

# Synthesiology

English edition

**Predictive modeling of everyday behavior from large-scale data**

**Expansion of organic reference materials for the analysis of hazardous substances in food and the environment**

**Modeling the social acceptance of industrial technologies**

**How Grid enables E-Science?**

**Basic materials research for the development of ubiquitous-energy devices**

**Innovation in distillation processes**

**Advanced in-silico drug screening to achieve high hit ratio**

*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 type of research where the theme is placed within a scenario of future society, and where a framework is developed in which researchers from a 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 type of research where the results and knowledge from *Type 1 Basic Research* and *Type 2 Basic Research* are applied to embody the use of a new technology in society.

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# Predictive modeling of everyday behavior from large-scale data

— Learning and inference from Bayesian networks based on actual services —

Yoichi Motomura

[Translation from *Synthesiology*, Vol.2, No.1, p.1-11 (2009)]

Daily life behavior modeling is discussed. This modeling framework consists of statistical learning, probabilistic reasoning, user modeling, and large-scale data collecting technologies. Bayesian networks can represent causality relationship as graphical structures. Such models should include situations and contexts of daily life behavior through real services. In order to collect large-scale data connected with them, we have to provide real services supported by many users. This concept is named “Research as a service” and discussed in this paper.

**Keywords :** Bayesian network, statistical learning, probabilistic reasoning, user model, behavior analysis, knowledge circulation

## 1 Introduction

The range of applications of information processing technology is steadily increasing. At the same time, information services to aid in everyday life are increasingly in demand. Therefore, a model is necessary which describes the activities of daily life in a quantifiable way, in terms of what a person is trying to accomplish in various circumstances. Using such a quantitative theoretical model, we consider a system that predicts background requirements and expected results from the user’s activities, rapidly implements them, and makes possible the development of new services that aid activities of everyday life. Additionally, by continuously implementing such cooperative operations with people during everyday life, it becomes possible to acquire meaningful data in large quantities not previously obtainable in a laboratory environment. Using this large-scale data, it is possible to bring about a cycle in which services continue to be used while the model is constantly being updated.

However, during these daily activities, information processing based on uncertain information (such as predictions that result in indeterminate or incomplete observational information) is of fundamental importance. What is needed is a paradigm shift from the deterministic approach, which has until now played a central role in system recording methods, to a non-deterministic approach. The non-deterministic approach is an approach to calculation in which ambiguous or uncertain information is processed *as is*, as far as possible. Calculations are made with the probability distribution as an object variable, along with the stochastic inference, which makes the prediction <sup>[1]</sup>. This stochastic inference has come to be used naturally as a naïve Bayes model or a Hidden Markov Model (HMM) using, for example, a pattern recognition device that maximizes the posterior probability. Further, in order to

control the system based on decision theory, express useful knowledge, and perform complex processing, calculations with high-dimensional probability distributions involving multiple variables are necessary. As the number of variables becomes enormous, calculations involving high-dimensional probability distributions become complex; therefore, one has no recourse but to approximate locally using low-dimensional probability distributions. In order to facilitate this, a graph structure is introduced which stipulates the relationship between variables. As a multidimensional probability distribution model having this type of graph structure, we have the example of a Bayesian network <sup>[2]</sup>. Bayesian networks are general models that stipulate dependencies among many variables by a conditional probability and network structure. Bayesian networks can construct a model by statistical learning from large-scale data, which in turn becomes an important feature in handling uncertainty.

In the current work, after discussing the non-deterministic approach and probabilistic modeling, together with Bayesian networks and techniques of constructing models that use them for predicting human activities in everyday life, actual cases in which they are applied are discussed. Finally, a hypothesis about “Research as a Service,” the construction of which has become inevitable in the process of implementation, is proposed and discussed.

## 2 Selection by Non-deterministic Approach

In real-world problems, we want to know the situation (value) or the possibility (probability) of objects that cannot be observed directly (latent variables). This type of uncertainty inevitably enters into computing when humans are considered as the object. When a system implements any task, the tasks are modeled within the system and considered to be the object

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of calculation operations. In other words, the program can be understood to be the model and computing operations of the object tasks, coded by means of a programming language. Further, the same operation cannot be performed for all users; rather, it is necessary to invoke both a model of the task and a model of the user within the system. Ordinarily, models of the task (process) can often be given clear descriptions; however, for users, in order to treat uncertainties associated with humans, a non-deterministic analytical model is often necessary. In the current state of affairs, clearly modeling the latent variables of human relations, such as the intentions or requests of users, is difficult; and one is compelled, in the first place, to describe this type of situation using a non-deterministic framework. In addition, when a variety of users utilize the system in various circumstances, stipulating beforehand all of the most appropriate operations the system should take is a difficult problem. The system designer should design in advance the capabilities offered by the system; however, answers to questions such as what the system user requests, how the user will react to information or services offered, were the system operations correct, were the user expectations met, etc., will not be known until the system is executed or even after it is executed. In other words, it is difficult to decide, in advance, the most appropriate design of operations for users. Consequently, merely using a non-deterministic framework to operate the system as requested by, or as expected by, users is inadequate; and having predicted user reaction at execution time, frameworks allowing dynamic construction of user models become very important in optimizing these reactions and evaluations. This is the uncertainty associated with humans.

Information to be calculated appears in large amounts, and large gaps emerge between computable amounts. However, handling uncertainty is necessary. For example, through the spread of the Internet, we find that limitations exist; and handling it directly necessitates facing an unwieldy amount of data. It is possible to calculate the frequency with which a given web page is read by all users; however, deterministic processing, such as counting this for all web pages, is not realistic. In this case, Google's PageRank is calculated by modeling the transition probability among web pages non-deterministically as a stationary stochastic process<sup>[3]</sup>. In other words, we describe deterministically the construction of source pages or related links, and although this is a computer-based or deterministic method, it is not contained within a deterministic framework. Being a strategy that uses a non-deterministic model, it can respond to an explosion in description quality or the number of data points. Coping with uncertainty in a system involving this type of real world or large-scale data that includes humans is highly desirable in an artificial intelligence system, in order to tackle real societal problems; and here, describing problems using a non-deterministic model is one solution.

Even if problems involving uncertainty are described by a non-deterministic computational model, the current deterministic computer processing brings to mind the computational theory of Marr<sup>[4]</sup> in which the following types of questions are considered independently: what is to be computed, how does the calculation method write the computational process (algorithm level), how is it to be implemented, etc. In other words, even if implemented by a program described by a deterministic computer language on a deterministic silicon chip computer, and, as in the previous web example, even if the original data or mechanism is deterministic, it can be profitable to think of the model as being calculated non-deterministically. As far as "toy problems" are concerned, it is sufficient to consider calculated quantities deterministically; however, one cannot avoid using a description with a non-deterministic framework when attempting to computationally model actual pressing problems in order to cope with the uncertainty existing within them.

