was used to seal the crucible in the Cu fixed-point device, an alumina tube was used instead of quartz in the new device since devitrification or softening of quartz occur at the Co-C eutectic point temperature.

Figure 6 shows the melting and freezing curves of the Co-C eutectic point. As a result of the uncertainty evaluation, it was found that thermocouples could be calibrated with the expanded uncertainly of 0.53 °C (level of confidence of approximately 95 %) at the Co-C eutectic point[6][7].

4.1.4 Pd fixed-point device

The wire-bridge method for realizing the melting point of palladium was mentioned earlier, and there were several techniques for attaching the fixed-point material to the thermocouple. As a result of experimental evaluation, it was found that attaching the coil-shaped palladium wire, as shown in Fig. 7, was effective in realizing a stable melting temperature[8]. Figure 8 shows the emf of a type R thermocouple with coil-shaped palladium wire when the furnace temperature was increased gradually after inserting the thermocouple in the Pd fixed-point device. In 150 seconds, the sustained melting temperature in the range of ±0.05 °C was observed while the attached palladium wire was melting, and the average emf value in this range was obtained as the calibration emf value of the thermocouple at the Pd fixed point. As a result of the investigations, it was confirmed that the melting temperature could be realized with reproducibility

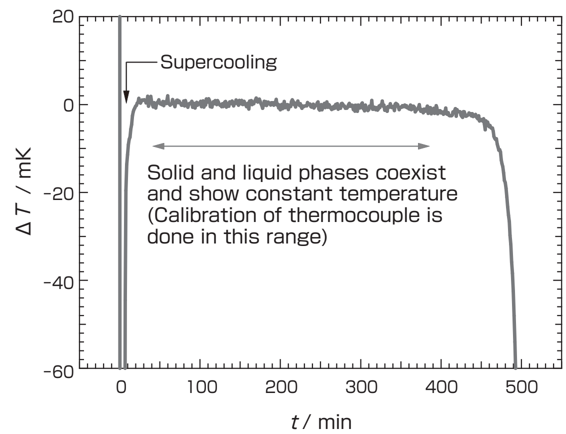

Fig. 5 Freezing curve at the Cu fixed point.

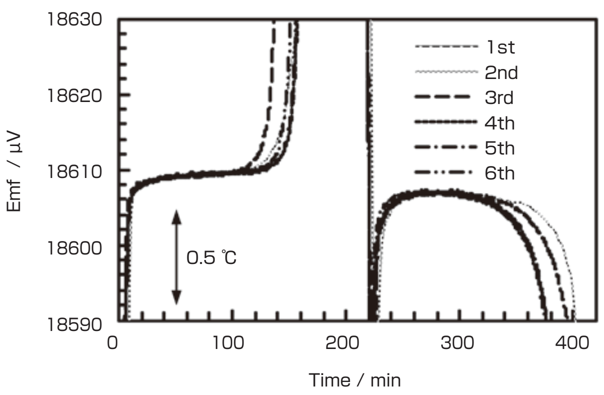

Fig. 6 Melting and freezing curves at the Co-C eutectic point.

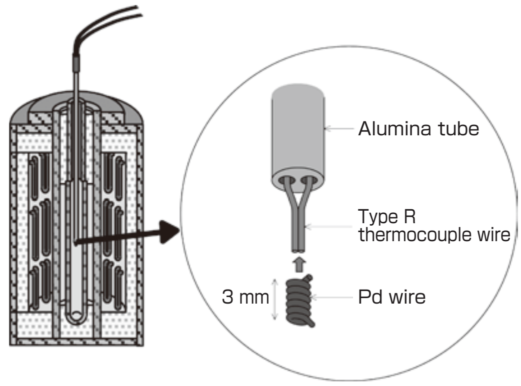

Fig. 7 Wire-bridge method to realize the melting point of palladium.

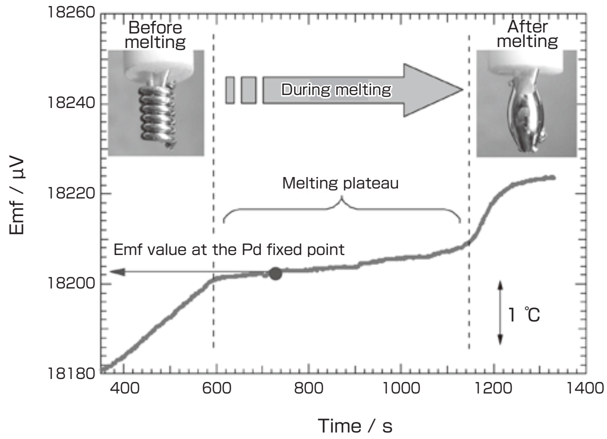

Fig. 8 Melting curve at the Pd fixed point.

of approximately 0.05 °C (standard deviation). By using this device, thermocouples could be calibrated with the expanded uncertainty of 0.79 °C (level of confidence of approximately 95 %) at the melting point of palladium.

4.2 Element 2: Technique for fabrication of stable Pt/Pd thermocouples

4.2.1 Drift and inhomogeneity of thermocouples

When transferring the temperature standard from the temperature fixed point to a thermocouple, the stability of the thermocouple itself is the largest component of uncertainty. Figure 9 shows the property changes of a new thermocouple when the thermocouple is inserted into a high-temperature furnace and the measuring junction is exposed to high temperature for a long time at a fixed insertion length. S is called the Seebeck coefficient of the thermocouple, and for simplification to consider, here, it is assumed that S has no temperature dependency. The E in the figure shows the electric field generated at the wire in the temperature gradient region, and the integration of E along the thermocouple wire is the emf that is actually observed using a voltmeter. E and S has the relationship $E = S\, dT/dx$[9][10]. Here, x is the positional coordinate along the wire of the thermocouple.

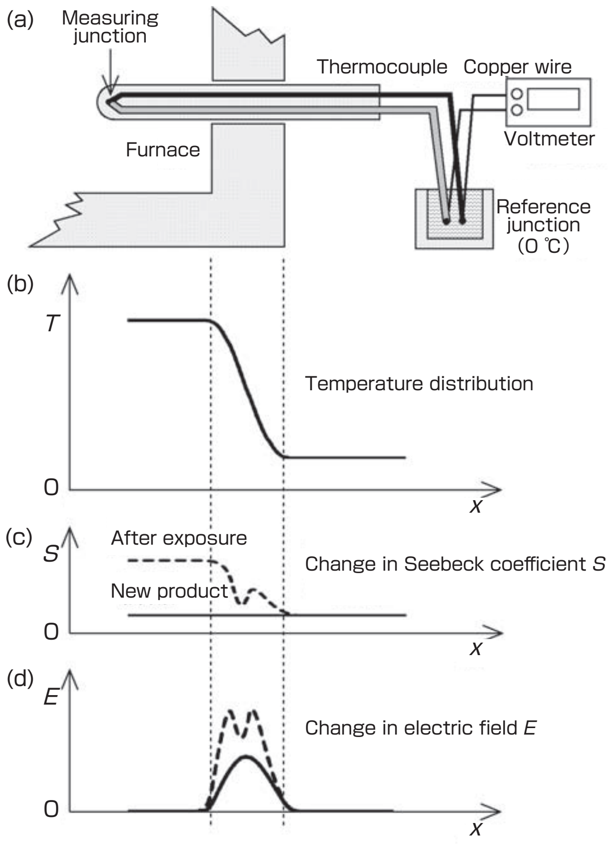

Fig. 9 Emf change by the exposure of thermocouple to high temperature.
The solid line indicates the Seebeck coefficient and the electric field of the new thermocouple, and the dashed line shows the values after exposure to high temperature.

When the new thermocouple is inserted into the furnace, in the beginning, the Seebeck coefficient S shows a constant value regardless of position x (this is called homogeneity), as shown by the solid line in Fig. 9(c). When the measuring junction is exposed to high temperature with the fixed insertion length of the thermocouple, the Seebeck coefficient of the part exposed to high temperature gradually changes due to the compositional and structural changes of the thermocouple wire and may become inhomogeneous in some parts, as shown by the dashed line in Fig. 9(c). With such changes in the Seebeck coefficient S, the electric field E changes as shown in Fig. 9(d), and the emf change is observed as a result. When the measuring junction is exposed to high temperature with the thermocouple fixed to a certain position, the emf change called the drift is observed. The tendency and magnitude of this emf change vary greatly depending on the type of thermocouples.

In the case where the temperatures of the measuring junction and the reference junction are constant, wherever the temperature gradient is on the position of the wire, the emf shows the same value regardless of the insertion depth, because the emf is determined by the temperatures of the measuring junction and the reference junction of the thermocouple that has homogeneous Seebeck coefficient S, as seen in the new thermocouple in Fig. 9(c). On the other hand, in the thermocouple that is exposed to high temperature for a long time in the furnace and a drift has been observed, the emf changes when the insertion length of the thermocouple

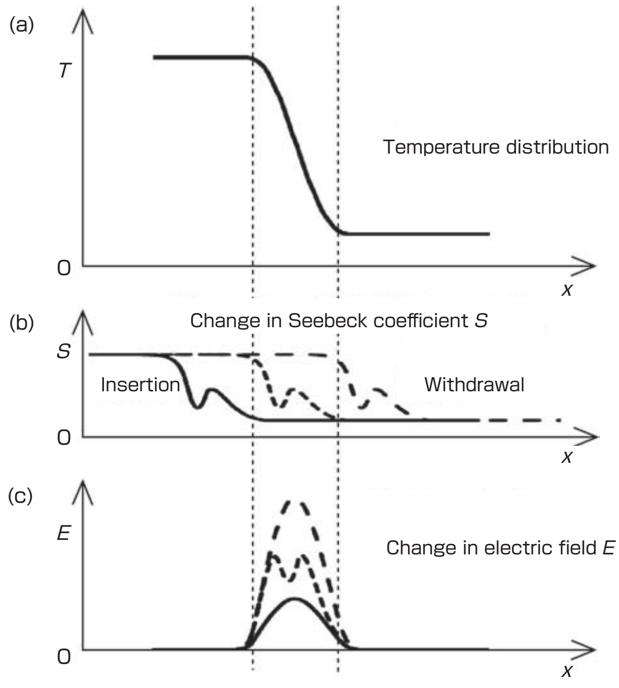

Fig. 10 Emf change when the insertion length of the thermocouple into high temperature furnace is altered.
The solid line shows the Seebeck coefficient and the electric field when the thermocouple exposed to high temperature is inserted, and the dashed line shows the values when it is withdrawn.

is changed as shown in Fig. 10. The thermocouple where the Seebeck coefficient differs according to the position of the wire is generally called the "inhomogeneous thermocouple." In actual temperature measurement, the emf change generated when the position where the temperature gradient falls is changed by altering the insertion length of the thermocouple is often called "inhomogeneous." In the inhomogeneous thermocouple, the emf is not determined by the temperature values of the measuring and reference junctions only, as it is dependent on the temperature distribution of the furnace. Therefore, the inhomogeneity may give erroneous standard if the calibrated transfer standard is used in different temperature gradient. The Seebeck coefficient S of the general thermocouple is temperature dependent, and a similar way of thinking is available.

4.2.2 Development of evaluation method of drift and inhomogeneity

As mentioned earlier, the drift and inhomogeneity of the thermocouple are extremely important factors when evaluating the stability of the transfer standard. Particularly, since the drift and inhomogeneity increase in the high temperature range, they become major components of the uncertainty of thermocouple calibration.

To evaluate the stability of the thermocouple, at first, we studied the drift and inhomogeneity of the Pt/Pd thermocouple fabricated according to the paper[11] of the joint research of the National Institute of Standards and Technology (NIST) (USA), and the Istituto di Metrologia "Gustavo Colonnetti" (IMGC) (Italy). Following this paper, the wire annealing was performed for 10 hours at 1200 °C by direct current application to the thermocouple wires. After assembling the thermocouple, the annealing in a furnace was performed for 3 hours at 1100 °C , and then 10 hours at 450 °C.

The Cu fixed-point device was used to maintain the measuring junction of the thermocouple at a constant temperature, and the drift and inhomogeneity of the thermocouple was measured simultaneously using the stability and the uniformity of the freezing temperature of the fixed-point device[12]. The measuring junction of the thermocouple was inserted to the position 1 cm above the deepest point of the measurement well of the Cu fixed-point device, the copper was repeatedly frozen and melted, and the emf changes were measured. The temperature control of the Cu fixed-point device was programmed to repeat the melting and freezing constantly, and the measuring junction of the thermocouple was always exposed to the Cu fixed-point temperature. Figure 11 shows the result of the measurement of *in-situ* drift for approximately 500 hours by fixing the position of the measuring junction. The emf of the Pt/Pd thermocouple changed markedly in the first 50 hours after starting the exposure, and showed almost constant value after 100 hours.

Figure 12 is a plot of the emf change when the thermocouple was moved up and down when the freezing of copper was in progress during the drift measurement. The position of the measuring junction when conducting the drift measurement was set as "0 cm". The 0 hour to 505 hours in the figure is the time lapse from the start of exposure. The data at the start of exposure (0 h) was the measurement of the emf change when the thermocouple was pushed in at the rate of 0.5 cm/min, and the other data were the measurements taken when the thermocouple was pulled up at the rate of 0.5 cm/min. The act of "changing the insertion length of the thermocouple" to obtain the data for Fig. 12 was the same as

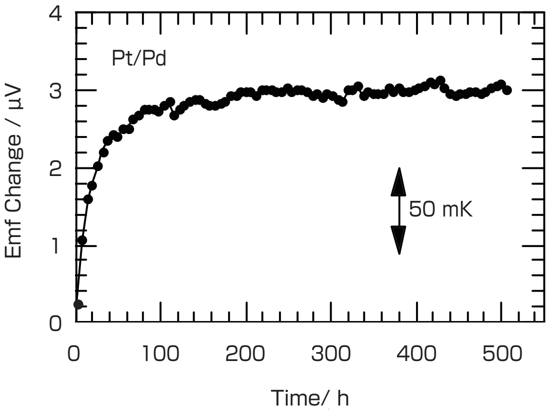

Fig. 11 Drift of the Pt/Pd thermocouple when exposed to the Cu fixed point.

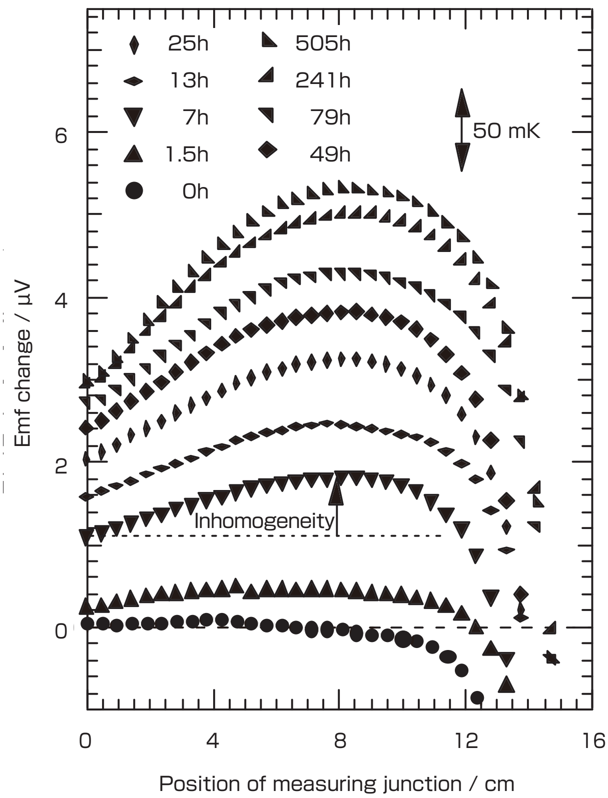

Fig. 12 Inhomogeneity of the Pt/Pd thermocouple when exposed to the Cu fixed point.

the act of “changing the temperature distribution along the wire of the thermocouple” while maintaining the temperature of the measuring junction, and the emf change reflected the inhomogeneity of the thermocouple. To quantitatively assess the inhomogeneity of the thermocouple, the emf change from 0 cm to upper 8 cm was defined as the “inhomogeneity” of the thermocouple, as shown in the example for 7 hours in Fig. 12.

The stability of the thermocouples at a temperature fixed point could be evaluated almost automatically in large amounts using this method, and the stable development and evaluation of the transfer standard that will be explained in the next section could be done efficiently.

4.2.3 Fabrication of the stable thermocouple

The Pt/Pd thermocouple is composed of the platinum and palladium wires that are pure metals, and it is reported that the emf change due to inhomogeneity is mostly related to the palladium wire[13]. To investigate the effect of the palladium wire from different lots, four Pt/Pd thermocouples were fabricated using the palladium wires from four different lots with the same nominal purity of 99.99 %[14]. Here, the four fabricated thermocouples will be called TC-a, TC-b, TC-c, and TC-d. Of the palladium wires from four different lots, the wires of TC-a and TC-b were made by the same manufacturing procedure by the same manufacturer. The wires of TC-c and TC-d were each purchased from manufacturers different from that of TC-a and TC-b. The electric current was applied to heat the wires for 10 hours at 1200 °C. After assembly, the thermocouple was annealed in a furnace for 3 hours at 1100 °C , and finally 10 hours at 450 °C.

Figures 13 and 14 show the results of the measurements of the drift and the inhomogeneity of these thermocouples, respectively. It can be seen that the changes of the drift and inhomogeneity differ by different lots even if the palladium wires were made by the same manufacturing procedure by the same manufacturer, as seen in TC-a and TC-b. On the other hand, TC-d showed small drift and inhomogeneity. This indicates that the drift and inhomogeneity can be greatly reduced by selecting an appropriate palladium wire lot. However, it is not easy to obtain a steady supply of the wire used in TC-d. Therefore, we investigated a method for reducing the drift and inhomogeneity using the wires that are relatively readily available, as used in TC-a, TC-b, and TC-c.

Since the heat treatment in the furnace was the final procedure in the heating history of thermocouples before they were actually used, we thought this was most deeply involved in the property of the thermocouples. Therefore, after 3 hours heat treatment at 1100 °C in the furnace to remove the wire strain, we fabricated a total of 11 thermocouples with different final heat treatments by conducting the final heat treatment at temperature points in the range from 450 °C to 1080 °C. For the palladium wire of the thermocouple, the wires from the same lot as TC-a that showed the largest drift were used. Also, since the emf of the Pt/Pd thermocouple in Fig. 11 stabilized at 100 hours, we selected 100 hours as the length of the final heat treatment.

Figure 15 shows the drift of the emf when the 11 Pt/Pd thermocouples fabricated as above were exposed to 1085 °C using the Cu fixed-point device, and Fig. 16 shows the inhomogeneity of the same thermocouples. The temperatures in the figure are final heat treatment temperatures. For reference, the result for the thermocouple annealed for 10 hours at 450 °C was plotted as black dots. In all thermocouples, the emf stabilized at approximately

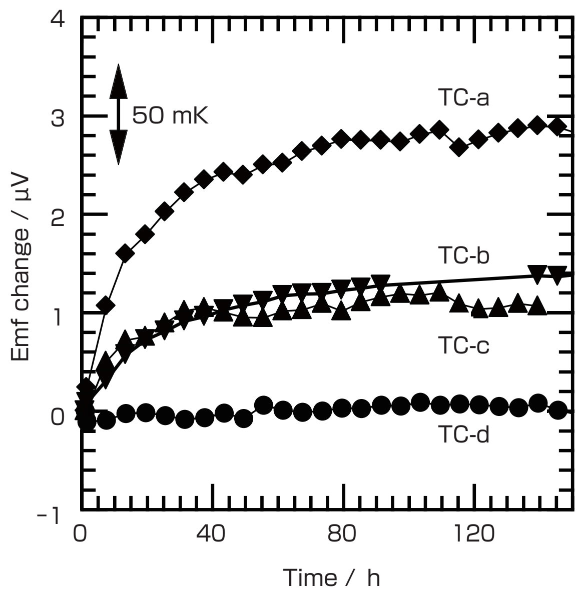

Fig. 13 Drift of the Pt/Pd thermocouples using palladium wires from different lots.

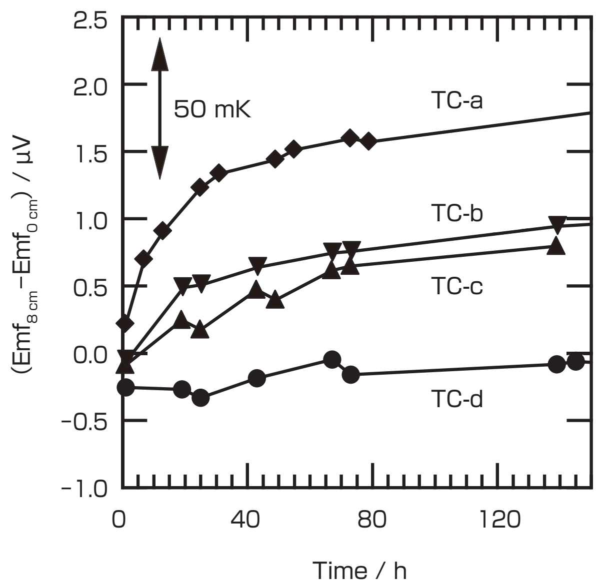

Fig. 14 Inhomogeneity of the Pt/Pd thermocouples using palladium wires from different lots.

100 hours after exposure to 1085 °C. Largest change was seen in emf at 100 hours at approximately 4 μV (corresponds to approximately 0.2 K) when the final heat treatment temperature was 730 °C. Here, it should be noted that the thermocouples that underwent 100 hours final heat treatment at 850 °C or 1030 °C showed very small drift and inhomogeneity. The emf change was within 0.5 μV (corresponds to 24 mK) over 150 hours, and this showed that the drift and inhomogeneity of the Pt/Pd thermocouple can be kept low by conducting appropriate heat treatment[12].

As a result of conducting similar measurement of the drift and inhomogeneity for the exposure to 962 °C using the Ag fixed-point device, it was found that the effect of the final heat treatment at 850 °C was effective for different lots of wire[15]. Also, as a result of similar measurement for the exposure to 1324 °C using the Co-C eutectic point, it was found that the final heat treatment at 1030 °C was effective in reducing the drift at the Co-C eutectic point[16]. In the exposure to temperature lower than the Ag fixed point, the drift and inhomogeneity of the Pt/Pd thermocouple decreased rapidly[17]. The above results mean that the drift and inhomogeneity of the Pt/Pd thermocouple at temperatures up to 1330 °C can be kept extremely small by selecting the appropriate wires, the fabrication method, and the heat treatment method[16]. We were able to find a method for reducing and stabilizing the drift and inhomogeneity at each temperature of the Ag fixed point, Cu fixed point, and Co-C eutectic point.

4.2.4 Comparison between Pt/Pd thermocouple and type R thermocouple

In case of the type R thermocouple, the emf tended to decrease gradually with exposure to 1085 °C, and drifted approximately 0.2 °C after 300 hours exposure[9][14]. In contrast, as shown in Fig. 15, in the Pt/Pd thermocouple with appropriate final heat treatment, the drift was held within 0.03 °C even after 150 hours exposure to 1085 °C. As in the drift, the inhomogeneity of the type R thermocouple continued to change gradually while the Pt/Pd thermocouple with appropriate final heat treatment showed almost constant value within 0.04 °C at approximately 150 hours, as shown in Fig. 16. Due to these clear differences, we selected the Pt/Pd thermocouple as the transfer standard for Ag fixed point, Cu fixed point, and Co-C eutectic point. On the other hand, since the Pt/Pd thermocouple used palladium as its wire, it could not be used at the Pd fixed-point temperature because it would melt. Therefore, we decided to use the type R thermocouple, which had been used widely for a long period of time in Japan, as the transfer standard for the Pd fixed point.

4.3 Element 3: Evaluation of the uncertainly of fixed-point calibration

There are several sources of uncertainty when providing the temperature standard at the temperature fixed point as the national measurement standard using the thermocouple as the transfer standard. As an outline, the sources are: "the uncertainty inherent in the fixed-point device," "the uncertainty inherent in the measurement system (voltmeter, reference junction device, etc.) when calibrating the thermocouple," and "the uncertainty arising from the drift and inhomogeneity of the thermocouple itself that is being calibrated." Table 1 shows the calibration uncertainty of the thermocouple at the Ag fixed point, Cu fixed point, Co-C eutectic point, and Pd fixed point. The expanded uncertainties (level of confidence of approximately 95 %) for the Ag fixed

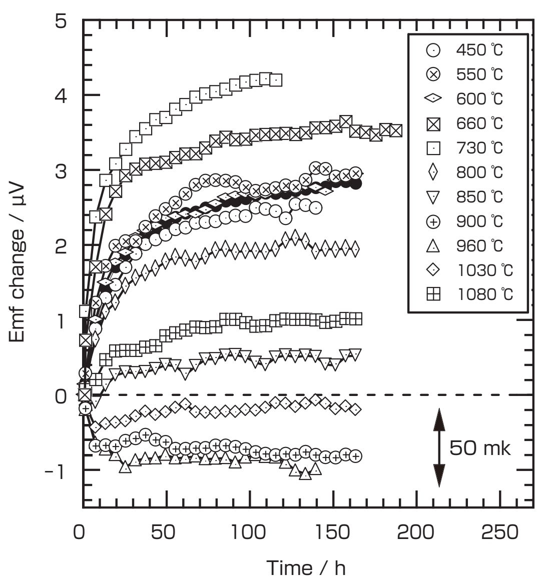

Fig. 15 Drift of the Pt/Pd thermocouples annealed at different temperatures as final heat treatment.

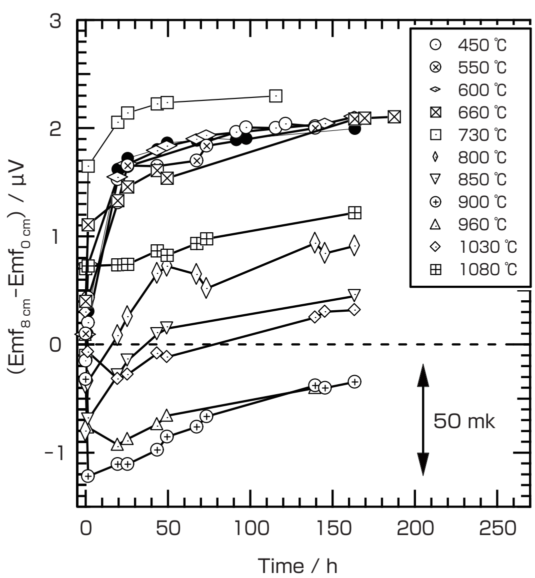

Fig. 16 Inhomogeneity of the Pt/Pd thermocouples annealed at different temperatures as final heat treatment.

point, Cu fixed point, Co-C eutectic point, and Pd fixed point are 0.09 °C, 0.11 °C, 0.53 °C, and 0.79 °C, respectively. This is the highest-level calibration capacity in the world, as described in the following section.

4.4 Element 4: Equivalence of the national measurement standard by international comparison

To investigate whether the realized fixed point was in accordance to the national measurement standards of other countries, an international comparison (APMP-T-S1-04) was conducted among the national metrology institutes of the Asia-Pacific region. Type R thermocouples were circulated among the participating institutes, each institute calibrated the type R thermocouple with their temperature fixed points, and the calibration values were compared with the value of the pilot laboratory. There were 12 national metrology institutes that participated: National Measurement Institute (NMIA) (Australia); National Institute of Metrology (NIM) (China); Standards and Calibration Laboratory (SCL) (Hong Kong); National Physical Laboratory (NPLI) (India); Research Center for Calibration, Instrumentation and Metrology, Indonesian Institute of Sciences (KIMLIPI) (Indonesia); Korea Research Institute of Standards and Science (KRISS) (Korea); Standards and Industrial Research Institute of Malaysia (SIRIM) (Malaysia); Standards, Productivity and Innovation Board (SPRING, currently NMC A*STAR) (Singapore); Council for Scientific and Industrial Research (CSIR, currently NMISA) (South Africa), National Metrology Institute of Japan (AIST/NMIJ); Center for Measurement Standards (CMS) (Taiwan); and National Institute of Metrology (Thailand) (NIMT) (Thailand).

Figure 17 shows the comparison result at 1084.62 °C, the freezing point of copper, and the differences of the calibration value between of the participating institutes and NMIA, which was the pilot laboratory, are presented with the calibration uncertainties of each institute. The calibration uncertainty of AIST/NMIJ was the smallest-level among the participating institutes, and it was confirmed that the calibration value at the Cu fixed point matched almost completely at the level of uncertainty claimed by other countries.

Table 1 Calibration uncertainty of the thermocouples at each temperature fixed point.

Transfer standards	Pt/Pd thermocouples			Type R thermocouple
Temperature fixed point used for calibration	Ag fixed point	Cu fixed point	Co-C eutectic point	Pd fixed point
Temperature of fixed point / ℃	961.78	1084.62	1324.0	1553.5
Uncertainty of measurement system / ℃	0.021	0.019	0.018	0.042
Uncertainty of fixed point realizing device / ℃	0.014	0.021	0.260	0.231
Uncertainty of thermocouple itself / ℃	0.034	0.045	0.060	0.315
Combined standard uncertainty of calibration / ℃ (Level of confidence of approx. 68 %)	0.042	0.054	0.267	0.393
Expanded uncertainty of calibration / ℃ (Level of confidence of approx. 95 %)	0.09	0.11	0.53	0.79

The combined standard uncertainty is the combination of individual uncertainty components, and is given by the positive square root of sum of squares of the uncertainties of the components.

The comparison of the calibration value at the Ag fixed point was conducted in the same international comparison, and as with the Cu fixed point, the calibration uncertainty of the Ag fixed point by AIST/NIMJ was the smallest-level, and the calibration values of each country matched almost completely at the uncertainty level claimed by them[18].

For the Co-C eutectic point, AIST/NMIJ joined the Euromet Project 857[19], a joint project of Physikalisch-Technische Bundesanstalt (PTB) (Germany), National Physical Laboratory (NPL) (UK), and Laboratoire Commun de Métrologie (LNE-Cnam) (France) that are the major European national metrology institutes. As the result of an international comparison in which Pt/Pd thermocouples and the Co-C eutectic cells were circulated, good agreement was obtained[20].

4.5 Element 5: Constructing and operating the quality managing system for thermocouple calibration

Based on the quality management system for the calibration and testing service conducted by AIST, a technical manual of the calibration service for thermocouples was generated in 2004. To meet the requirements of the ISO/IEC 17025, the international standard for the calibration and testing laboratories, the particulars of personnel, facility and environmental condition, calibration method, equipment, traceability, handling of the calibrated device, reporting, and others were determined. According to this manual, the calibration would be conducted and the calibration records would be in safekeeping. The evaluation method for the drift and inhomogeneity that are uncertainty sources unique to the calibration of thermocouples were described in detail,

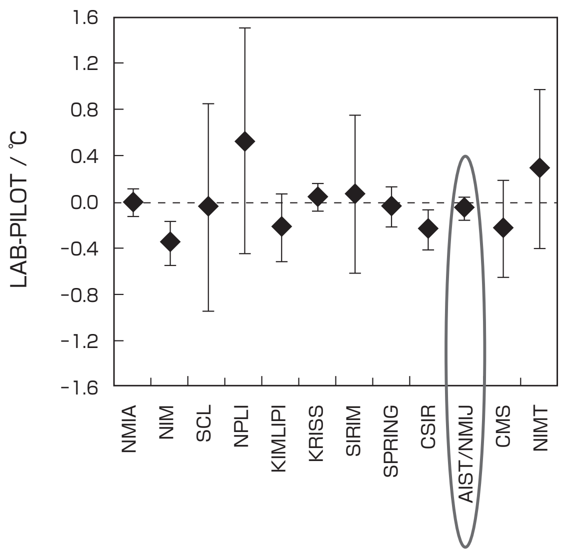

Fig. 17 The result of international comparison of the calibration value of type R thermocouple at the Cu fixed point (1084.62°C).

◆ indicates the difference between the calibration values of the participating institutes and NMIA, and the error bar indicates the calibration uncertainty of each institute.

and the procedure for quantitatively evaluating the effects on the calibration value and uncertainties of the thermocouple was also described in the technical manual. In May 2006, the calibration service of the thermocouples by AIST was certified to be in accordance to the international standard under the certification program provided by the National Institute of Technology and Evaluation (NITE). The quality management system is the element that is necessary to regularly maintain the technique, where the calibration method for the thermocouples was established by careful evaluation of uncertainty and then verified by international comparison. It raises the reliability of thermocouple calibration conducted by AIST both domestically and internationally.

5 Element 6: Establishment of the traceability system

5.1 Design of the traceability system for thermocouples

The traceability system for temperature was constructed based on the JCSS[Term 4] system according to the “Measurement Act” in Japan. In this traceability system, the national measurement standards are used to calibrate transfer standards of the calibration laboratories which calibrate thermometers used in industry. As the national measurement standards, the fixed-point devices for the Ag fixed point (in 2002), the Cu fixed point (in 2002), and the Pd fixed point (in 2005) of AIST were designated as national primary standards by the Measurement Act. By following this Act, AIST provides the transfer standards with calibration values at these three points as the standards to the calibration laboratories [21][8]. The calibration laboratories calibrate their temperature scales by transferring the standard from the transfer standards to their fixed-point devices. However, for the Pd fixed point, the laboratories are allowed to select the method of transferring the standard by comparison calibration to working standard thermocouples instead of their fixed-point devices.

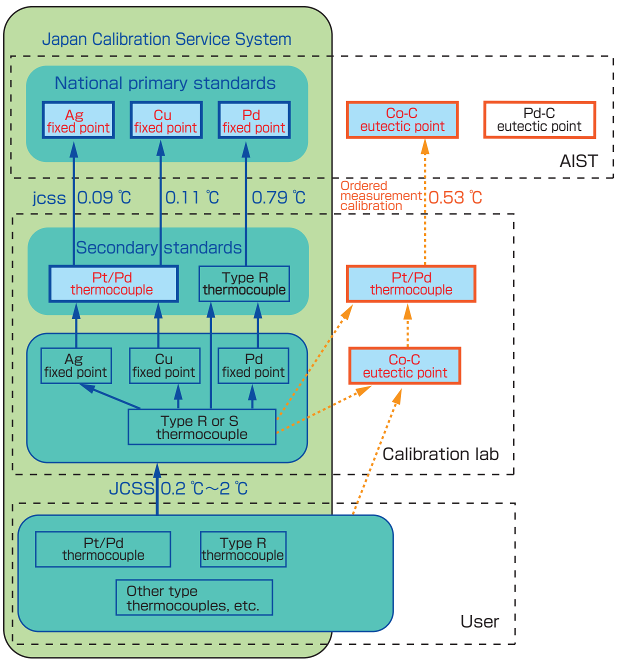

Fig. 18 Diagram of the traceability system of thermocouples for high temperature range (as of February 2010).

The transfer standards calibrated by AIST are the secondary standards as designated by the Measurement Act, and Pt/Pd thermocouples were employed for the Ag and the Cu fixed points and a type R thermocouple for the Pd fixed point. By providing the standard at the Pd fixed point using the thermocouple as the transfer standard, as shown in Fig. 18, calibration laboratories are now able to have the temperature standards up to 1554 °C for the working standard thermocouples, and to calibrate various thermocouples including the type R thermocouple using their working standard. Currently, AIST conducts approximately 10 calibrations a year for the secondary standards using the national primary standards, and issues the calibration certificates with the “jcss” mark designated by the Measurement Act to indicate that they were calibrated using the national primary standards.

Apart from the jcss calibration, AIST started the provision of the temperature standard at Co-C eutectic point upon request in 2009[7]. This enabled a more accurate verification of the temperature scale created by the calibration laboratories.

The calibration laboratories registered to the JCSS can flexibly select various calibration services according to their own equipment, including the calibration of various fixed-point devices up to the Cu fixed point, fixed-point calibration up to the Cu fixed point for noble metal thermocouples (types R, S, B, and Pt/Pd), base metal thermocouples (types N, K, E, J, and T), and thermometers with indicators for high temperature range, as well as the comparison calibration of thermometers at temperature range to a maximum of 1554 °C[22].