### 3 Bayesian Networks

#### 3.1 Probabilistic Modeling

As one non-deterministic approach, there are probabilistic methods. By using probability, it becomes possible to quantitatively model the non-determinism of phenomena and to treat it strictly by means of axiomatic probability theory. The probability values to be assigned to observable phenomena can be obtained from a large quantity of observational data; and for unobservable phenomena, estimates may be made by Bayesian probability theory (Bayesian hypothesis). This models the uncertainty of variables and the relationships between them through conditional probability and is easy to understand when considered as a way of determining the uncertainty of a particular variable, given information about other variables. Since this unknown probability distribution is treated as a subjective prior distribution in the conventional Bayesian hypothesis, it has been criticized by non-Bayesian statisticians. Recently, however, as large amounts of data have become more manageable, it has become possible to empirically construct this probability distribution from large statistical data sets and this approach is promising as a practical method in domains having a large amount of uncertainty.

For example, consider a stochastic framework for treating totally unobservable phenomena. There is a large amount of uncertain information in the real world, such as future weather conditions, noise signals, or user intentions, for which it is difficult to determine a specified value. We introduce a stochastic framework in order to systematically cope with these. An object that includes indefiniteness, such as complex factors or the influence of noise, will be represented as a random variable denoted by  $X$ , and the concrete values this variable can take will be represented by  $x_1, x_2, \dots, x_n$ .

Next, consider dependencies between variables. For

example, when it has been established that the variable  $X_j$  becomes  $y$  if  $X_i$  takes the value  $x$ ,  $X_j$  can be considered to be dependent on  $X_i$  (if  $X_i=x$  then  $X_j=y$ ). When considering complex phenomena that actually occur, the dependencies among multiple variables become complicated, and explicitly enumerating all relationships, such as “if  $X_1=x_1, \dots, X_i=x_i, \dots$ , then  $X_j=y$ ”, is not very realistic. In addition, even if this type of If-Then rule were enumerated extensively, in practice, there are exceptions, and always describing the situation completely is probably difficult. Therefore, we abandon the exact expression, focusing only on the primary variables; and in order for a rule to quantitatively demonstrate the extent of confidence, we introduce the following probabilistic expression: “when  $X_i=x_i$ , the probability that  $X_j=y$  is  $P(X_j=y | X_i=x_i)$ .” A unique dependence between the two quantities  $x$  and  $y$  can be represented, for example, by the function  $y=f(x)$ ; and in the same way, the dependence between the random variables  $X_i$  and  $X_j$  can be represented by the conditional probability distribution  $P(X_j|X_i)$ .

This shows that the distribution for  $X_j$  is influenced by the values taken by  $X_i$  and that the quantitative version of this dependence is established by the conditional probability distribution  $P(X_j|X_i)$ . Further, quantitative dependence among multiple random variables can be modeled by a set of a graph structure and conditional probability tables defined on each variable, that is Bayesian network.

The fact that arbitrary variable probability distributions can be calculated efficiently, with no distinction between predictor variables and criterion variables, is also a strong point of the Bayesian network construct; and models can be reused in various applications.

A framework that determines model or system behavior by providing data consisting of groups of desired inputs and outputs is referred to as machine learning or statistical study. A Bayesian network can also be constructed through statistical studies from actual data. Calculations of probability distributions performed on Bayesian networks are called probabilistic inferences. Below is a simple discussion of the construction of models and probabilistic inferences from

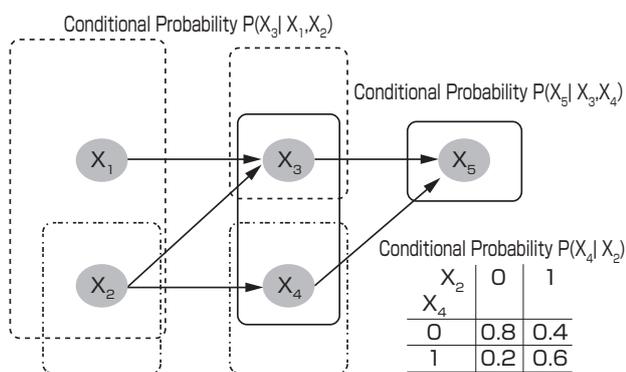


Fig. 1 Bayesian network.

models and data.

### 3.2 Bayesian Network Model

Mathematically, in Bayesian networks, a model is defined by a graph structure, which considers random variables to be nodes, and in which a conditional probability distribution is allotted to each node (Fig. 1).

In the case of discrete random variables, the conditional probability distribution of each variable is given by means of a conditional probability table (CPT). Giving a table of conditional probabilities in this way allows the probability distribution to be expressed with more degrees of freedom than is the case by specifying a density function and a parameter. In other words, it is useful as a non-deterministic modeling procedure when the nature of the object is not known in advance.

Destination variables that give the conditional probability are referred to as child nodes. In this way, directed acyclic graphs defined by a conditional probability table, variables, and graph structures are constructed as Bayesian network models.

### 3.3 Model Construction from Model Data

When Bayesian network models become large, it is not easy to determine the network structure or the entire conditional probability table manual. In such cases, a procedure is necessary for constructing a model from statistical studies of large amounts of data.

Utilized data sets that include cases which deal with all items in the conditional probability table are called complete data. In this case, the statistical data is counted to obtain the frequencies; and these, when normalized, become the most likely estimators of the conditional probability values. In the case of incomplete data having deficiencies, conditional probability values are presumed, compensating for various types. There are instances when it is desirable to construct the model network from data. Studies of the construction then search for the graph structure from some initial conditions. As a measurement criterion for the appropriateness of a graph structure, information criteria other than likelihood, such as AIC, BIC, or MDL, etc., are used. When the graph node number is large, the search space increases explosively, and from a computational load perspective, searching all graph structures is difficult; therefore, it is necessary to use a greedy algorithm or various types of heuristics to search for quasi-optimal structures. The K-2 algorithm<sup>[5]</sup> is a study algorithm for this type of graph structure. This search algorithm is as follows:

Table 1 Conditional Probability Table (CPT).

$P(y_1   Pa(X_i)=x_1)$	...	$P(y_1   Pa(X_i)=x_m)$
:	...	:
$P(y_n   Pa(X_i)=x_1)$	...	$P(y_n   Pa(X_i)=x_m)$

(i) for each node, limit the candidates that can become new nodes, (ii) select a child node, add and graph the new candidate nodes one by one, (iii) decide on and evaluate the parameters on which the graph is based, (iv) only when evaluated highly, use as a new node, (v) when there are no more new node candidates to add, or when the evaluation does not increase even if a new candidate is added, move to another child node, (vi) repeat (i) – (v) for all child nodes.

In general, new search spaces increase combinatorically; therefore, a device is needed to avoid an increase in computational load by limiting combinations of new nodes that become ranked from the beginning to be candidates. Furthermore, we consider independently the search portion of the graph (ii), (v), and the mode evaluation portion (iii) and think about various study methods.

One can expect that the use of a Bayesian network would be an effective approach to construct a non-deterministic model from large amounts of data by means of statistical learning. However, obtaining a causal structure from only statistical data is fundamentally difficult, and the task of searching the graph structure is NP hard. In such cases, it is actually necessary to skillfully implement the variable candidates or search range limitation, or to introduce appropriate latent variables.