5.2 Joint research with Japanese calibration laboratories and drafting of the technical documents

To disseminate the Pt/Pd thermocouple as the standard thermocouple, the parties took a circulating test of the Pt/Pd thermocouple from June 2001 to March 2002 in the working group of the Temperature Measurement Subcommittee, under the 36th Committee on Industrial Instrumentation of the Japan Society for the Promotion of Science. With the objective of assessing the drift of thermocouples during calibration at the Cu fixed point, four Pt/Pd thermocouples were fabricated under the same condition from platinum and palladium wires taken from the single lot, and were subjected to tests. These thermocouples were transferred from “AIST → four labs → AIST,” and after conducting recovery annealing, they were sent to “AIST → remaining four labs → AIST" to investigate the degree of change of calibration values in the Cu fixed-point calibration by each calibration laboratories. Prior to the tests, investigations were performed based on the thermocouple fabrication facilities and calibration equipment of the calibration laboratories and AIST, of the specification of the materials such as the thermocouple wires and insulation tube to fabricate the Pt/Pd thermocouple, the assembling conditions such as the pretreatment of wires and insulation tubes as well as the heat treatment after assembly, and the condition of usage.

In the same working group, two joint experiments were conducted in 2004 by seven laboratories including AIST as the "Joint Experiment including the Calibration of Type R Thermocouples at Pd Fixed Point "[23]-[25].

For the calibration laboratory to register to JCSS, it must comply with the guideline for the technical requirement items. This guideline is to clarify the technical requirements established by the international standard ISO/IEC 17025 and to provide explanation to the calibration laboratories. This technical document was published and issued by NITE. This also serves as technical criteria by which the third party recognizes the technical competence for the calibration conducted by a calibration laboratory. The conditions for the secondary standards or the regular reference standards were determined based on the results of the above joint experiments. Cautions pertaining to the handling of inhomogeneity were also described [26].

6 Impact of standard development and future issues

6.1 Effect of the development of the traceability system for thermocouples

As the actual effect of constructing the traceability system for thermocouples, the temperature range of the JCSS has increased, and also the number of JCSS certificates issued by the registered calibration laboratories has increased. The number of JCSS certificates issued was approximately 2000 in FY 2002[27] while there were approximately 10000 in FY 2008[28]. It indeed increased five times in these six years. The certifications of standard conformity and calibration values issued by the thermometer manufacturers and the calibration laboratories ensure the reliability of the thermometers used widely in our society.

6.2 Dissemination of the Pt/Pd thermocouples to industry

Research work has shown that the Pt/Pd thermocouple developed as the transfer standard can gain extremely high performance by conducting appropriate heat treatment. In the beginning, this thermocouple was distributed as an R&D product with charge by AIST, and the target was limited to the calibration laboratories that had plans to ask AIST for calibration. We transferred this technique for fabricating the thermocouple to a private company, thereby enabling a wider range of users to use the Pt/Pd thermocouple. The developed Pt/Pd thermocouple was launched for sale in April 2006 from Chino Corporation to which the fabrication method was transferred[29].

The Pt/Pd thermocouple is expected to become a thermocouple for general temperature measurement, as well as for a transfer standard. To promote its industrial use, AIST worked on the standardization by IEC, and as an outcome, it was standardized as IEC 62460 in 2008[30].

6.3 Development of the Pd-C eutectic point

As described in chapter 3, we aim to provide the temperature standards at four fixed points (Ag fixed point, Cu fixed point, Co-C eutectic point, and Pd-C eutectic point) using the Pt/Pd thermocouples as the transfer standards in the future. Therefore, we are currently working actively to develop the Pd-C eutectic point and its evaluation[5]. We have participated in the joint project (Euromet Project 857) as in the Co-C eutectic point, to conduct the international comparison of the temperature values at the Pd-C eutectic points with the representative European national metrology institutes including PTB (Germany), NPL (UK), and LNE-Cnam (France).

Table 2 shows the projection of how the calibration uncertainties at each temperature fixed point including the Pd-C eutectic point can possibly be reduced in the future. Currently, the metal-carbon eutectic point is not assigned as the defining fixed point in the 1990 International Temperature Scale (ITS-90)[Term 5]. Therefore, the temperature value using the Co-C eutectic point cell for thermocouple calibration was measured and determined using the radiation thermometer calibrated based on ITS-90. One of the sources of calibration uncertainty of the thermocouple at the Co-C eutectic point shown in Table 1 includes "the uncertainty of the fixed-point device," and this is the largest uncertainty component of 0.26 °C. This uncertainly component includes the uncertainty of measurement using a radiation thermometer[6]. In the future, the uncertainty due to the radiation thermometer measurement is expected to decrease, and as a result, the expanded uncertainties (level of confidence of approximately 95 %) of the thermocouple at the Co-C and Pd-C eutectic points are expected to fall to approximately 0.3 °C. When this is achieved, it will be

Table 2 Calibration uncertainty of the Pt/Pd thermocouple at each temperature fixed point expected in the future.

Temperature fixed point	Ag fixed point	Cu fixed point	Co-C eutectic point	Pd-C eutectic point
Temperature of fixed point / ℃	961.78	1084.62	1324.0	1491.9
Expanded uncertainty of calibration / ℃ (Level of confidence of approx. 95 %)	0.09	0.11	0.3	0.3

possible to provide the standards with smaller uncertainty in the temperature range up to 1500 °C using the Pt/Pd thermocouple as a transfer standard.

7 Conclusion – significance of the Measurement Standards Development Program

Since the latter half of the 1990s, AIST/NMIJ has been establishing the traceability system by setting the Measurement Standards Development Program based on the social demand in Japan. Of course, the establishment was done by closely following the trends of our industry. The execution of the 10-year period of the Measurement Standards Development Program started in 2001 is now coming to an end. Throughout this period, when and which measurement standards would be prepared and disseminated by AIST were clearly presented to the companies that place importance on quality control including the calibration laboratories. The system was built by discussing a system for measurement standards that was most appropriate to serve the demands for Japan. This means that the necessity of fusing the technological foundation to ensure the reliability that has been built by industry, and the metrology traceability established by AIST/NMIJ, has been well understood.

The development of the temperature standards is considered to be an excellent example that promoted the use of JCSS[31]. It was indeed a result of the synchronization of the expanded range of national measurement standards provided by AIST and the vast variety of calibration services conducted by the private companies. This required the integration of the various elemental technologies described in this paper; including the setting of the national measurement standards, the technological development of the transfer standards, the evaluation of uncertainty, the establishment of the quality management system, the execution of the international comparison, the construction of the traceability system, the drafting of the technical documents for calibration, and others. It was a long-term effort that started in the late 1990s, and now, has grown to be a strong system that guarantees the reliability of the temperature measurement up to 1550 °C which has been established in Japan. The authors will continue the technological development for further advancements as described in section 6.3, and will engage in the activities to promote and spread the use of our traceability system.

Acknowledgements

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Terminology

Term 1. Thermocouple: Highly practical thermometer made of two different kinds of metal or alloy wires. It can measure extremely low temperature of -270 °C to ultra high temperature of 2400 °C depending on the wire selected. Currently, the Japan Industrial Standard (JIS) designates eight types: types T, J, E, K, and N thermocouples using base metal; and types S, R, and B thermocouples using noble metal.

Term 2. Temperature fixed point: Heat equilibrium where the phase transition occurs at constant temperature. The calibration of thermometers is conducted at this point because it has excellent reproducibility and stability. Some well known fixed points are: the triple points of water (the temperature at which gaseous, liquid, and solid phases coexist) and the freezing point of pure metals such as copper, silver, zinc, and others.

Term 3. Eutectic point: The melting or freezing temperature of alloys when two or more solid phases separate out from a solution and freeze to become a densely mixed substance. The melting or freezing temperature of alloy becomes minimum at the eutectic composition.

Term 4. Japan Calibration Service System (JCSS): This was started as an accreditation system for the calibration laboratories based on the Measurement Act in November 1993, and became a registration system in July 2005. The calibration laboratory undergoes screening to see whether it fulfills the requirements of the calibration institution standard (ISO/IEC 17025) set by the International Standard Organization (ISO) and the International Electrotechnical Commission (IEC). The calibration laboratory is registered if it meets the necessary requirements. The registered laboratory may issue the calibration certificate bearing the JCSS mark.

Term 5. The International Temperature Scale of 1990 (ITS-90): The temperature scale that approximates the thermodynamic temperature based on the international agreement among the member state of the Metre Convention. It is defined by the temperature values at several fixed points and the interpolations (interpolation thermometer and interpolation function). The ITS is reviewed approximately every 20 years, and currently, the temperature scale based on the technique available in 1990 is used.

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Discussions with Reviewers

1 Motivation of the research

Comment and question (Akira Ono, AIST)

This paper describes excellent *Type 2 Basic Research* and *Product Realization Research* where the traceability system for the thermocouples in Japan was designed from a bird's-eye perspective, various elemental techniques were integrated while developing a new elemental techniques, and the traceability system acceptable by society was constructed, all while working with the international movement. Since the many thermocouples are commonly used the social and industrial effect of the increased reliability of the temperature measurement is immense.

One issue, the engineers mainly of the iron and steel manufacturing industry have often indicated that there are some serious problems in the reliability of thermocouples at high temperatures. On the other hand, thermocouples have been generally used as thermometers for a very long time, and some have said that there might not be no more room for advancement, and the research in Japan has not been active. With this background, I am quite surprised the authors sought a new research subject in the thermocouples, and were able to construct a traceability system for thermocouples with exceedingly high reliability. What was your motivation for starting this research, and what do you think was the factor of success? Can you please reply based on your experiences as researchers who were directly involved.

Answer (Masaru Arai, Hideki Ogura, and Masaya Izuchi)

The greatest motivation was to set our minds on tackling the inhomogeneity of thermocouples. As mentioned in the paper, the thermocouple is affected by temperature gradient due to inhomogeneity. Therefore, in other national metrology institutions, there is a limitation tacked on to the thermocouple calibration that the value is applicable only if it is used under the same condition that the thermocouple was tested. But that means the user of the calibrated thermocouple could not use the values as they are. When we started the research, we faced the issue of how to handle the uncertainty evaluation considering that the inhomogeneity caused bias rather than variation, and that this increased with longer exposure to high temperature. We attempted to solve the problem by taking the following procedures: (1) reduce the inhomogeneity of the thermocouple itself, (2) evaluate the inhomogeneity appropriately, and (3) check the adequacy of the evaluation method by having the users submit the temperature distribution data of the calibration device they possess.

The reason we succeeded is, using perhaps an overused phrase, we simply "never gave up and went all the way." Following the inhomogeneity increase over time is a work that requires endless patience, but one of the factors of success was we developed a highly accurate calibration device and established an efficient and precise thermocouple evaluation method using this device. The precise evaluation to the fine level as we did this time was never done before because it took so much time and effort. Yet now, the evaluations can be done much more efficiently, and we can conduct experiments in many different conditions. As a result, we were able to build a traceability system for thermocouples with exceeding reliability.

2 Factors for the stabilization of Pt/Pd thermocouples

Comment and question (Jun Hama, Evaluation Division, AIST)

Authors clarified heat treatment conditions to reduce the drift and inhomogeneity, which cause the uncertainty sources of calibration of the Pt/Pd thermocouples, and developed uncertainty evaluation method to the establishment of the calibration method. These results are helpful to the development of the transfer standards with high precision and to supply them to industry.

To understand these results more clearly and to consider the possibility of further increasing their reliability, please teach why the drift and inhomogeneity stabilize in the case of the Pt/Pd thermocouples, although the authors described the guidelines for heat treatment conditions to reduce the uncertainties due to these factors. In the type R thermocouples, why don't the drift and inhomogeneity decrease at similar heat treatment temperature?

Answer (Masaru Arai, Hideki Ogura, and Masaya Izuchi)

In Fig. 9(c), only the tendency for increased Seebeck coefficient is presented schematically, but in case of the Pt/Pd thermocouple, there are temperature ranges where the Seebeck coefficient may become large or small by exposure to the temperature range from room temperature to 1300 °C. Therefore, by conducting preliminary heat treatment for sufficiently long time at an appropriate temperature, the change in the integral value of the electric field generated in the wire along the thermocouple can be kept very low. Moreover, in the Pt/Pd thermocouple, the change in the Seebeck coefficient due to exposure tends to become saturated over time, and the emf ultimately stabilizes. On the other hand, in the type R thermocouple, the composition of the Pt-Rh alloy continues to change at around 1000 °C. Therefore, the Seebeck coefficient continues to decrease without saturation, and as a result, the drift does not become saturated and the emf continues to decrease.

3 Microscopic factors for the instability of the Pt/Pd thermocouple

Question (Akira Ono)

That the drift and inhomogeneity can be significantly reduced by final heat treatment of the Pt/Pd thermocouple at a specific temperature is a major finding of this research. The authors stated that the cause of drift and inhomogeneity is in the palladium wire, but palladium is pure metal, and I don't think its composition changes by exposure to high temperature. I suppose the cause of decreased drift and inhomogeneity may be some suppression of microscopic structural change in the palladium wire, but what is the view of the authors? To what extent can the microscopic changes that occur in the palladium wire be explained in terms of material science and solid state physics?

Is there any other way than maneuvering the heat treatment condition based on some different principle that can reduce the drift and inhomogeneity of the thermocouple?

Answer (Masaru Arai, Hideki Ogura, and Masaya Izuchi)

We are certain that the microscopic structure change of the palladium wire has something to do with this. Currently, other researchers report the cause of the drift and inhomogeneity of the Pt/Pd thermocouple, and these can be roughly divided into: the oxidation of the impurities in the palladium wire, and the growth of crystal grain in the palladium wire.

If the cause is the impurities in the palladium wire, the impurities in palladium oxidize, and change from conductor to insulator, thereby changing the emf. Therefore, if the refining technique advances in the future, and we are able to fabricate highly pure palladium wire or remove the impurities that enhance the inhomogeneity, then we may be able to inhibit the inhomogeneity. On the other hand, if it is caused by the growth of crystal grain in the palladium wire, we can sufficiently grow the crystal by preliminary heat treatment, or add additives to inhibit the crystal growth to the level that it will not alter the emf.

Currently, the cause of the drift and inhomogeneity of the Pt/Pd thermocouple is not fully clarified, and to further reduce the calibration uncertainty of the thermocouple is a future research topic.

4 Contribution to the Japanese industry and its level

Comment and question (Akira Ono)

The authors established the traceability system for thermocouples with thorough consideration of the technological status of the Japanese industry. I think there is a Japanese characteristic in the traceability system compared to the that in other countries. Many of the Japanese private calibration laboratories possess fixed-point furnaces of high temperatures that can be used for calibration services, though the furnaces may not be advanced like the AIST's national measurement standards. The authors took into account the equipment and experiences of the private calibration laboratories, and I think that it is the reason the authors were able to construct a traceability system at the highest level of reliability in the world. What do you think about that point? The authors repeatedly emphasize "the technique that has been nurtured by the private companies" in the paper and I wonder whether you are referring to this.

It was demonstrated by the international comparison that the technological level of AIST is high. If there was an international comparison among the I suppose the Japanese calibration laboratories would perform extremely well. What is your thought? I would suggest some activities so that the high technological reliability of the Japanese private calibration laboratories are recognized better in the world.

Answer (Masaru Arai, Hideki Ogura, and Masaya Izuchi)

In Japan, the introduction of the fixed-point device to raise the reliability of temperature measurement started early. Also, for the thermocouple calibration device using the Co-C eutectic point, which is our latest research mentioned in the paper, the Japanese calibration laboratories have developed products jointly with AIST, and several laboratories are already preparing to use these devices. As you can see, the technological level of the Japanese calibration laboratories is extremely high. If there is an international comparison among the calibration laboratories, the Japanese laboratories will certainly demonstrate high reliability. Also, in the working group of the Temperature Measurement Subcommittee, under the 36th Committee on Industrial Instrumentation of the Japan Society for the Promotion of Science, the thermocouple calibration laboratories and AIST are collaborating to study the thermocouple calibration technique, and we would like to present the research results at international conferences.

5 Reliability of the thermocouples at temperatures above 1550 °C

Question (Akira Ono)

This paper describes the traceability system of thermocouples in the temperature range up to 1550 °C. Thermocouples are also used as the major thermometer for above 1550 °C. What do you think is the reliability of the thermocouples in this temperature range? If you were constructing the traceability system in the temperature range above 1550 °C in the future, what kind of research approach would you take?

Answer (Masaru Arai, Hideki Ogura, and Masaya Izuchi)

The thermocouple is a major thermometer for high temperatures above 1550 °C. In industry, tungsten-rhenium thermocouples are used for temperatures up to over 2000 °C. However, in practice, the reliability of tungsten-rhenium thermocouples are not really known. For example, with approximately 100 hours of use, approximately 5 °C thermoelectric drift is expected at around 1700 °C, and the drift will increase in higher temperatures.

In this temperature range, it is difficult to create a stable and homogeneous temperature field to begin with, and in addition, since the reactivity of the substance increases, the effect of the insulation and protection tubes on the thermocouple wire must be studied. To construct highly reliable thermocouple traceability, we think it is important to engage in R&D to solve the elements for evaluating the stability of the thermocouple. We would like to continue the research by actively incorporating the high reproducibility of metal-carbon eutectic point that is the result of our latest research.

Biomarker analysis on microchips

— Development of POCT device for multi-marker analysis —

Masatoshi Kataoka*, Shouki Yatsushiro, Shouhei Yamamura, Masato Tanaka and Toshihiko Ooie

[Translation from *Synthesiology*, Vol.3, No.1, p.16-25 (2010)]

Point of care testing (POCT), the analysis of biomarkers at the patient's side, is a continuously expanding trend in the practice of laboratory diagnosis. Although some POCT devices for the analysis of blood glucose and/or several infectious diseases have been developed, many laboratory tests in almost all hospitals are contracted out to clinical laboratory companies. However, outsourcing of biomarker analysis is time-consuming, high in cost, and requires much blood and reagents. Consequently we are constructing a biomarker analysis system on microchips for the POCT device. In this paper, we show the core technology for the analysis of biomarkers on microchips, and describe the problems and its solutions in the application of microchips for POCT device.

Keywords **:** Laboratory testing, biomarker, POCT, microchip electrophoresis, microchip, multi-marker analysis

1 Introduction

To achieve a high quality life of good health and longevity, it is necessary to prevent various diseases by ultra early detection or predictive diagnosis, particularly of lifestyle-related diseases such as diabetes. To do so, it is necessary to monitor several biomarkers related to various diseases on a daily basis at a personal level, and to establish a network and a diagnostic system of the data obtained. To achieve these goals, we are working to construct a device to measure multiple biomarkers that can be used by patients. Ultimately, it is necessary to establish a technology to detect multiple biomarkers that are present in the humoris such as blood, in the setting of people's daily lives and homes. To realize this, the device must: combine the processes of blood sample collection, pretreatment, separation, reaction, and detection; be compact and easy to use so it can be installed and used at home; and also enable analysis of multiple biomarkers for accurate diagnosis. The biomarker analysis conducted to observe the *in vivo* biological or biochemical changes of protein, glucose, and lipid in the blood is exactly the same as the clinical test conducted when a patient visits a hospital.

Recently, there is an increased demand for "clinical tests at patient's side" or point of care testing (POCT) in the field of clinical tests[1]. In current clinical testing, it is rare that the results be available on the same day as the test. Several days are required before the results become available, and this may prevent swift diagnosis and treatment. Other than the fact that the biomarker measurement itself is time consuming, large and expensive precision measurement device is necessary, and the economic burden on the medical institution is great including the cost of labor for lab technicians. Therefore, many medical institutions outsource the clinical tests to private clinical laboratories. Figure 1 shows the schematic diagram of the clinical test outsourcing based on the brain-to-brain loop model suggested by Lundberg *et al*[2][3]. In contrast, POCT allows the sampling and selection of tests to be done at the patient's side, and the results can be obtained directly from the tests conducted on the spot. This enables definitive diagnosis at the patient's first visit to a medical institution, and this will allow a swift start of the treatment, increased treatment efficiency, reduced load of repeat visits, and reduced medical expenses. This in turn will be beneficial to the patient, the medical institutions, and to society. As a benefit for the clinician, it will enable obtainment of useful, on-the-spot information for determining the treatment method, such as the presence of infections or systemic diseases and their clinical conditions in cases that may require emergency surgical intervention. Currently, POCT devices have been developed and introduced in the clinical practice for conditions that

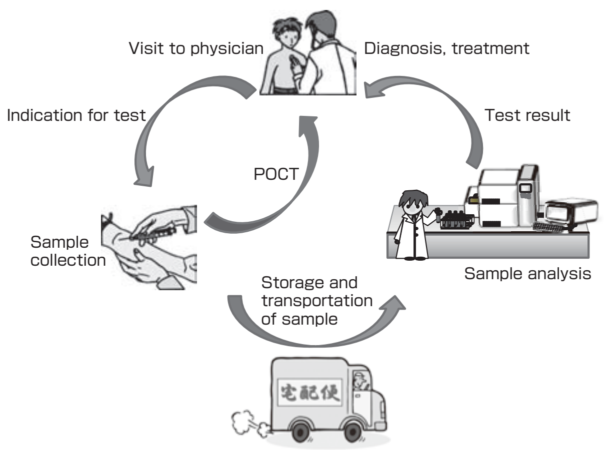

Fig. 1 Flow of tests currently dependent on clinical testing companies.

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require immediate diagnosis, particularly in acute diseases and infections, such as cardiac infarction, influenza diagnostic kit, blood glucose measurement, as well as blood gas measurements in the operating room. However, these products target biomarkers only of specific diseases, and have problems since many detection methods are qualitative. The development a POCT device that can solve these current problems and quantitatively analyze multiple biomarkers will be a core technology for a personal-level multiple biomarker monitoring in the future. Only when the POCT technology is established and its efficacy is recognized in clinical practice, the personal health monitoring technology will be recognized by society (Fig. 2). To do so, it is necessary to realize the POCT device that allows quantitative analysis of multiple biomarkers as soon as possible. Due to the advances in recent analysis technology using nanotechnology, high speed, smaller sample, and higher sensitivity are achieved in testing, as well as the downsizing of device. The development of a device using various microchips is a typical topic of such technological development. Such a device provides benefits to POCT, as explained in the following chapter, and as a personal-level biomarker device. Therefore, as a step for achieving the above goal, we present the application of the nano biodevice to the development of the POCT device by combining the existing microchip core technologies such as the glucose analysis using the commercially-available microchip electrophoresis device for nucleic acid analysis, and the construction of the antigen-antibody reaction system on the micro flow channel using microfluidics. The issues that are yet to be solved will be described from the standpoint of a biological user with clinical experiences.

2 Requirements of the POCT device

The POCT device must allow measurement of a biomarker quickly in the doctor's office or the hospital ward, provide analysis within 30 min[1], possess sensitivity and reproducibility usable for clinical diagnosis, enable measurement equivalent or superior to the current clinical

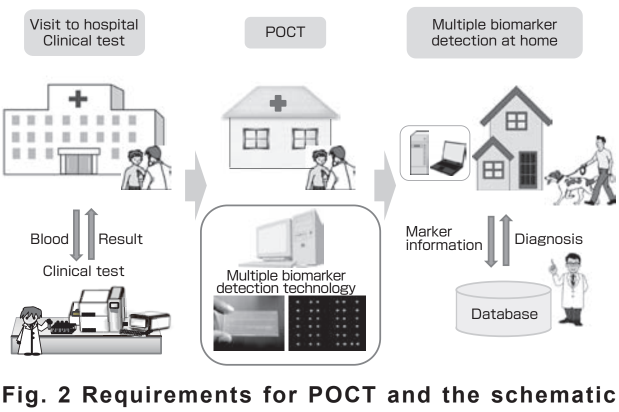

Fig. 2 Requirements for POCT and the schematic diagram of the integrated microchip substrate.
The plasma separation mechanism is installed onto the microchip substrate. There are flow channels for microchip electrophoresis and microfluidics system.

test method, have compactness that enables installation in the office, and be operable for physicians while interviewing patients. Regular blood tests require several ml of blood per test item, and that is not only stressful to the patients, but also is costly since it necessitates large quantities of reagents for the test tube analysis. Therefore, analysis with microscale samples is in demand not only in POCT but also in clinical tests in general. Also, since the test samples include blood, the device material must be easily sterilized after testing. Also, considering the needs of a device that allows the detection of multiple test items, we focused on the microchemical chip technology based on the microfabrication technology, or the microchemical analysis system where the procedures for chemical and biochemical analyses such as the pretreatment, separation, reaction, and detection are integrated on a microchip of few centimeter square size. Aiming at the application to the POCT device, we clarified the conditions for optimal detection of commercially-available individual biomarkers using the microchip electrophoresis and microfluidics, and worked on the on-chip mounting of the biomarker detection system.

3 Application of the microchip substrate to the POCT device

3.1 Construction of the biomarker measurement method using the glucose analysis by microchip electrophoresis

3.1.1 Application of the microchip electrophoresis to biological and biochemical analysis

Microchip electrophoresis devices have been developed and are commercially available. In these devices, electrophoresis is conducted in the micro flow channel with μm-level width and depth formed on the microchip made of plastic or glass material of a few centimeter square size using the microfabrication technology for semiconductors. Compared to the conventional electrophoresis method for the separation analysis of nucleic acid and proteins, the microchip electrophoresis has high separation capacity by application of high voltage, because the sample volume can be reduced by using the micro flow channel, and because the efficiency of heat release during electrophoresis is increased due to the increased surface volume against the sample volume in the flow channel. Moreover, higher sensitivity can be achieved by using the LED-excited fluorescence detection system. These devices, however, are not sufficiently diffused in the biology and biochemistry labs of the universities that are expected to be the main users. The main reasons are because their usage is limited to the separation analysis of nucleic acids, the price of the electrophoresis device is higher compared to the conventional agarose electrophoresis, and the cost of microchips and gel necessary for the analysis per sample is about 200 times higher. Therefore, we attempted using the device for purposes other than nucleic acid separation without changing the electrophoresis chip, the device, or the analysis software, by optimizing the electrophoresis conditions by considering the gel and buffer solution compositions. We found that in the various experimental methods conducted daily in the biology and biochemistry laboratories, the presence of the proteins such as enzymes and ions such as Mg^{2+} ions necessary for restriction enzymatic activities did not affect the electrophoresis, by conducting the electrophoresis analysis after the on-chip restriction enzymatic treatment using the sample reservoir as a reaction field. Based on this result, we designed the on-chip restriction enzyme treatment method, and conducted quick restriction fragment length polymorphism (RFLP) analysis. We also reported that a biology researcher could conduct the mitochondrial membrane potential measurement, as well as application to synthetic RNA analysis and DNA ligation reaction analysis, simply by changing the electrophoresis condition, without changing the electrophoresis device or the analysis software. We also reported the high applicability of the microchip electrophoresis to biological and biochemical analyses utilizing the advantages, as it allows not only for nucleic acid separation analysis but also rapid, small sample, and high sensitivity analysis and various enzyme treatments[4]-[8]. These results indicate that the microchip electrophoresis can be applied to various experimental procedures, and cost reduction can be expected.

3.1.2 Application of the microchip electrophoresis to blood glucose analysis

Based on these findings and considering the application to POCT, we applied the blood biomarker analysis using the commercially-available microchip electrophoresis device and microchip. The Hitachi SV1100 was used as the microchip electrophoresis device, because it allowed easy handling of the solution by Pipetman due to its 10 µl reservoir capacity, and the gel and buffer solution could be changed easily. The supplementary chip was used as the microchip. Figure 3 shows the *i*-chip made of polymethylmethacrylate (PMMA) to be used with the SV1100. The *i*-chip has three micro flow channels with width of 100 µm and depth of 30 µm, and simultaneous analysis of three samples was possible (Fig. 3A).

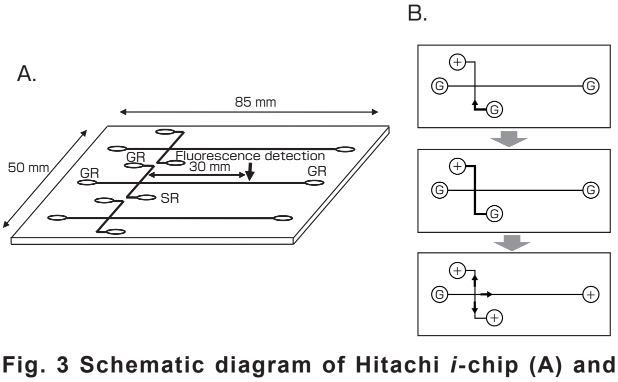

Fig. 3 Schematic diagram of Hitachi *i*-chip (A) and sample separation in the cross flow channel (B).
The "+" indicates the anode, "G" indicates the ground, and arrows show the migration direction of the sample DNA.

The electrophoresis procedure is simple. After adding the gel from the gel reservoir (GR), total 10 µl sample solutions including the internal control DNA were placed in the sample reservoir (SR). Electrophoresis and separation were conducted, and the separation and analysis of the DNA were done by fluorescence detection (Fig. 3B). In this microchip electrophoresis, the detection sensitivity was about 10 times higher than that of conventional agarose gel electrophoresis with fewer samples. The analysis result was obtained in a few minutes after the start of the electrophoresis, and the DNA could be separated with error of only a few bases. We focused on the high DNA separation capacity including the glucose structure of the microchip electrophoresis, and used the supplied DNA analysis software for the analyses for blood glucose and amylase that have glucose structure or use glucose as enzyme substrates[9][10].

In the blood glucose measurement, we reported that the blood glucose could be specifically detected, after directly fluorescence-labeling the glucose by adding the fluorescent pigment 2-aminoacridone (AMAC) to the blood plasma, and then charging the glucose negatively using the boric acid buffer solution as the driving force of electrophoresis (Fig. 4A)[8]. It was found that the separation and analysis by electrophoresis of fluorescence-labeled glucose could be done in the blood plasma sample in which diverse proteins and other substances were present. This method had detection limit of 0.92 µM, allowed quantitative detection in the range of 1~300 µM, and enabled detection of blood glucose as accurate as the blood glucose level obtained by the conventional clinical test. Moreover, it showed high reproducibility both in within-a-day and between-days reproducibility, and indicated the possibility of practical application to blood glucose measurement by microchip electrophoresis. In the hexokinase-G-6-P-dehydrogenase method used in current clinical tests, there is a major problem where the value higher than the actual glucose measurement is obtained due to the presence of the disaccharide maltose in the infusion. However, by using the microchip electrophoresis, the monosaccharide glucose and the disaccharide maltose can be easily identified due to the difference in migration time[11]. As a result, the risk of hypoglycemia due to the false high-value reading of the glucose measurements in patients receiving infusion containing maltose can be prevented.

3.1.3 Measurement of blood amylase activity by microchip electrophoresis

Blood amylase is a biomarker used in the diagnosis of pancreatitis and sialadenitis. Amylase hydrolyses the glycoside bond and converts starch into glucose, maltose, and oligosaccharides. In the current clinical test, the oligosaccharide is used as the enzyme substrate and a qualitative measurement is done by the colimetric method[12]. Since it is already known that amylase is hydrolyzed into maltohexaose (G6) and maltotriose (G3) that are oligosaccharides, we focused on the high separation capacity of the fluorescence-labeled glucose using the microchip electrophoresis that became apparent in the blood glucose measurement. We used the APTS-G6 that was fluorescence-labeled by 8-aminopyrene-1,3,6-trisulfonic acid (APTS) as a substrate, separated the breakdown product APTS-G3 by microchip electrophoresis, and then quantitatively measured the amylase activity (Fig. 4B)[10]. Here, the boric acid buffer solution was used as the driving force of migration, as in the blood glucose separation. In this method, the quantitative detection of blood amylase activity was possible in the range of 5~500 U/L at detection limit of 4.38 U/L. There are two isozymes of blood amylase originating from the pancreas or the salivary gland. By conducting the plasma pretreatment using the anti-amylase antibody of salivary gland origin for the differential diagnosis of pancreatic disease, the specific measurement of pancreatic-origin amylase activity became possible. When the plasma sample was used, it was shown that the amylase activity measurement was accurate as the current clinical testing method, and this indicated the possibility for practical application of the microchip electrophoresis in amylase activity measurement.

In the glucose and amylase measurements described above, about one hour is necessary for blood glucose labeling and enzyme treatment of APTS-G6, and the treatment time must be reduced for application as POCT. Therefore, it is necessary to shorten the detection time by achieving high sensitivity by changing the fluorescence material or the detection system. However, the blood glucose and amylase activity are measured using the supplemented DNA analysis software, after the fluorescence-labeling and electrophoresis of the plasma using the commercially-available microchip electrophoresis device and the supplemented electrophoresis chip, or by mixing the fluorescence-labeled oligosaccharide with the plasma and then conducting electrophoresis. The major advantages are that the quantitative detection can be done extremely easily, and that it has accuracy and reproducibility equivalent to the current clinical test method. Also, only µl level of plasma sample is required, the device is compact, and the plastic substrate can be sterilized in an autoclave. Combining all these factors, the high potential of the microchip electrophoresis in biomarker analysis such as blood glucose and amylase is indicated. However, the glucose and amylase measurements are relatively inexpensive at 110 yen per test as covered by the National Health Insurance system, and the economic feasibility is low when only one item is tested with the microchip electrophoresis. However, sufficient economic feasibility can be maintained by measuring a combination of multiple test items, such as the detection of various blood proteins that will be mentioned later, on one chip for a particular disease.

3.2 Construction of the antigen-antibody reaction system on the microchip substrate

3.2.1 Construction of the sandwich ELISA on the micro flow channel

Many of the biomarkers in the blood are various metabolites and proteins, and specific detection is possible even in blood in which many foreign substances are present. In the current clinical test methods, the antigen-antibody reaction system that does not require molecule sorting by electrophoresis is widely used. In the current clinical test methods, the antigen-antibody reaction using 96-well plate is generally used, but over one hour is needed for the reaction time, and several tens of µl of samples are necessary. Therefore, we attempted construction of the antigen-antibody reaction system in the

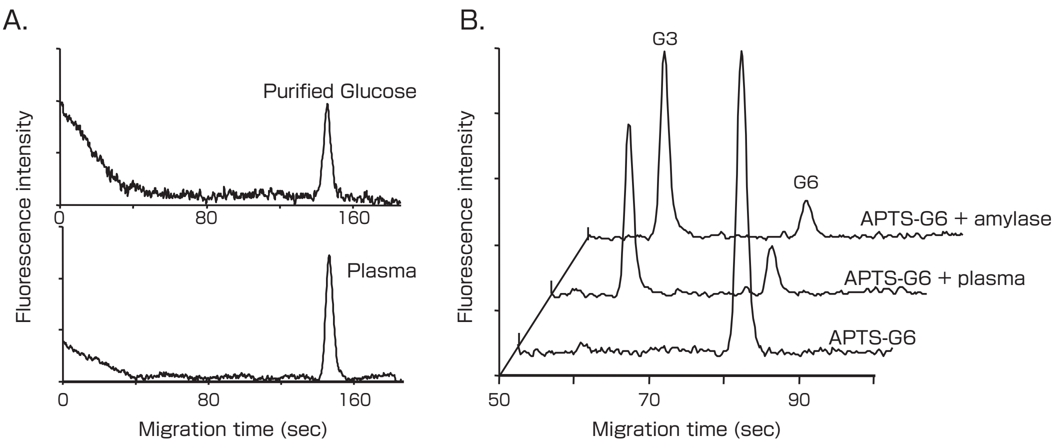

Fig. 4 Measurements of blood glucose (A) and amylase activity (B) using the microchip electrophoresis.

(A) A peak for plasma glucose was observed in a similar migration time as the glucose preparation. The blood glucose concentration was measured by calculating the calibration curve from the fluorescence intensity of the glucose preparation with known concentration.

(B) A single peak was observed in the solo electrophoresis of APTS-G6. Treatment of APTS-G6 with purified amylase, the single peaks of APTS-G6 and APTS-G3, its breakdown product, were observed. By reacting the APTS-G6 with plasma, it was broken down into APTS-G3 by the action of blood amylase. The blood amylase activity was measured by calculating the calibration curve from the fluorescence intensity corresponding to APTS-G3 by treatment of APTS-G6 with amylase with known concentration.

micro flow channel on the microchip to reduce the sample quantity and to reduce the antigen-antibody reaction time by molecular scattering using the microspace. We investigated the sandwich enzyme-linked immuno-sorbent assay (ELISA) method (Fig. 5A) that is widely used for biomarker detection and has excellent quantitative quality.