### 3.4 Probabilistic Inference

There are other types of models that possess a graph structure; however, many of them are often used to visualize graph structures that explain data. On the other hand, by constructing them with discrete random variables and conditional probability tables, Bayesian networks very efficiently implement the probabilistic inference algorithm, which estimates the probability distribution of arbitrary random variables in the model. This is a significant advantage over other graphical models and is a crucial feature in operating an intelligent learning system with a realistic computational load.

Probabilistic inference on Bayesian networks is implemented by the following procedure: i) assign the value of an observed variable (e) to a node, ii) assign a prior probability distribution to both new nodes and nodes having no observed value, iii) calculate the posterior probability distribution  $P(X|e)$  of the desired object value (X).

In order to find the posterior probability in item ii), a probability propagation method is implemented which renews the probability distribution of each variable according to the dependence between variables.

When all paths within a graph structure that does not consider the direction of links of the Bayesian network do not possess loops, the Bayesian network is called a *singly connected* network. In this case, even networks with structures in which

multiple new nodes and child nodes exist, the calculation is completed by utilizing its conditionally independent character by performing, for each node, probability propagation calculations of 4 types: propagation upstream, downstream, from upstream, and from downstream (Figure 2).

These computations are completed in order of network size (number of links), and the calculation efficiency is extremely high. When the network is viewed without considering the direction of links and there is a portion in which even one path is somehow looping, this Bayesian network is called *multiply connected*. In this case, there is no guarantee of an exact solution; however, probability propagation can be applied as an approximate solution method; this is called the Loopy BP method.

## 4 User Modeling

Based on the fact that the information system and the user advance processing conversationally, and that this information system is a portion of the entire system, which is subject to operations, the information system, the user, and even the environment and surrounding circumstances, must be considered. Consequently, viewing the entire system as a control object, human behavior and response should be thought of as one component of the object of calculation. In this case, we want to evaluate what the user is requesting under given circumstances and how to react to the system output results obtained. In the system, it is necessary to describe the cognitive state of such users in terms of computable user models.

Machines (programs) learn from data by the development of machine learning. In other words, the approach wherein models are constructed from data and revisions are made sequentially [iteratively] is feasible. In the construction of machine learning models, statistical tests are repeatedly implemented to act as an automated model selection process, based on information criteria; and the result is considered to be the appropriate model. In other words, a statistically meaningful model is chosen through machine learning from within an extensive search space.

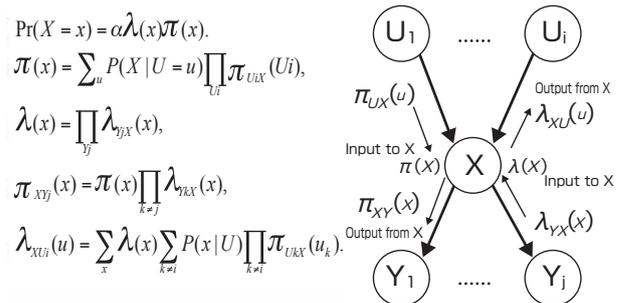


Fig. 2 Belief propagation.

$$\begin{aligned} \Pr(X = x) &= \alpha \lambda(x) \pi(x). \\ \pi(x) &= \sum_u P(X = u) \prod_{U_i} \pi_{U_i X}(U_i), \\ \lambda(x) &= \prod_j \lambda_{Y_j X}(x), \\ \pi_{X Y_j}(x) &= \pi(x) \prod_{k \neq j} \lambda_{Y_k X}(x), \\ \lambda_{X U_i}(u) &= \sum_x \lambda(x) \sum_{k \neq i} P(x | U) \prod_{k \neq i} \pi_{U_k X}(u_k). \end{aligned}$$

Further, by using a probabilistic model, it is also possible to model abstract and diverse elements, including, for example, the idiosyncrasies of individuals, making it possible for conventional psychology to attempt to deal with a universal human model. This is an important viewpoint for models that implement individual adaptation or personalization crucial in information processing associated with recent human centered design and usability aspects. There have been various implementations of user modeling which use a Bayesian network as the probabilistic model<sup>[6]</sup>. In order to model, in particular, constructions of human cognition and evaluation as Bayesian networks, interview methods used in clinical psychology or marketing are applied<sup>[7]</sup>. In this way it is possible to infer acceptability or intention by modeling and implementing probabilistic inferences of the system and services of the user.

## 5 Modeling of Everyday Activities

As an actual example of computing uncertainty, the standpoint of user modeling has been discussed above; however, when considering everyday life assistance as various actual services<sup>[8]</sup>, modeling of the living person, each day, as a user, is vital. Until now, sensors have been installed in a home, or a “sensor house” has been proposed for research and development in order to analyze everyday activities<sup>[9]</sup>. Until now, several applications have been proposed wherein abnormalities are judged by detecting outlying values while modeling patterns in measured data as stationary distributions; however, for broader applications, modeling with only stationary distributions is inadequate. Rather, it is necessary to consider optimizing the utility, or value, depending upon user intentions. In other words, in order to predict the intentions, impressions, and assessments of the user, which cannot be observed directly, from observable actions, higher-order inference is necessary. To accomplish this it is necessary to model dependencies and causal relationships, such as how results turn out in response to certain circumstances and activities; to accomplish this, it is necessary to record, not only action data, but comprehensive data involving causal variables, and to search for causal structure from relationships among a large number of variables.

This can be considered as a new kind of analysis of behavior, opened up by sensor technology and modeling technology. Behavior analysis was established by Skinner in the mid 1900s as a field of research making use of the behavioral science approach within psychology<sup>[10]</sup>. In this context, human activities are referred to as antecedent and behavior contingencies, and expected changes in environment, as the result of actions, are thought to be determined from relationships among three items. Further, the causal relationships between antecedents and behavior contingencies are clarified when focus is on a certain activity. While modeling this explicitly and by causing changes in those

behavior contingencies and antecedents, control of behavior is implemented.

It is necessary to interpret video images of observed activities and to perform a labeling procedure in order to discover the cause and effect of activities. Performing this manually, however, requires an enormous amount of time and effort; therefore, it is difficult to efficiently analyze natural activities in an everyday life environment. In addition, performing this interpretation manually allows only a small number of objects to be analyzed as control variables of the activities. Technology capable of automatically handling large amounts of observational data is necessary in order to analyze everyday activities.

In such cases, observing actions automatically by a sensor network embedded in the environment, and utilizing statistical study techniques comes to mind. By constructing a Bayesian network model through statistical learning from the large amount of sensor data gathered, it is possible to connect the inevitability amid the reasons and purposes for actions, which become candidate behavior contingencies, and the environment and situations, which become antecedents. In this way, it is expected that behavior analysis will be developed largely by contributions from model construction technology that extracts variables with strong causal relationships from sensor technology that can comprehensively observe daily activities, and from the data observed thereby. Through modeling of actions based on Bayesian networks and ultrasonic sensor networks, research has, until now, been aimed at analysis of everyday life behavior<sup>[11]</sup> and at applications such as injury prevention for children<sup>[12][13]</sup>. An example of inferring the behavior of children<sup>[14]</sup> is introduced below.

Attach an ultrasonic transmitter to a person or object in the room. Then, at regular intervals, position information (x, y, z coordinate data) of the person or the objects can be captured by ultrasonic receivers embedded in the sensor room. A fisheye camera (camera with a wide-angle lens) installed on the ceiling of the room simultaneously photographs the circumstances of the person’s activity in the room as a video. For the activities of the person in this photographed room, the video images are labeled manually at one-second intervals. For example, a detailed database is collected giving action labels such as “the person is walking,” “sitting,” “standing.” Modeling of everyday activities is performed using this data, and experiments of behavior inference are performed based on the video.

Considering the problem as the system’s observation of the behavior by means of sensors and images, it can be formulated as a type of pattern recognition problem. Since data arising in the everyday real world considers human life activities and the living environment as a background, the nature of the state

space in which the data arises and the bias are reflected in ways that resonate with human activity and semantics. In the space in which this type of data arises, peculiar restrictions and deviations in the frequencies of occurrence can be treated in terms of a probability distribution. Enumerating all the causal structures established in the world, as is the case for physical laws, is difficult because of the quantity of such descriptions; however, expressing the important elements as probabilities is an effective approximation. Work has been done to model this type of probabilistic construction by a Bayesian network in the actual space and to utilize it in Bayesian inference<sup>[15]</sup>.

In Bayesian inference, multiple class labels are taken to be  $C_i$ , and a posterior distribution combining both the likelihood  $P(x|C_i)$  for a signal pattern  $x$  and prior distribution  $P(C_i)$  which determines the class label  $C_i$ , such that

$$P(C_i|x) = P(x|C_i) P(C_i) / \sum_j P(x|C_j) P(C_j) \quad (1)$$

is maximized. It is known that this makes possible optimal recognition that minimizes the Bayes error probability. The fit of the data is represented by the likelihood, and prior knowledge is represented by the prior probability distribution. Learning from data and prior knowledge are naturally integrated by considering the maximized prior probability, which is the product of both of these, to be the inferred result.

In cases when the frequency of occurrence of class labels depends upon the observation time and place, the prior distribution  $P(C_i)$  depends on the situation  $S$ . In such cases, consider this to be the conditional probability  $P(C_i|S)$ , replace this with  $P(C_i)$  of equation (1), and obtain a class which maximizes the posterior probability of (2):

$$P(C_i|x, S) = P(x|C_i) P(C_i|S) / \sum_j P(x|C_j) P(C_j|S) \quad (2)$$

The second term in the denominator of the right-hand side of Eq. (2) is the prior probability of the activity label  $C_i$ , which is in situation  $S$  in the label space. Here, we will consider the stochastic causal structure in the label space. When we construct, as a Bayesian network, a causal structure among a series of places and actions, for example, when we introduce advance knowledge with a causal structure of the following form: "If activity  $C_i^t$  occurred in circumstance  $S$  at time  $t$ , it is easy for activity  $C_i^{t+1}$  to occur at time  $t+1$ ," the probability of an action when a person enters domain  $S$  is expressed as  $P(C_i^{t+1} | C_s^t, S)$  and can be modeled by a Bayesian network. Having constructed the model by means of statistical studies on the data set of observations of activities when children are playing in an experimental environment imitating a living room, aside from past activities, dependencies between the relative distance of, for example, the sofa or wall in the room, the speed of movement, etc. are confirmed. Having studied the Bayesian network and naïve Bayes by means of activity data of other

children, and inferred the activities of other children through Bayesian inference via Eq. (2), the identification rate was found to be approximately 50 % or less according to the most likely inference of naïve Bayes only, and could be increased to approximately 60 %~80 % by Bayesian inference, using a Bayesian network<sup>[14]</sup>. By means of this behavior inference algorithm, it is possible to efficiently form action-labeled data from observational images of everyday activities.

## 6 Research as a Service

Now that large-scale data can be measured in daily life, complicated problems can be handled through statistical learning. However, a characteristic problem of statistical learning is that as models become complicated at a high level, the amount of data necessary for learning increases. Sensor data observable superficially can be dealt with comparatively easily. However, the internal state of human behavior is a psychological aspect; therefore, a questionnaire survey used on test subjects is a necessity, and this entails a high cost. In addition, when acquiring data, practical problems exist, such as the problem of privacy and the fact that cooperation for the purpose of the research is simply difficult to obtain. Furthermore, even if a phenomenon is easily observable in terms of external factors, in order to completely collect predictor variables with high environmental dependence at the scene where they will actually be used, it is necessary that the environment wherein data is observed be controlled, so as to simulate the everyday environment as accurately as possible. Therefore, for this type of problem, the author considers it obligatory to unify actual service, investigation, and research. In this connection, the author lectures on the concept of "Research as a service"<sup>[22]</sup>. This clarifies the "means-end chain" as behavioral contingencies of humans in the context of behavior analysis, making it easy to make comprehensive models while including environmental dependence. Consequently, the results of the observations, evaluation questionnaires, and user feedback (psychological investigation), obtained while implementing the information service in society, are collected without separating the investigation and modeling procedure from the applications that use the model. This is known historically in cybernetics and in reliability engineering as the Deming cycle: PDCA (Plan, Do, Check, Action), in which a model is continuously corrected while cycling through actual problems.

For an essential resolution of the uncertainty issue, an approach is necessary in which a cycle is permanently continued that collects additional data while using and controlling the model, with modeling based primarily on actual data. This is not limited to simply collecting actual data, but from the standpoint of research, implies that the researcher is imbedded in the field, which leads the way to new research that will bring about new values and evaluations<sup>[16]</sup>.

It is also necessary to implement an applied system that can be embedded as infrastructure within society, as a product that can be tolerated as an actual service.

## 7 Bayesian Network Applied System

The applied system of the Bayesian network can be developed by implementing a probabilistic inference algorithm or model construction algorithm as a computer program. Building on work in the Real World Computing Project, the IPA Unexplored Software Project, and other such projects prior to 2001, and by searching Bayesian networks from large amounts of data in 2002, the author developed the software BayoNet that can perform probabilistic inference based on this work<sup>[17][18]</sup>. This software has been licensed to private enterprise and commercialized; however, due to the fact that a high degree of specialized knowledge is necessary in order to apply it to the resolution of particular problems and the fact that the utilization procedure is not self-explanatory, it has been somewhat difficult to train users who can fully utilize the software. If it is software developed for highly specified purposes, it is not necessary; however, software featuring a Bayesian network emerging as purely fundamental research on mathematical models can be applied for extremely broad purposes; and at the point in time when it can be utilized in practice, new investigations resulting in even more valuable purposes can occur. Therefore, a taskforce of the strategic center for venture development was started in 2003, and researchers personally had the opportunity to begin a search for business models that use this technology. At this point in time, many research results have remained as essential technologies, such as algorithm refinement and acceleration or inference precision improvements; however, we have felt resistance to further development of technologies in circumstances in which the outcomes were not obvious. Therefore, we decided to prioritize the search for outcomes by problem resolutions that had the possibility of being adequately treated, given the efficiency at the time.