The blood procollagen I carboxyterminal propeptide (PICP), which is a biomarker for osteoporosis and cancer metastasis in which highly specific antibodies are commercially available, was selected as the measurement model. In the sandwich ELISA method, the primary antibody is fixed on to the solid phase[13]. In the conventional test, the 96-well plate (Fig. 5B) was mainly used as the solid phase, but here, the microchip (Fig. 5C) was used. After fixing the antibody and conducting blocking[Term 1], the plasma sample or the purified PICIP with known concentration and the peroxidase-labeled secondary antibodies were added. Fixing on to the solid phase was done via the bonding of PICP bonded to the labeled secondary antigen to the PICIP primary antibody. After washing away the labeled secondary antibody that did not bond to the antigen, peroxidase substrate was added, and the chemiluminescence was detected by a CCD camera. When using this as the POCT device, the user carries out the procedure after the blocking procedure. In the conventional 96-well plate, three hours was needed for the antigen-antibody reaction using 20 µl plasma. The cyclic olefin copolymer (COC) (Sumitomo Bakelite Co., Ltd.) substrate, in which the surface is treated to fix the protein and has three micro flow channels on one microchip, was used as the microchip substrate. The introduction of each solution at µl level into the micro flow channel was done using the Pipetman. Blocking was done after introducing the primary antibody from the sample well (1) in the direction of (2) and fixing it, and the antigen and the peroxidase-labeled secondary antibody were introduced in the direction from (3) to (2). Washing was done after the antigen-antibody reaction, the enzyme substrate was added in the direction from (1) to (2), and chemical luminescence was detected. The amount of plasma necessary per micro flow channel was 1 µl or less, and the antigen-antibody reaction time was 30 min. Dramatic reduction of the detection time and the sample volume was realized compared to the conventional method.

For the antigen-antibody reaction in microspace, the method in which the micro-beads with diameter of several µm were fixed on the antibody, and then introducing and fixing the beads in the micro flow channel had been reported. In the beads method, there are issues such as a necessity of designing a micro flow channel with a complex shape to contain the beads in the channel. Therefore, we selected the method of fixing the antibody directly to the micro flow channel surface. As shown in Fig. 5C, the increased chemiluminescence intensity was observed in accordance to the concentration of the purified PICP, but the uneven luminescence in the same flow channel was observed, and it could be seen that quantitative property was not maintained. The reasons were thought to be: 1) uneven fixing of the primary antibody in the flow channel surface, and 2) insufficient washing or partial residue of labeled secondary antibody in each steps of blocking. In the Y-shaped flow channel used (Fig. 5C), the increased chemical luminescence was observed particularly at the fork point of the flow channel. It was necessary to design a flow channel that could be washed easily. Therefore, we attempted improvement of the quantitative property by fixing the primary antibody to the specific part of the micro flow channel using the inkjet for 1), and by increasing the washing efficiency by changing the flow channel design for 2).

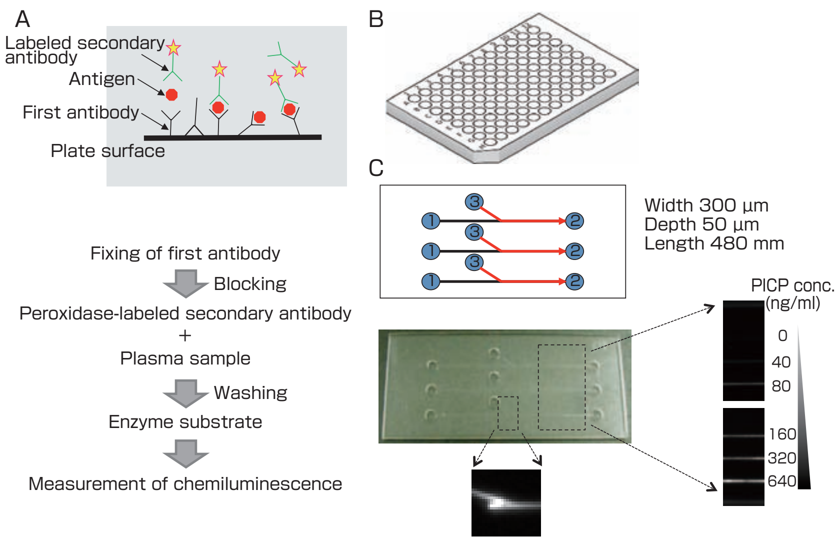

Fig. 5 Antigen-antibody reaction by sandwich ELISA method.
Principle of the sandwich ELISA method and its experimental procedure (A), 96-well plate (B), and PICP detection in the micro flow channel (C).

3.2.2 Fixing the antigen to the micro flow channel surface using the miniaturized inkjet

To fix a certain amount of antigen on to an arbitrary part on the micro flow channel, miniaturized inkjet that can be programmed to discharge ultralow volume of solution at pl level was used. The miniaturized inkjet used was the piezo-driven Pulse Injector (Cluster Technology Co., Ltd.) (Fig. 6). This inkjet device could discharge 65 pl of diluted anti-PICIP primary antigen in one droplet. When 100 droplets of primary antibody was discharged and fixed using this device, the droplet diameter reached approximately the width of the flow channel, and the anti-PICIP primary antibody was fixed (Fig. 6). As mentioned earlier, in the design of the micro flow channel with a fork, nonspecific chemiluminescence[Term 2] was seen, where a strong chemiluminescence was observed in the fork part due to the problem of washing, and it was difficult to maintain the quantitative property. Therefore, four linear micro flow channels that allowed easy washing was formed on one COC microchip (Fig. 7A) to construct the quantitative detection system. After discharging and fixing the primary antigen to the micro flow channel surface using the inkjet, blocking and washing were done in the direction of (1) to (2) to prevent the nonspecific adsorption and residue antibody, and after 30 min of antigen-antibody reaction, the chemiluminescence was detected using a CCD camera (Fig. 7B). In this reaction system, the amount of plasma needed per micro flow channel was 1.8 µl and the antigen-antibody reaction time was 30 min. These were 1/10 or less and 1/6, respectively, compared to the conventional 96-well plate method, and a low sample, high-sensitivity detection system was constructed. As a negative control, the antibody for the cardiac infarction marker, heart type fatty acid binding protein (H-FABP), that did not recognize the PICIP was discharged and fixed on to the micro flow channel surface using the inkjet. No nonspecific luminescence was observed for H-FABP, and good quantitative property was observed in the concentration range of 0~600 ng/ml (Fig. 7B, C). In the case where the plasma sample was used, rapid, low-volume, and accurate detection system that allowed measurement accuracy equivalent to the current sandwich ELISA method using the 96-well plate was possible. By conducting the antigen-antibody reaction in the micro flow channel, we were able to construct a blood protein detection method that could be applied to the POCT technology.

In the method where the antibody is discharged and fixed in the micro flow channel using the miniaturized inkjet, the discharge and fixing of an arbitrary amount of antibody on to an arbitrary part becomes possible (Fig. 7D). The principle of the blood protein detection by sandwich ELISA method is basically similar regardless of the type of biomarker. Multiple types of antibody solution can be discharged by changing the head of the inkjet including the antibody solution, and multiple biomarker detection is possible from only 1.8 µl plasma sample in one micro flow channel. Currently, we are investigating the concentrations of the various primary and secondary antibodies as optimal conditions of the antigen-antibody reaction system to quantitatively detect multiple types of blood biomarkers on one micro flow channel. We are aiming to fabricate the multi-marker detection microchip, particularly the diagnostic chip for diabetes and osteoporosis that are gathering attention as life-style related diseases. For the diabetes diagnosis, in addition to blood glucose, measurements of insulin and high-sensitivity CRP that could be detected by antigen-antibody reaction could be mounted on the chip for accurate diagnosis with very small amount of blood. In osteoporosis, the detailed state of the disease can be observed by measuring both the osteogenesis marker PICP and the absorption marker NTx. Considering the cost advantages, the current insulin test is

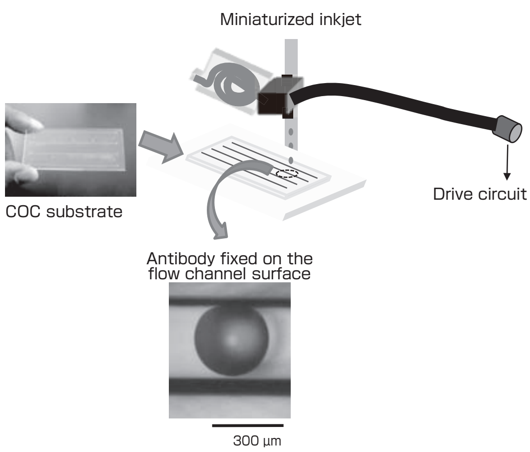

Fig. 6 Schematic diagram of the antibody fixing on the micro flow channel using the miniaturized inkjet, and the antibody fixed on the flow channel surface.

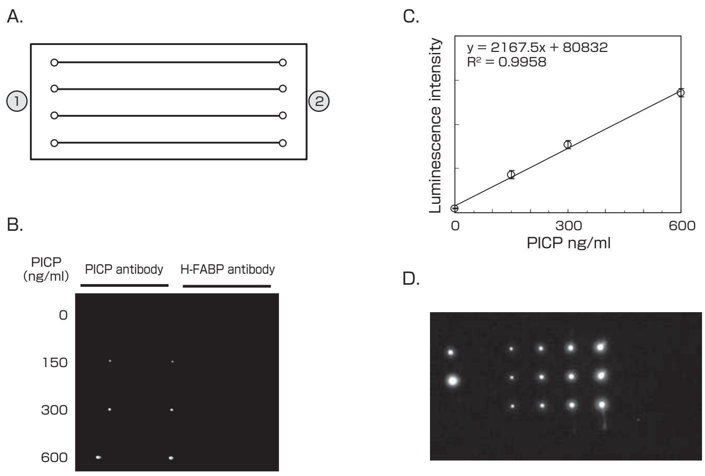

Fig. 7 Schematic diagram of the microchip substrate with micro flow channel (A) and the PICP detection image using this chip (B), calibration curve (C) and the image of chemiluminescence when antibody of arbitrary amount is fixed on each flow channel (D).

2640 yen while CRP measurement is 1560 yen, and adding the blood glucose measurement, the total is 4310 yen for the three items. In osteoporosis, the PICP measurement is 1700 yen and the NTx measurement is 2900, requiring a total of 4600 yen. The cost of the antigen-antibody reaction system is dominated by the cost of antibody used as the reagent. Therefore, if the antibody fixing method using the inkjet is employed, the amount of antibody used is about 1/10,000 in PICP compared to the 96-well plate method, and the cost of antibody can be reduced drastically. Also, by fixing multiple types of antibody on to one micro flow channel, the amount of detection reagent used can be greatly saved, and used with plastic substrate made of inexpensive material, sufficient economic feasibility can be expected.

4 Future issues

We have been working to construct the biomarker detection system based on the existing technologies such as the microchip and the electrophoresis using microchip from the standpoint of users in the biology field. For the microchip electrophoresis, we were able to present the high potential of the current individual technologies in relatively short time, without spending time and effort on the development of the new device and software, but using the commercially-available chip, electrophoresis device, and analysis software for application to the biology and biochemistry experiments and clinical tests. However, for the realization of the POCT device, besides the biological approach, it is necessary to collaborate with engineers and researchers across the fields, including engineering and medical fields focusing on microfabrication, information fields for future database construction.

While we were able to construct the core technology for the biomarker analysis on the microchip for glucose and protein, the following issues remain before the POCT device can be used in actual clinical practice. In the above microchip, the analysis is conducted after the conventional blood cell separation by centrifugation, and then adding the plasma components to the microchip. Therefore, to do the blood test during interviews by physicians in clinical practice, the blood cell separation process must be simplified. Therefore, it is required that the analysis, including blood cell separation, can be accomplished simply by adding the whole blood to the microchip. To enable tests with ultralow volume blood at μl level, we are working on an on-chip plasma separation system with a micro flow channel that incorporates a filter for separating the erythrocyte components from the blood drawn using currently available disposable microsampling needles. Moreover, we must construct a solution sending system using a micropump to send the necessary amount of plasma automatically and quantitatively to the sample well in the flow channel of microchip electrophoresis or microfluidics. Also, for the realization of the multiple biomarker detection chip, a complex micro flow channel design is required. In the design, it is necessary to install the separation and analysis systems that have different principles on one microchip, including the electrophoresis system where the substance is separated by the difference of migration speed due to the charge, size, and shape of the substance, and the micropump[Term 3] used in antigen-antibody reaction system by sending ultralow volume liquid. For this, it is necessary to collaborate with companies with expertise in microfabrication technology including plastic forming.

In addition to the above technological issues, a prototype of the POCT device will be fabricated as soon as possible, by integrating and constructing the peripheral technology such as the development of the detection system and analysis software. In this case, the subject will be the diagnostic chip for diabetes and osteoporosis that affect several million to ten million patients among Japanese adults. The efficacy as a POCT device is verified by comparisons with current clinical test data through joint research with university hospitals and specialized hospitals. Data will be collected to obtain approval of the Ministry and Health, Labour and Welfare based on the Pharmaceutical Affairs Law as a medical test device. After introducing this POCT device to clinical practice, we shall work on the introduction of the biomarker measurement device to monitor health at home.

Terminology

Term 1. Blocking: Prevention of the nonspecific bonding of the antibody to proteins other than the antigen proteins or to solid phase surface. Bovine serum albumin, gelatin, and skim milk are often used as the blocking agents.

Term 2. Nonspecific luminescence: Luminescence caused by the breakdown of peroxidase enzyme substrate, after the peroxidase-labeled secondary antibody bonds nonspecifically to the protein or solid phase surface, due to insufficient blocking or cleansing. It becomes background noise.

Term 3. Micropump: Liquid control element that generates pressure to move the ultralow volume of liquid.

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Completed the course at the Graduate School of Dentistry, The University of Tokushima in 1990. Doctor of Dentistry. Worked as a dentist specializing in periodontal disease at the Faculty of Dentistry, The University of Tokushima from 1990 to 2002, and studied the genetic analysis of the periodontal pathogenic factor. Engaged in research for the biological analysis using the microchip electrophoresis as an associate professor of genetic expression field at the Institute for Genome Research, The University of Tokushima until 2004. Joined the Health Technology Research Center, AIST Shikoku as a senior researcher in 2006. Leader of Biomarker Analysis Team from 2007. Leader of Biomarker Analysis Group, Health Research Institute, AIST from 2010. Works on application of the microchip to biomarker analysis including electrophoresis. In this paper, constructed the biological analysis method using the microchip and coordinated the overall concept.

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Masato Tanaka

Joined the Shikoku National Research Institute, Agency of Industrial Science and Technology, Ministry of International Trade and Industry in 1988. Engaged in research for the mechanical system control and the measurement technology using ultrasound. Became a senior researcher of AIST in 2001. Doctor (Engineering) from The University of Tokushima in 2002. Senior researcher of the Biodevice Team, Health Technology Research Center, AIST Shikoku from 2005. Senior researcher in Health Research Institute, AIST from 2010. Currently studies the microfabrication technology and the ultralow-volume droplet control technology for biodevice construction. In this paper, worked on the discharge and fixing of antibody using the miniaturized inkjet.

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Leader of Biodevice Group, Health Research Institute, AIST from 2010. Specialty is microfabrication using lasers. Develops the plastic disposable chip, the units to be embedded in integrated chip, and others to enable multi-item diagnosis using blood, to realize a device that can numerically express the human health condition. In this paper, constructed the discharge and fixing of antibody using the miniaturized inkjet for multi-marker analysis.

Discussions with Reviewers

1 Practical use

Question (Kazunori Nakamura, Evaluation Department, AIST)

The authors mention, “There are many issues that remain before this can be actually used as a POCT device in clinical practice,” and I think the technology is still quite far from practical use. You should add this point to the title and the introduction of the paper to let the readers know.

Please provide an analysis of the many remaining issues, organize their solutions and the actual efforts, and summarize the future direction. Also, before the device and the method can be used in actual clinical tests, there are issues of cost and approval by the Ministry of Health, Labour and Welfare, as well as its quantitative property and reliability. Since getting the MHLW approval involves setting the National Health Insurance points, it is important to establish the cost efficiency compared to the existing method. What is your thought on this?

Answer (Masatoshi Kataoka)

The future issues were described in chapter 4. The technologies include (1) mounting the blood cell separation system on to the chip, (2) construction of pump system using the micropump, and (3) micro flow channel design. The prototype of the device will be fabricated, and its efficacy as a clinical test device must be demonstrated. Also, we described the necessity of the approval as a medical test device according to the Pharmaceutical Affairs Law. On the issue of cost, we explained that there is sufficient economic feasibility when compared to the current test costs in terms of the NHI points.

For the title, we changed it to emphasize the development of the core technology.

2 Comparison with current technology

Comment (Kazunori Nakamura)

This technology is applied to the measurement of blood glucose and amylase activity. Particularly for blood glucose, the glucose sensors that the patient can use daily are already widely in use. Therefore, please state the issues in the currently used methods, and clarify the things you did to solve those problems. You also mention that the method in this study has equivalent performance to the current clinical test method, and therefore, I think you should explain the future developments such as whether this method will replace the current clinical test, whether there is possibility of diffusion as a POCT device, and the path to practical use including the cost aspects.

Answer (Masatoshi Kataoka)

As you mentioned, there are blood glucose sensors that are commercially available as POCT device. However, in the glucose measurement using the hexokinase-G-6-P-dehydrogenase method, higher-than-actual glucose value may be indicated because the disaccharide maltose is identified as monosaccharide glucose. This is a major issue when the patient is receiving infusion that contains maltose (there are actual fatal cases due to hypoglycemia). In such cases, the identification of monosaccharide and disaccharide by electrophoresis based on the migration time provides great clinical advantage.

For amylase measurement, we described that the conditions needed as a POCT device are cleared, such as quantitative property, simple operation, smaller amount of samples, compactness of the device, and chip that can be autoclaved. In terms of cost, we described that the cost of the electrophoresis device will be reduced due to the high universal application of the microchip electrophoresis to various experimental procedures. Also, we explained that in clinical tests, because the costs of blood glucose and amylase measurements are already low in the NHI, the cost of a new device will not be feasible for single tests, but the cost competitiveness will be sufficient if it is used as a multiple analysis chip where several test items are combined.

3 Performance of individual technologies

Comment (Kazunori Nakamura)

You indicated the problem of sandwich ELISA currently used. However, it is not really clear how effective the reduction of measurement time is in the diagnosis of the long-term disease like osteoporosis. You write that the reaction time was reduced from conventional three hours to 30 minutes, but the measurement principles are the same as the antigen-antibody reaction and enzyme reaction, and you don’t sufficiently explain why it is reduced even if they are basically the same principle.

Comment (Motoyuki Akamatsu, Human Technology Research Institute, AIST)

Please explain, why the microchip electrophoresis can use small amounts of samples and have high detection sensitivity compared to the conventional agarose electrophoresis.

Answer (Masatoshi Kataoka)

When constructing the antigen-antibody reaction system, the antigen identification capacity of the antibody becomes the issue. We selected the PICP because: it is a marker for osteoporosis, which is a social issue being a life-style related disease with high number of patients (fracture due to osteoporosis may cause geriatric patients to become bedridden); the highly specific antibody is readily available (the antibody is commercially available independently); and the PICP blood concentration is measurable in healthy individuals (data is always obtainable from the blood sample; markers such as inflammatory cytokine will fall below measurement limit in healthy individuals, and data analysis is difficult → difficult to establish an experiment system). We added these points to the paper.

Since the principle of antigen-antibody reaction is basically the same regardless of the marker type, the basics are the same whether it is PICP or any other marker under investigation. Therefore, we selected PICP for investigation because it is an osteoporosis marker for which highly specific antibody is commercially available. The reduction of time from three hours to 30 minutes will allow use in a doctor’s office, which is a requirement of POCT. In antigen-antibody reaction, specific bonding starts with the collision of the antibody and antigen in space. In the microspace, the dispersal time is reduced due to the molecular dispersal effect, and this, as a result, is thought to lead to the reduction of antigen-antibody reaction time. We also added this explanation.

For electrophoresis, we stated: “Compared to the conventional electrophoresis method for the separation analysis of nucleic acid and proteins, the microchip electrophoresis has high separation capacity by application of high voltage, because the sample volume can be reduced by using the micro flow channel, and because the efficiency of heat release during electrophoresis is increased due to the increased surface volume against the sample volume in the flow channel. Moreover, higher sensitivity can be achieved by using the LED-excited fluorescence detection system.”

4 Approach based on clinical experience

Comment (Motoyuki Akamatsu)

While I understand that the approach from the standpoint of biological researchers with clinical experience is highly valuable, what exactly is based on clinical experience is not explained. For example, one could readily see, even without clinical experience, that the treatment time and device size are issues to be solved. I think you should clearly describe the points seen from the clinical side.

Answer (Masatoshi Kataoka)

In the construction of the personal-level health monitoring system for home use, we are considering an approach for the development of the POCT device, toward the construction of the blood biomarker device that can be used in daily living. Therefore, we are aiming to realize the device as soon as possible, using the microchip substrate that is a currently available technology. We also added that from a clinical standpoint, in cases where emergency surgical procedure is necessary, the device will allow obtaining information useful to determine the treatments, such as the presence and status of the infections or systemic disease.

5 Approach of combining the existing technologies

Comment (Motoyuki Akamatsu)

I understand that the individual technologies are not original, but the combination of these technologies makes this research original. However, when you claim the originality of the combination technology, I would like to see the discussion of why you did not select the other elemental technologies. Overall, there are explanations about the things that were done using the technologies that you selected. However, as a *Synthesiology* paper, I would like you to explain how you selected the technologies.

Answer (Masatoshi Kataoka)

As you indicated, cost reduction can be expected because the commercially-available microchip electrophoresis device, supplementary chip, and analysis software can be used directly for the various biological experimental methods. We explained this point. For the selection of the elemental technologies, we addressed the combination of existing technologies in the selection of the microchip. Also, we explained that the reason for selecting Hitachi SV1100 was because the migration gels and buffer solutions could be changed easily. The reason for focusing on the hydrolysis of G6 and G3 in the amylase measurement was because they could be easily separated by electrophoresis. The reasons for selecting the PICP were because of its high disease specificity (as osteoporosis and cancer metastasis markers) and because highly specific (good) antibodies are commercially available. The antibody specificity is extremely important, and we placed weight on this point. Also, for the antibody fixing method in the antigen-antibody reaction in microspace such as the micro flow channel, we added the comparison with the beads method.

We also described that we were able to demonstrate the potential of the current individual technologies without spending much time, and yet for the future product realization as a device, collaboration with engineering and medical fields is necessary.

6 Amylase of pancreatic and salivary gland origin

Question (Motoyuki Akamatsu)

In section 3.1.2, you explain the necessity of separating the amylase of pancreatic origin and the one of salivary gland origin. However, in actual clinical practice, the presenting symptoms are completely different (swelling occurs in different places) in pancreatitis and sialadenitis, and there is very low chance of missing the diagnosis. Even so, is it necessary to separate the two? Of course, there is the advantage of detecting the disease before the symptoms manifest, but looking at the patients, I think there are very few people with which the disease must be caught before the inflammations occur. What do you think?

Answer (Masatoshi Kataoka)

As you mentioned, the parts affected by pancreatitis and sialadenitis are completely different. Therefore, differential diagnosis can be made easily from the clinical symptoms such as swelling and inflammation, but blood amylase is measured as a marker to see the clinical state of the diseases. As described in the text, there are two types of blood amylase, one of pancreatic origin and other of salivary gland origin. About 40 % originates from the pancreas, and 60 % from the salivary gland. This ratio depends on the individual, age, and gender. Therefore, to understand the clinical state and to determine the treatment efficacy, it is necessary to accurately measure the amylases originating from each organ. The pancreatic-origin amylase is also used as a marker in the follow-up observation of acute pancreatitis, chronic pancreatitis, and pancreatic carcinoma.

Development of primary standard for hydrocarbon flow and traceability system of measurement in Japan

— Approach to construction of an effective and reliable traceability system —

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It is of importance to establish the hydrocarbon flow standard which acts as the basis for vast dealings and taxation for hydrocarbons, enforcement of the policy on energy savings and high quality management of industries. As a result of investigation into calibration methods, reliability, and effectiveness, the specification of the national primary standard and the traceability system for hydrocarbon flow in Japan was designed. We took the technical initiative in establishing the traceability system using JCSS (Japan Calibration Service System) as basis of the national primary standard in the limited region of flow rates and various kinds of liquids. The national primary standard of high accuracy and safety has been developed. This project was evaluated through verification of international consistency by way of international key comparisons.

Keywords **:** Flow rate, uncertainty, measurement, traceability, national primary standard

1 Introduction

The measurement of hydrocarbon flow is important as a basis of quantity for the trade and taxation of petroleum products, and for the production control at the petrochemical plants. The accuracy of the flowmeter used in flow measurement is influenced by the property of liquids, the condition of flowmeter installation, and the condition of the flow. Therefore, to operate the flowmeter in a condition that ensures high accuracy, it is necessary to conduct a calibration where the flowmeter is adjusted to indicate the correct value or to calculate the correction value by flowing the liquids in the flowmeter at a standard flow rate and comparing the standard flow rate and the readings of the flowmeter. Also, regular calibration is necessary to guarantee the performance of the flowmeter currently used.

Until now, strict quality control for the hydrocarbon flowmeter used in trade was practiced according to the law, but with the advances in measurement technology, there is a rising demand for the ability to conduct voluntary advanced quality control using high accuracy flowmeters. There are demands for accuracy, low cost, and coverage of varied calibration subjects, including the demand for establishment of a highly accurate flow standard for diverse petroleum products, as well as the demand for international integrity. However, in flow measurements, National Institute of Advanced Industrial Science and Technology (AIST) possessed the national primary standards for water and air flow only. There was no national primary standard for hydrocarbon flow, and the demands of industry could not be met. Therefore, AIST newly constructed the national primary standard facility for hydrocarbon flow in 2001, and after conducting the uncertainty evaluation and building up the quality system, it was designated as the specific standard for hydrocarbon flow according to the Measurement Law of Japan in 2005. Since the range of the national primary standard for hydrocarbon flow was limited, under a government-supported research project and with cooperation from private petroleum companies, the technologies to expand the range of liquid types and flow range were developed at the level of secondary standards that were in possession of the calibration laboratories. This completed the traceability system of measurement in Japan, and the Japan Calibration Standard Service (JCSS) for hydrocarbon flow was established utilizing the capabilities of the private companies.

2 Social objective for creating the hydrocarbon flow standard

The annual petroleum trade in Japan is approximately 29 trillion yen[1], and the merchandise value is said to be several times that amount. Tens of thousands of hydrocarbon flowmeters that provide the basis for the quantity entered on the trading certificates are in operation in the petrochemical complexes throughout Japan. Accurate measurement using the hydrocarbon flowmeter is in demand by industry and society. The range of flow measurement is mostly 1~1000 m^3/h, and particularly the measurement of several hundred m^3/h used for tanker truck is most frequently used. There are many types of petroleum, including gasoline, kerosene, light oil, heavy oil, and crude oil. Positive displacement flowmeter and turbine flowmeter are

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used most frequently. Currently, the precision demanded of flowmeters is very strict, and the level of uncertainty required for hydrocarbon flow standard is high.

Until now, the standard tested (accepted or rejected) by AIST was used to test many hydrocarbon flowmeters. This standard is a device used by the prefectural inspection agencies to test the small-diameter hydrocarbon flowmeters for commercial use, to prevent disadvantage to the general consumers of Japan, that is, to guarantee fairness. In a system using this standard, the public institute tests a certain function using an appropriate method, and this is expected to greatly reduce the cost of managing the measurement device in society as a whole.

On the other hand, with the advance in measurement technology, there has been a recent increase in the demand for highly accurate flow measurement exceeding the range of this system, as well as for measurement of more types of petroleum products and wider flow range, so that the companies can perform voluntary highly accurate quality control on their own. Moreover, with the internationalization of economic and production activities, the international trade of the Japanese petroleum products is increasing, and it is mandatory to guarantee the integrity of the international flow measurement values. Therefore, there is a demand to provide a standard with international integrity to the users and to also offer choices of maintaining the metrological traceability in accordance to the international system. However, there was no calibration facility that could be used as the national primary standard of hydrocarbon flow, and the work of setting up the flow rate using physical quantities such as mass, volume, time, density, temperature, pressure, and others were left to the flowmeter manufacturers and users. Also, since the definition of metrological traceability was scientifically established, the metrological traceability could no longer be maintained with the conventional system that did not address uncertainty.

The petroleum tax on the domestic trade of petroleum products is very large at about 6 trillion yen annually[1], and measurement is socially very important. Therefore, the tax office meter (hydrocarbon flowmeter) must have a highly accurate control of instrument error (deviation from standard value) within ± 0.2 %[2]. Currently, several tens of thousands of custody meters are said to be in operation at the petrochemical facilities throughout Japan, as mentioned before, and rationalization is highly in demand since great cost and human resources are needed to maintain precision.

3 Technological objective for creating the hydrocarbon flow standard

Some people may misunderstand that to measure the hydrocarbon flow or the quantity (volume or mass) of the petroleum products, the flowmeter can be easily calibrated with high accuracy by calibrating the volume tank (volume prover) or the weighing scale (mass comparator) with high accuracy because they are parts of the calibration device. Although the uncertainty of the volume or mass is part of the source of calibration uncertainty, there are several other sources that significantly affect the calibration uncertainty such as: temperature, pressure, and density measurements; leakage of test liquid from the branch of the connecting pipe used in calibration; and the effect of the flow velocity distribution and flow velocity fluctuations in the pipes. In practice, these factors may turn out to be dominant in the overall calibration uncertainty in many cases, and it is necessary to evaluate these uncertainties. In the actual measurements using the flowmeter, there are many cases where the conditions in which the flowmeter was calibrated and the condition in which it is actually used are different. Therefore, it is necessary to evaluate the effects of the pipe formation, temperature, pressure, properties of the test liquid, and others on the flowmeter characteristic, and to estimate the measurement uncertainty in the actual measurement condition. Since it is impossible to conduct these evaluations for all measurement conditions due to cost and time restraints, it is necessary to pinpoint the source of uncertainty according to the requirements and to estimate the uncertainty efficiently.

In petroleum products, liquid expansion of about 0.1 % is seen every 1 ºC. However, in the petroleum products trade, the measured volume is used as is without necessary corrections according to the temperature of the measurement environment. On the other hand, the petroleum products, which are energy resources, technically should be traded by mass, and it is necessary to supply the flow standard as mass flow in addition to volume flow for the new national flow standard.

4 Investigation of method for the provision of hydrocarbon flow standard

4.1 Provision of hydrocarbon flow standard

In the actual on-site measurement of the hydrocarbon flow, it is necessary to conduct the flow measurements with minimum uncertainty using minimum resources (cost, time, etc.), and the reliability must be guaranteed. Since the flow standard is set up using other physical quantities such as mass, volume, time, density, temperature, and pressure, it is necessary to clarify "who and where" the set up of the standard flow from other standards will be done in providing the national standard. Since there was no calibration device for hydrocarbon flow that could be used as a national standard in Japan, the work of setting up the flow rate from other physical quantities was left to the flowmeter manufacturers and users, and the reliability was unknown. The provision of the flow standard can be categorized roughly into the following three:

(1) Method where the NMI provides the flow standard

If the national metrology institute (NMI) sets up the flow standard as a national standard, it will be highly reliable, and an ideal traceability system could be constructed. However, there is a diversity of petroleum products and the range of flow rate is extremely wide, and it is not realistic to create and provide the flow standards for all liquid types and flow ranges used in society. Even if all flow standards with small uncertainties at a national standard level can be provided to fulfill the diverse flow measurement conditions actually used, such systems will be extremely expensive. As a result, the user who pursues a balance of uncertainty and cost will most likely select the service of the calibration laboratory described in (2).

(2) Method where the calibration lab calibrates the flowmeter using the standards for other physical quantities (such as volume)

This is a method where the calibration laboratory conducts the calibration of flowmeters using not the national flow standard, but instead, for example, the mass and density standards. In this method, even in a case where the calibration lab uses the mass and density standards, if the calibration of the flowmeter is done using inappropriate combinations, it may lead to problems such as missing an important correction value or underestimating the uncertainty. Also, establishing the technology to achieve small uncertainty is a great burden on individual calibration labs, and it may result in increased social cost of measurement control. It is also difficult to guarantee reliability, and this may be a disadvantage to the users. On the other hand, this method is highly expandable, and the calibration lab can adapt this method to diverse liquid types and flow rates.

(3) Method of using the flow standard provided by overseas institutes

Although the flow standard is employed in many countries, this method will force dependence on foreign standards, and it is difficult to achieve small uncertainty required in Japan. Also, the flowmeter must be transported abroad for calibration, and the reliability decreases in that process.

Figure 1 shows the outline of the representative standard service systems for hydrocarbon flow. In Europe, basically method (1) is employed, and in ranges where the flow standard is not supplied, the approved institution verifies the adequacy of the set-up of flow rates using method (2). To guarantee the performance capacity of the calibration lab, the international standard (ISO17025) requires a skill test, but in several cases this is not conducted appropriately and this is becoming a problem. Therefore, the expansion of the provided range of flow standards is in progress, such as constructing the calibration facility at the level of the national standard for hydrocarbon high-flow (maximum flow of 5000 m^3/h).

In the United States, method (2) is mainly employed, and the calibration labs set up the flow rates according to the principle of market mechanism. The accreditation of the calibration lab is done by the accreditation authorities. However, there are some labs that are accredited for technologically inadequate uncertainty, where they claim uncertainty much smaller than the national standard with the least uncertainty in the world. To address this issue, the United States has a law to collect a certain ratio of the sales of petroleum products for the American Petroleum Institute (API), and this fund is used to establish and enforce the technical standard (API standard) for guaranteeing the reliability of flowmeter calibration. There is effort for maintaining the reliability of the standard at a civilian level, without depending on the government agencies, but aiming for a small government. For Japan that does not have such a system, it is probably difficult to introduce method (2) directly.

Since there was no national standard for hydrocarbon flow in Japan until now, method (2) was employed using a standard established by the law for the calibration and testing of specific measurement devices for trade. However, it became necessary to establish a national flow standard due to the recent increasing

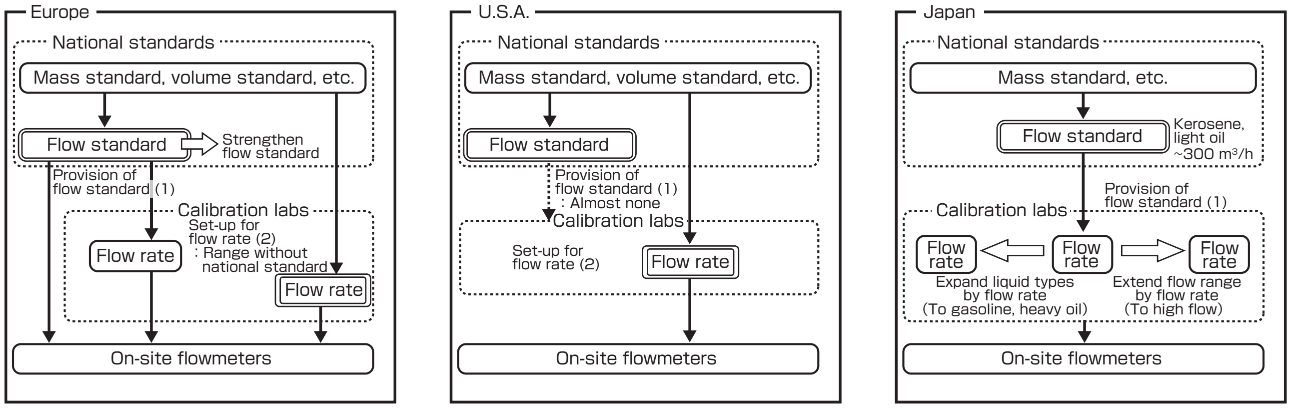

Fig. 1 Outline of the hydrocarbon flow standard system.

demand for the calibration of devices that cannot be covered by method (2), including highly accurate flow measurement, measurement of diverse liquid types and flow ranges, and measurement that guarantees international integrity. Therefore, the combination of method (1) that achieves reliability and (2) that focuses on expandability was selected. This is a method where AIST provides the flow standard with high accuracy (small uncertainty) for core flow rates and liquid types, and the calibration lab extends the ranges of standard flow rates and expands the liquid types using the calibration device it already owns, by utilizing the JCSS. Figure 2 shows details of the division of labor between AIST and the calibration lab for the liquid types and flow ranges. Assuming the flow ranges of the flowmeter used for tanker shipment, 300 m^3/h was set as the maximum flow rate in this national standard, and the liquid type was set as kerosene and light oil because their viscosity is of medium level.

4.2 Calibration method of the national standard and survey and comparison of the elemental technologies

When the calibration lab tries to expand the range of liquid types and flow rates, its calibration uncertainty increases compared to the uncertainty of the national standard on which it is based. To reduce the burden on the calibration lab in attempting to reduce the uncertainty, it is necessary to conduct calibration using the national standard at uncertainty as small as possible. The flowmeter used for measuring the quantities for taxation of the petroleum product must maintain an instrument error (deviation from the standard value) within 0.2 %[2]. Therefore, the goal value of the uncertainty of the national standard for hydrocarbon flow was set at 0.04 % or less for the volume flow standard. This is the highest-level goal value compared to the NMIs of other countries. Several technological challenges were expected, but we decided to overcome those challenges to establish the national standard.

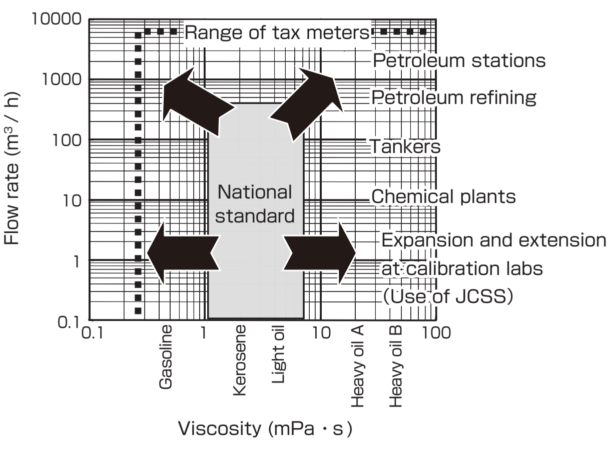

Fig. 2 Diagram for the work division according to liquid types and flow ranges between the national standard and the calibration labs.

The calibration of the flowmeter is conducted by comparing readings of the flowmeter to be calibrated to the readings of the flowmeter through which the standard flow passes. The representative methods for calibrating the hydrocarbon flowmeter are categorized below[3][4]. The eliminated methods include: the comparison method in which the flowmeter is used to calibrate another flowmeter, because this necessitates the calibration of the flowmeter used as standard to be calibrated at a calibration facility; and the dynamic calibration method where the instant flow passing the flowmeter is measured because it is difficult to keep the uncertainty small.

(1) Categorization by types of flow

- Standing start and stop method: The method in which the flow of the flowmeter to be calibrated is stopped before and after the calibration. While the calibration facility can be constructed at relatively low cost, the transient state between the stop state and the flow state may affect the flowmeter.
- Flying start and stop method: The method where the flow rate of the flowmeter to be calibrated is not changed between the calibrations. There is no effect of the transient state of the flow.

(2) Categorization by types of reference standard

- Volumetric method (volume tank): The method where the volume is measured by sending the test liquid into the volume tank equipped with preliminarily calibrated volume scale. While it has been used widely in general petroleum facilities, it is necessary to evaluate the effect of the test liquid that may remain on the inner wall of the volume tank, and to take highly accurate temperature measurement of the test liquid in the volume tank to reduce the effect of volume expansion by temperature.
- Volumetric method (pipe prover): The method where the flowmeter is calibrated by calibrating the volume displaced by a piston moving inside the pipe. Calibration is then conducted using the conduit. Since there is no part open to the atmosphere (closed loop), the effect of evaporation does not have to be taken into account, and this has been used in many petroleum facilities. To achieve high accuracy, it is necessary to investigate the effects of the device to detect the position of the moving body, the temperature measurement in the measurement volume, the leakage between the moving body and the wall of the pipe, and the expansion/contraction of the moving body.
- Gravimetric method (weighing scale): The method where the test liquid is introduced into the weighing tank, and the mass of the liquid is measured using a weighing scale. While high accuracy can be achieved, the scale may be affected by the impact of the test liquid when the test liquid is poured into the tank from a high place. It is also necessary to have a mechanism

where any exterior load on the weighing tank be eliminated during the mass measurement.

(3) Categorization by a flow switching method in the flying start and stop method

- High-speed valve method: A method in which the flow of the test liquid from the test line is switched to the storage tank and the standard, by rotating the valve at high speed. While it is less expensive than the diverter method, large pressure change occurs when switching is done at high speed, and there is a limit to the switching speed. The effect of switching on the flowmeter to be calibrated cannot be neglected. Also, there are problems in the symmetry of the flow, and achieving high accuracy is limited.
- Diverter method: A diverter is a device for switching the test liquid that jets out of the nozzle opened to the air to the storage tank and standard. Since the flow fluctuation during switching is small, it has absolutely no effect on the flowmeter to be calibrated. It has been used in water flow standard facilities, and there is a possibility for achieving high accuracy. On the other hand, since the liquid flows freely as a jet from the nozzle, there are dangers of explosion due to static electricity generated by mist. Also, the oil vapor and droplets released into the air may become sources of uncertainty. When the test liquid is poured in torrents into the weighing tank, large amount of air bubbles are formed, and when the test liquid containing the bubbles are circulated in the test line, the remaining gas may be a source of uncertainty.

Table 1 shows the calibration capacities and the methods of the NMIs of other countries for the hydrocarbon flow

Table 1 Uncertainties and calibration methods of the national standard for hydrocarbon flow of various countries.

Country	NMI (National Metrology Institute)	Flow rate (m³/h)	Uncertainty** (%)	Test liquid	Temperature (℃)	Pressure (MPa)	Viscosity (mm²/s)	Calibration method	Reference
Austria	BEV	0.0018 ~90	0.07 ~0.1	Gasoline, light oil	14 ~ 17	0.05 ~ 0.6		Volumetric method, standing method	Volume tank
Taiwan	CMS	18 ~360	0.05	Light oil, spindle oil (machine oil)	10 ~ 45	< 0.5	2.5 ~ 150	Gravimetric method, standing method	Weighing tank
Cuba	INIMET	3 ~ 300	0.1 ~ 0.2	Gasoline, kerosene, light oil, heavy oil	Wait-and-see	< 0.8		Volumetric method	
Czech Republic	CMI	0.29 ~396	0.15 ~0.30	Kerosene, light oil, petroleum, LPG	0 ~ 85	0.1 ~ 3.5		Volumetric method, flying method	Pipe prover (piston)
Denmark	FORCE	0.4 ~400	0.03	Petroleum products				Volumetric method, flying method	Pipe prover (piston)
Germany	PTB	0.6 ~250	0.1	Petroleum	Wait-and-see	0.35	0.77 mPas	Volumetric method, standing method	Volume tank
Italy	IMGC	0.0036 ~3.6	0.1	Kerosene, light oil	Wait-and-see	0.15		Volumetric method, flying method	Pipe prover (piston)
Japan	NMIJ*	15(3)~ 300	0.03	Kerosene, light oil	15 ~ 35	0.1 ~ 0.7	1.4~1.9, 4.4~7.8	Gravimetric method, flying method	Weighing tank
Korea	KRISS	1~ 14.8	0.11	Spindle oil (machine oil)	15 ~ 30	0.1 ~ 0.3	600 ~ 2200	Gravimetric method, standing method	Weighing tank
Mexico	CENAM	0.002 ~ 340	0.06 ~ 0.08	Petroleum products	0 ~ 82	0.1 ~ 0.4	0.5 ~ 10	Volumetric method, flying method	Pipe prover (piston)
Poland	GUM	0.4~ 400	0.1	Light oil	Wait-and-see		0.3 ~ 300	Volumetric method, flying method	Pipe prover (piston)
Sweden	SP	0.36~ 1260	0.1	LPG, light oil, etc.	−20 ~ 120		LPG~300	Volumetric method, flying method	Pipe prover (prover)
The Netherlands	NMi -VSL	0.001~ 250	0.04	Gasoline, kerosene, light oil		0.4	0.7, 1.8, 5	Volumetric method, standing method	Volume tank
U.K.	NEL	0.00012 ~720	0.03 ~0.08	Kerosene, light oil, heavy oil	5 ~ 50	0 ~ 0.8	2.2 ~ 30	Gravimetric method, standing method	Weighing tank

*) NMIJ : National Metrology Institute of Japan, AIST
**) Uncertainty: Here, for simplification, the values for expanded uncertainty (95 % confidence level) are presented.

standard. Here, the calibration capacity is presented quantitatively by the uncertainty based on the international comparison conducted under the Convention du Mètre. This can be considered the evaluation result of the most authoritative national standard, where all the participating institutes agree to the technological basis of the uncertainties that are presented by each other. In the calibration of the hydrocarbon flowmeter in overseas national standards, the liquid flow method using the volume pipe and the stop method using the volume tank are used frequently. However, as mentioned earlier, these methods have several technological issues in achieving the high level of uncertainty. Also, in the standing method, the transient state of the flow may become a major source of uncertainty, depending on the type of the flowmeter. In some calibration methods, the type of the flowmeter to be calibrated may be limited. On the other hand, the gravimetric method with flying start and stop using the diverter, which is frequently employed in the calibration facilities for water flowmeter, is rarely employed for petroleum products since they are hazardous materials with risk of explosion due to static electricity. If this point can be overcome, there is high possibility for achieving small uncertainty. Therefore, AIST selected the "gravimetric method with flying start and stop using the diverter" as the calibration method of the national standard facility, to realize a national standard with the highest accuracy in the world, and developed the elemental technologies to achieve the high accuracy and took measures to ensure safety.

5 Construction of the hydrocarbon flow standard

5.1 Calibration facility for hydrocarbon flow

Since this facility will store and use large amounts of kerosene and light oil, it must be designed in accordance with the Fire Service Law as a place for handling hazardous materials. Also, a safety management system must be established, and measures to prevent the leakage or outflow of the test liquid are required in consideration of the surrounding environment. Because the risk factor increases, as mentioned in the previous chapter, in the "gravimetric method with flying start and stop using the diverter," it is mandatory to take sufficient safety measures. In Japan, there were almost no cases of a large indoor facility where a large amount of petroleum products, which are hazardous materials, was allowed to flow, but its construction was approved by the fire service authority because of its importance as a national standard and the implemented special safety measures. Figure 3 shows the safety measures and the relationships to the elemental technologies for uncertainty.

To prevent leakage of oil, dual measures were taken where the entire facility was surrounded by an oil dike, and a pit and an oil-water separator were installed around the building. The roof was made of light corrugated sheets with an explosion-release structure to release the pressure upward in case of an explosion, but had insulation to improve the temperature stability in the building. The hazardous area containing the test line through which the petroleum products will circulate and the nonhazardous area such as the operating room where the control computer will be installed were clearly demarcated. The test line would be monitored from the operating room, and a refractory glass and refractory shutters were installed to enable quick response in case of emergency. In the hazardous area, oil-proof floor was installed to prevent underground permeation of oil, the two 43 m^3 storage tanks were placed in the underground pit, and the weighing tank was installed in the room with the underground pit, to prevent leakage to exterior environment in case of any accident.

Figure 4 shows the diagram of the hydrocarbon high-flow calibration facility[5] which is a real-flow calibration facility for hydrocarbon flowmeter, and Table 2 shows the sources of uncertainty[6][7]. This calibration facility is composed of two test lines for kerosene and light oil, and the flow range

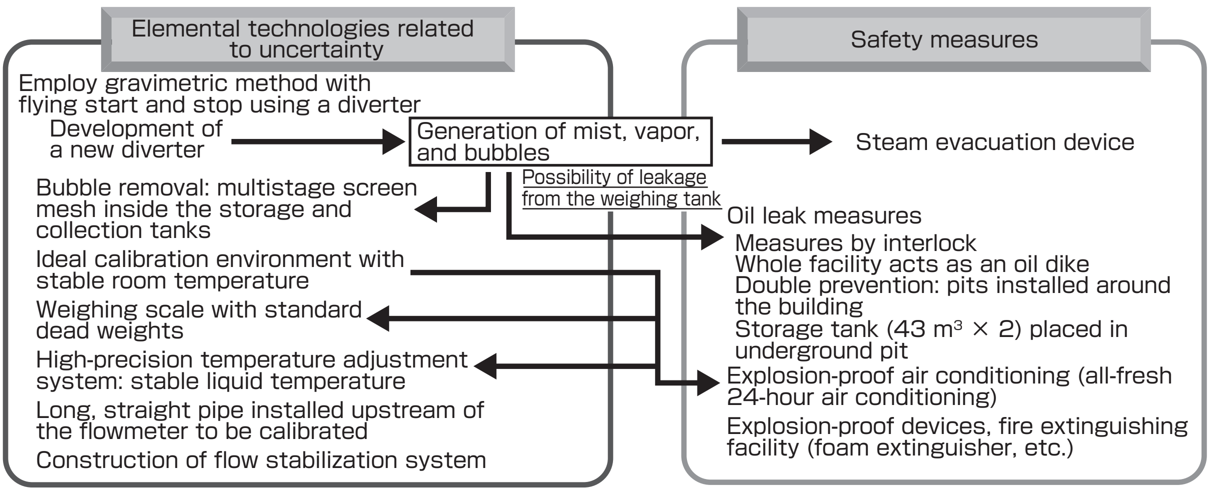

Fig. 3 Elemental technology developed for hydrocarbon high-flow standard.

is 3~300 m^3/h for both lines. The facilities for kerosene and light oil are completely independent of each other, but since they have common temperature adjustment device for the test liquid, the two facilities cannot be operated simultaneously.

This facility employs gravimetric method with flying start and stop using diverters. The test liquid (kerosene or light oil) that passes the flowmeter to be calibrated is run for a certain time from the diverter nozzle to the weighing tank installed above the weighing tank, the standard mass flow rate is obtained by dividing the inflow mass measured by the weighing scale by duration time, and the figure is converted to standard volume flow rate by dividing the mass flow rate by the density of the test liquid. The calibration is done by comparing these standard flow rates and the readings of the flowmeter to be calibrated.

As mentioned in the previous chapter, the characteristic of the calibration method using diverters is that there is little change in flow rate during the measurement compared to switching the flow using a valve. A newly developed diverter was used[8]. This diverter shifts the diverting wing in the same direction and at the same speed as the free jet flow at the beginning of the measurement when the flow is diverted to the weighing tank and at the end of measurement when the flow is diverted to the bypass. It has been employed in the national standard (water flow) of the United States and France, as well as calibration labs (water flow) of Japan, and is becoming a world standard in the liquid calibration labs. Although the diverter could not be used directly in the hydrocarbon flow calibration facility due to safety concerns, the generation of static electricity was successfully controlled while increasing the jet flow speed, by controlling the outlet surface area of the free jet flow inside the diverter, and this in turn led to successful decrease of the uncertainty of collection time in the calibration uncertainty of the flowmeter.

To prevent the vapor or droplet of the test liquid generated in the free jet flow from flowing into the measurement room, adjustments were made so the interior of the diverter would be slightly lower in pressure than the atmospheric pressure,

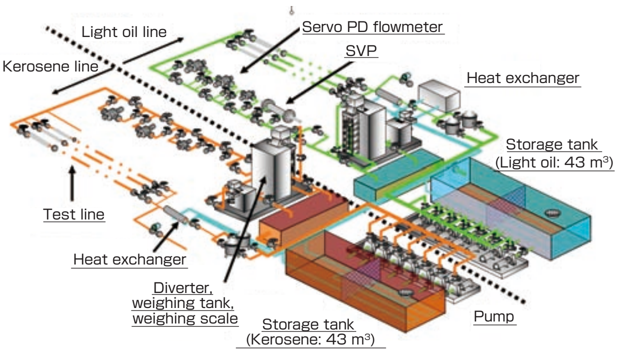

Fig. 4 Diagram of the hydrocarbon high-flow calibration facility.

Table 2 Sources of uncertainty in the national standard (kerosene test line).

Source of uncertainty	Relative uncertainty
1) Flowmeter pulse counting time	0.0028 %
2) Mass change in the connecting pipe	0.0008 %
3) Effect of fluctuation in flow or density	0.0002 %
4) Mass measurement of test liquid (the effect of vapor and droplets)	0.0054 ~ 0.0154 % (0.0030 ~ 0.0146 %)
5) Density measurement of test liquid in flowmeter	0.0124 ~ 0.0146 %
6) Collection time to the weighing tank	0.0032 ~ 0.0042 %
Calibration uncertainty of volume flow (relative) : 1) +2) +3) + 4) + 5) + 6)	0.016 ~ 0.022 % (Simplified to 0.03 %)
Calibration uncertainty of mass flow (relative) : 1) +2) + 4) + 6)	0.008 ~ 0.016 % (Simplified to 0.02 %)

Note) Relative uncertainty: The components that are considered to be the cause of the sources of each uncertainty are given, among the relative amount (calibration uncertainty) obtained by dividing the uncertainty of flow rate indicated by the flowmeter by the flow value.

the vapor was forcefully evacuated from the room, and the oil vapor and droplets were condensed and collected as waste oil. Due to the forced evacuation of the vapor and droplets, the calibration uncertainty in the kerosene line deteriorated, and it was found that this was a dominating source in the kerosene line for certain flow range. Compared to the kerosene line, the effects of vapor and droplets were smaller in the light oil line. To remove the large amount of bubbles caused by the diverter, multistage screen mesh was installed in the 43 m^3 storage tank and the buffer tank, and the bubbles could be sufficiently removed.

The flowmeter to be calibrated was set in the test line with a diameter of 50~150 mm. To create an ideal flow, a straight pipe with a diameter 100 times larger (15 m) was installed upstream of the flowmeter to be calibrated. To reduce the pulsations caused by the pump, three centrifugal pumps with equal performances were operated in parallel. We also developed a method for reducing the flow fluctuation during supplying into the weighing tank[5].

In the weighing room where the weighing scales were installed, the temperature was controlled within room temperature of 20 ± 5 ºC and the humidity at 30 % or above, as countermeasures against statics throughout the year using an explosion-proof air conditioning device. These also contribute to the reduction of the uncertainty of the weighing system. By calibrating the weighing scale before the measurement by loading ten 1000 kg standard dead weights for the 10 t scale and five 200 kg standard dead weights on the 1 t scale, the effect of reproducibility of the weighing scale was minimized[7]. Also, since several sources of vibrations such as the pump were installed in the same building, sufficient anti-vibration measures were taken by devising the pile foundation, to improve the uncertainty of the weighing scale that is sensitively affected by very small vibrations.

To reduce the uncertainty due to the temperature expansion of the test liquid, it is necessary to stabilize the temperature of the test liquid. Sufficient temperature stability of the test liquid (± 0.05 ºC or less) was obtained by devising ways to reduce the time change of the load on the heat exchanger, such as maintaining a stable room temperature using the explosion-proof air conditioning facility, and keeping the constancy of flow that passes through the heat exchanger that controls the temperature of the test liquid. As a result of such technological developments, the uncertainty of "5) Density measurement of test liquid in the flowmeter" and "2) Mass change rate in the connecting pipe" in Table 2 were minimized[6].

For the purpose of checking the reproducibility of the calibration system, a servo positive displacement (PD) flowmeters with excellent reproducibility[9] were developed, and three of them were installed permanently in the test line for kerosene and light oil. The adequacy of the calibration could be checked at all times by calibrating the servo PD flowmeter while calibrating the flowmeter, and then comparing the result with the past calibration values.

As an assumption of calibration, the check of residual gas in the pipe and the check of leakage of the test liquid that occurs from the valve at the branch pipe are incorporated in the calibration routine.

By incorporating the above safety measures and elemental technologies for reducing the uncertainty, the calibration uncertainty of the volume flow was 0.03 %, which was superior than the goal value 0.04 %. The world's highest accuracy of 0.02 % was achieved for mass flow[5].

5.2 Verification of the validity of the developed flow standards

The developed hydrocarbon high-flow calibration facility is designated as the specific standard for hydrocarbon flow by the Measurement Law. It is extremely important to verify the validity of the absolute value and the uncertainty of the value of the hydrocarbon flow to be calibrated, and to check the international equivalency, to guarantee the reliability of the hydrocarbon flowmeter of Japan.

As a result of conducting bilateral international comparison with the SP Technical Research Institute of Sweden (SP) (see Table 1), the calibration results at the calibration facilities of NMIJ and SP matched in the range of each other's uncertainties[5]. We also participated in the international comparison test for hydrocarbon flow conducted under the Convention du Métre, with National Engineering Laboratory (NEL) of U.K. as the officiating country[10]. The initial participants included five European countries, two Asian countries (including Taiwan), and two North American countries, a total of nine nations. Since a flowmeter for international comparison with excellent reproducibility and flow characteristic was damaged during transportation, the comparison was carried out over a two-year period from 2005 to 2007. The calibration values of the flowmeters of all participating countries are shown in Fig. 5. The calibration values of the two countries, Mexico and Canada that were dropped midway in the comparison, were greatly divergent from the values of other countries. For these two countries, the calibration was conducted by transporting the calibration device using the pipe prover (small volume prover) or the volume tank to external facilities (such as the petroleum company). This implies that it is technologically difficult to set up a highly accurate flow standard just by maintaining the traceability for individual measurement devices such as the volume tank, as mentioned before, and it is necessary to reduce the uncertainty source of the entire calibration device including the calibration environment. The Japanese national standard values are distributed in the center of the overall calibration values, as can be seen in Fig. 5. Moreover, it was confirmed that the Japanese values match within the range of the internationally agreed values and uncertainties obtained by statistic analysis[10].

6 Effort to create an efficient JCSS traceability system

To respond to the demands of industry that uses the flowmeter for diverse petroleum products at wide flow range, it is necessary to expand the flow range and the range of liquid types from the national standard through the Japan Calibration Service System (JCSS). Therefore, in a government-supported research project[11], we developed the technology to enable easy expansion to different liquid types by adding an advanced analysis to the characteristic of the flowmeter that is dependent on the liquid viscosity, and the technology to extend the flow range by the parallelization of the flowmeters[11][12]. Figure 6 shows

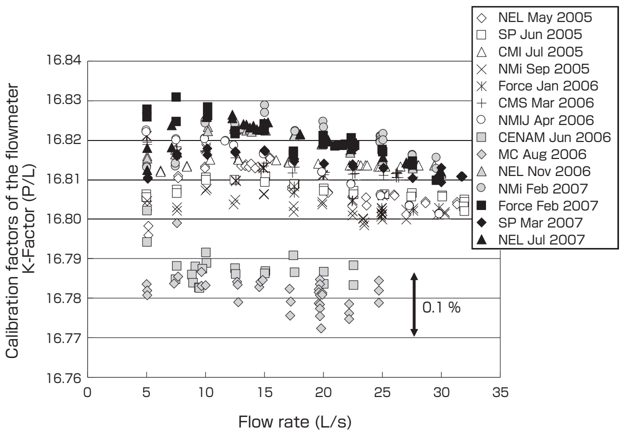

Fig. 5 Measurement results of the international comparison for hydrocarbon flow.
The participating organizations and countries are: NMIJ: Japan, NEL: UK, SP: Sweden, CMI: Czech Republic, NMi: The Netherlands, Force: Denmark, CMS: Taiwan, CENAM: Mexico, and MC: Canada. The data in Fig. 2 of the *International Key Comparison*[10] were re-plotted.

cases where the calibration capacity of Japanese calibration laboratories was surveyed to verify the adequacy of these new calibration technologies. As shown in the result for 2005, the calibration facility that originally had deviations of − 0.05 % ~ + 0.10 % from the national standard significantly improved the calibration capacity to match within ± 0.03 % of the national standard, by calibrating its facility using the flowmeter calibrated by the national standard. Moreover, the values for heavy oil that is out of the range of calibration using the AIST national standard matched ± 0.03 % of the values of the overseas calibration institutes, and this implies that the method for expanding the liquid types, developed for the project, was adequate.

We also drafted the Guidelines on the Technological Requirement[13] to technologically support the National Institute of Technology and Evaluation (NITE) that accredits the calibration labs that receive the national standard. As a result, the number of accredited and registered calibration labs are increasing as a new business.

We are also continuing the development of the high-precision flowmeter jointly with flowmeter manufacturers to improve the work efficiency and to reduce the uncertainty arising from the viscosity property of the flowmeter, by applying the expansion technology for liquid types.

By dividing the roles with the JCSS calibration labs, the national standard has become a facility with the world's highest precision level, although in a limited range, and is taking on an important function as a development platform for the flowmeters among the measurement device industry.

7 Summary

In this paper, we discussed the positioning of the national standard for hydrocarbon flow from the perspective of pursuing socially practical application, and reported on the selection process of the calibration method for the national standard of hydrocarbon flow, the elemental technologies to reduce the uncertainty, and the maintenance of safety. We also reported on the adequacy of the national standard and the construction of the traceability system that could be used by the user. Currently, we are providing technical support to calibration labs that wish to register to the JCSS, to achieve efficiency of the precision management of the flowmeters used in practice. There is a movement away from petroleum due to environmental issues, but with the rising prices of petroleum products as exemplified by the recent rise in the crude oil price, further high-precision measurement will be in demand. In the future, it is necessary to design traceability systems for LPG and LNG that are low temperature liquids for which the systems of flow rate standard have not been organized, as well as for highly viscous grade C heavy oil. Since high-performance mass flowmeter is being developed, there is a possibility of a shift from the currently used volume-based trade to mass-based trade. In the future, there are necessities for the establishment of new technological standards, the technological advices for changed regulations, and the improvement of the traceability systems to meet the social demands.

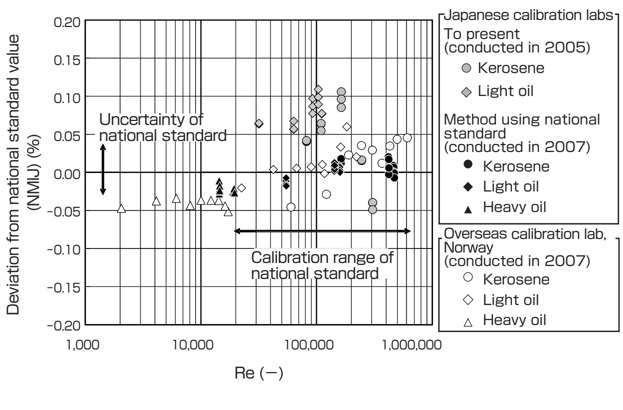

Fig. 6 Deviation from the national standard value (NMIJ).

The Re number on the horizontal axis do not match since the flowmeters used in 2005 and 2007 were different. The calibration range of the national standards is provided as reference.

Acknowledgements

The surveys of the technological trend among the flowmeter calibration laboratories and the NMIs of various countries played important roles in this research. These were obtained as the research results of the Hydrocarbon Flow Research Consortium Session, in which the petroleum companies and the flowmeter manufacturers participated, organized by the Japan Measuring Instruments Federation. Also valuable were the cooperations of: the International Accreditation Japan, National Institute of Technology and Evaluation; the Measurement and Intellectual Infrastructure Division, Ministry of Economy, Trade and Industry; and the Petroleum Refining and Reserve Division, Agency for Natural Resources and Energy.

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Discussions with Reviewers

1 Standard and the calibration of the tax meter

Comment (Mitsuru Tanaka, Research Coordinator, AIST)

In the researches for measurement standards, I think the methodology to present the technological basis on which the government makes decisions in the management of the system is "synthesiology". The content of the paper steps deeply into the discussion assuming the decision by the government, and I am afraid that it may mislead the readers. Therefore, why don't you focus on the descriptions for technology synthesis and the evaluation only from the objective attributes such as precision, cost, diversity of calibration subject and range, or international competition?

Answer (Takashi Shimada)

In chapter 1 and chapter 2, we corrected that the new service system for hydrocarbon flow standard was constructed, because there were rising demands for ranges that fall outside of the precision, liquid type, and flow range of the conventional standard system.

2 Title of the paper

Comment (Mitsuru Tanaka)

The original title "Establishment of the hydrocarbon flow standard" makes it unclear what point is described, in the range of topics from elemental technology development to political decisions. To emphasize "synthesiology", please revise the title so one can readily see whether the subject is a measurement standard for the entire Japan, is limited to national measurement standard for which AIST is responsible, or encompasses the international measurement standards.

Answer (Takashi Shimada)

Since the subject is a system for the entire Japan and the Japanese national measurement standard, we revised the title from that standpoint.

3 Elimination of overlap with existing research papers

Comment (Yasuo Hasegawa, Energy Technology Research Institute, AIST)

Since there are already detailed papers written for this research, and to have the readers understand the essence of "synthesiology", why don't you eliminate the descriptions that overlap with the existing papers and simplify the text?

Answer (Takashi Shimada)

We added figures and tables to briefly present the technological content, and rewrote the paper so the relationship between the result of synthesiology research and the administration in charge of metrology can be seen more clearly.

A field-scientific approach to Clinico-Informatics

— Towards a methodology for technology transfers —

Yoshiki Kinoshita * and Toshinori Takai

[Translation from *Synthesiology*, Vol.3, No.1, p.36-46 (2010)]

We propose clinico-informatics, as a research field for dealing with risks of information systems based on informatics. In this paper, we consider a model of technology transfer from the authors' experiences, i.e. transferring verification technology to industry in the various fields which involves information system development. A scenario for technology transfer is proposed with the methodology of field-science and we discuss roles of the techniques used in the scenario, for instance, fieldwork, interviews and participant observation.

Keywords : Clinico-informatics, qualitative research, risk, fieldwork, dependability, formal method, model-checking

1 Introduction: clinico-informatics

Anyone involved in informatics would naturally be led to the study to reduce risks related to information processing by applying results of the study in informatics. There are three principal subjects of study to that end:

1. methods to analyze the situation in the field (which corresponds to *diagnosis* in medicine,)
2. methods to improve the situation in the field (which corresponds to *therapy* in medicine) and
3. methods to propagate the technologies.

The methods in 3 are methods to propagate methods, so it is in a sense of a different level to that of 1 and 2. It corresponds to the activities in clinical medicine where the results of research are conveyed to medical practitioners for use in their own therapy, where medical associations and other organizations play important roles. Because of this analogy, we shall call the study, *clinico-informatics*, the study about information processing which aims at these three subjects. We borrow the word "clinico-" or "clinical" from clinical medicine. We emphasize that clinico-informatics does not mean a branch of informatics which is applied in clinical medicine. Rather, by clinico-informatics we mean the study of therapies of information systems which corresponds to clinical medicine which is a study of therapies of human beings.

Therefore, technology transfer is one of the three subjects of clinico-informatics study. While diagnosis and therapy has natural analogues in medical care, the analogy does not extend so naturally to technology transfer. Technology transfer itself is usually not considered as a subject of clinical medicine. It would, however, naturally be a subject of clinico-informatics, as technology transfer is nothing but a flow of information.

During the 16th century or so-called the Age of Exploration, European people were suddenly exposed to those with totally different cultures and such experiences soon spread out all over. Initially, the dominant view was that the differences in culture could be explained simply by means of *advancement*; everything was considered to be in a development process, so either culture was seen to be more advanced or the other was considered to be behind in the development. In the 20th century, however, the study of cultural anthropology and ethnology started, where cultures are studied as evolution in many directions according to regional and historical characteristics; much more delicate argument about *differences* of cultures was made instead of simple arguments based on *advancement* and *development*. It was recognized, as a result, that the difficulty of mutual understanding between people in different cultures lies in different ways of looking at things, rather than the lack of the ability on the side of the "developing culture". We are now facing a similar *cross-cultural exchange* in technology transfer; academia and industry just have different cultures and neither culture is more advanced than the other.

To see how such cross-cultural exchange happens in modern information processing, consider the first two of the three subjects of clinico-informatics we listed: methods of analysis and improvement of information processing systems. In the study of methodology in general, one inevitably analyzes the situation on site and tries to improve the situation. The scientists and engineers must work together there. Since the information technology nowadays provides basic methods in many technologies, however, the variety of fields of the engineers who deal with the information system on site is

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extremely wide. It varies from electronic and mechanical engineering to chemical process, and more. It is therefore necessary for those who study clinico-informatics to communicate with the engineers of various fields and to exchange information for analyzing and improving the diverse and the complex. Therefore, it is often necessary, as our own experience shows, to start technology transfer by conveying background knowledge such as mathematical logic that is totally foreign to the engineers. We regard it natural to consider such a process as a cross-cultural encounter and exchange.

Thus, we regard the technology transfer process as a kind of cross-cultural exchange. It would then be natural to apply methods in ethnology and scientific technique of other fields to study technology transfer. The techniques to deal with diverse and complex situations include qualitative research, ethnography, and fieldwork or field science. The techniques such as interviewing, participant observation and the KJ method[1][2][3] are used in sociology and nursing as well as ethnology. Incidentally, Kyoto University, from which a respectable tradition of fieldwork has emerged, has recently proposed *field informatics*. They say, however, "Solutions for problems in the field are proposed from the viewpoint of informatics and the various issues that arise in the field[4]," which shows their approach is somewhat different from ours, as we would have said "Solutions for problems *in informatics* (or information processing) are proposed *from the viewpoint of fieldwork*."

The Research Center for Verification and Semantics (CVS), AIST, conducts the study of verification using the Mathematical Methods to check whether a given information system operates as intended. The properties to be verified include: deadlock-freeness (it never stuck), liveness (appropriate service will be eventually provided), termination (execution does not fall into infinite, endless loop), correctness (correct result is calculated), etc. The verification by Mathematical Methods involves the process of representing such properties by means of logical formulae and proving that the implementation of the system meets those properties. If the system has a fault, the proof should not succeed, and in that case a counterexample is often obtained. In some cases the proof is done by a person (Semiformal Methods) and in other cases it is done by a machine (Formal Methods).

CVS has conducted several joint research projects with industry. Those projects are in general called *fieldwork* and include the study in clinico-informatics for the technology called "model checking[5][6]." We start with the *analysis* of the situation by talking with the partner, consider the ways of carrying out the model checking that *improve* the situation most effectively, and then try to *transfer the technology* to the partner. Methods in fieldwork such as participant observation play central roles here. The term *field science* was introduced by Kawakita Jiro[Note 1)] and it includes the *KJ method* (named after Kawakita Jiro). We try to give a systematic account of the technology transfer process of informatics research results, using our experiences of fieldwork as examples and Kawakita's field scientific methods as leading principles.

This paper is written as follows. In chapter 2, we explain the technology called model checking, which we transferred to our partners of joint research projects. In chapter 3, we try to give a systematic account of technology transfer using Kawakita's notion of field science and related models for problem-solving. The general scenario of technology transfer in clinico-informatics is presented in chapters 4 and 5; the scenario for technology transfer that we have conducted is described in chapter 4, and the outline of some of the element techniques used for technology transfer is explained in chapter 5. In chapter 6, we present two of the most typical technology transfer projects that we conducted, and try to evaluate the outcome. Finally in chapter 7, the proposed model for the technology transfer process is discussed, as well as issues left for future work.

2 Technology transferred: model checking

This chapter is a short introduction to the model checking[Note 2)] for readers not familiar with informatics. Model checking is the technology which was used in our joint work with industry in verification and diagnosis of the system (fault removal[Note 3)]).

Model checking is one of the technologies in software development methodology called *Formal Methods*. Formal Methods is, in a sense, nothing but a scientific approach to software development, where one describes and proves propositions according to mathematical logic. In application of Formal Methods, one first sets up a *formal language*, in which data and the propositions about them can be written as *terms* and *formulae*. Upon that language, a *formal theory* is built, where *axioms* and *rules of inference* are provided. Then an *interpretation* is given that specifies the mathematical objects and their properties as the *denotations* of terms and formulae of the formal language. The fact that a proposition ψ is true under an interpretation M is written as $M \models \psi$, and we say ψ is true under M. An interpretation under which all axioms of the formal theory are true is called a *model*. When ψ is true under any model, we write $\models \psi$, and we say ψ is *valid*. One is usually interested in the validity of propositions, but in some cases, one is rather interested whether a proposition is true or false only under a given specific model. Checking whether a proposition is true or false under a given model is called *model checking*. Model checking under formal theories of a special kind, i.e., formal theories in *temporal logic*, are target of our interest here. Temporal logic is useful in describing dynamic properties of control programs and nowadays is one of the indispensable methods in program verification. Model checking in formal theories in temporal logic is our principal concern here. A model of a formal theory in temporal logic is usually given in the form of a *transition system*Note 4).