The advantage of using Bayesian networks is that by performing probabilistic inferences, we can determine the probability distribution of arbitrary variables and conduct quantitative evaluations in various situations. In many conventional multivariate analysis procedures, quantitative relationships are often modeled based on a covariance relationship that assumes linearity among variables (linear independence). In the Bayesian network model, quantitative relationships are represented by a conditional probability table. In a conditional probability table, a family of conditional probability distributions are not hypothesized, but rather, the table forms a model in which non-linear, non-normal relation interactions can be represented with great freedom. In addition, predictor variables and objective variables are not clearly distinguished; therefore, introduction of latent [implicit] variables is also straightforward. In other

words, even variables that cannot be observed can be treated as latent variables. Therefore, latent variables are introduced that become categories, and when analyzing the statistical data of a user or customer, we can extract attributes of groups that perform the same activities, classify constituencies, and that can even be utilized in customer segmentation.

It is extremely important that these characteristics respond by recommending information or products that are acceptable matches, depending upon the user or customer activities (Web browsing history, etc.), attributes, or circumstances. In collaborative filtering, information or products desired by customers or users cannot reflect situation dependence when displayed by a portable telephone or car navigation system. Information recommendation technology for such activities that change depending upon the environment is important, even in ubiquitous computing, in which a variety of situation changes in actual space are imagined.

### 7.1 User- and Situation-Dependent Information Recommendation in a Car Navigation System

It sometimes happens that the driver of a car wants to stop somewhere while driving. For example, while driving for some purpose, the driver decides to stop to eat at a restaurant. In conventional car navigation systems, a category is specified, and all corresponding restaurants are listed in order by distance. The user must find the appropriate restaurant from within the list; however, the user has to operate a touch switch or remote control in order to see detailed information about restaurants, so it is not easy for the driver to locate the desired restaurant.

Therefore, if a car navigation system were to model the driver's preference of various restaurants, given various situations and criteria using a Bayesian network, and, using a probabilistic inference from this, if the system replaced the driver while driving, and automatically selected the appropriate destination, it would be an extremely practical function. A person's taste depends largely upon their personality and upon the situation while driving. While driving, it is necessary to select the most appropriate choice at the time, among conditions that change moment by moment.

To illustrate this dependence on situations and personal differences, a Bayesian network can be efficiently applied that can model complex relationships among variables and uncertainty. Therefore, we test and evaluate a car navigation system that suggests content appropriate for the user<sup>[6]</sup>. This system possesses, as a Bayesian network, a user taste model within the vehicle information system. Content, such as restaurants or music, is suggested by content providers, and a score showing how appropriate it is for the user and conditions at the time is calculated as a conditional probability when the situation and user attributes are given.

It then recommends items with a high score, limiting them to superior content. For 182 actual restaurants in the Shinagawa neighborhood, a questionnaire was conducted among 300 test subjects, causing desired store locations to be selected in six situations (scenarios). A model was constructed from the gathered data. Restaurants desired in six situations (scenarios) were selected from the 182 restaurants in the Shinagawa neighborhood. Concerning the selection procedure, firstly, the user was queried about desired categories, and stores corresponding to those categories were displayed. If disliked, the next genre was chosen by the same selection method as in currently existing car navigation systems. There were multiple answers for selected restaurants, and ultimately 3778 records were obtained. There were 12 situation attributes, 17 restaurant attributes, and 12 user attributes. The model in Fig. 3 was constructed as a result. There are four attribute nodes representing users, three representing situations, and six representing restaurants. The model consists of all 13 of these random variables, and the probability distribution of restaurant attributes favored by specific users in a given situation is calculated by probabilistic inference.

In the model of Fig. 3, for drivers with a light driving history, the probability is high that franchise restaurants such as family restaurants and fast food chains will be chosen; conversely, for extensive driving histories, the probability that these restaurants will be chosen is low. Franchise

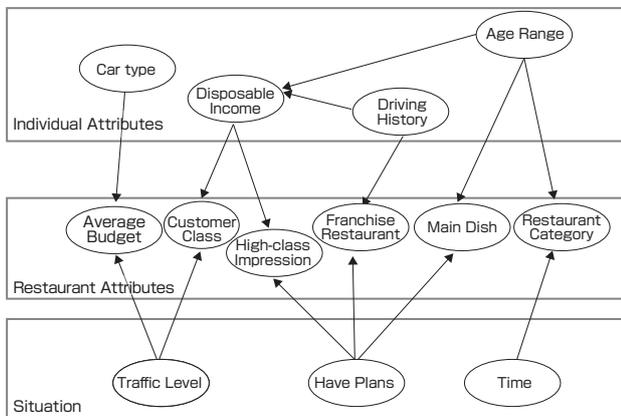


Fig. 3 Restaurant preference Bayesian network model.

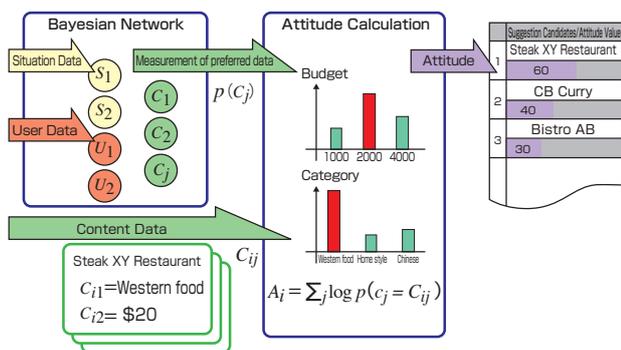


Fig. 4 Outline of restaurant recommendation system [6].

restaurants often provide parking areas and show a tendency to be favored by young or beginning drivers. In addition to “driving history”, there is a “have plans” interaction. This reflects the tendency that even in cases wherein the driving history may be long, in situations when the driver has plans and must hurry, there is a high probability that a franchise restaurant will be used. The proper tendency is obtained intuitively for other relationships, such as that between budget level and vehicle type.

Using the model depicted in Fig. 3, a prototype of a restaurant recommendation system was also designed (Fig. 4). Favored content attributes are forecast as probability distributions from user variables and situation variables.

$$A_i = \sum_{j=1}^n j \log p (c_j = C_{ij}) \quad (3)$$

By recommending content for which the value of this score is high, a car navigation system appropriate for the situation and the user can be implemented. Upon comparing this prototype system and a conventional car navigation system, its effectiveness was confirmed by the fact that prediction results for restaurants matched the users' preferences and the situation.