Software which automatically performs model checking is called a *model checker*. A model checker is given two input data: a model and a property expected to hold for the model. The model checker reponds on whether the former satisfies the latter in the form of YES or NO. When the answer is NO, it normally gives a counterexample, too. In the case that the formal theory is in temporal logic, a model checker usually gives a counterexample in the form of an execution trace (state sequence) of the transition system. Hereafter, we only consider model checkers for formal theories in temporal logic; so the formal theory concerning model checkers is assumed to be in temporal logic.

Faults in an information system may be detected using a model in the following way. First, a user defines a transition system that represents the system. The transition system will work as a model of the formal theory of concern. Now, information systems are in the *real world*, while transition systems are in the *mathematical world*. So, the defined transition system is different from the information system. We say that the transition system is obtained from the information system through (mathematical) *abstraction*. While abstracting the information system, one intends to retain every feature which affects the addressed property. There are, however, no mathematical ways to make sure that every such feature is really retained, since the information system lies outside the mathematical world. The defined transition system may not sufficiently retain the property of the original information system. We shall come back to this problem later. Hereafter in this chapter, we shall exclusively consider the transition system rather than the original information system to be verified, unless otherwise stated.

Now, whether the transition system has the expected property boils down to whether the property is true under the model given as a transition system. So, it can be checked by a model checker. If the model checker answers NO and gives a counterexample, which indicates a candidate of the malfunction of the original information system, then the counterexample, given in terms of execution trace of transition system, is interpreted in terms of the original information system and judgment whether it does give an example of malfunction of the original system is done by the information system designer, not the verification engineer. Even if the model checker says YES (satisfied), however, it does not necessarily mean that there are no faults in the original information system (false positive). This is because it is not clear whether the transition system given as a model adequately represents the original information system.

As shown above, the model checker checks the transition system. To use the model checker to check the original information system, some manipulation is necessary to fill in the gap between the original information system and the transition system. For example, even if the model checker answers NO, one cannot conclude immediately that there is a fault in the system (false negative), and the counterexample should be analyzed. The issue is who does such analysis. Ideally, someone from the development team participates in the analysis in addition to the people doing the verification (fault finding), and the final decision on whether it is a fault or not is done by the development team.

3 Field scientific method of technology transfer

In this chapter, we give a systematic account of technology transfer by applying the W-model for problem solving attributed to Kawakita. The *Full Research* model, which has been discussed since the establishment of AIST, is also applied and is compared with Kawakita's model.

3.1 Kawakita's W-model for problem-solving

Kawakita observed that study in science is classified into three categories: bibliographical science, experimental science, and field science[1]. Study in bibliographical science is conducted on desktop using the *earlier literature* by means of *deduction*. Mathematics is its typical example. Experimental science is an *inductive* study where a reproducible phenomenon is recreated in the laboratory through *experiments* and one investigates whether a hypothesized theory holds with respect to the phenomenon; an example is experimental physics. These two kinds of study are based on some given theory, but field science focuses upon *abduction* where one goes out to the *field* to observe a possibly non-reproducible phenomenon on site in order to set up a theory or a hypothesis. What occurs in civil society immediately after an earthquake is an excellent example of such an observation. The difference between these three kinds of study is purely methodological, and so the field is

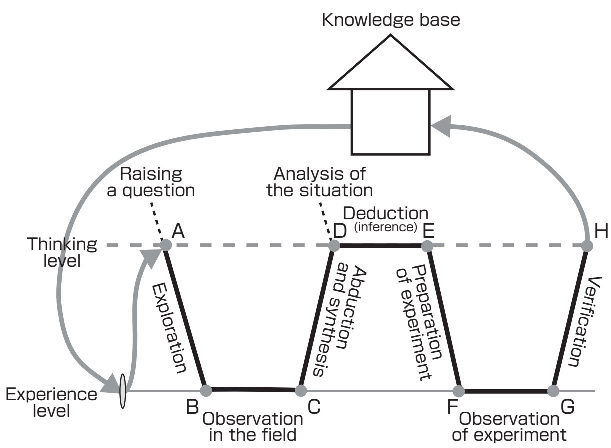

Fig. 1 Kawakita's W-model for problem solving. (taken from [1] and reconstructed)

not necessarily outdoors, but may well be on desktops in your bibliography or, in the case of informatics, in the office of software development. The relationship between these three kinds of study is depicted in the W-model for problem solving shown in Fig. 1[2].

The technology transfer is a way of problem solving, so we set up our hypothesis that the process of technology transfer can be understood using the Kawakita's W-model for problem solving. With this approach, we try to give a systematic account of technology transfer, occasionally referring to our own experiences.

We apply the Kawakita's W-model for problem-solving to technology transfer as follows. First, under a vague expectation or problem proposal that some technology may be useful somewhere in some society, one visits (make exploration) there and observes the situation (field observation)[Note 5]. As a result of the observation, one determines the way the technology which initially seemed useful can in fact be made useful (abduction). Other technology may turn out to be necessary in this phase (integration). Then one goes back to the laboratory, the overall situation is overviewed (understanding the situation), and it is decided whether the initial plan is to be performed or not. In the former case, the specific procedure of technology transfer is designed in detail (reasoning), and the experiment that allows the procedure to go forward is prepared and performed. The result of experiment is observed, verified and evaluated.

If the technology transfer is conducted without such a systematic view as above, at least three problems arise, according to our experience.

1. If some technology is transferred without sufficient understanding of the overall situation due to insufficient social observation (field observation), we may just hard-sell a technology not suitable in the situation.
2. Technology transfer is a difficult and large scale process that takes at least several months, or even several years in some cases. A comprehensive understanding of the whole technology transfer process would help the stakeholders much because they can then understand where they stand in the whole process. Such an understanding would especially help the involved engineers and scientists, when they face with difficulty in the process. Also, such a picture will make it easier to provide explanations to other stakeholders (especially the project sponsors).
3. Although the concrete technology transfer process itself is unique between a research institute and its industrial partner, there are cases where several similar cases are discussed all together. Such a comprehensive discussion would only be possible under the existence of a general theory of technology transfer.

In particular, the target of technology transfer of concern in this paper is for a methodology of software development in general, not a method or know-how of developing specific software, such as an algorithm or even a parameter of some algorithm. In the former case, systematic training of engineers (knowledge transfer) would be inevitable, while a need for such training is not so obvious in the latter case. It seems that the difficulty arising with knowledge transfer has an aspect of a *complex system* issue, and it is where Kawakita's W-model for problem-solving could come in.

3.2 Full Research and W-model

Type 2 Basic Research[7] was first proposed by Hiroyuki Yoshikawa as a process of conveyance of knowledge (results of study) *from abstract to concrete*. It is a part of the life cycle of research called *Full Research*[8][9], which consists of the three processes: *Type 1 Basic Research*, *Type 2 Basic Research*, and *Product Realization Research*. As both Yoshikawa's *Full Research* and Kawakita's W-model are frameworks of problem solving, the following comparison could be made.

Since Kawakita's model is intended for problem solving in general, it can be applied comprehensively at various levels; Kawakita himself in fact proposed that the W-model process should be repeated six times for large-scale problems. In particular, we can apply Kawakita's model to the overall life cycle of *Full Research*, as well as to the individual processes of *Type 1 Basic Research*, *Type 2 Basic Research*, and *Product Realization Research*.

In both *Full Research* and the Kawakita model, abduction plays an important role, no less than deduction and induction. The Kawakita model has the processes of *experiment* for induction and exploration for abduction; the Yoshikawa model, on the other hand, has a process called *synthesis*, which seems to correspond to a mixture of experiment and exploration in Kawakita's terms.

The levels of thought which are called *concrete* and *abstract* in the Yoshikawa model corresponds to the *experience* and *thinking* level in the Kawakita model. So, the slogan "from abstract to concrete" of *Type 2 Basic Research* corresponds to the transition from the thinking level to the experience level in the Kawakita model. As shown in Fig. 1, there are two types of transitions, exploration and experiment preparation. If we apply the W-model to the whole life cycle of *Full Research*, *Type 2 Basic Research* corresponds to the V-shape on the left half [Note 6] of the W-shape. The other V-shape to the right where reasoning, experiment, and verification are done would be understood as *Type 1 Basic Research*. Our explanation here may sound as though *Type 1 Basic Research* is always done after *Type 2 Basic Research*, but the order is not a major issue here, since the whole research activities are cyclic where the results of the *Type 1*

Basic Research are stored in the *warehouse of knowledge*, according to Kawakita, and are supplied to the *Type 2 Basic Research* process in the following cycle.

There were considerable amount of discussions to clarify what *Full Research* is, but it seems there has not been enough discussion on how *Full Research* is done. On the other hand, the KJ method, which was initially proposed as a method to support abduction, is now extended to the method to support the whole processes in the Kawakita W-model. The reviewer informed us of Reference [10] by Nakashima. Although it is interesting that the importance of abduction is also discussed in [10], we wish to discuss about it from our viewpoint in detail in another, proper context.

3.3 Qualitative research and quantitative research

Qualitative research nowadays is often discussed in contrast to quantitative research. In physics and chemistry, qualitative research tends to be undermined as being less accurate or not very precise. This is wrong. There *is* accurate and precise qualitative research and it often even provides foundations of quantitative research. The validation of selection of parameters used in a quantitative research, for instance, is inherently qualitative, so all arguments which follow the selection of parameters are based on qualitative research.

Incidentally, real numbers are often used to represent quantity, but there are other mathematical objects which could be used here. There are many cases where the quantitative argument can be carried out by means of only the ordering (comparisons) and limits (maximum and minimum). In such cases, the argument can be given by only using the structure of *partially ordered sets*, *lattices or complete lattices*, but not by using the whole structure of real numbers.

Nevertheless, qualitative research can be conducted without losing preciseness, and are actually used widely in ethnology, sociology, and nursing. Common to these fields are the facts that they deal with phenomena which are related to human beings, that the subjectivity is involved in the subject of study[Note 7], that they deal with phenomena which are not reproducible or hard to reproduce, and that the subject of study is complex. Parameters used to examine complex subject of study, in general, should be chosen with care. The validity and adequacy of the selection must be thoroughly and carefully studied, but such is only done by qualitative research, as we explain above. Qualitative research is important here and we need a methodology for it. The KJ method[1][2][3] by Kawakita and the grounded theory approach by Glaser and Strauss[11] are examples of such methodologies.

It would be appropriate, in the study of technology transfer from the viewpoint of clinico-informatics, to take the qualitative research approach to grasp the right direction of the research. The reason is that technical transfer involves human beings and, like other such humanistic subjects, it concerns with wide and complex variety of phenomena. The decision of whether a specific enterprise employs the new technology is entirely subjective, like all other decisions. Moreover, technology transfer in an individual enterprise is a non-reproducible process.

So, qualitative research plays a large role in the study of clinico-informatics, at least in its earlier phases. There can, however, be much use of quantitative research in the study of clinico-informatics. The authors are not totally negative about quantitative research, but qualitative research must come before it. It is only necessary to give serious thought about the selection of quantities to be investigated before starting quantitative approach, and such thought would unavoidably lead to qualitative research.

4 A scenario of technology transfer

We present, in this chapter, a typical scenario for the technology transfer process abstracted from our fieldwork experience in transferring the model checking technology.

1. [Interview] At first, the research team *interviews* its industrial partner in order to collect detailed explanations of the situation.
2. [Trial experiment] The *participant observation* process is repeated through the trial experiment where the model checking (technology to be transferred) is applied to development projects conducted by the industrial partner. This is done jointly by the research team and its industrial partner.
3. [From *engawa* (entrance) to *oku-zashiki* (backyard)] The trial experiment is started targeting system development with smaller risks of failure; this we call the *entrance* stage. As the trials are repeated several times, the target developments are chosen from those with larger risks of failure, and we call this process being introduced *backyard*. An example of development with little risk is a prototype which was once developed some years ago; the experiment can be done using left records of the prototype project. Development of test products has more risk, and that of commercial products for sale would have the largest risk for industrial partners.
4. [Training of engineers] The trial experiment is initially conducted solely by the research team, but in due course it should be taken over by the industrial partner, because that is the goal of technology transfer. In order to enable it, training for the use of technology is given to the industrial partner. The objective is to impose technological discipline on engineers so that they can carry out the trial experiments on their own.
5. [Objective achieved] The objective of technology transfer (such as manual writing and state-of-the-art engineer training) is achieved.

While we set up the above scenario, we followed several rationales based on our experiences in our fieldwork conducted through joint research with industry. Some of the rationales are listed here.

a) Some of the industrial partners asked the research team to develop an automatic checker that checks the correctness of software in response to a press of a button. The research team did not, however, agree to do it. There are at least two reasons:

(I) It is known in mathematical logic that there is no such general procedure that automatically proves whether an arbitrary given program satisfies an arbitrary given specification (undecidability of Church's first-order predicate logic).

(II) Even though the model checker itself is an automatic checker, the whole verification process using it is an interactive process because the property to be checked is usually found by try and error. On some occasions the property must be changed because there was a misunderstanding or impreciseness in setting it up; on other occasions, too much resource, memory or CPU time, is required by the verification software that the property must be divided into smaller ones or some other action is necessary. Such iteration seems to be inherently interactive and non-automatic, so, the research team was rather negative against the effort to increase the degree of automation.

It seems our industrial partner wished (I) because they considered the technology transfer for detecting faults by model checking as merely a flow of information. However, it involved a more complex phenomenon than a mere flow of information, as described in b) in the actual technology transfer process.

b) The verification technique, including model checking that we used as the subject of technology transfer, is a part of design technique. Design is a dynamic process rather than a static knowledge. The written texts and lectures on technical information does not convey by themselves the whole skill needed. It was necessary to convey the way how one uses the knowledge in a face-to-face manner. Here we see a kind of cross-cultural encounter; the culture of engineering or industry and the culture of academia. Incidentally, this is the reason why the technology transfer must be done as a *joint* work with a research team and an industrial partner, rather than as a contract and merely delegating the whole work to either side.

To exemplify how the basic knowledge differs from one field to another, take the basics of mathematical logic, which is necessary to describe the logical formula to be checked in verification. Such subject is not taught at all in high schools and in most university courses, as opposed to basics of linear algebra and analysis. Even most university courses in computer science in Japan do not teach it. So there is a rather large gap between the engineer's background and what is required for a person who uses model checking in verification in industry. According to our experience, it normally takes a few months or even a year to fill this gap, i.e., to teach the necessary basic facts about mathematical logic to the engineers who need to acquire model checking technique.

c) Another reason for us to employ fieldwork for technology transfer is that we have to show to the management of our industrial partner how effective the technology of concern is in the context of actual work done at their own site.

For our industrial partner to fully deploy the technology, it is necessary for them to evaluate the technology with their own eyes in their own context. But it takes time for the situation to come to that stage, as we wrote in 3 in the scenario, and the scientist in charge can often be frustrated, which of course would result in no good results. With the slogan of "moving from entrance to backyard" in mind, the scientist in the research team should try to observe where in the stage of technology transfer he/she stands, and that helps him/her keep himself/herself away from any frustration.

d) Each fieldwork project started training or education of engineers individually, but it did not take long for us to realize the need of a systematic way of training. We needed an education specifically meant for engineers at work. Therefore, we developed an independent training course of model checking for engineers and have provided it to the project participants[12]. The course has been designed so that the engineers are thoroughly drilled on the basics of mathematical logic, and that the facts independent of each particular tools are emphasized and clearly distinguished from tool-dependent knowledge.

e) The goal of model checking technology transfer is diverse. How our industrial partner wishes to incorporate the technology of model checking into their own development process differs much according to their culture and strategy. Some industrial partners tried to eliminate dependency on experts as much as possible by means of providing manuals. Other industrial partners tried, on the contrary, to depend on experts as much as possible, so we first trained a small number of engineers, and then those engineers trained other engineers after going back to industry.

Finally, we discuss which step of our scenario corresponds to which process of Kawakita's W-model for problem-solving. 1) The *interview* corresponds to the *exploration* on the leftmost edge of the W-shape where the flow goes from the thinking level to experience level. It is a step for gathering information to analyze the situation. 2) *Trial experiments* correspond to *field observation* and, in some cases also to *experimental observation*. The *model experiment* and *restoration experiment* that will be mentioned later also correspond to field observation, and the *blind experiment* and *man-hour measurement by engineers* to experimental observation in the laboratory. 3) What we call "*from entrance to backyard*" is nothing but the cycle of the entire W-shaped process; a perfect model solving process in the KJ method is a six time iteration of the W-shaped process. 4) *Training of engineers* corresponds to the path from the "warehouse of knowledge" to the starting point of the problem solving cycle in the left top of the W-shape. The knowledge is given to the engineer, and the next cycle of the W-shaped process is started. 5) The final step corresponds to "*abduction and integration*". For example, after the procedure is written as a manual, the adequacy of the manual is checked by experiment.

5 Element techniques for technology transfer

In this chapter, we discuss several element techniques for technology transfer that may be used in the scenario described in the previous chapter.

5.1 Fieldwork of technology transfer

Technology transfer may be conducted by a research team in the form of fieldwork. As mentioned earlier, fieldwork in clinico-informatics is not methodologically organized compared to fieldwork in the fields of ethnology and sociology; there are many to be learned from these fields of study, especially methods for information gathering or exploration. At any rate, we conducted our fieldwork with the following slogans.

a) Proceed according to the values in the field

The fieldwork of technology transfer should be conducted according to the values in the field rather than that in academia. To solve the problem in the field takes priority over writing a research paper on each element techniques[Note 8)].

So, the specific technique to be transferred should not be selected for the sake of applying a particular research result of a research team. This does not necessarily mean, however, that the research team must swallow every bit of what people in the field say; on the contrary, the research team may occasionally have to be opposed to the opinion of the people in the field, provided they think in terms of the values in the field, not in academia. In spite of initial possible disagreement, however, it is important for both to come to an agreement to proceed further.

For example, there was the aforementioned case where the industrial partner insisted in development of a fully automatic tool, but the research team did not regard it as a good solution. It should be emphasized that the research team in this case totally took the standpoint of the values in the field. In another example[13], the industrial partner requested the problem to be solved in the implementation process. It is, however, usually considered more effective to apply Mathematical Methods to processes in logically upper levels such as the requirement analysis process and the design process in software development. Accepting the industrial partner's requirement, the research team in this case made several trial experiments, through which they even developed some element techniques. As a result, they confirmed that the model checking technology was also effective in the implementation procedure. This is a case where the request from the field was incorporated successfully.

b) Principle of 4:6

Scientists involved in the research team of fieldwork are expected not only to be competent in scientific research, but also to be able to think and work in context of the field—in our case, industry. From the viewpoint of administration of research, it is important to organize a system where scientists involved are well motivated in fieldwork; in other words, there should be some academic element in their work. Also, we expect some bidirectional and mutual reaction between thought in an industrial context and that in an academic context. The slogan we made up to proceed in this direction is the principle of 4:6, which means researchers involved in fieldwork should use 40 % of their effort for fieldwork and 60 % for traditional academic work, that is, work in bibliographical science and experimental science. The idea is that traditional scientific work not only motivates scientists but also enables the use of methods and knowledge of the frontier of basic science in the fieldwork. In that way, a new direction of academic research may well be created, reflecting the issues in the field. It is often essential to evaluate the results of the fieldwork from the viewpoint of academia, but in such a case, knowledge and ability of the involved scientist in basic science is important[Note 9)].

Here is a case study in verification of software in industry[14]. The target was the design of web user interface, and there were two specifications: one for the screen transition as seen from the user, and the other was a flowchart that described the control flow of the program. The request from our industrial partner was to check for the *consistency* between the two specifications. The research team attempted to clarify the word "consistency" used in the field, and it was found that the word in their context meant a certain *simulation relation*, which nowadays is one of the basic notions in programming semantics. Fortunately, the research team was able to introduce an essential and effective model of the system by use of the notion of simulation relation in this case. This is an example that the knowledge in basic science worked well enabling such an effective model to be obtained because the research team had known the notion of simulation relation well before this industrial collaboration.

The processes of our technology transfer fieldwork were conducted almost precisely according to the description in chapter 4. The element techniques used in this procedure are explained below. Section 5.2 is an explanation of the interview technology used in the first step. Section 5.3 discusses the participant observation used widely in fieldwork. Finally in section 5.4, the model experiment, predevelopment experiment, post-development experiment, restoration experiment, and blind experiment used in trial experiments are described.

5.2 Interview

At the start of fieldwork in technology transfer, the research team must learn the domain knowledge of the field. In most cases, some written material about the domain knowledge is available, and the research team can ask questions, to which the industrial partner answers. We call this step the *interview*. Since the knowledge and the background or culture of the research team and the industrial partner differ, one must choose the vocabulary carefully during the interview. Yet the communication between the research team and the industrial partner often is so hard at first that it looks almost impossible. This is why we say technology transfer is a cross-cultural exchange. The techniques of interview overlap in a large part with *requirement analysis* in system and software engineering.

Interview is done during the whole process of fieldwork, not just at the start. So, the project should be scheduled taking the time for interview into account. Another thing to consider is that the interviewee is not necessarily cooperative to the interview, especially when he/she is not a member of the project, as the interview must occasionally be done with a person who is not a project member. Special preparation for interviews should be considered for such cases.

5.3 Participant observation

Participant observation is one of the standard techniques in qualitative research. The observer becomes a part of what is observed, therefore the act of observation itself may effect the result of observation. It is widely used in ethnology and sociology.

Processes of information system design and development are typical examples of non-reproducible processes. If the methodology of experimental science is applied simple-mindedly, one would immediately face with difficulties caused by the non-reproducibility, as well as the influence of the observer on the object.

5.4 Trial experiment

There are several objectives in trial experiments.

1) To give examples of application of the technology of concern in the context of the industrial partner, in order to make it easier for them to evaluate the value of the technology.
2) To exemplify applications of the technology of concern.
3) To ease the learning of the technology by the industrial partner, by means of tutoring by the research team.

Of these, 1) and 3) are for the interest of the industrial partner, while 2) is for that of the research team. No special method is necessary for 2) and 3), but we make a list of some specific methods for 1) (Fig. 2).

a) [Model experiment] Trial experiment for past prototypes and past development cases
   The risk is small since there is no damage even if the technology application fails.

b) [Reconstruction experiment] Take an old system development, for a part of which the recorded document is missing. Reconstruction experiment is conducted by tracing exactly the old development according to the recorded document wherever it is available and making up the undocumented part by doing new development. For example, the specification is rebuilt in consultation with the preserved source code if the specification document is missing, and model checking is done according to the newly built specification document and the source code.

c) [Pre-development experiment] Trial experiment for a commercial product under development or for its development process

d) [Post-development experiment] Trial experiment for a commercial of products already available in the market
   This includes conducting analysis of failures reported

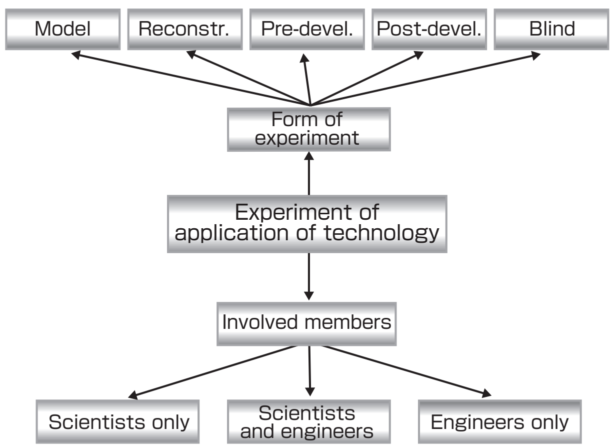

Fig. 2 Classification of experiments of application of technology.

from, for instance, the market.

e) [Blind test] Take an old development with some properties (nice or bad—it can be a fault). It is assumed that the technology of concern can ease the findings of those properties. The properties are hidden from the research team who tries to clarify them using the technology of concern and evaluating the results of the process. For instance, take an old development with some known, recorded faults. These faults are hidden from the research team who tries to find them using model checking. This can be a good way to evaluate the value of model checking.

Who exercises the technology of concern? There are at least three possibilities.

i) By a team composed only of members of the research team
ii) By a team composed of a mixture of members of the researchers and those of the engineers
iii) By a team composed only of engineers of the industrial partner

In early stages, one tends to follow i) to display the effect of the technology of concern; then the technology is gradually transferred to the industrial partner by means of ii), and finally, the trial experiment is conducted by iii) to evaluate the cost.

6 Two case studies

Amongst many fieldworks of ours, there were two cases that were continued for more than three years which were concerned, as a result, not only with a short term goal but also with a middle term one. In this chapter, these two works are presented and we try to evaluate their outcome.

6.1 Industrial partner P

The fieldwork done jointly with our industrial partner P started in response to a demand by P for introducing model checking into their development process. P reached model checking after their search for a method of developing reliable software with high quality.

1. A “Model experiment” was conducted for a small piece of software of P. Model checking was conducted for about one month, and an engineer on the side of P learned the process of verification using model checking, while the research team learned how to read the specifications written in P and the basic domain knowledge. This was repeated several times.

2. A “Blind test” was conducted after repetition of 1. All the faults that should be discovered were found by applying model checking. A good set of examples showing the effectiveness of model checking was obtained through this Blind test.

3. Up to this point, the work of model checking itself was done by the research team. At this point, the project decided to write a manual which enables engineers of P to conduct model checking without assistance of experts. To that end, model checking is now done jointly by the research team and engineers of P and this joint team repeated “pre-development experiments” and “post-development experiments,” several times to write down a guideline for a verification process using model checking, and a manual to verify a module in nine days. The guideline was written jointly but the manual was completed solely by the engineer team.

Unfortunately, we have not received any report from P about how model checking was introduced into their own development process after this fieldwork was completed. We assume it has not been deployed in a large scale, to our disappointment. Note that, however, P is a world wide enterprise having more than a hundred thousand employees, so for them to deploy a new technology would itself be a huge project.

For a technology transfer project to succeed, there are various points that must be considered, other than technical problems that would be solved by trial experiment as discussed above. We realized through this fieldwork that the research team must set up a view about intellectual properties; that is, it must have a fixed strategy concerning which results would contribute to intellectual properties and which results would contribute to academic publications, and such strategy should be set up at an early stage of the whole project. Take, for example, the writing of a manual as described in 3 above. The manual was written only by the engineers of P and no one from the research team participated in the writing. This, however, prevented information sharing between the engineers and researchers. In retrospect, the researchers should have supported the manual writing much more because some information which must be written down in a manual is not so important as an intellectual property or as a result of academic research but, at the end of the project, we tended to regard every information written in the manual as valuable either as an intellectual property or an academic result.

6.2 Industrial partner Q

A fieldwork for technology transfer jointly with our industrial partner Q started when engineers of Q became interested in model checking, and the top management of Q dispatched one engineer to AIST for two years.

While the fieldwork with P was done with the intention to write a manual to propagate model checking to exclude the dependency on experts, in the case of Q, technology transfer took place in an extremely expert-oriented style where the technology was thoroughly taught to one engineer. This engineer participated in several research projects at CVS and went back to Q, after two years, with ample experience in conducting "restoration experiments" and "pre-development experiments."

As a result, the trained engineer has been active and has established a study group of model checking after the completion of the fieldwork project. The group extended even to other companies and he created his own model checking training course for engineers, which is readily used in Q.

The two cases of fieldwork above differ in their strategy for propagation of the technology inside the industrial partners, even though both were trials to apply the same technology. The reason seems to lie in the diversity of software development. The field to which the information technology is applied tends to be diverse and that implies that qualitative research is effective here.

7 Discussion and conclusion

7.1 Issues

We are still in the process of collecting experiences in the fieldwork for technology transfer. Therefore, the scenario presented in this paper should be regarded as tentative. There are, however, at least two issues for the future.

a) There is room for further systematic study on observations obtained through our fieldwork. It seems qualitative approaches, such as the KJ method, are effective for such a study.
b) While there are active discussions on measurements and quantity for the software development processes[15][16], in clinico-informatics, how to use such measurements in concrete technology transfer[Note 10)] still remains as an issue to be discussed.

Just as there are issues of finding the cause of a disease and clarifying the mechanism of a disease in clinical medicine, there are issues of finding the cause of risks and clarifying the mechanism of faults in clinico-informatics, and these issues must be solved by collaborating with the basic research of informatics. The risks (or dependability, if one looks at the other side of the same phenomenon) of information systems are widely studied nowadays, and an approach that takes into account the diversity and complexity of information processing, as presented in this paper, seems to be worth emphasizing more.

7.2 Conclusion

In this paper, we attempted the systematization of clinico-informatics based on the field scientific methodology by Kawakita. The KJ method seems particularly effective as a method of information gathering in the requirement analysis, as it is one of a few methodologies about abduction. To apply the KJ method to the actuality of clinico-informatics is our future theme.

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This study was done using the experiences of the technology transfer activities conducted by a succession of research groups: Collaborative Research Team of Informatics, Laboratory for Verification and Semantics and Research Centre for Verification and Semantics, which continues since the establishment of AIST. We are grateful to all enterprises involved, the engineers thereof, and the researchers of AIST who participated and contributed to these technology transfer activities. Professor Hideyuki Nakashima and Professor Naoto Kobayashi kindly reviewed the paper, and provided several essential, *synthesiological* comments. In many cases in the review process, the authors' understanding was improved in an essential way. We are deeply grateful to be given this opportunity of writing this paper and of discussion.

Note

Note 1) We write Kawakita's family name before his given name, as is usual in Japanese. We guess he had a definite opinion on how his name should be put, from the fact that the KJ method was named as it is after his own name.

Note 2) Model checking is a technique (or technology) in system and software engineering. It is an application of mathematical logic to software engineering, which is generally called Formal Methods. For an overview to Formal Methods, refer to Reference [17].

Note 3) Reference [18] is a proposal for the terminology of the dependability and risk of information systems such as fault, error and failure. We try following them. The notion of *fault removal* is explicitly defined in [18], and it includes *verification* (finding the fault).

Note 4) A transition system is a mathematical structure given by a pair (S, R) of a set S, whose member is called state, and a binary relation R, which is called the transition relation, on S. If $s\ R\ t$ holds between states s and t, we say there is a transition from s to t. Automaton is obtained by adding some additional data such as input and output symbols and relations around them to a transition system. A state transition diagram often used by programmers may be seen to denote a transition system. In that sense, transition systems are widely used in practice as a mathematical model of information system.

Note 5) In some cases, all stakeholders come to an agreement on what the problem in the field is. It may also be a case, however, where stakeholders do not come to such an agreement because some stakeholders do not have a clear understanding of the essence of the problem the field faces. Even in such a case, the research team involved may be able to capture, because of their academic background, the essential problem there; that many other issues would automatically be solved if that problem is solved. The role of a research team here would be to detect such an essential problem, explain it to the stakeholders and propose a solution to it. *Exploration* of the situation and observation with open eyes with as little bias as possible would make it possible for the research team to play such a role.

Note 6) This is a point indicated by the main reviewer. The authors initially objected to the comment, but after thinking through, we changed our position and came to this conclusion.

Note 7) This does not necessarily mean that we are stating that these disciplines engage in subjective discussions.

Note 8) As a result, some of the authors' colleagues suffered from lack of volume in their publication lists. We emphasize that there are people even in academia who understand the importance and difficulty of fieldwork and that being seriously involved in fieldwork inevitably implies a small number of academic publications. Having said this, we must observe that there are still many who do not recognize this causality and tend to accuse scientists in fieldwork of lack of academic publications.

Note 9) Consider a researcher in clinical medicine who is not trained in basic science such as molecular biology and he/she tries to connect a result of a clinical study to basic science. It is widely known that he/she may go round and round for years over the same topic because he/she does not have the overall view of the whole picture, and it is often attributed to lack of his/her ability in basic science. Such a phenomenon is called PAIDS (paralyzed academic investigator's disease)[19].

Note 10) It seems the KJ method could be used effectively as a method for system analysis (requirement analysis, safety analysis, etc.). Conceptual tools such as Goal Structuring Notation (GSN) and Claim, Argument and Evidence (CAE), based on the operation of relating different objects by arrows, are recently used widely for safety cases, but the KJ method, based on the operation of putting things together by circles, seems to work from different perspectives. This is, however, an open issue to be investigated.

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Declaration

This paper was written based on the two authors' discussions and collaboration. Therefore, there is no "principal author" in this paper, but the two authors made equal amount of contribution.

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Discussions with Reviewers

1 "Clinico-informatics"

Question (Hideyuki Nakashima, Future University Hakodate; Naoto Kobayashi, Center for Research Strategy, Waseda University)

Although the meaning of "clinico-informatics" is clearly explained in the text, I am afraid that a careless reader may easily misunderstand the word to mean "informatics for clinical treatment." What do you think of using the term *rinjo johogaku* or "on-site informatics"?

Answer (Yoshiki Kinoshita, Toshinori Takai)

Even outside of medical domain, the term *clinical psychology*, for instance, has been widely accepted. We agree, however, there is a possible misunderstanding which you pointed out, so we rewrote the text to avoid it. It could also be said that clinico-informatics is a study of therapy for systems, or *systemtherapy*.

2 Technology transfer

Question (Naoto Kobayashi)

You write that 1) analyzing the situation (diagnosis), 2) improving (therapy), and 3) deciding and executing the improvement policy (technology transfer) are the three principal subjects of study in clinico-informatics, making analogy with clinical medicine. I am anxious to clarify the chronological order of these activities; in particular which of 2) improvement and 3) technology transfer comes first in chronological order? It seems that 2) usually comes after 3). Is it the case that 2) is first done by the research team and then 3) the technology is transferred to industry step by step, or that 2) improvement and 3) technology transfer are done in parallel? Could you clarify the chronological order of 2) and 3)?

Is there no transfer of technology (of medical treatment) from medical doctors to clients (of course there is none because of the law), while there may be advice about treatment and prevention? If you include nursing, however, technology transfer does occur from medical doctors to nurses.

Answer (Yoshiki Kinoshita, Toshinori Takai)

2) comes after 1), but 3) is to shape the technology of 1) and 2) into a form that can be used (deciding the improvement policy) by general engineers (general physicians), and to communicate (execute). 1) and 2) are activities at a level different to that of 3), so there is no specific chronological order between 2) and 3).

The technology transfer we are considering as an example corresponds to a flow of knowledge from research institutes to the medical doctors, not from medical doctors to clients. Since it is done between medical doctors with proper licenses, (i.e., from those working in research institutes to those working in clinics,) the limitation by law does not matter here.

Question (Naoto Kobayashi)

I understand your notion of technology transfer and the analogy to what happens in clinical medicine, but I still do not understand that "3 to propagate the technologies" comes after "2 to improve the situation in the field" It would be strange if a medical doctor cares for the patient before deciding the therapeutic policy, wouldn't it? Could you explain more about what you mean by "to propagate the technologies"?

Answer (Yoshiki Kinoshita, Toshinori Takai)

After giving another thought, we concluded that analysis of the situation, improvement, and propagation of the technology transfer are *subjects* of study in clinico-informatics, and the propagation itself is not part of the study of clinico-informatics; clinico-informatics studies *methods* for propagation. We rewrote the text to emphasize this distinction. We appreciate your point.

3 W-model for problem solving

Question (Hideyuki Nakashima)

You compare the W-shaped and V-shaped processes in chapter 3. Is not a W-shaped process a repetition of two V-shaped processes? (Refer to: H. Nakashima: Discipline of constructive research fields – Toward formalization of *Synthesiology*, *Synthesiology*, 1 (4)) Moreover, I do not think Yoshikawa's model is wrong; I would rather think processes of his model is repeated in reality.

Answer (Yoshiki Kinoshita, Toshinori Takai)

The V-shaped part on the left of the W-shaped process is a stage of abduction where the theory emerges, while deduction and induction are performed based on the theory emerged there. Therefore, we think the W-shape is not a repetition of the V-shape. We added some explanation about this point to the text.

By the way, we do not at all say that the Yoshikawa model is wrong. Our point is that the methodology for abduction has not been discussed at all or the discussions have been far from sufficient, if any.

Question (Naoto Kobayashi)

You wrote that the V-shaped part on the left side of the W-shaped process was missing in the Yoshikawa's framework of *Full Research*. If so, the process for the left V-shaped part is predetermined in the framework of *Full Research*. However, such a situation is rarely found in reality, but there usually must be a process of the research team going out to society or industry to observe the situation. The difference of *Full Research* and your fieldwork may be as follows. In the case of fieldwork, the two V-shaped parts in the W-shaped process are always linked serially and the W-shaped process is repeated again and again several times. On the other hand, the left hand side V-shaped part is assumed not to be repeated usually in the case of *Full Research*.

Therefore, it seems to me that the whole W-shaped process also exists in *Full Research* but it is not symmetric, and the study in most cases is performed by repeating the right hand side V-shaped process.

Answer (Yoshiki Kinoshita, Toshinori Takai)

We did not intend to say, "The research theme is predetermined," but we do intend to say, "Discussion on the process for determining the research theme has been missing." Therefore, I absolutely agree with you in that "such a situation is rarely found in reality, but there usually must be a process of the research team going out to society or industry to observe the situation."

By the way, the difference between *Full Research* and the W-model is the emphasis of the presence of the left hand side V-shaped part and the presence of a methodology for conducting it. The difference is not the number of times the left V is repeated. Whether it be *Full Research* or anything else, the left hand side V-part, i.e., abduction stage, is there, and what matters is whether one is conscious of that part and look at it with emphasis or not.

Question (Naoto Kobayashi)

In Kawakita's W-model for problem solving, I think the left hand side V-shaped part ("exploration," "field observation," and "abduction and synthesis") is important. In the process of the application of model checking, you wrote "under a vague expectation or problem proposal that some technology may be useful somewhere in some society, one visits (make exploration) there and observes the situation (field observation)." In practice, however, don't you conduct technology transfer to respond to some clear issue that your industrial partner has? Or, do you mean that the problem of your industrial partner is clear, but how to solve it is vague? Could you clarify the word "vagueness" in your statement here?

Answer (Yoshiki Kinoshita, Toshinori Takai)

The industrial partner involved does not necessarily have the full understanding of the essence of the problem. Therefore, there may be a more pressing issue touching to the essence. That issue must be solved first; the other issues are often automatically solved as soon as such an essential problem is solved. It is the responsibility of the research team, which is equipped with more of scientific knowledge and experience, to explore and observe the field with open eyes with as little bias as possible.

Acquisition of skills on the shop-floor

— Visualization and substitution of skills in manufacturing —

Norio Matsuki

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For the purpose of assisting skill transfer training in small and medium manufacturing industry, an acquisition method of judgment skills of experienced factory workers on shop-floors of metal processing such as forging, casting and plating is proposed. Several software applications based on the method that have been developed and evaluated in the manufacturing factories are also presented. The future vision of skills and skilled workers in the manufacturing industry is also discussed.

Keywords : Skill, tacit knowledge, skill acquisition, skilled worker

1 Introduction

The objective of this paper is to discuss the results of the research on the "Skill Acquisition Method" that was the subject of R&D in the "Project to Support the Transfer of Small Core Technology," a project of the New Energy and Industrial Technology Development Organization (NEDO) conducted from 2006 to 2008, for the purpose of acquiring the skills of expert skilled workers of the small manufacturing factories and to smoothly transfer those skills to the successors. Changes in the research scenario will also be discussed. The content of the research described in this paper is the result of the effort of all who participated in the NEDO project, and the author, who was the project leader, shall outline the project as a representative.

In this research, the aspects of physics and engineering were considered for the expert skills in manufacturing technology, while the aspects of cognitive science and business management were eliminated as much as possible. Such a stance was not clearly defined in the initial research scenario. In the beginning, we did not consider the significance of clearly setting such a stance. However, as the research progressed, it became necessary to clarify the positioning of the skill research.

Since this project was supported by the Small and Medium Enterprise Agency, the purpose was to support the small companies. Therefore, the output of the project should be a skill transfer tool that could be used effectively by the small companies. Rather than being an innovative research, the development of an evaluation index which would be popularly used among the companies was important. The recent R&Ds through competitive funding have promoted the so-called outcome orientation where the contribution to the creation of a market after the completion of the project is emphasized. Many researchers in the basic fields feel this is a hindrance. In this paper, we shall also discuss how the demand, "develop a technology that can be used on site," affected the R&D scenario.

2 Outline of the skills investigated

2.1 Skill and tacit knowledge

The *gino* or "skill" of manufacturing that will be investigated as the subject of this study is defined as "the ability to take actions and to make decisions that are useful in manufacturing, from design to production, although the exact reason why cannot be explained." The opposing concept is the *gijutsu* or "technology." Technology is defined as "something for which the rationale and the mechanism of actions taken and decisions made can be explained clearly to a third party, and the third party can reproduce the actions and decisions based on that explanation." The *jukuren gino* or an "expert skill" is used in this paper to mean a skill that was learned through the long experience of working in manufacturing, and is generally highly advanced and highly useful. A worker who works for a manufacturing company and has this ability is a *jukuren ginosha* or an "expert skilled worker." Therefore, the method for acquiring expert skills is the method for replacing the skill with technology. This is sometimes called "turning a skill into technology." The method for acquiring expert skills in this research can be considered a method for turning the skill into technology.

Tacit knowledge is a term related to skills. Michael Polanyi, who was the first to propose tacit knowledge, discusses tacit knowledge in terms of the knowledge associated with physical action that cannot be described verbally, such as the knowledge of riding a bicycle[1]. On the other hand, tacit knowledge[2] in the SECI model of Ikujiro Nonaka is defined as "the knowledge based on experience and insight

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that cannot be expressed verbally.” The difference between Nonaka’s tacit knowledge and what is defined in this paper is how to address the action skills. Since action is influenced by knowledge, the boundary is not clear, but there is no discussion that encompasses the manual skills of an expert skilled worker in Nonaka’s tacit knowledge. The skill discussed in this paper perhaps corresponds to the knowledge ability that combines the tacit knowledge of both Polanyi and Nonaka. On the other hand, Nonaka’s formal knowledge overlaps to a great extent with the definition of technology. Therefore, excluding the action skills, the conversion of tacit knowledge into formal knowledge in the SECI model and the conversion of skills into technology are synonymous. Also, this paper will not discuss the tacit knowledge of a group that plays an important role in the SECI model.

By the way, is one person’s tacit knowledge, tacit knowledge for other people also? There may be cases where a certain person is incapable of providing a verbal expression or cannot explain the reasons, but the subject might have been studied elsewhere and had already become formal knowledge. This is one assumption in this study. The knowledge of physics, chemistry, and engineering needed in materials and manufacturing is substantial, and we think that the assumption that a worker in a factory can be knowledgeable in everything is not practicable. It is more natural to think that an individual understands only part of the scientific and engineering findings made by humankind. As an assumption of this study, many of the tacit knowledge and the skills of the expert worker have already become formal knowledge (technology). Here, the phrase “does not understand” includes the nuance “has not solved the ‘application’ of how it affects the workings in the factory even though the principle is known.” Although we did not conduct a survey that allows numerical expression, the company engineer who is a world leader in some specialty understands the formal knowledge of that specific narrow field while, in general, a worker at a family-run factory may not have a wide range of formal knowledge. Due to such an assumption, clarification of tacit knowledge that humankind does not yet know and the pursuit of the formal expression of such knowledge are not the subjects in the research for the expert skill acquisition method. This research does not investigate “tacit knowledge” in its true sense.

2.2 Traditional research of skills

The tacit knowledge of Polanyi and Nonaka discussed in the section is briefly explained. Michael Polanyi is a doctor of medicine, chemistry, and a philosopher. He thinks that there is a process in the human action where complex controls are conducted implicitly without explicit cognition, such as riding a bicycle. He calls this process tacit knowledge. If it cannot be essentially verbalized, Polanyi’s tacit knowledge cannot be turned into formal knowledge or technology. Therefore, following Nonaka’s definition, tacit knowledge will be re-defined as an “action based on experience and insight, and the verbal expression for its control mechanism is difficult,” and this will be the subject of investigation in this research. In engineering, researches had been done on the automatic control of motorcycles, and the control system as an alternative to tacit knowledge for riding the bicycle has been realized. Considering this point, the tacit knowledge in Polanyi’s sense will not be the subject of this research.

Nonaka, who is a scholar of business management, defines tacit knowledge as a keyword to analyze knowledge management in business, particularly in the Japanese manufacturing industry. He proposes the SECI model where the individual and group tacit knowledge and formal knowledge change and develop as a knowledge spiral. SECI is an acronym for socialization, externalization, combination, and internalization. What we are interested in is the content of the skill expressed as tacit knowledge. It is important to know the engineering meaning of the expert skill that works effectively in response to a new situation. In this sense, our standpoint for tacit knowledge differs from the one that covers business management.

In cognitive science, researches on the skill acquisition mechanism have been done. For example, Ericsson *et al.* point out the importance of training in acquiring expert skills[3]. While this is an extremely interesting topic, how a worker acquires a skill is not the subject of this research.

In engineering, there are proposals of skill transfer using virtual reality (VR)[4] and corporate attempts at digitizing and visualizing the skills for TIG welding[5]. Both researches are technologies to supplement and support on-the-job training (OJT).

Our stance is that it may be possible to express expert skills as formal knowledge, as described in the previous section. The basic policy for establishing the expert skill acquisition method in this research is to express the expert skill using the formal knowledge that has been already established.

2.3 Types of skills under investigation

In discussing expert skills, the mass media often portrays an expert craftsman of a family-run factory using exceptional manual skills to create beautiful parts, and transmits the message that this supports the Japanese manufacturing industry. This will be discussed later, but the skills investigated in this research are the skills related to various decision-makings rather than the skills of action.

The skills used at the processing factories are presented in Table 1. The subject of this research is mainly the skills related to preparations conducted before starting the work, such as the set-up. Particular attention is given to the skill of decision-making. The skill of decision-making is a skill for determining the specific figures, not just determining the right-wrong of a certain action. For example, in forging, such skills include the estimation of the necessary process pressure by looking at the plan and material of the ordered parts. The decision of whether a product can be manufactured by the machines available in the company factory is extremely important in the forging industry, and often depends on the expert skilled worker's assessment.

One of the reasons for looking at the skill of decision-making is because the output of this research is a skill transfer tool that can be used on site. To create the tool, it must be implementable on the computer, in such ways as entering some figures that will produce some figures or graphs. Therefore, it is necessary to look at skills that can be expressed in numbers, and the skills of decision-making became the main subjects of this research.

The goal of the NEDO project under which this research was conducted was to select four core processing technologies – casting, forging, plating, and heat treatment, to select 10 different skills for each processing methods, to extract individual skills, and to develop a skill transfer tool that can be used on site. This project was a joint project by AIST and RIKEN, and RIKEN conducted the research for metal cutting and metal stamping. These processing methods were selected among those set forth in the Act on Enhancement of Small and Medium Sized Enterprises' Core Manufacturing Technology, as enforced by the Small and Medium Enterprise Agency.

3 Research scenario

The development of the skill acquisition method of an expert skilled worker means that the acquired skill must function independently and autonomously from the skilled worker. It means to build a computer system that will be an alternative to the skilled worker, as shown in Fig. 1. Although we were aware of this concept only vaguely at the start, we became conscious of it when we actually executed the R&D. The construction of this alternative became the methodology for skill acquisition in this research. In this chapter, the path we followed is discussed in retrospect.

We started the research by learning how the expert skilled worker conducts decision-making. The case studies of decision-making done at companies were collected, and their importance and qualities were studied. This was the collection of the decision results or the output. Next, we considered the whole body of information that was used for that decision-making. This was the collection of the input for decision-making.

Although it is very interesting to recreate the thought process that takes place in the mind of an expert skilled worker, it is very difficult. Therefore, we built an algorithm that was established from the input and the output. This involved building a computer system using the known formal knowledge. The algorithm was inferred from the output, and the input to establish that algorithm was inferred. This was verified through interviews at the company, and then the algorithm and the input were reviewed. The creation of the alternative of decision-making by the expert skilled worker was the method for skill acquisition in this study.

Since the subjects were the input and output only, as a result, we decided not to consider the thought process of the expert skilled worker at all. Although the subject was skill acquisition, the expert worker was not the subject of analysis. We became clearly conscious of this at the late stages of the research. In this research, a device for observing the actions of the expert worker was developed, and we felt we were observing the expert worker at all times, but that was not the case. In the early phases of the research, consideration of the difference in methodologies for acquiring the different skills – decision-making and action control – was insufficient.

In contrast to the fact that the research for tacit knowledge and skills from the viewpoint of business management focuses on the role of the expert skilled worker and the process of knowledge creation, attention was given to the skill itself in our engineering research. However, neither the business management research and our method considered the thought process of the expert worker, and in that sense, the two were the same. The issue of the tacit knowledge in the brain is an issue for cognitive and brain sciences.

Table 1. Skills in processing.

Category of ability	Ability of expert skilled worker				
	Ability to set up		Ability during work (based on perceptivity)		Others
	Ability to plan	Ability to adjust	Ability to determine situations	Manual skills	Ability to respond to trouble, etc.
Example of on-site skills	· Processing method planning · Riser arrangement planning	Adjustment of additives according to the day's weather	· Tapping timing; "Take it out now"	· Pouring · Polishing · Burr removal	Capable of responding quickly to new trouble
Difficulty of measurement	Easy	Relatively easy	Relatively difficult	Difficult	Difficult

← Before work — Immediately before work — During work →

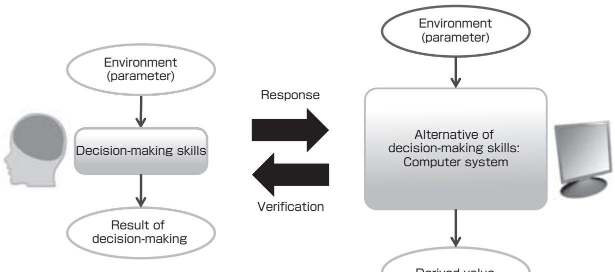


Fig. 1 Model for acquisition of the decision-making skills.

4 Research result

In this chapter, the skill acquisition method that was finally organized will be described. More accurately, the framework for acquisition is presented. This framework fails to propose the meta-structure for skill acquisition that allows acquisition of a desired skill with ease. However, it may provide a certain viewpoint when acquiring the skills and when considering the meaning of the expert skilled worker in future manufacturing.

4.1 Overall structure

The result of this research can be organized as shown in Fig. 2. The computer system as an alternative has a derived model for outputting the decision value. The derived model is composed of the derived algorithm that calculates the decision value by entering measurements or some derivable values from the work environment.

The excellence of an expert skilled worker that became clear by studying this derived model is the “ability to simplify the problem.” For example, in forging, the important role of the expert skilled worker is to calculate the pressure needed for manufacturing the product. Here, the expert worker seems to simplify and categorize the complex product shape to calculate the processing pressure. It is assumed that by doing so, the parameters to be considered can be greatly reduced and the sufficiently precise answer can be given for deciding whether a product can be forged using the machines at the company. The derived model as an alternative is quite different from an expert worker, yet there is a similarity that the complex phenomenon is simplified. As the research progressed, we thought that the greatest characteristic of an expert skilled worker was the ability to simplify the subject and to quickly come up with reasonably accurate answers. The ability to discern the simplification process is the true value of the expert skilled worker.

Simplification is important in the derived model for alternatives. The on-site environment is often complex, and it often becomes an extremely complex and unstable system if all the influences of the related factors are taken into account. It is necessary to build the derived model to enable decision-making by selecting the truly dominant factors. Also, obtaining useful results from simple input means that the operation on site is easy. The limitation of “developing a technology that can be used on site” actually played an important role in discovering the ways of simplification. In this research, the condition that it must be usable on site was effective in keeping the research activity sound.

Looking at the skill transfer tools created, they can be organized into several types. Following are the explanations of the types.

4.2 Derivation by theoretical formula

In the cold forging treatment, the desired part is shaped by stamping the metal at high pressure. It is known that the deformation resistance and restraint coefficient play important roles as shown in Fig. 3 in the process of metal deformation. From various experiences, it could be estimated that approximate value can be obtained by fitting the shapes of the part shape into some patterns for the purpose of considering the forging pressure, even though the shape of the parts are different. It was also found that by using iron as a standard for estimating the property values, this could be applied to other materials such as magnesium and aluminum.

The derived model for pressure values needed in cold forging was created from the companies’ experience and knowledge of metal plasticity, as well as the drawings and materials of the parts to be manufactured. Figure 4 shows the interface of the implemented computer system. We were also able to create a derived model for the temperature increase of the product during forging.

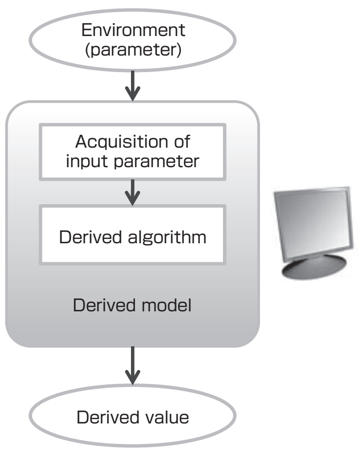
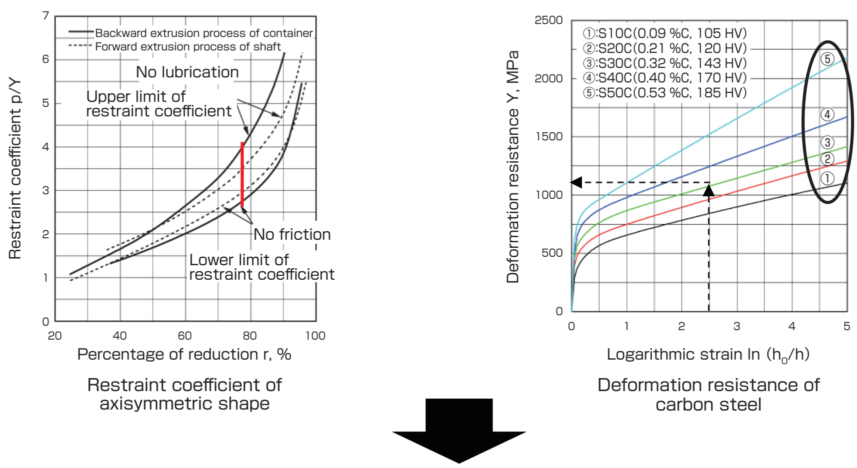


Fig. 2 Structure diagram of the counterpart to decision-making skills.



Processing pressure = Restraint coefficient × Deformation resistance

Fig. 3 Model for calculating the processing pressure in forging.

By fusing the theoretical model where the processing pressure is expressed as a product of the restraint coefficient and deformation resistance, and the model for simplifying the product shape based on experience, we created a computer system that serves as an alternative to the decision values that relied on the decision-making by an expert skilled worker. The measurement values of pressure used in actual processing can be entered and stored in this computer system. By doing so, the values dependent on the factory environment or the processing machine can be estimated.

This computer system is one type of simulation for cold forging. In skill transfer, this cold forging simulation can play the following role. First, it can be used as an alternative to the expert skilled worker. If the simulation is perfect, it will be finished there, but the materials and lubricants change with time. Good results may no longer be obtained using the same process if the situation changes. Therefore, the successor must understand the derived model and algorithm that are the basis of this simulation. By understanding the procedure and the principle of the computation, the successor will be able to respond to new situations. In the manufacturing industry that faces severe competition, the ability to do the same work constantly is not sufficient, and the ability to respond to new issues is demanded. In this sense, the simulation in which the principle and the processing procedure are clear can be considered one of the most effective ways to support skill transfer.

4.3 Derivation by experimental formula

In casting, the hardening process of metal plays an important role. The casting technology is a method where precise shapes are created by finely controlling the process of metal solidification. It is possible to an extent to conduct theoretical derivation by entering vast amounts of parameters such as detailed shape of the part, production condition and temperature environment, humidity and temperature of the mold, various properties of the molten metal, and others. However, measuring these figures on site, and entering them to conduct the simulation are very difficult. Also, in casting, the number of parts to be produced with one pour greatly influences the production efficiency and the resultant cost. Company cannot be managed by looking only at the product quality.

Considering the various conditions, we thought a mechanism for collecting and storing data that included the algorithm for experimental production based on estimates to some degree was more effective than the simulation format. The material deforms during the heat treatment. It is important to estimate the degree of this deformation. For this purpose, we conducted preliminary experiments at research institutes or companies, selected the degree of deformity and the main parameters that govern the process, and then created the experimental formula. We employed the derived model based on the experimental formula as an alternative to the expert skill of estimating the deformation in heat treatment (Fig. 5).

To handle new situations, successors have to employ new experimental formulas as derived models. Therefore, they need to learn the knowledge of physics pertaining to metal materials and to understand engineering to see how the simplification is done. We believe this is the skill turned into technology that the successor should inherit.

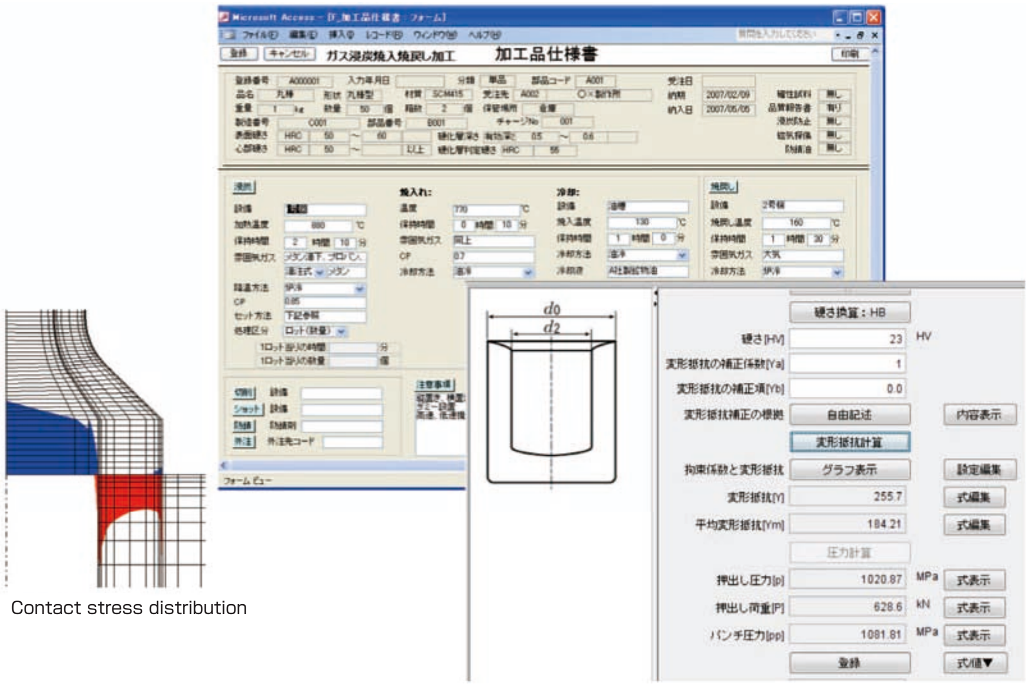


Fig. 4 Example of a system for decision-making skills.

4.4 Derivation by data mining

In manufacturing, responding to various troubles is an important skill. In plating, we built a mechanism for organizing the case studies of defects, to collect and to accumulate the relationships between the candidate causes of defects and the correctional procedures from the past data.

The troubles are categorized, and when a trouble actually happens, it is determined to which category a defect belongs. The past data are searched based on the situation where the defect occurred as additional parameter, and countermeasures are taken. This is a type of data mining. This is a method for obtaining the appropriate information from the past storehouse of data, for cases where the theoretical or experimental formulae cannot be estimated. Cluster analysis, neural network, and genetic algorithms may be effective, although these were not conducted in this research. In casting, we use a search method with an interface as shown in Fig. 6 to search the past case studies. This is a method called Eagle Search developed at the Center, and is characterized by the flexibly interchangeable search keys.

The fact that the derived model is based on data mining indicates that the derived model under investigation is not sufficiently clarified. If the cause can be theoretically pursued from the troubles that occur and the response can be clarified, a theoretical derived model can be built, rather than using data mining. However, in actual situations, theoretical pursuit may not be possible because the defect is not reproducible or the cost of reproduction is too great. Therefore, data mining where the past case studies and their solutions are accumulated and searched is effective as a skill for responding to trouble.

The three derived models were presented above. Comparing them, the method based on theoretical formula seems to be the most effective and reliable. That is because the derivative method can be explained theoretically. The method by experimental formula seems to be reliable following the theoretical formula method since the assumed parameters and their mutual relationships are clear. The method of data mining seems to be the least reliable since the cause-and-effect relationship is unknown. Therefore, the derived models should be reviewed constantly, and a method based on a theoretical formula must be investigated as much as possible.

However, the differences among these methods are not necessarily clear. The difference between the derivations by theoretical and experimental formulae is the difference of whether the theory is established or not. For data mining, as the range of the issues become clear and the data are accumulated, the estimation of an experimental formula may become possible. When using this research result, the derived model should be reviewed according to the changes in the situation and the method with higher reliability should be explored further.

4.5 Other derivative methods

For the decision-making skills, we believe the above three methods are typical. However, there are skills other than decision-making that must be transferred. In metal stamping that was studied by RIKEN, the processing methods are different according to the types of parts under investigation. This means that the most important skill is the skill of selecting the processing method according to the characteristic of the parts, and the skill of discerning the points that must be focused on in selecting the processing method. The selection of the processing method design is too complex to be called a simple chain of decisions. In this project, we worked on skill transfer by creating a meta-flow

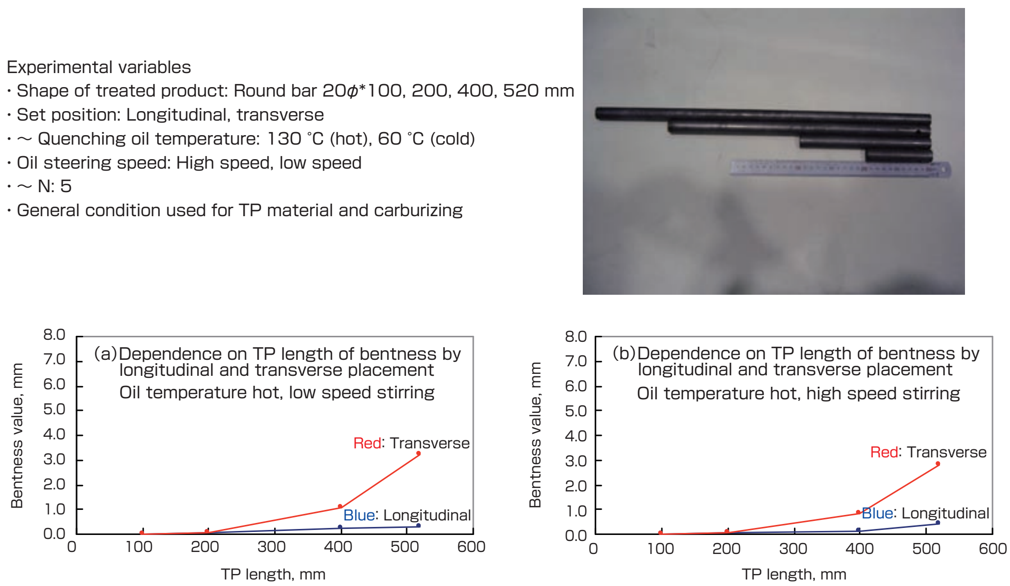


Fig. 5 Example of derivation of experimental formula in heat treatment.

model, but it is difficult to discuss this within the range of the above-mentioned three methodologies. This will be a topic of future research.

4.6 Measurement of the action of expert skilled worker

For the skill of action of the expert skilled worker, the following study was conducted in this study. One was the visualization of the pouring action in casting. As shown in Fig. 7, a device to measure the flow rate of the molten metal was developed by attaching a strain sensor to the neck of the ladle used in pouring. By doing so, we tried to visualize the expert skill of “fast in the beginning, slow in the middle, and push it in at the end!”

While visualization became possible, it is known that fine adjustments are done depending on the situation such as the number of parts produced and the form by which the parts were linked, and such control mechanism is not simple. To analyze the action, the meanings of the actions become apparent only by interviewing the expert skilled worker on how to control what, and then analyzing the relationship of the action and the flow rate and temperature of the molten metal. The analysis of the action skill requires the clarification of the meaning of the control, but that level has not been achieved in this research or in a similar research on welding.

5 Skills in future manufacturing industry

We discussed the research scenario and the result of acquiring the decision-making skills of the expert skilled workers, and described some examples of decision-making skills and the visualization of the action skills. Would expert workers in companies become unnecessary as such researches progress? We would like to discuss the training of future skilled workers and the positioning of expert skills.

The issue of expert skills is an issue for large corporations as well as small companies. For example, painting and welding are done almost entirely by robots in the automobile industry. The setting of the action is done by a method called “teaching,” and the actions of the robots are determined by the expert skilled worker. However, as the factories became automated and the skilled workers lost their workplace, the companies are now facing the problem where people who can determine the appropriate painting and welding conditions for new materials and new paints are no longer present. This also points to the problem that the companies do not fully understand the control mechanism of such actions.

As discussed in the section of the derivation by theoretical formulae, it is important that the successor who inherits the decision-making skills fully understands the physical and engineering meaning of the actions. It is necessary for the skilled worker of the future to engage in decision-making and action with sufficient engineering knowledge, at least in related fields. The worker must observe the actions objectively, and play the role of creating new skills by adapting to the new environment as an expert skilled worker. The future image of the expert skilled worker is to be an advanced engineer on site at the factory.

The fully analyzed skill is converted to technology, and automation will be realized by robots. The worker himself will then go on to study the next topic. The author believes that the future skilled worker should take on the role as an engineer. The companies and the society must favor such human resources in terms of status and income, or else the future of Japanese manufacturing, which is currently considered to be the top in the world, will be in question.

The skills of the current expert skilled worker are the results of long, hard efforts by excellent human resources who were the young people called the “Golden Eggs” who came from

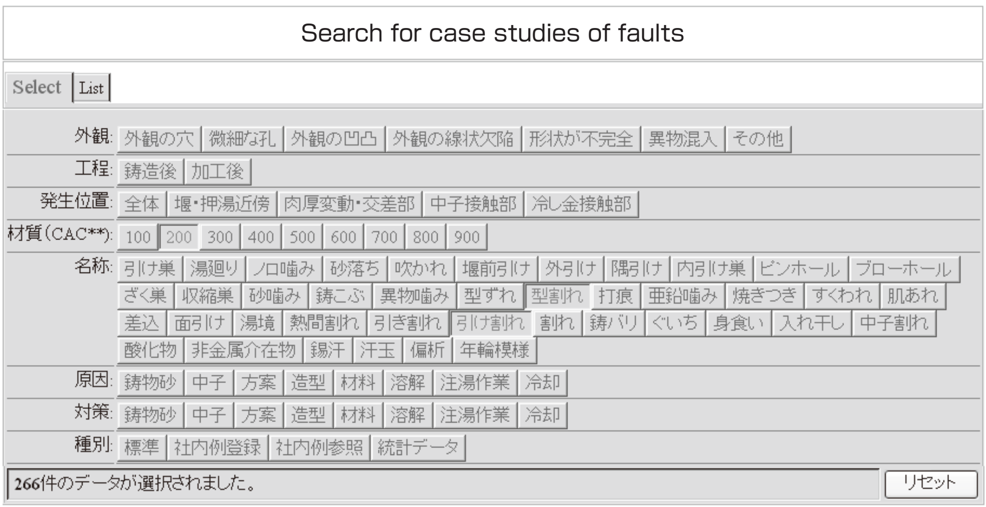


Fig. 6 Example of screen for data mining.

the rural areas to work in the large cities. I think we have come to the end of the age of manufacturing where high school graduates are called skilled workers while the college and graduate school graduates are called engineers. At the same time, the mass media message saying that the expert artisans of the family-run factories support the Japanese manufacturing industry must be corrected. While their role is not small in terms of required precision and cost, the future cannot be warranted by exaggerating the image of the artisans.

Finally, I shall discuss to whom the expert skills belong. Discussion on the possession of invention by the corporate researcher started with the blue diode incident, but the possession of the skills of the expert skilled worker is hardly discussed. When the skills for processing that was cultivated carefully over time is converted to technology, is the skilled worker left with nothing? Recently, the problem has been raised on the outflow of skills when the corporate retirees are invited by foreign companies to provide local training overseas. However, we must first discuss the subject of the possession of skills. I think there must be serious discussion by various parties involved.

6 Conclusion

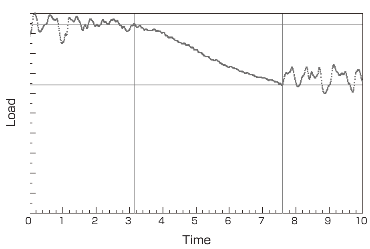
The outline of the research scenario for the acquisition of expert skills and the results of the research were described. The results obtained in this research are as follows:

(1) The method by computer system construction as an alternative of the expert skilled worker was proposed for skill acquisition; and

(2) The alternative computer systems including the ones based on theoretical formula, experimental formula, and data mining were described.

We also discussed the position of expert skills in the future manufacturing industry.

The Digital Manufacturing Research Center has conducted research with the objective of "studying manufacturing scientifically." I think the R&D for the acquisition and the visualization of expert skills has clarified the relationship between expert skills and manufacturing better than ever before.



Temporal change of load on ladle

Fig. 7 Expert skill in casting and its visualization.

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Author

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Completed the master's course in Mathematics at the Faculty of Science and Engineering, Waseda University in 1980. Worked at Nihon UNIVAC, Ltd. (currently Nihon Unysis, Ltd.), and then joined the Mechanical Engineering Laboratory, Agency of Industrial Science and Technology in 2000. Doctor (Engineering). Became the leader of the System Technology Research Team, Digital Manufacturing Research Center, AIST in 2001. Became the Director of Digital Manufacturing Research Center in 2006. Became the director of Collaboration Promotion Departmet in 2010. Specializes in shape modeling, and leads the R&D project for IT technology for supporting processing technology, skill transfer technology, and manufacturing.

Discussions with Reviewers

1 Structure of the paper

Question (Kanji Ueda, AIST)

It is unclear whether the title, objective, method, result, and discussion of the paper are exactly the same as the NEDO project "Skill Acquisition Method." Is the first section a part of the latter section, or is it reconsideration from a different point of view?

Answer (Norio Matsuki)

This paper is intended to be a description of the NEDO project "Skill Acquisition Method" from the viewpoint of the twists and turns in the research scenario. It was unclear at what point this view was taken, and the paper was revised to clarify that point.

2 Changes in setting of the scenario to match the actual situation

Question (Kazuo Igarashi, Measurement Solution Research Center, AIST)

You wrote that the direction was shifted to create an effective tool and allowed the use of methods outside the initial scenario because the initially set scenario could not be executed by ignoring the demands on site. However, estimating from the content of the factors that prompted the change, I think the items described here are important subjects that should have been studied and discussed in the beginning when the project was proposed.

Answer (Norio Matsuki)

As you indicated, they should have been studied beforehand. However, the actual situation of skills at the companies is complex, and there were many things that we would have never known until we started the project. I think this research could have resulted in a tool that could be utilized effectively on site even with the initial assumptions only, but we believe better results were obtained by changing the scenario according to the situation.

3 Clarity of the components

Question (Kanji Ueda)

For the derived model, is the content of “as derived model, theoretical formula… experimental formula… data mining…” related to Fig. 7 (Expert skills in casting and its visualization) or does it refer to the hypothesis or the obviosity?

Answer (Norio Matsuki)

These are the hypotheses of this research. If possible, we would like to continue our research of skills and continue investigating these hypotheses.

4 Future of expert skilled worker

Question (Kazuo Igarashi)

You say: as a result, it is necessary to have sufficient engineering knowledge to be a successor of an expert skilled worker in decision-making and action. You also say: the future image of the expert skilled worker is an advanced engineer on site. Certainly, this conclusion is in one direction, and while it may be applicable to large corporations, I don’t think this is feasible in middle and small businesses that were the subject of this research, due to the resource recruiting problem. Is it appropriate to draw such definitive conclusions in this paper?