### 7.2 Information Recommendation Appropriate for User and Situation with a Portable Phone

Information recommendation technology appropriate for various users and situations is important in next generation portable phone services. Examples of application of Bayesian networks in a movie recommendation service in portable phone services have been introduced [19][20]. For approximately 1600 test subjects, their content evaluation history, user and content attributes were collected via a questionnaire that suggested movie content. Other than demographic attributes such as age, gender, employment, etc., questions regarding lifestyle, appreciation frequency as attitude attributes concerning movie viewing, concern over movie selection time, the primary purpose for watching movies (seven questions about wanting to be emotionally moved), evaluation of content (good/bad), one's mood at the

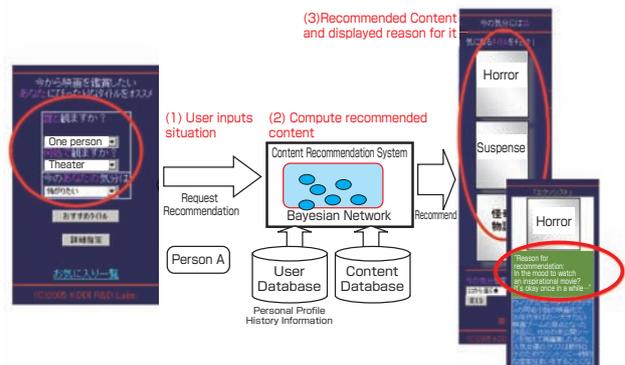


Fig. 5 Mobile information service system that recommends movies depending upon the user and situation [19][20].

time (seven questions about being emotionally moved) were collected. Furthermore, for approximately 1000 people, all of the following were collected separately as free-form text: the content of each movie, what kind of feeling or situation, (theater, DVD, etc.), with who, with how many people, what time of day, was the movie appreciated. This data was input into BayoNet<sup>[17][18]</sup>, the Bayesian network construction software developed by the author, and a Bayesian network model was constructed automatically. Through the Bayesian network constructed in this way, a prototype of the portable information system was developed that makes movie recommendations, based on situation and user tastes. If the user sends requests to services from the portable phone, together with information about the situation, the system implements the probability inference using registered user attribute and situation information from the database. Content whose probability of being selected is judged to be high is recommended as superior (Fig. 5). This movie recommendation system was also developed into an Internet service at *auOne* lab (<http://labs.auone.jp>) and released generally in 2007 with approximately 7000 recommendations implemented. Further, the model is being restudied from this recommendation history, and experiments are being conducted to improve recommendation precision. Using the calculation model for movie selection constructed in this way, we also proposed cooperation with a movie distribution company to optimize sales strategies for DVD content for which the movie release period has passed<sup>[21]</sup>.

As this information service spreads and multiple users utilize the system, the history of selection content accumulates ever-larger amounts of statistical data. Improvements in the Bayesian network model resulting from that data will increase the appropriateness and inference precision of the model, create a self-supporting feedback loop, and allow horizontal development of other services to be realized. Data obtained from the market through actual services becomes reusable knowledge for the calculation model; this

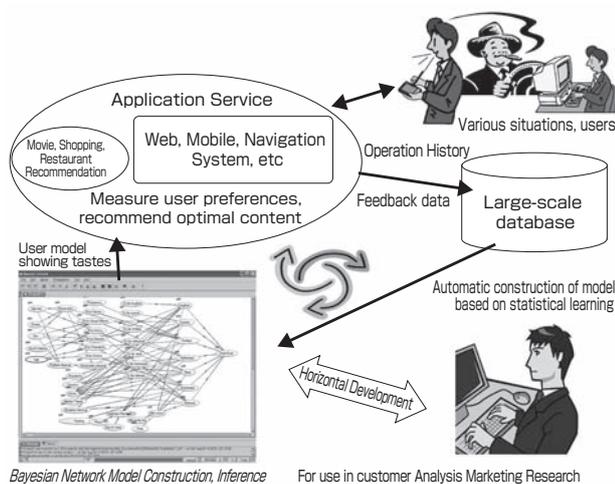


Fig. 6 Knowledge cycle service due to Bayesian network.

knowledge cycle, reflected in the next service, can be called “Research as a Service” as noted earlier (Fig. 6). Research activities through this type of actual service can even be put into practice in a service engineering research center through construction of a calculation model from large-scale data and through implementation of an optimization design loop in the field. Such research activities are proposed as a business to improve the productivity of the service industry<sup>[22]</sup>.

## 8 Conclusion

In the present research, the development of software could be categorized as pure or basic research; however, software development which excludes the initial step, which is obviously outcome oriented, could be considered applied fundamental research. It seems that there were several conditions that implied that we rethink the criterion for application selection intuitively recommended in that process.

1. There are unresolved problems in existing procedures.
2. There were problems actualized by user requests.
3. There are stakeholders that profit from resolutions of these problems and bear the corresponding cost and risk.

In these types of conditions, using Bayesian networks to model human behavior, forecasting customer or user activities, and achieving improvements in value and efficiency by optimization of associated services is thought to be an appropriate outcome. Client enterprises that can realize these outcomes exist in industry types that possess contact points (channels) with various customers. Selecting the outcomes mentioned above, the appropriate fields become channels that can collect large amounts of data from customers such as the Internet, portable telephones, car navigation systems, and call centers. However, among these choices, two necessary types are: being able to

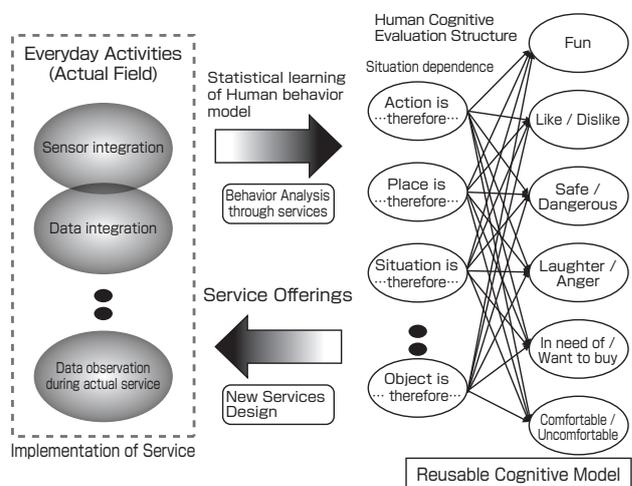


Fig. 7 Reusable model of human cognitive and evaluative structure.

adequately respond by transferring the present technology, and the development of additional technology for outcome realization. In the former, the venture responds; in the latter, the choice is made to promote cooperative research between AIST and enterprises.

Engineering implementation and societal implementation differ. In engineering, even if the technology is already established, in order to produce societal value, participation of many more stakeholders is necessary. It is necessary to convey value to these stakeholders, which will not necessarily have an engineering background, in order to persuade them to bear the cost and risk; and it is necessary to demonstrate that the outcome has high reliability. Therefore, societal implementation through department-level cooperative research and technology transfer to AIST Ventures is necessary, and results need to be proven in the field. In other words, evaluation of the outcome and societal implementation occurs simultaneously.

In order to clarify the conditions under which implementation in society is possible, a marketing research was performed in the Venture Task Force. The cost benefit analysis, which did not need consideration in the first type of basic research, was critical. In order to smoothly advance societal implementation, reductions of cost and risk are sought while improving benefits. At this step, the outcome itself is corrected, and there is a possibility of motivating fundamental research out of necessity for a new outcome. This promotes fundamental research, becomes feedback to fledgling basic research, and is represented in the policy statement of the Digital Human Research Center: "Application driven fundamental research." It has also become possible to acquire large-scale data that includes situations and context involving the results of activities through actual services and actual users. Bayesian networks constructed from this data forecast the cognitive and evaluation structures and behaviors of existing consumers and others. Being causal models rather than merely descriptive models of the data, they are cognitive models with high reusability and potential for horizontal development (Fig. 7) in other services<sup>[23]</sup>.