Answer (Norio Matsuki)

The manufacturing industry faces severe global competition regardless of the size of the company. While this may sound like an extreme conclusion, I think even the small and minute companies can no longer afford to employ unskilled laborers in a traditional manner, and must move in this direction.

Secure implementation of cryptographic modules

— Development of a standard evaluation environment for side channel attacks —

Akashi Satoh *, **Toshihiro Katashita and Hirofumi Sakane**

[Translation from *Synthesiology*, Vol.3, No.1, p.56-65 (2010)]

The use of cryptographic modules is rapidly expanding throughout the world. Because of this, it is necessary to standardize a security evaluation scheme and to establish a public evaluation and validation program for these modules. Side channel attacks, which extract secret information from the cryptographic module by analyzing power consumption and electromagnetic radiation, are attracting a lot of attention. Research activity on such attacks has intensified recently. However, it is difficult to compare evaluation schemes proposed by different researchers because of differences in the experimental platform or environment. This makes it difficult for other researchers to repeat and verify the results. Therefore, we have developed cryptographic hardware boards and analysis software to serve as a common, uniform evaluation platform for side channel attacks. We have distributed this platform to government, industry, and academic research labs throughout the world in order to facilitate the development of an international standard.

Keywords : Cryptographic module, cryptographic hardware, side channel attack, differential power analysis, fault injection attack, security evaluation scheme, SASEBO

1 Introduction

The fast expansion of the broadband network as well as the popularization of high-performance, rich-featured information appliances, IC cards, and RFID tags hasten the advent of a ubiquitous information society. On the other hand, the exchange of a vast amount of information in every aspect of our daily life raises security threats including eavesdropping and falsification of communication data to the surface. Cryptography is a fundamental technology indispensable to coping with such threats. With more and more use of the technology in consumer products, a number of active studies have been conducted not only on theoretical analysis for cryptographic algorithms but also on security assurance of implementation of practical devices such as cryptographic chips. In particular, many researchers have paid significant attention to physical attacks, which observe the measureable phenomena of operating devices such as power consumption, electro-magnetic radiation, and operating times and estimate the internal cryptographic key from the leaked information on the measurement results without invading or destructing the target device. This class of attacks is called side-channel attack since such attacks exploit the information on channels other than the intended input- or output-channels. Today, while the formulation of international security evaluation standards with regard to side-channel attacks is in progress, the efforts are confronting the following difficulties. First, there is no justification for us to oblige industrial parties such as IC card vendors to supply their cryptographic products for evaluation testing or to provide their proprietary information. Second, universities or other academic institutions may publish their experimental results, but third parties can hardly trace the results produced at the different experimental environments unique to each of them. Therefore, we have developed a standard experimental environment and published information about side-channel experiments in order to contribute to the standardization activities from the neutral standpoint of the National Institute of Advanced Industrial Science and Technology (AIST) as a pubic research institution. In addition, we are pursuing collaborations with domestic and overseas research institutions, private companies, and universities toward operations of security evaluation systems for cryptographic modules.

In this paper, we first present a comprehensive vision of these standardization activities and our role in them. Secondly, we explain our effort in developing a standard evaluation environment for side-channel attacks and demonstrate the current status of side-channel attacks through experiments with the environment. Thirdly, we introduce our vision for future research on fault-injection attacks and invasive attacks, which require higher techniques, and on system dependability and security assurance against accidental errors and faults in addition to attack-basis security issues.

2 Expanding application and security evaluation of cryptographic technology

2.1 Standardization of cryptographic algorithms

The invention of writing made non-oral information propagation and knowledge accumulation possible. Since then, humankind has devised various measures for preventing a third person from discovering the information or knowledge. Cryptographic technology is one of them.

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Cryptographic algorithms and cryptanalysis techniques made dramatic advances particularly in wartime. Cryptography seen in mystery novels and suspense films mostly uses a secret algorithm that only the involved parties know, so it seems to be a puzzle-solving game different from the one in information security. Third parties, however, can decipher such cryptography once they discover the algorithm or the secret of the puzzle.

On the contrary, in today's cryptography, the key of the secret lies in the cryptographic key. Even the same message is enciphered into different ciphertext by using a different key. Therefore, if a third party obtains one key, the communicators can keep the confidentiality of messages with another key. Likewise, the Enigma machine, a mechanical cipher machine the German army used during World War II, separates the initial device setting, treated as a cipher key, from the algorithm of the machine. However, since the algorithm still involves an important hint for cryptanalysis, secure management of not only the key but also the machine itself is essential.

After the war, bank businesses and governmental operations began using cryptography for securing information, motivated by DES (Data Encryption Standard)[1] that the National Institute of Standards and Technology (NIST) established as a U.S. Federal standard in 1977. Most of previous cryptographic schemes did not clearly separate the algorithms and keys like the Enigma machine. In addition, their algorithms were not willingly made public because of their specific purposes. In those regards, disclosing the algorithm of DES was epoch-making. In the same year, Rivest, Shamir, and Adleman at the Massachusetts Institute of Technology (MIT) devised the RSA[2] (named after the inventors' surnames) scheme, which is suitable for digital signatures as well as encryption. DES is categorized as *symmetric-key cryptography* since, with the DES algorithm, encryption and decryption both use the same key. On the other hand, RSA is classified into *public-key cryptography* as it uses an encryption key and a decryption key different from each other and making the encryption key public does not affect confidentiality.

While cryptography had been considered equivalent to military technology and severely restricted to use and to import and export until the late 90's, the restrictions have gradually been relaxed since before or after 2000. Subsequently, more and more consumer products have begun using various cryptographic algorithms for different purposes. Meanwhile, the remarkable advancements in cryptanalysis techniques and computer's performance made the cryptographic strength of DES questionable. Thus, NIST called for stronger cryptographic algorithms for AES (Advanced Encryption Standard)[3] worldwide. Cryptographers and other specialists discussed the security issues and evaluated the performance of the implementations for AES algorithm proposals at three public standardization conferences[4]. Since NIST determined one as a new U.S. federal standard in 2001, several international standards have adopted AES.

The AES project triggered various evaluation and standardization works such as CRYPTREC (Cryptography Research and Evaluation Committees)[5] the security evaluation project for Japanese e-government recommended ciphers, the European Union's NESSIE project (New European Schemes for Signatures, Integrity and Encryption)[6], and ISO/IEC 18033[7]. Once it was thought that keeping the cryptographic algorithm secret provided attackers with fewer clues for cryptanalysis. However, there have been many incidents compromising proprietary algorithms that leaked through some channel or were reverse-engineered. Therefore, standard cryptographic algorithms such as AES are typically published so that many researchers and engineers can pursue various analyses for security verification of the algorithms throughout the world.

2.2 Security evaluation for cryptographic implementation

Enthusiastic security verification for standard cryptographic algorithms performed by a number of specialists ensures that there is little worry of a potential sudden exposure of a security flaw in the algorithm. Nevertheless, even with presumably secure algorithms, cryptographic key leakage may still occur due to a flaw in the software or hardware implementation of the algorithm. Unfortunately, it is hard for users to verify whether the implementation is secure or not. Thus, international standards were established for public institutes to perform security evaluation on security and cryptographic products for users' convenience, such as ISO/IEC 15408 (Common Criteria)[8][9] and ISO/IEC 19790[10].

ISO/IEC 15408 provides an evaluation framework for general information security products, including cryptographic modules, so that evaluators can verify the sound implementation of such products based on a Security Target (ST) determined by the developers. It also specifies Evaluation Assurance Level (EAL) in seven grades that express evaluation depths. The levels are roughly classified into two groups, which are EAL 1 to 4 for commercial use and EAL 5 to 7 for military and governmental secret agencies. Note that the EALs do not express the security strength of the product but indicate that the implementation of the security functions was properly conducted based on the specified ST. The security evaluation described in ISO/IEC 15408 mainly deals with logical functions, but physical security functions or hardware issues are not sufficiently mentioned. Under certain conditions, hardware security may be considered properly managed. However, this premise is not true when the attacker possesses the cryptographic hardware module such as a smart card. To address this issue, the JIL (Joint Interpretation Library) Hardware Attacks Subgroup (JHAS), mainly consisting of European IC vendors, users, evaluation laboratories, and certification authorities, published a supporting document[11] that defines smart card physical security. Although the JIL has also accumulated the knowledge and technology about practical attacks and countermeasures on smart cards, it will not publish them.

ISO/IEC 19790, a modification of the U.S. Federal standard FIPS (Federal Information Processing Standard) 140-2[12], addresses security requirements for cryptographic modules comprising software, firmware or hardware in ten areas of different design and implementation aspects. The standardization of the testing items for the security requirements, based on the FIPS 140-2 DTR (Derived Test Requirements)[13], resulted in a separate document known as ISO/IEC 24579[14]. Cryptographic module testing under ISO/IEC 24579 judges the target module with the security levels specified in ISO/IEC 19790 ranging from 1 to 4 for each of the ten areas and eventually with the overall level indicating the minimum level across all the areas. Unlike ISO/IEC 15408, the level represents a security strength.

In Japan, Information-Technology Promotion Agency (IPA®) operates the following programs: JISEC (Japan Information Security Evaluation and Certification Scheme)[15] is based on ISO/IEC 15408. JCMVP® (Japan Cryptographic Module Validation Program)[16] is based on JIS X 19790 Security Requirements for Cryptographic Modules, which is equivalent to ISO/IEC 19790.

Since FIPS 140-2 was signed-off, more than eight years has passed, and side-channel attacks, which examine the internal activities of a cryptographic module to extract its secret key with various physical measures, have become a more and more serious threat. To reflect the changing cryptographic situation, in 2005, NIST began the process of transitioning from FIPS 140-2 to FIPS 140-3 and published the first public draft of FIPS 140-3[17] in July 2007. The revising process for ISO/IEC 19790 will proceed accordingly. In Japan, the Cryptographic Implementation Committee formed by the National Institute of Information and Communications Technology (NICT) and IPA, and the Side-channel Security Working Group under the committee are discussing security evaluation guidelines for implementations within CRYPTREC.

Side-channel attacks have drawn significant attention not only for standardization activities but also in academia, in which the international conferences on information security, hardware, or the like have held more and more sessions relevant to the attacks. In fact, technical papers on side-channel attacks account for a remarkable portion of the accepted papers in the Cryptographic Hardware and Embedded Systems (CHES)[18] workshop, which has a particularly high profile among such workshops.

3 Unification of hardware experimental environments and standardization of evaluation method

3.1 Research position

We are studying cryptographic hardware as one of the fundamental technologies that support the advancement of information network society. Our efforts include research on countermeasures and security evaluation methods against physical attacks, side-channel attacks in particular, as well as development of compact, high-speed and power-saving implementation technology in preparation for further expansion of the use of cryptographic hardware.

CRYPTREC is working for the revision of the E-Government Recommended Ciphers List scheduled for 2013. Involved with this, we are supporting CRYPTREC in their work on performance evaluation of hardware implementations of cryptographic algorithms and tamper resistance evaluation against side-channel attacks. In the development scheme for the current Recommended Ciphers List, security evaluations of theoretical aspects and performance evaluations of software implementations were performed for the proposed algorithms. While the software performance evaluations were carried out on the real processor platform specified by CRYPTREC, the hardware performance was not sufficiently evaluated and hardware implementations mainly provided by the proposers were merely presented as reference information. At that time, side-channel attacks had just emerged and were thus excluded from the evaluation elements. Thereafter, various attacking and protection schemes have been proposed and real platform evaluations with hardware have also been conducted. However, these changes have posed a problem such that third parties can hardly verify such evaluation results since each evaluator uses different experimental environments. In this regard, it may be possible to make a market-available cryptographic hardware product a common experimental platform for evaluators. However, evaluation results that may contain information about a serious vulnerability of such products should not be disclosed by third-party evaluators.

To address the construction of a common experimental environment for security evaluations for cryptographic hardware, we developed the Side-channel Attack Standard Evaluation Board (SASEBO)[19] in collaboration with Tohoku University within a project commissioned by the Ministry of Economy, Trade and Industry, and have promoted its utilization for domestic and foreign research bodies. We have also conducted various experiments ourselves with the SASEBO platform and actively published the information on newly developed countermeasures and evaluation techniques on it. The SASEBO has become available on the market through domestic circuit board vendors, intended for users such as universities and companies who plan to engage in cryptographic hardware implementation or side-channel attack research. It is expected that this activity would further speed the promotion of side-channel attack research. At the same time, such an activity might be suspected of being an antisocial behavior encouraging malicious hackers. Comparing this situation with the case of security evaluation for cryptographic algorithms will lead to the answer to this question. The development of security evaluation schemes corresponds to that of attack schemes by a researcher of goodwill. The previous chapter demonstrated that making cryptographic algorithms open to the public for experts' third-party evaluations, rather than hiding them, will turn out to be an advantage. The same can be said for the security evaluations of cryptographic hardware implementations. In other words, through the evaluations done on the common experimental platform by many researchers, the evaluation framework efficiently determines the effective countermeasures and the effective evaluation (or attacking) techniques from various proposals, accumulating and utilizing the know-how of implementations and measurements. On that basis, we conduct the research activities with the goal of improving the security of information security products as well as contributing to constructing a dependable information network infrastructure, taking advantage of this knowledge.

3.2 Formulation of international standard specification and expansion toward security evaluation business

Toward the above-mentioned goals, as a public research institution, AIST addresses not only technological development but also various tasks as shown in Fig. 1 in cooperation with companies and related organizations domestic and overseas.

Firstly, AIST has sent a researcher to NIST to pursue collaboration works for contributions to international standardization of security evaluation schemes for side-channel attacks. While there is no question that the standardization activity by public research institutions of the U.S. and Japan is important for each of them individually, it was also important for AIST to demonstrate to NIST the advantages of working together. Therefore, we promoted our in-depth academic knowledge and advanced technology by showing a demonstration of an evaluation system prototype using the SASEBO as well as introducing AIST's activities in major related academic societies. In consequence, we took charge of the input for the description in the Physical Security – Non-Invasive Attacks section of the FIPS 140-3 second draft[20] published in December 2009. In addition, we have taken the lead in developing the evaluation testing technology for side-channel attacks.

Meanwhile, in Japan, to take advantage of the opportunity provided by the revisions of FIPS 140-3 and ISO/IEC 19790, CRYPTREC is advancing the discussion of the security evaluation guidelines for side-channel attacks. In the endeavor, AIST plays a central role and provides domestic companies and universities with a variety of technologies such as the SASEBO. Through information sharing in the CRYTPREC activity, AIST promotes not only gathering of domestic knowledge and the technological advancement but also improvement of the testing environment for a new evaluation system for cryptographic modules.

The aforementioned JHAS, in their ISO/IEC 15408 activity, is exchanging information on a variety of physical analysis methods including side-channel attacks targeting smart cards. However, they will not disclose details of such information because it contains proprietary information on their individual products. This may be considered as a way of assuring the security by hiding. However, remember that in our research activities for standardization of FIPS 140-3 or ISO/IEC 19790, disclosing the analysis results of individual products or implementation know-how is not our primary goal either. Our primary goal is to demonstrate the effectiveness and versatility of the attack methods and countermeasures through experiments on the common evaluation platform SASEBO and to formulate a security evaluation standard. In fact, even a JHAS member is not allowed to analyze a smart card of another member's without proper consent. In this respect, they are demanding a cryptographic LSI or an evaluation platform on which unrestricted analysis experiments for technology accumulation are allowed. Thus, we plan to be providing JHAS with the SASEBO technology through IPA, which is the contact point of JHAS in Japan.

Although ISO/IEC 19790 and ISO/IEC 15408 have different standardization directions, our analysis technology is applicable to the evaluation work under either one. It is difficult for cryptographic product vendors to disclose their know-how related to such analysis technology. At the same time, from the viewpoint of fairness, it is objectionable that the vendors whose products are evaluated lead the standardization of evaluation. Hence, it is significant in the standardization movements that AIST pursue the research

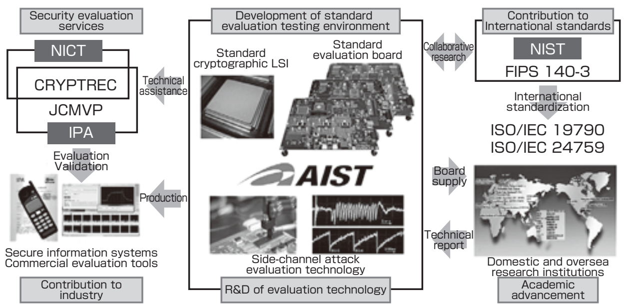

Fig. 1 Research activities for cryptographic module evaluation at AIST.

on security evaluation technology, cooperating with other organizations including NIST and CRYPTREC in its neutral position, listening to industry's voice.

In operation of an evaluation system, every participating testing laboratory is required to produce the same evaluation results if they use the same target cryptographic module. In order to ensure uniform evaluation environments and analysis skills, we plan to conduct a skill test for the testing laboratories with the SASEBO implementing a cryptographic circuit. We are also developing an analysis tool for the testing laboratories, who would then demand a training program using the board or the tool. To develop and operate such a training program will require much money and human resources, but it is difficult to keep acquiring public funds for it. Note not only that the entire society obviously benefits from the improvement of the cryptographic products security, but also that cryptographic product vendors and the testing laboratories running a security evaluation business benefit from this security evaluation movement. Therefore, we should take advantage of the vitality of corporations for the realization of higher security and the advancement of the evaluation systems. To realize this, we have brought the SASEBO to market through a few Japanese circuit board vendors toward popularization of the evaluation and countermeasure technologies. We are also planning to expand the distribution channel overseas. There are two companies in Europe and one in the U.S. which run smart card evaluation tool businesses. The negotiations we had with each of the three companies resulted in having all their tool products support the SASEBO. In addition, discussions are in progress to offer their evaluation tools and training programs to the testing laboratories with the analysis scheme AIST is developing. As a public research institution, AIST will control the fundamental subjects such as the standardization of evaluation method and the development of analysis technology with other organizations including CRYPTREC and NIST and pursue further cooperation with domestic and overseas companies toward more efficient operation of the system.

4 Practical side-channel attacks

4.1 Various physical analysis attacks against cryptographic modules

Physical analysis attack methods against cryptographic modules are classified roughly into *invasive attacks* and *non-invasive attacks* as shown in Fig. 2. Invasive attacks require expensive equipment and sophisticated technical skills to depackage the LSI, which is the core part of a cryptographic module, and to analyze its insides directly. In contrast, side-channel attacks[21][22], proposed by Kocher *et al.*, are non-invasive attacks, which do not make modifications to the modules. They exploit the internal activity information leaked through side-channels in the form of power consumption waveforms, electromagnetic waves, or timing of the operating LSI that are different from the normal I/O channels. Side-channel attacks only require relatively cheap equipment such as an oscilloscope and a personal computer to acquire and analyze the information, but they are a remarkably strong attack method. While side-channel attacks, which observe the operating states of the LSI from outside, are classified as a passive attack method, fault-injection attacks, which inject noise into the power line or clock signal to induce false operations on the LSI and analyze its response, are classified as a more sophisticated attack. It is necessary to carry out the standardization of security evaluation schemes for fault-injection attacks, following that of side-channel attacks.

4.2 Side-channel attack standard evaluation board (SASEBO)

To construct a security evaluation standard platform, we have developed the SASEBO boards and the cryptographic LSIs shown in Fig. 3 and Fig. 4, respectively. The SASEBO-G and SASEBO-B employ Xilinx® and Altera® FPGAs (Field Programmable Gate Arrays), respectively, which offer users reconfigurability of circuit functions for cryptographic algorithm implementation on different device architectures. To enable various side-channel attack experiments on these boards, we have designed the circuits of all the ISO/IEC 18033-3 standard block ciphers and the RSA scheme, the public-key cipher standard, and published the source codes of those on our partner's web site[23]. These boards offer not only hardware experiments, but also cryptographic software evaluation experiments with the Xilinx® FPGA's embedded processor or a processor macro. The cryptographic LSIs shown in Fig. 4 were fabricated in a 90-nm and a 130-nm CMOS standard cell process and have the published cryptographic circuits. These LSIs are designed to be mounted on the SASEBO-R. The SASEBO-GII, the latest SASEBO board, is equipped with a Xilinx® FPGA, and has a four to seven times larger logic capacity than SASEBO-G, while achieving a significant reduction of the board area to one third the size with a much higher density. It also features the cutting-edge partial-reconfigurability for uses other than side-channel attack experiments so that research on even higher level hardware security systems is possible.

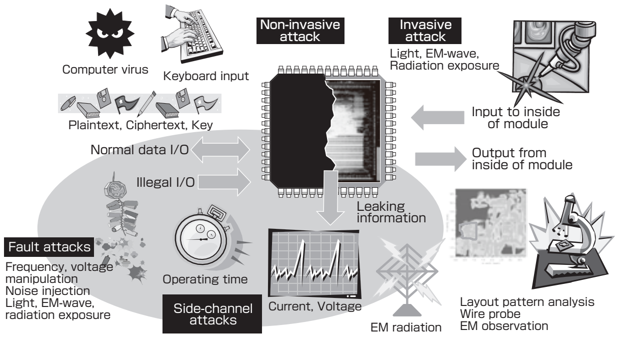

Fig. 2 Various physical attacks against cryptographic modules.

Meanwhile, the initial version of SASEBO board obtained the first JCMVP® certification[24] for a hardware module. As a secure implementation example, all of its design information and source codes are available to the public on the SASEBO web site. By the same token, we will attempt to obtain a JCMVP® certification for the SASEBO-GII.

4.3 Simple power analysis on an RSA cipher circuit

This section presents a practical side-channel attack example with the RSA scheme implemented on the SASEBO's FPGA and LSI and the experimental results from Simple Power Analysis (SPA), which extracts the cryptographic key directly from the power traces (namely, the waveform of power consumption).

The modular exponentiation operations expressed in Eq. (1) and Eq. (2) define the RSA scheme encryption and its inversion as the decryption, respectively. The plaintext x, the data before encryption in Eq. (1), will be encrypted with e and n, both of which form the public key, into the ciphertext y, while in Eq. (2) the ciphertext y will be decrypted with the secret key (a.k.a. private key) d into the plaintext x. In these computations, 1,024-bit or longer precision integers are typically used for every variable except e so that it can be computationally difficult to obtain the secret key from the public key, while still theoretically possible.

$$\text{Encryption} : y = x^e \bmod n \qquad (1)$$

$$\text{Decryption} : x = y^d \bmod n \qquad (2)$$

The modular exponentiation operation in the RSA scheme is realized by iterating modular multiplication and modular squaring operations, reflecting the bit pattern of the exponent e or d. SPA attempts to acquire the secret key d by examining the computation times of each operation[21] or the differences in the power traces of each operation. Figure 5 represents an example of the left binary method, which begins the bit-wise test for the exponent d=25=$11001_{(2)}$ from the left end. As the result of each test, a bit '0' involves a modular squaring operation, whereas a bit '1' invokes both modular squaring and multiplication ($\times x$) operations. If one can distinguish between the power traces of every squaring (S) and multiplication (M), the result represents the secret key directly.

However, the difference between squaring and multiplication is not necessarily observable for the intermediate value derived from the input data differing every time. In this regard, some attack methods that enhance the difference of the operations on the power trace by manipulating input data have been studied. Figure 6 depicts parts of the power traces measured for the running RSA circuits on the 130-nm cryptographic LSI (represented as ASIC in the figure) and on the FPGA mounted on the SASEBO-R and SASEBO-G, respectively. It is difficult to distinguish between the power traces of multiplication and squaring on either circuit for random input data. However, by providing the input with the particular value x=2^{-1024} that is effective for the attack against the 1,024-bit Montgomery multiplication algorithm adopted in the circuits, the results show the clear distinction between multiplication (M) and squaring (S).

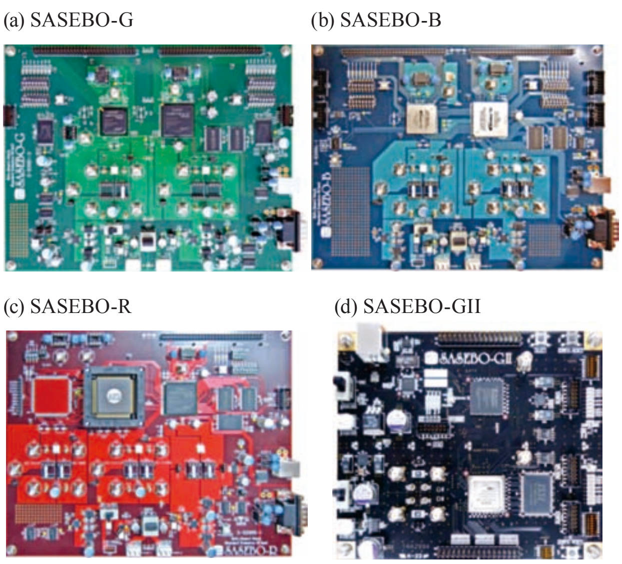

Fig. 3 SASEBO Board.

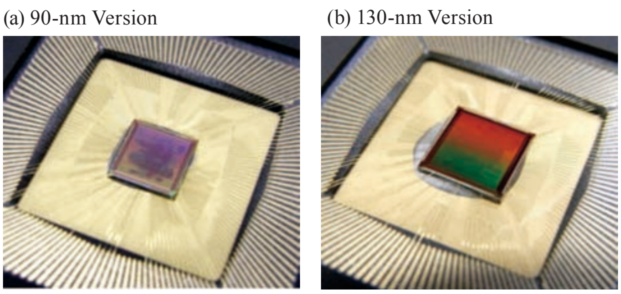

Fig. 4 Cryptographic LSI.

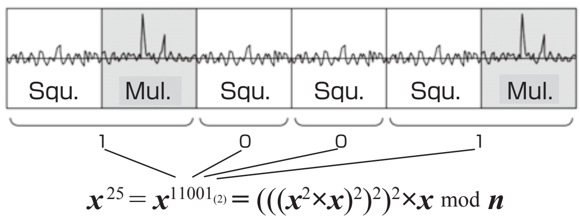

Fig. 5 SPA against RSA implemented with the left binary method.

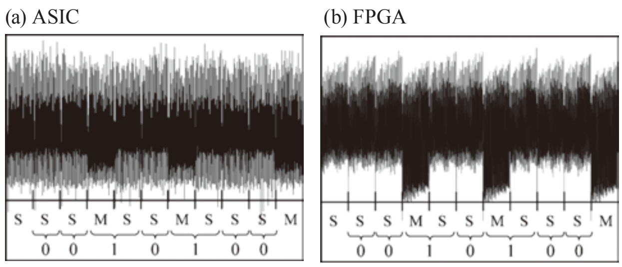

Fig. 6 SPA against RSA implemented on SASEBO-R and SASEBO-G (x=2^{-1024}).

The simplest and most basic SPA countermeasure for the RSA scheme is to insert a dummy multiplication operation after the squaring operation of every ‘0’ appearing in the secret-key bit pattern. However, some other attack methods with input-data manipulation techniques, which can determine such a dummy multiplication, have been proposed. We are exploring the effectiveness of various attack methods and countermeasures through experiments with the SASEBO, and also attempting to find and develop new attack methods and countermeasures.

4.4 Differential power analysis on an AES cipher circuit

This section explains the AES algorithm, which is the standard symmetric-key cipher that is most widely used today, and demonstrates the Differential Power Analysis (DPA)[22] attack, which processes a multitude of power traces.

AES encrypts a 128-bit data block with a 128-, 192- or 256-bit key. Figure 7 illustrates the encryption algorithm with a 128-bit key. The 128-bit data is arranged into a 4 × 4 array of bytes to be processed in 10 rounds, each of which forms a round function and consists of four transforms: SubBytes, ShiftRows, MixColumns, and AddRoundKey, except for the last round excluding MixCoulumns. The 128-bit secret key will be transformed iteratively by a simple key scheduler into the 10 × 128 bits round keys to be provided to each round. Each of the round keys is used for the exclusive logical OR (XOR) with the corresponding data block in the AddRoundKey function. SubBytes is a collection of 16 S-boxes where the byte-wise non-linear transform for each byte of the 4 × 4 array is performed individually. In ShiftRows, the cyclic shift for each row of the 4 × 4 array is performed individually. MixColumns consists of 4 of the 4-byte linear transforms for each column.

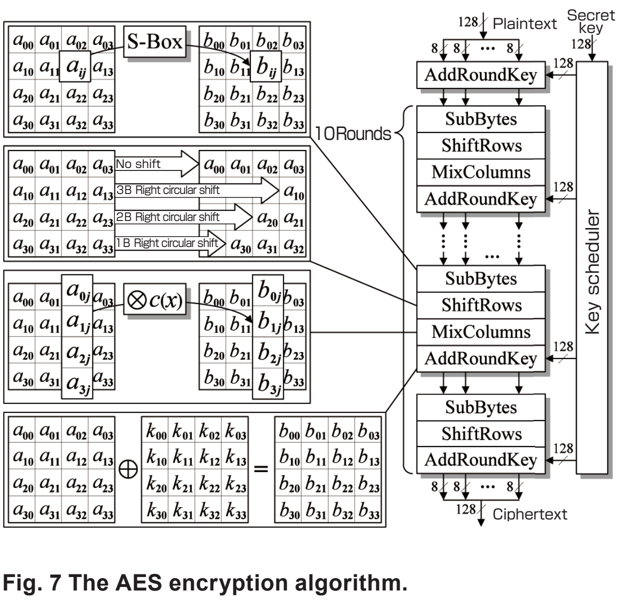

Fig. 7 The AES encryption algorithm.

A typical circuit implementation of AES employs a loop architecture that iteratively uses one round function for 10 times. Figure 8 shows the power traces measured for the AES circuits implemented on the cryptographic LSI and FPGA mounted on the SASEBO-R and SASEBO-G, respectively, indicating the saw-teeth shaped peeks corresponding to each round. Unlike an SPA case on the RSA scheme where the secret-key bit sequence reads on the power trace as a form of geometric pattern, the key cannot be extracted in that way for AES because all the 128 key bits are XORed in a moment and the difference contributed by each bit on the power trace is too small to read. By contrast, DPA is the key extraction scheme that applies a statistical technique to thousands of or tens of thousands of power traces. It builds a set of power models each based on a different partial key estimation, examines the correlation between each model and the power traces acquired for different input data, and determines the most probable partial key corresponding to the power model that indicates the highest correlation with the measured data. Since SubBytes is a byte-oriented transform, ShiftRows has shift operations along with the byte boundaries, and AddRoundKey is a bit-wise XOR, an individual operation at every byte will be performed at the last round, which skips MixColumns. Therefore, the 128-bit key can be analyzed at every byte. Because an eight-bit value has possible 256 combinations from 0 to 255, the estimation for an eight-bit partial key requires one to build and to examine as few as 256 power models. Accordingly, for the whole 128-bit key, only 16 individual analyses have to be done. During the analysis for an 8-bit part of the key, the power consumption component based on the operations for the other 120 bits behaves as noise. Note that, however, since a cryptographic circuit is considered to be a sort of random number generator, the power consumption of the unrelated part will be uncorrelated with the part being analyzed. That is, the influence of random noise components can be reduced by a statistical process on a number of power traces.

Figure 9 is a screen shot of the power analysis attack evaluation tool for AES circuits we developed. This instance is performing the CPA (Correlation Power Analysis)[25], focusing on the intermediate value register, with the power model based on the hypothesis that the power consumption will be proportional to the number of transitioning bits (Hamming distance) at the last round. The lower half of the

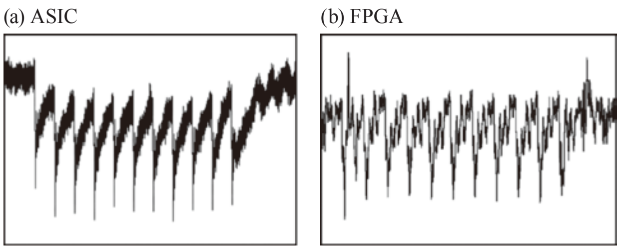

Fig. 8 Power traces for AES circuit.

figure shows the 16 partial key bytes represented as 16 boxes each with 256 vertical lines displayed in the box. The height of each line indicates the strength of the correlation between each model based on the partial key hypothesis ranging from 0 to 255 and the actual power consumption of the AES circuit. The tool determines the partial key hypothesis that indicates the highest correlation among the 256 candidates as the right partial key in each box. For a circuit without a countermeasure, it can extract the entire correct key in only a few minutes even with a cheap oscilloscope of around 200,000 yen to capture up to several thousands of power traces and with a low-end personal computer of as cheap as a few tens of thousands of yen.

As well as CPA, many other attack methods against AES have been emerging. In addition, more and more countermeasures have been proposed, too. We are pursuing verification of the effectiveness of those and have begun implementing them on our evaluation tool.

4.5 Development of more sophisticated attack methods and formulation of new evaluation guidelines

Along with the advancement of LSI analysis technology, research on security evaluation schemes for active attacks such as fault-injection attacks and invasive attacks is becoming more and more important. Examples of fault-injection attacks include, for an AES circuit with the loop architecture, the technique that induces a false operation in the circuit to pull out an intermediate value processed before the last round, and the technique that investigates how the error caused at a specified round propagates to the output. However, there is no guarantee of successful fault injection convenient for analysis. Even with a high success rate of triggering, the types of errors to be induced greatly depend on the circuit implementation. Furthermore, to publish experimental results, it is important that the cryptographic module can be attacked freely. Consequently, to conduct research on fault-injection attacks, use of a common experimental platform with a real cryptographic hardware module such as the SASEBO is necessary.

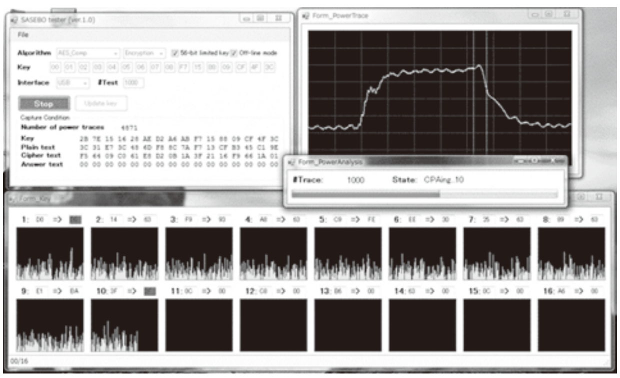

Fig. 9 AES circuit evaluation tool.

Invasive attacks are capable of observing not only the information buried in the total power consumption of an LSI, but also a local signal in the cryptographic circuit with such an LSI measuring system as shown in Fig. 10. However, such an existing system is not designed for an attacking purpose. Therefore, it is necessary to develop a system suitable to observe leaking information and sophisticated measurement technologies. We have seen that the quality of power traces and electromagnetic waveforms significantly influences the analysis results also in side-channel attack cases. Thus, we are also working on the development of new measurement technologies and the standardization of measurement environment.

Further, it is important not only to publish experimental results of successes or failures for each attack, but also to provide such security guidelines as criteria for designing tamper-resistant cryptographic modules against side-channel attacks through such experiments. This will require analysis of the mechanism of information leakage and in turn construct models that explain it qualitatively and quantitatively.

In developing cryptographic modules, perfect security is not necessarily required; rather, the implementer must consider the balance between the cost to implement countermeasures and the value of the protection. Conversely, from the attackers' point of view, the attacking costs should be worth the benefits. Even for standard cryptographic algorithms such as AES and RSA, brute force attacks would compromise them. Practical limitations of time and cost, however, do not allow successful searching in the entire key space. Thus, we will also be considering how to perform the security evaluation for cryptographic module implementations in the attacking cost aspect.

5 Conclusion

In this paper, we have discussed security evaluation for cryptographic module implementations, focusing on the side-channel attacks, and AIST's efforts toward the formulation of international standards and their significance. With the

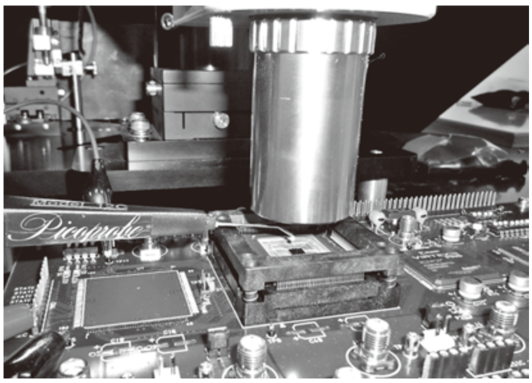

Fig. 10 Invasive attack on the cryptographic LSI on SASEBO-R.

cryptographic circuits implemented on the SASEBO boards developed as part of constructing a standard experimental platform, we showed that power analysis attacks successfully compromise such implementations, if they lack proper countermeasures, even with inexpensive measurement instruments, suggesting that urgent action is required. We also pointed out that it is necessary to immediately begin developing proper countermeasures and evaluation methods even for attacks requiring higher skills such as fault-injection attacks and invasive attacks.