Concerning issues required for implementation in society, and from the standpoint of fundamental research, whether or not a quick response can be given is thought to be an important issue associated with establishing fundamental research on problem resolutions requested by society in the future. The very fact that speed is requested of technology in society requires that many "buds" be nurtured for the future. Such choices can only be performed by those thoroughly grounded in fundamental research; consequently, in order to perform fundamental research, views aimed at societal technology that clearly envisions the future are surely required.

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## Author

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The team leader of large scale data based modeling research team, center for service research(CfSR) and the senior research scientist of digital human research center (DHRC) at National Institute of Advanced Industrial Science and Technology (AIST) in Japan. He received M.Sc from The University of Electro-Communications and then joined the Real World Computing project in the electrotechnical laboratory, AIST, MITI (the ministry of international trade and industry, Japan) in 1993. In this project, he developed Bayesian network modeling and inference system, BayoNet. His current research works are statistical learning theory, probabilistic inference algorithms on Bayesian networks, and their applications to user modeling and human behavior understanding and prediction from sensory data. He also conducts the venture company, Modellize Inc., as the chief technology officer and applies Bayesian network technologies to many variety applications in Japan. He also wrote four textbooks on Bayesian networks, and gave many lectures on Bayesian network researches and applications. He received a best presentation award, research promotive award from Japanese Society of Artificial Intelligence, Docomo Mobile Science award and IPA super creator award.

## Discussion with Reviewers

### 1 Clear description of the originality as synthesiology

#### Question and comment (Hideyuki Nakashima)

The author described the difficulty of the modeling of daily-life behaviors and the significance of machine learning approaches for the modeling in chapters 1 and 2. The part should include more concrete examples for the improvement of readability of ordinary readers.

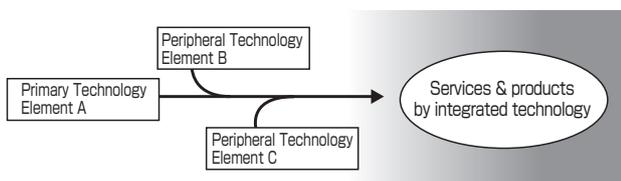


Fig. a Breakthrough model.

The author has described “Research as a service” in chapter 2, and I believe that this part is the most essential part of the presented paper. This part should be expanded.

#### Question and comment (Masaaki Mochimaru)

I guess the paper can be understood as presenting a breakthrough-type *Full Research*. The core technology of the paper is the Bayesian network with sensing technology and/or interview. The result of the study is a *Synthesiology* that realizes the solution of problems in the real world. The method and results are not just integration of the peripheral technology. The originality of the paper as *Synthesiology* is the suggestion of the concept of “Service as a research”. That is a social-circulation-type *Full Research*. This paper has embodied the concept of *Synthesiology* more than the past articles in *Synthesiology*, so, the author should explain the concept of *Synthesiology* explicitly.

#### Answer (Yoichi Motomura)

I have revised the abstract, title, the concept of “Service as a research”.

## 2 The composition of the paper

#### Question and comment (Masaaki Mochimaru)

This journal is not for artificial intelligence but *Synthesiology*, so, the author should write “the dream” realized through the integration technology in the introduction. It would be a description that the dream (the realization of daily-life-support-service by a system that understands the purpose of human behavior) and the concrete examples in order to give example images to readers. The breakthrough point for realization of the dream is “description, understanding and realization of daily-life in computer”. The difficulties of the realization of the dream are as follows: (1) human behaviors include some unclear and uncertain elements and the author has introduced the Bayesian network which is a non-deterministic modeling framework as a solution for the unclear and/or uncertain modeling, (2) the difficulty for using the Bayesian network is the necessity of a large scale dataset. This difficulty can be solved by the ubiquitous sensing technology and “Service as a research” in the real world. This composition can improve the readability of the paper.

#### Question and comment (Hideyuki Nakashima)

The logical connection between chapter 1 and chapter 2 is not good. Could you add a brief summary of the rest of the paper at the last part of chapter 1?

#### Question and comment (Masaaki Mochimaru)

The description of chapter 2 has prevented the smooth story expansion of the paper as indicated by Prof. Nakashima. I suggest three solutions as follows: (1) add the abstract to the last part of chapter 1 as say Prof, Nakashima, (2) change the position of chapter 2 and chapter 3, (3) move chapter 2 to the last of chapter 8.

I recommend the solution (3), because “selection of non-deterministic approach for human behavior model”, “Bayesian network as a non-deterministic approach” and “Research as a Service” are written in the paper. For readability it is not good to show the concept suddenly. So, I suggest the following storyline.

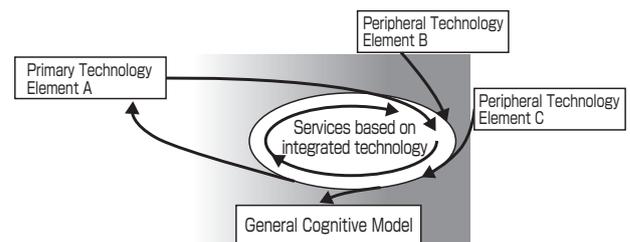


Fig. b Society cycle model.

- (i) Description of “non-deterministic approach”.
- (ii) Description of the concrete examples.
- (iii) Description of the need of a meaningful large scale data for realization of the examples.
- (iv) Description of the proposal of “Research as a service” as the methodology of the study to obtain a large scale data.
- (v) Description of the essentiality of cooperation of some stakeholders for the “Research as a service”.

**Answer (Yoichi Motomura)**

Thank you for your suggestions. I have revised the composition based on proposal 1.

**3 Additional description of specific examples**

**Question and comment (Hideyuki Nakashima)**

“As this information service spreads and multiple users utilize the system, the history of selection content accumulates ever-larger amounts of statistical data. Improvements in the Bayesian network model resulting from that data will increase the appropriateness and inference precision of the model, create a self-supporting feedback loop, and allow horizontal development of other services to be realized”, this part is the most important in the presented paper. Please describe more concretely about the spiral - what happened actually. I appreciate that you carried

out the verified test of the proposed system to over 1000 people, however, you cannot say that the system is practical just by this. For example, it is usual to use the questioner dataset which is over 1000 samples in social science. In IT field, construction and evaluation of pre-production system is not enough to say that you actually used the system - To provide the actual service in the real world” is the significant step.

**Answer (Yoichi Motomura)**

I have added the description with respect to the examples.

**4 Description of the reusable model**

**Question and comment (Masaaki Mochimaru)**

The figure which shows the concrete image of “reusable model” corresponds to “general knowledge model” shown in comment 1. The interest as *Synthesiology* is in that the model can be horizontally developed into other applications (services). On the other hand, “the study is done through the service circulation in the real world. Additionally, the reusable model is generated”. This concept’s description maybe excess information for readers, and readability is not good. So, I suggest that the author describes the concept in chapter 8 with a figure.