Research on information security subjects including cryptography aim to construct protection measures against attackers with malicious intent. At the same time, as information systems are becoming more and more complex, the development of technology that prevents damage from incidental errors or faults is also in great demand. For example, although software bugs can be fixed on the running system even over the network, hardware bugs or faults not only require the system to halt, but also may take much time, in the case of a remote site, to be treated. To address this problem, the dynamic partial reconfiguration technology of FPGA, which enables altering a part of the logic circuit with the system operating, is offering a promising solution. The SASEBO-GII, the latest in the series, is equipped with functions that make possible research and development of dynamic partial reconfiguration, and has already begun driving research on applications of online circuit reconfiguration. Once it becomes possible to exchange hardware configuration information through the network, new threats including potential theft and falsification of such information, and hardware viruses involving a system failure may emerge. Therefore, these future pressing issues will also need to be addressed.

Our ultimate goal is to construct a *dependable information system* where highly-improved security and reliability of the entire hardware system are achieved following the fulfillment of the research on cryptographic hardware security. Toward this goal, we will pursue the research and development of the new hardware technology that will be in demand in the future.

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Discussions with Reviewers

1 Synthesiological descrption

Comment (Hideyuki Nakashima, Future University Hakodate)

Although the description of the synthesiological aspect of this research is rather weak, the paper is well written as a tutorial of the side-channel attack in cryptography, which is not necessarily widely perceived.

Comment (Masaaki Mochimaru, Digital Human Research Center, AIST)

The article is clearly written for non-specialists. The ideas of encryption, security evaluation, side-channel attack, and historical background, which are necessary items to understand this article, are well written. Note that this journal is about "synthesiology" as titled, intending to inform readers of synthesiological points of the authors' work. By following this concept more closely, and making such points clearer, the authors can make the article more informative of "the approaches and 'synthesiology' of the work" even to readers in different fields.

I think that how the AIST's action involved the stakeholders and synthesized them to achieve the goal would be central to "synthesiology". The authors might want to revise the article by elaborating how they changed the stakeholders and changed society to connect them to the goal.

Answer (Akashi Satoh)

We changed the last half of chapter 3 into "3.2 Formulation of international standard specification and expansion toward security evaluation business", wrote up a large part about AIST's activity in the section, and made the collaborations shown in Fig. 1 more obvious. The description of "Side-channel attack standard evaluation board (SASEBO)" was moved to section 4.2.

Synthesiology on the Second Anniversary

[Translation from *Synthesiology*, Vol.3, No.1, p.77-82 (2010)]

We have just completed the second year of *Synthesiology* which was launched in 2008. Four issues each of Volumes 1 and 2 were published during the two years, including 49 research papers and 14 articles and interviews. We received various responses from the readers through the questionnaires in each issue. The editors of the journal held a round-table talk on the second anniversary to reflect on the past two years and to project what lies ahead.

***Synthesiology* Editorial Board**

Participants of the round-table talk

Hiroyuki Yoshikawa	Grand Emeritus Advisor, AIST
Akira Ono	Editor in Chief, AIST
Naoto Kobayashi	Senior Executive Editor, Waseda University
Motoyuki Akamatsu	Executive Editor, AIST
Koh Naito	Executive Editor, AIST

The second anniversary of *Synthesiology*

(Ono)

We have just completed the second year of *Synthesiology* which was launched in January 2008. I would like to welcome today the round-table talk participants who were involved in starting the journal. Please give your comments on the second anniversary.

(Akamatsu)

I have gone through all of the published research papers, and I feel that more people are becoming conscious of what “synthesiology” is. Such papers are written differently from conventional papers, and often speak “passionately” about how the authors carry out their researches. On the other hand, there were some authors who had difficulties in switching over from conventional paper writing. I am not sure whether every researcher of AIST understands “synthesiology” clearly, but I think anyone will be able to understand how to write a *Synthesiology* paper after reading its papers and articles.

(Kobayashi)

I sent two copies of *Synthesiology* last year to the President of Technology Management Council, IEEE of the United States, and I received a very sincere response: “I was extremely impressed.” Also, we received a submission of paper from abroad, and I am glad to see that our effort of publishing the English version is slowly but steadily producing results. I hope we can further raise the awareness of the journal internationally.

I transferred to a university last spring. Since the university is organized according to specialties, it is quite difficult to conduct research across the disciplines. In my university we have been discussing how to establish interdisciplinary research projects since last April. “Creating research” is one aspect of synthesis, and I really feel it is necessary to nurture “synthesiology” as scholarly pursuits.

(Naito)

When I reread all the papers of the issue to write the “Letter from the Editor”, I found the authors write in manners unseen in conventional analytical research papers. They are gaining “insights” across the disciplines. I strongly feel that the style of writing and reading papers of synthetic approach is becoming established. This was unthinkable two years ago when *Synthesiology* was launched, or eight years ago when

Dr. Koh Naito

we started to discuss *Full Research*. I enjoy working as an editor as I see the style gradually become established.

(Ono)
I would like to share with you now two of my recent experiences. I gave a lecture "Synthesiological research and innovation" in Taipei, Taiwan last September. After that I dropped by at the Industrial Technology Research Institute (ITRI) in Hsinchu, and was asked on short notice to give a lecture under the same title to an audience of about 100 researchers including the director of ITRI. I talked about "*Full Research* and *Synthesiology* to express it". Interest was high and many questions were asked. To the question, "How is it in the United States?" I answered: "I think America is a country of pragmatism, and therefore something like *Full Research* is done in actuality. The mental barrier between academia and industry is low in the States, as seen from the fact that the university professors often set up venture businesses. Yet they do not consider the industry-academia collaborations or the venture activities as research itself. While research and business are conducted without border, those are distinctly research and business. The Americans do not publish a journal like *Synthesiology*, and do not think in terms of accumulating such knowledge. I may be going too far, but I don't think the Americans see the necessity of thinking how business is related to research, as long as the business is successful." Another question asked was, "What was your motivation for starting *Synthesiology*?" I answered: "I think I have virtually practiced the equivalence to *Full Research* and *Type 2 Basic Research* ever since I started working at the Agency of Industrial Science and Technology so long ago. I started the journal to redefine these researches, to appropriately respect the activities of the *Type 2 Basic Research* and *Product Realization Research*, and to put the people who engage in these researches into the spotlight." I think those are my sincere feelings. Since the people of ITRI have the same objectives as AIST, they seemed to share my feelings and therefore, to thoroughly sympathize with my lecture.

The second story I'd like to share is that I had an opportunity to speak with the chief editor of a famous academic journal of the American Chemical Society, when he was visiting Japan. I brought up *Synthesiology* and said, "I'm working on this journal." He was astonished by the disclosure of the reviewers' names. In fact, before I brought up *Synthesiology*, I asked, "Where do you put in the most effort to make a good journal?" The editor answered: "I take extreme care on reviewing. The reviewers are anonymous, and I try to make the authors anonymous to the reviewers, too. Also, I am trying to refine the review system by allowing the authors to appoint or reject the reviewers in an appropriate manner." When I said, "In *Synthesiology* the reviewers are revealed and the discussions are disclosed", he was so surprised he fell silent for a moment and then said, "That's really impressive."

Language in which science and society speak with each other

(Yoshikawa)
I'd been thinking ever since I was young how "synthesis" could become a discipline, and I feel that my grand dream has been realized here. There is the background where *Full Research* is practiced thoroughly at AIST, and certainly, *Synthesiology* is the crystallization of the efforts of many AIST researchers who work to make "synthesis" into a systematic discipline. I am hopeful for the future. Moreover, the editors and reviewers are extremely passionate, and there's a feeling that AIST is really a great place to be. That's my first impression.

More specifically, there is a development of a language with which the researchers can speak to people who are not specialists of the same discipline. The Science and Technology in Society (STS) Forum is a gathering of scientists, politicians, and businessmen, but its greatest difficulty is the lack of a common language. When a specialist talks about some specialized subject, the politician gets angry saying, "I don't understand a thing." What I claimed was: "The specialists speak in a language necessary for their research, which is jargon. When speaking to people outside their own disciplines, the researchers can explain what they are doing only in terms of what benefit will be brought by the results of their research. That is extremely difficult, because at times it will be a projection, and at times it may be vague. However, the researchers must spend effort to reduce the vagueness and raise the accuracy of the projection." The fact that a reader can read *Synthesiology* papers and understand other fields is a proof that a very valuable methodology in terms of "verbal communication" is developing. That means a language of communication between science and society is being created. To this I shall give full marks.

Next, I won't say there is something that only gets a zero mark, but I shall point something out. The papers are all fun and I feel the "passion". The verbal quality is communicated through the passion, so I understand what the authors wish to accomplish. While "passion" is necessary, the

Dr. Hiroyuki Yoshikawa

explainable structure in the form of “synthesiology” is not yet established. I can see it by reading each paper, but I’m not sure whether the common structure is apparent to a third party who reads the paper. As I wrote in the “Introduction to service engineering” in Volume 1 No. 2, I think there is a temporary area of discipline. This temporary discipline is like a logical system that the researchers set up to solve a certain problem. Say there is an interesting device and the researcher must figure out how to create a concrete device from some abstract basic principle, and how to discuss it with the manufacturer, and in doing so the verbal quality must be raised to a logical level. I, however, can’t see that level being achieved in the papers even if I read between the lines or even through the lines. I think it will be better if the authors can present some logical quality.

Deepening “synthesiology”

(Ono)

We are working on “synthesiology” that seeks logical and common principles by accumulating the results of synthetic and integrating research activities, and it is necessary to deepen this practice. Dr. Akamatsu, you gave a lecture called “Expectation for ergonomics as ‘synthesiology’” at the annual conference of Japan Ergonomics Society.

(Akamatsu)

I compared the developments of the endoscope and the x-ray in the lecture. It took 100 years for the realization of the endoscope, while the x-ray was employed in medicine in less than a year. The negative aspects of the x-ray were unknown when it was employed, and lots of harm was done. I suggested that perhaps some period of “valley of death” is necessary. After that, I talked about “discipline”, “relationship between social expectations and academics”, “why ‘synthesiology’ is difficult”, “‘synthesiology’ and engineering”, and “ergonomics as ‘synthesiology’”.

Concerning “discipline”, Dr. Yoshikawa suggested that in contrast to the “scientific discipline” of the natural sciences, we create a “temporary discipline” by focusing the target of the issue to be solved, and this will grow into a “mature discipline”, which shall be called “engineering”. While the “temporary discipline” attempts to solve the actual problem for some specific artifact, it becomes more abstract as the discipline advances, and when the temporary discipline becomes a mature discipline, and then becomes a scientific discipline, it tends to fall back to the analytical method. How one can stay adequately in the temporary discipline is necessary in synthesis. This is because when the researchers create a language for a discipline and seek law and principle, they start working to elaborate the law. Naturally, they delve into analysis to pursue consistency in the discipline and try to create a beautiful system, and this poses the danger of weakening the dynamics to face society. This is related to “Why is “synthesiology” difficult?” When we cannot communicate with people in other disciplines, it is difficult to integrate and instead we turn to analysis.

In “‘synthesiology’ and engineering”, what we call *kogaku* is a Japanese translation of the English “engineering”, but the word origin of engineer is “wise and skillful people making things”. Originally there was no meaning of discipline in “engineering” but “synthesiology” is trying to make it into a discipline. *Engineering*, a temporary discipline, is created from the works of the people who are capable of creating complex artifacts. That is exactly the objective of “synthesiology”.

For “ergonomics as ‘synthesiology’”, when we define innovation as the introduction of scientific knowledge into society, “ergonomics is the study of creating an artifact that can adapt to human beings”, and it may play an important role in “synthesiology”. It may seem that something that is suitable for humankind can be made using knowledge of human beings, but things are not that simple. If the human characteristics can be known, we should be able to evaluate a product based on that. But unfortunately, current ergonomics cannot make something creatively. What is lacking? For example, “noisy” is a physical property of sound pressure, but the common issue today is that the noise from the floor above becomes bothersome in a quieter environment. When living conditions were poor, this issue could be explained by physics or the language of natural science, but when the poor living conditions improved, it became something that could not be discussed by the language of natural science. Here, the researchers realize for the first time that they cannot make something that is truly useful to human beings unless we study humankind thoroughly. Rather than creating a scientific discipline that studies a natural subject, we must practice “synthesiology” for making things that “will be used” in science of “society” that is created by human activities. This is the “social” science as proposed by Dr. Yoshikawa.

(Kobayashi)

In a recent experience, I helped an energy project at my university. The project never took off, but I had conversations

Dr. Motoyuki Akamatsu

with people of an automobile manufacturer, a battery manufacturer, a power network, and others. We set up a system starting from elemental technology, and were able to draw the image of the project in its entirety. I don't know whether this was because I was trained in synthesiology or whether because I worked at AIST, but I really felt that any research project or program must be set up with a synthetic approach.

Quoting the methodology of synthetic research

(Ono)
Dr. Naito, you also think that "research of synthesiology" is important, don't you?

(Naito)
Right now, I think it is seen merely as an extension of case study research. In the future, I think the true theory will be created when *Synthesiology* itself will become the subject of research, a model proposed by Dr. Kobayashi is applied, it is further developed for education and design, and we get an output in the form of some kind of design manual. I think personally this is the period where more case studies are collected, and after some accumulation, the researchers who wish to study this subject will be attracted, and the discipline as well as the education and design as its application will be ultimately formed.

(Akamatsu)
I want the authors to state, "the *Synthesiology* paper that I wrote has the same approach to some papers published before in this journal". Dr. Naito mentioned that a third party could use these papers as subjects of research. As a research discipline, when a researcher quotes his/her own paper, he/she must take a stand such as, "My method is similar to this-and-that research approach, but is different here and there". I feel that part is still lacking while the authors can talk passionately.

(Ono)
I feel the same way. I don't know whether the researchers cannot do so because they didn't think synthesiologically in setting the scenario or because they are unable to re-organize the actions they took as a process of synthesis.

Bronze and iron experiment methodology and methodology of synthetic approach

(Yoshikawa)
I think it is the latter. Although I may be thinking in my favor, I believe that people who conducted and created good synthesis were thinking synthesiologically.

Suppose that, in engineering, an experiment was done with some material, or in mechanical engineering, a detailed change in shape was observed with high speed, and then a theory was made. Suppose also that one researcher did it with copper, and another did it with iron. The latter can write a paper with iron in the same manner, but that would be copying the former following a superficial process. Yet, the former who did it for the first time was not superficial, but engaged in an analytical research by setting up a program of how to investigate the essence of a material. There is bound to be some synthesiological element like this in true research.

(Kobayashi)
When I reviewed a paper, although the author was not conscious that a synthesiological way of thinking was employed, I mentioned, "Didn't you get to this because you made your strategy step by step in the process of strategic selection?" The author realized, "Oh, so this is what it's all about." That was a case of discovery through the discussion between the author and the reviewer.

(Ono)
Taking a deeper look, it can be said the author himself already engaged in synthesiological thinking, and that it manifested itself when he was given a chance to write this type of paper.

(Kobayashi)
The paper of "Study on the PAN carbon-fiber-innovation for modeling a successful R&D management" in Volume 2 No.2 was written by Osamu Nakamura and others when they saw that the polyacrylonytrile (PAN) carbon fiber, which was invented by Dr. Akio Shindo at the former Osaka National Research Institute of the Agency of Industrial Science and Technology in the 1960s, eventually developed into business. There are a few points to be raised here. It is true that the carbon fiber was originally an excellent material, but one day he was told by some American military personnel: "This has excellent mechanical strength. This can be useful." Then, "synthesis" started in an aspect totally different from the original scenario. I think the important point here is the "meeting with people," that the logic alone does not lead to success. It seems to finally become something through turning points including random chance.

Dr. Naoto Kobayashi

Synthesiology listens to social wishes

(Yoshikawa)
That story is really important. When the American military personnel said, “We need something strong”, he was expressing what I call the “social wish”. Such things exist outside research, and the researchers are often not aware of them. A social wish and scientific ability meet, and I call that “chance meeting”. How would they meet? In the 19th and the 20th century, “synthesiology” was suited in areas where new discovery produced new functions. Now, the social wish is greater, and there is a sense of risk that unless we invent such-and-such a thing the earth will be destroyed, or in other words, the expectations for some power that will enable overcoming the risks spur research.

(Akamatsu)
The people who were involved in the carbon fiber research were trying to look at the property of carbon fiber from various aspects, and recognized its potential when “strength” was mentioned. The reason of its success was the presence of a social wish. There are many elemental properties to be investigated. Therefore, when the researchers are left to decide for themselves which property of carbon fiber they should study deeply, they may jump right in, and they may end up nitpicking the corners.

(Yoshikawa)
When they start nitpicking, it means they do research that’s easy to write out as a paper. The motivation to do research is that the researchers must do something that has never been done before, and if they find a corner that has never been explored, they will dig deeper there. In contrast, it is not easy to write a *Synthesiology* paper, but they will move in that direction because there is a social wish.

Expansion of *Product Realization Research* in industry

(Ono)
There are many people who regard *Synthesiology* as the “study of synthesiology”, and we are getting submissions of such papers. People who are engaged in “research that stretch across various disciplines”, or those who are trying to do new research based on such results are becoming interested. In addition, I would like to see submissions from industry.

(Akamatsu)
I also want more submissions from industry, so I am considering the “*Product Realization Research* paper (tentative title)”. I am thinking about making a collection of case studies of product realizations by having industry submit papers of actual product realizations that are valuable for “synthesiology”.

(Yoshikawa)
When a company develops a product, aside from the actual product to be sold, they also produce an invisible product called the thinking methodology, but it is discarded. While it remain in the head of the researcher and may remain as skills and experiences, it cannot be seen by a third party.

(Ono)
That part vanishes into air, but I think that is the source of corporate power. The “Technical Reports” published by companies present some aspects, as they show which items were successful along with scientific backgrounds, but I wish they would write what lies underneath. I think sharing this knowledge in depth will further strengthen the Japanese companies.

Educational material at the Innovation School

(Ono)
We train young, post-doctorate researchers at the AIST Innovation School. The students were divided into groups of ten to take turns doing paper reports of *Synthesiology*. Some commented, “It captures the social trend and presents the total picture, and it helps me see where I stand.” Many post-docs felt fresh surprise, and it gave them quite an impact. Dr. Akamatsu was also a moderator of the School. What did you think?

(Akamatsu)
At the paper reports session, I provided supplemental explanations, and the post-docs were able to read from the perspective of “What is “synthesiology”?” There were six moderators, and one of them said, “The students really thought it through, and now I finally understood what *Synthesiology* is from their reports.” Some papers state, “It is important to occasionally return to *Type 1 Basic Research* when doing *Type 2 Basic Research*”, and the students were happy to see that perspective. When one is deeply involved in a topic, one may unconsciously create a sanctuary. It seems that the students learned the importance of looking at the big picture, drawing a scenario, and going forward without getting entangled in something immediately in front of their eyes.

Dr. Akira Ono

(Yoshikawa)
Those were the greatest objectives of the Innovation School: to actually create something by breaking the rock-hard specialism supremacy, and to have wide-ranging contact with society. It is good that they were able to learn that.

(Ono)
We send post-docs for a few months to companies, and have them experience corporate OJT. They become new channels for communication between AIST and the companies, and it is an important experience for us. The people of the companies that accepted the students evaluate the OJT and provide comments, and they are mostly very positive. Normally, the companies do not have the opportunity to work with young doctoral researchers, and they see it as a new opportunity and are surprised that we’ve got good researchers here.

(Yoshikawa)
It’s a learning experience for companies. That is good. The Innovation School is one model where one can learn while working. The students are learning that “it is not good to be fixed in a narrow field”, and also learn what synthesis is through *Synthesiology*. They understand that to engage in a new work is to “think”.

Future expectations and prospects

(Ono)
How about the future expectations and prospects for *Synthesiology*?

(Akamatsu)
One of the students of the Innovation School commented: “The papers are good because the quality of the reviewers are high. To continue being a good journal, you must nurture good reviewers that can review in terms of what is ‘synthesiology’”. I felt that was important. The reviewers function as a kind of connoisseur. The reviewers are trying to bring the “synthesis” out of the papers, and we would be in trouble when we step down for the next generation if they are unable to do the same. This is a future issue.

(Kobayashi)
I’ve been thinking about the exact same thing. We ourselves grew up in the past two years, but I feel we must increase the number of people who share “synthesiology” as a discipline. We must do more symposia and workshops and communicate the concept through word of mouth. We must also spend effort to increase the reviewers, particularly getting people outside AIST to participate, and to raise the awareness of *Synthesiology*.

(Naito)
It is really fun to discuss various points with the authors in the process of a review, and I think the quality of both the authors and the editors is raised through this dialog. Perhaps the number of submissions may increase if we create some mechanism where the author-editor dialog is enhanced further, and if we carry on such dialog with outside people. I think we will be able to learn many things from each other if we set up symposia, seminars, and lectures as part of this activity.

(Ono)
My comments are the same as everyone. By doing the review, the reviewers have fun making new discoveries and getting inspiration, and I myself am surprised at how much I can understand the values of other research fields.

(Yoshikawa)
Since Japan’s population is small, the ratio of GNP will decrease. It is now a 9 % nation, but in 2050, it will become a 3 % nation and its presence will decline. What we have to do to avoid this is to increase the number of researchers. If the number of researchers increases within the same population, the presence will increase at least in terms of science. I call this “policy to double the number of researchers”, but it won’t be good if we simply double the number of closed, sectionalized researchers. We want to have researchers who are all-inclusive including the developers that write papers in the Technical Reports. At the same time, we need a kind of a social passage where there is a professional continuity from secluded researchers to corporate developers, and people should be able to move freely. I think *Synthesiology* will be a powerful tool to accomplish this, and I think it can become a kind of social movement.

(Ono)
Thank you very much for discussing such a wide range of interesting topics today.

Editorial Policy

Synthesiology Editorial Board

Objective of the journal

The objective of *Synthesiology* is to publish papers that address the integration of scientific knowledge or how to combine individual elemental technologies and scientific findings to enable the utilization in society of research and development efforts. The authors of the papers are researchers and engineers, and the papers are documents that describe, using "scientific words", the process and the product of research which tries to introduce the results of research to society. In conventional academic journals, papers describe scientific findings and technological results as facts (i.e. factual knowledge), but in *Synthesiology*, papers are the description of "the knowledge of what ought to be done" to make use of the findings and results for society. Our aim is to establish methodology for utilizing scientific research result and to seek general principles for this activity by accumulating this knowledge in a journal form. Also, we hope that the readers of *Synthesiology* will obtain ways and directions to transfer their research results to society.

Content of paper

The content of the research paper should be the description of the result and the process of research and development aimed to be delivered to society. The paper should state the goal of research, and what values the goal will create for society (Items 1 and 2, described in the Table). Then, the process (the scenario) of how to select the elemental technologies, necessary to achieve the goal, how to integrate them, should be described. There should also be a description of what new elemental technologies are required to solve a certain social issue, and how these technologies are selected and integrated (Item 3). We expect that the contents will reveal specific knowledge only available to researchers actually involved in the research. That is, rather than describing the combination of elemental technologies as consequences, the description should include the reasons why the elemental technologies are selected, and the reasons why new methods are introduced (Item 4). For example, the reasons may be: because the manufacturing method in the laboratory was insufficient for industrial application; applicability was not broad enough to stimulate sufficient user demand rather than improved accuracy; or because there are limits due to current regulations. The academic details of the individual elemental technology should be provided by citing published papers, and only the important points can be described. There should be description of how these elemental technologies are related to each other, what are the problems that must be resolved in the integration process, and how they are solved (Item 5). Finally, there should be descriptions of how closely the goals are achieved by the products and the results obtained in research and development, and what subjects are left to be accomplished in the future (Item 6).

Subject of research and development

Since the journal aims to seek methodology for utilizing the products of research and development, there are no limitations on the field of research and development. Rather, the aim is to discover general principles regardless of field, by gathering papers on wide-ranging fields of science and technology. Therefore, it is necessary for authors to offer description that can be understood by researchers who are not specialists, but the content should be of sufficient quality that is acceptable to fellow researchers.

Research and development are not limited to those areas for which the products have already been introduced into society, but research and development conducted for the purpose of future delivery to society should also be included.

For innovations that have been introduced to society, commercial success is not a requirement. Notwithstanding there should be descriptions of the process of how the technologies are integrated taking into account the introduction to society, rather than describing merely the practical realization process.

Peer review

There shall be a peer review process for *Synthesiology*, as in other conventional academic journals. However, peer review process of *Synthesiology* is different from other journals. While conventional academic journals emphasize evidential matters such as correctness of proof or the reproducibility of results, this journal emphasizes the rationality of integration of elemental technologies, the clarity of criteria for selecting elemental technologies, and overall efficacy and adequacy (peer review criteria is described in the Table).

In general, the quality of papers published in academic journals is determined by a peer review process. The peer review of this journal evaluates whether the process and rationale necessary for introducing the product of research and development to society are described sufficiently well.

In other words, the role of the peer reviewers is to see whether the facts necessary to be known to understand the process of introducing the research finding to society are written out; peer reviewers will judge the adequacy of the description of what readers want to know as reader representatives.

In ordinary academic journals, peer reviewers are anonymous for reasons of fairness and the process is kept secret. That is because fairness is considered important in maintaining the quality in established academic journals that describe factual knowledge. On the other hand, the format, content, manner of text, and criteria have not been established for papers that describe the knowledge of "what ought to be done." Therefore, the peer review process for this journal will not be kept secret but will be open. Important discussions pertaining to the content of a paper, may arise in the process of exchanges with the peer reviewers and they will also be published. Moreover, the vision or desires of the author that cannot be included in the main text will be presented in the exchanges. The quality of the journal will be guaranteed by making the peer review process transparent and by disclosing the review process that leads to publication.

Disclosure of the peer review process is expected to indicate what points authors should focus upon when they contribute to this journal. The names of peer reviewers will be published since the papers are completed by the joint effort of the authors and reviewers in the establishment of the new paper format for *Synthesiology*.

References

As mentioned before, the description of individual elemental technology should be presented as citation of papers published in other academic journals. Also, for elemental technologies that are comprehensively combined, papers that describe advantages and disadvantages of each elemental technology can be used as references. After many papers are accumulated through this journal, authors are recommended to cite papers published in this journal that present similar procedure about the selection of elemental technologies and the introduction to society. This will contribute in establishing a general principle of methodology.

Types of articles published

Synthesiology should be composed of general overviews such as opening statements, research papers, and editorials. The Editorial Board, in principle, should commission overviews. Research papers are description of content and the process of research and development conducted by the researchers themselves, and will be published after the peer review process is complete. Editorials are expository articles for science and technology that aim to increase utilization by society, and can be any content that will be useful to readers of *Synthesiology*. Overviews and editorials will be examined by the Editorial Board as to whether their content is suitable for the journal. Entries of research papers and editorials are accepted from Japan and overseas. Manuscripts may be written in Japanese or English.

Required items and peer review criteria (January 2008)

	Item	Requirement	Peer Review Criteria
1	Research goal	Describe research goal ("product" or researcher's vision).	Research goal is described clearly.
2	Relationship of research goal and the society	Describe relationship of research goal and the society, or its value for the society.	Relationship of research goal and the society is rationally described.
3	Scenario	Describe the scenario or hypothesis to achieve research goal with "scientific words" .	Scenario or hypothesis is rationally described.
4	Selection of elemental technology(ies)	Describe the elemental technology(ies) selected to achieve the research goal. Also describe why the particular elemental technology(ies) was/were selected.	Elemental technology(ies) is/are clearly described. Reason for selecting the elemental technology(ies) is rationally described.
5	Relationship and integration of elemental technologies	Describe how the selected elemental technologies are related to each other, and how the research goal was achieved by composing and integrating the elements, with "scientific words" .	Mutual relationship and integration of elemental technologies are rationally described with "scientific words" .
6	Evaluation of result and future development	Provide self-evaluation on the degree of achievement of research goal. Indicate future research development based on the presented research.	Degree of achievement of research goal and future research direction are objectively and rationally described.
7	Originality	Do not describe the same content published previously in other research papers.	There is no description of the same content published in other research papers.

Instructions for Authors

Synthesiology Editorial Board
Established December 26, 2007
Revised June 18, 2008
Revised October 24, 2008
Revised March 23, 2009

1 Types of contributions

Research papers or editorials and manuscripts to the "Readers' Forum" should be submitted to the Editorial Board.

2 Qualification of contributors

There are no limitations regarding author affiliation or discipline as long as the content of the submitted article meets the editorial policy of *Synthesiology*, except authorship should be clearly stated. (It should be clearly stated that all authors have made essential contributions to the paper.)

3 Manuscripts

3.1 General

3.1.1 Articles may be submitted in Japanese or English.
Accepted articles will be published in *Synthesiology* (ISSN 1882-6229) in the language they were submitted. All articles will also be published in *Synthesiology - English edition* (ISSN 1883-0978). The English edition will be distributed throughout the world approximately four months after the original *Synthesiology* issue is published. Articles written in English will be published in English in both the original *Synthesiology* as well as the English edition. Authors who write articles for *Synthesiology* in Japanese will be asked to provide English translations for the English edition of the journal within 2 months after the original edition is published.
3.1.2 Research papers should comply with the structure and format stated below, and editorials should also comply with the same structure and format. Subtitles and abstracts are preferable but not necessary. Manuscripts for "Readers' Forum" shall be comments on or impressions of articles in *Synthesiology*, or beneficial information for the readers, and should be written in a free style of no more than 1,200 words. Editorials and manuscripts for "Readers' Forum" will be reviewed by the Editorial Board prior to being approved for publication.
3.1.3 Research papers should only be original papers (new literary work).
3.1.4 Research papers should comply with various guidelines of research ethics.

3.2 Structure

3.2.1 The manuscript should include a title (including subtitle), abstract, the name(s) of author(s), institution/contact, main text, and keywords (about 5 words).
3.2.2 Title, abstract, name of author(s), keywords, and institution/contact shall be provided in Japanese and English.
3.2.3 The manuscript shall be prepared using word processors or similar devices, and printed on A4-size portrait (vertical) sheets of paper. The length of the manuscript shall be, about 6 printed pages including figures, tables, and photographs.
3.2.4 Research papers and editorials shall have front covers and the category of the articles (research paper or editorial) shall be stated clearly on the cover sheets.
3.2.5 The title should be about 10-20 Japanese characters (5-10 English words), and readily understandable for a diverse readership background. Research papers shall have subtitles of about 15-25 Japanese characters (7-15 English words) to help recognition by specialists.
3.2.6 The abstract should include the thoughts behind the integration of technological elements and the reason for their selection as well as the scenario for utilizing the research results in society.
3.2.7 The abstract should be 300 Japanese characters or less (125 English words). The Japanese abstract may be omitted in the English edition.
3.2.8 The main text should be about 9,000 Japanese characters (3,400 English words).
3.2.9 The article submitted should be accompanied by profiles of all authors, of about 200 Japanese characters (75 English words) for each author. The essential contribution of each author to the paper should also be included. Confirm that all persons who have made essential contributions to the paper are included.
3.2.10 Discussion with reviewers regarding the research paper content shall be done openly with names of reviewers disclosed, and the Editorial Board will edit the highlights of the review process to about 3,000 Japanese characters (1,200 English words) or a maximum of 2 pages. The edited discussion will be attached to the main body of the paper as part of the article.
3.2.11 If there are reprinted figures, graphs or citations from other papers, prior permission for citation must be obtained and should be clearly stated in the paper, and the sources should be listed in the reference list. A copy of the permission

should be sent to the Publishing Secretariat. All verbatim quotations should be placed in quotation marks or marked clearly within the paper.

3.3 Format

3.3.1 The headings for chapters should be 1, 2, 3…, for subchapters, 1.1, 1.2, 1.3…, for sections, 1.1.1, 1.1.2, 1.1.3.
3.3.2 The text should be in formal style. The chapters, subchapters, and sections should be enumerated. There should be one line space before each paragraph.
3.3.3 Figures, tables, and photographs should be enumerated. They should each have a title and an explanation (about 20-40 Japanese characters or 10-20 English words), and their positions in the text should be clearly indicated.
3.3.4 For figures, clear originals that can be used for printing or image files (resolution 350 dpi or higher) should be submitted. In principle, the final print will be 15 cm × 15 cm or smaller, in black and white.
3.3.5 For photographs, clear prints (color accepted) or image files should be submitted. Image files should specify file types: tiff, jpeg, pdf, etc. explicitly (resolution 350 dpi or higher) . In principle, the final print will be 7.2 cm × 7.2 cm or smaller, in black and white.
3.3.6 References should be listed in order of citation in the main text.

Journal – [No.] Author(s): Title of article, *Title of journal* (italic), Volume(Issue), Starting page-Ending page (Year of publication).

Book – [No.] Author(s): *Title of book* (italic), Starting page-Ending page, Publisher, Place of Publication (Year of publication).

4 Submission

One printed copy or electronic file of manuscript with a checklist attached should be submitted to the following address:

Synthesiology Editorial Board
c/o Publication Office, Public Relations Department, National Institute of Advanced Industrial Science and Technology (AIST)
Tsukuba Central 2, 1-1-1 Umezono, Tsukuba 305-8568
E-mail: synthesiology@m.aist.go.jp

The submitted article will not be returned.

5 Proofreading

Proofreading by author(s) of articles after typesetting is complete will be done once. In principle, only correction of printing errors are allowed in the proofreading stage.

6 Responsibility

The author(s) will be solely responsible for the content of the contributed article.

7 Copyright

The copyright of the articles published in “*Synthesiology*” and “*Synthesiology English edition*” shall belong to the National Institute of Advanced Industrial Science and Technology (AIST).

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Letter from the editor

Two years have passed since *Synthesiology* was first published, and we are grateful to all those involved for their cooperation, support, and understanding.

In this issue, there is an article on the round-table talks held by core members of the editorial board and Dr. Yoshikawa, Grand Emeritus Advisor of AIST, reflecting over the passed two years. During the talks, the direction to which *Synthesiology* is aiming and the passion with which we strive to establish “synthesiology”, the study of synthesis, were discussed. Dr. Yoshikawa used the keyword, “social wish”, and clarified the significance of *Synthesiology* from the viewpoint of connecting with society in response to and with the awareness of the social wishes. His talk suggests much to all those involved in research and development.

There are several papers, in this issue, with the point of view of meeting the social wishes. Particularly, the papers on standards for hydrocarbon flow and temperature standards state how standard supply systems were established by solving both the technological issues involved in developing standards of the highest level and problems of making adjustments while incorporating the standards into the societal system. These are typical examples of research and development advanced in connection with society.

In the paper on the acquisition of expert skills on the shop-floor, research results on the acquirement of skills from expert skilled workers in manufacturing and the alternative method are discussed. It is stated in the paper that research and development was done under the demand to “develop a technology that can be used on site”, and that this condition, in fact, served to maintain the research sound. At sites of research and development, one sometimes forgets the primary purpose of research, or loses awareness or forgets what the research is to serve. This paper reminds us of the essential spirit of research and development, and it is written with a strong awareness of research that is acceptable to society.

Concerning the relation between research and development and society, there is a paper on research assessment. It is interesting to note that this paper discusses the importance of program assessment, and compares program assessment with the significance of *Synthesiology*. The research and development at AIST must always be done conscious of its significance in society, and the paper makes one aware that, in doing so, research assessment is precisely what is important.

There are papers of various research fields in this issue. Through the evolvement of *Synthesiology*, regardless of field, I hope that as many researchers appear who can “naturally” discuss and practice matters of their research, not only academically but also “synthesizing” approach in the context of “social wishes”.

Synthesiology will be included in Scopus, the database of Elsevier B.V. Inc..

We are looking forward to your paper submissions.

Senior Executive Editor
Masahiro Seto

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Messages from the editorial board

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