**Answer (Yoichi Motomura)**

I have revised chapter 2 and chapter 8.

# Expansion of organic reference materials for the analysis of hazardous substances in food and the environment

—Realization of an efficient metrological traceability using the quantitative NMR method —

Toshihide Ihara<sup>1\*</sup>, Takeshi Saito<sup>1</sup> and Naoki Sugimoto<sup>2</sup>

[Translation from *Synthesiology*, Vol.2, No.1, p.12-22 (2009)]

Reference materials are indispensable for accurate analysis of hazardous substances in food and the environment. For organic substances, however, the dissemination of reference materials is hopelessly unable to catch up with today's rapidly proliferating analytical needs. To solve this problem, analytical techniques were improved to develop a method in which a single primary reference material could provide accurate quantitative measurements for a wide variety of organic compounds. In pursuit of this goal, we turned our attention to the <sup>1</sup>H NMR method. We improved upon the method to allow precise comparisons of signal quantities from protons with different chemical shifts, enabling calibration at an acceptable level of uncertainty for a variety of organic reference materials using a primary reference material for protons. This result opens the prospect of highly efficient metrological traceability, reducing the required number of national reference materials to a minimal level.

**Keywords :** Chemical metrology, metrological traceability, reference material, nuclear magnetic resonance spectroscopy, primary method of measurement

## 1 Introduction

Our modern lives are surrounded by chemical compounds, and a wide range of laws and regulations controls these chemical compounds, to ensure safety and to prevent adverse impact on the environment and human health. In recent years, public concern for safety has increased in Japan, prompting an increase in the number of chemical compounds subject to regulation, limitations, and other regulatory controls. For example, in May 2006, the Food Sanitation Law was revised to introduce the "Positive List System<sup>Term 1</sup>" for agricultural chemical residue in foods. With the enforcement of stringent regulations, the number of control subjects expanded from approximately 250 to about 800 kinds of agricultural and other chemical compounds traded domestically and internationally. At the same time, several new Official Methods of Analysis<sup>Term 2</sup> were established to measure the regulated chemical compounds, and as result, the use of advanced analytical equipment capable of conducting multiple simultaneous measurements, such as gas chromatograph/mass spectrometer (GC/MS) and liquid chromatograph/mass spectrometer (LC/MS), increased in food and environmental analyses. In this situation, many laboratories that inspect and test chemical compounds are increasingly employing GC/MS and LC/MS to conduct analyses.

While these analytical equipment are capable of simultaneously measuring multiple components, it is necessary to calibrate the sensitivity of the analytical instrument for each analyte in the samples to ensure the reliability of analytical results. To perform this calibration, reference materials (RMs) that serve as "yardstick" are

required for individual analytes. In this type of analysis, the accuracy of inspection and testing results are crucial, and the reliability of the "yardstick" is of paramount importance. The use of certified reference materials (CRMs)<sup>Term 3, [1]</sup> or equivalent RMs is highly recommended in such cases, and therefore various testing and inspection laboratories are working swiftly to acquire the RMs necessary to handle the ever-increasing list of regulated materials.

## 2 Current problems with RMs

The characterization of RMs by metrologically appropriate procedures is achieved by using measurement methods that offer traceability<sup>Term 4</sup> to SI definitions (in this case, amount-of-substance). Normally, this is a task performed by the national metrology institute<sup>Term 5</sup> of a country, and the RMs produced are known as the national reference materials (primary RMs). Generally, national RMs offer the highest standards of accuracy, and are scrupulously prepared with labor, time, and expense. Normally, they are not transferred directly to the inspection and testing laboratories that perform the actual analysis, because this is not practical due to the quantities and costs involved. Instead, secondary RMs are calibrated based on the national RMs, and working RMs are in turn calibrated using the secondary RMs. In this way, a pyramid structure is constructed, with few higher-order RMs at the top and a larger population of lower-order RMs reproduced below. Order in this proliferation of RMs is enforced through traceability to the original set of accurate "yardstick" or the national RMs. In essence, this concept is similar to the traceability systems where scales are calibrated using a series of weights, and the current RM traceability

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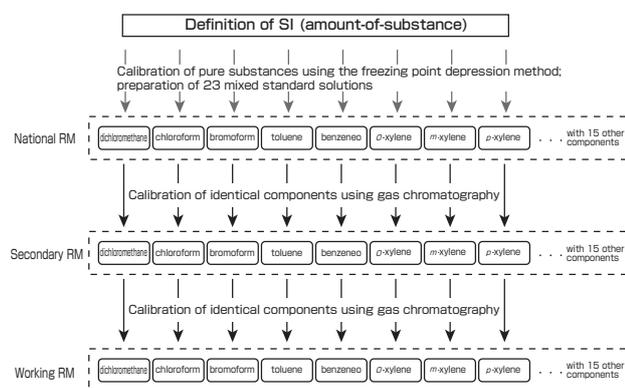
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system is not unique to reference materials. However, it is different from the weight system in a number of ways.

Figure 1 is a schematic diagram of the traceability system for the RMs used in the analysis of volatile organic compounds that are used to test the quality of river and tap water in Japan. The national RM is in the form of a single solution incorporating 23 volatile compounds. Traceability to SI is obtained using pure substances for each component that is valued using the freezing point depression method. The secondary and working RMs also consist of a single solution incorporating 23 volatile organic compounds, but in this case, calibration from upper-order to lower-order standards is conducted separately for each component. Because the lower-order traceability system requires a one-to-one correspondence, the pyramid structure breaks down for these RMs. In other words, the national RM for a given component must be used to calibrate the secondary RM for the same component, and calibration of working RMs for the same component is performed using this secondary RM. Because this is one-to-one calibration of the same chemical compounds, commercially available analytical technologies such as gas chromatography can be used for calibration down to the working RM level while maintaining excellent reliability. This practical system of traceability is used throughout the world.

The drawback of this traceability system is that it requires a wide array of national RMs to match each chemical compound subject to be analyzed. Development of these national RMs is a major bottleneck in the traceability system because it requires enormous time, labor, and expense. The construction of a more efficient traceability system based on an entirely new concept is needed to address the rapidly proliferating demand for RMs prompted by increasingly tight regulation of chemical compounds through the positive list system discussed above.

### 3 Research target: Construction of an efficient traceability system



**Fig. 1** Traceability system for RMs used in analysis of volatile organic compounds.

To recapitulate the previous chapter, the problem with present traceability system for RMs lies in the dependence on national RMs. Because the system consists of the series of “calibration chains” for the same chemical compound, the system cannot respond promptly to the need for RMs to analyze the growing number of chemical compounds. Although this problem can be solved if minimum types of higher-order RMs could be used to calibrate a wide range of working RMs, this is not possible with current calibration technology, which is designed to calibrate like chemical compound with like chemical compound. An entirely new calibration technology must be developed and introduced: a universal calibration technology capable of analyzing chemical compounds independently of their molecular structure.

The aim of this study is to develop a new calibration technology to realize a system that efficiently secures traceability to the wide range of working RMs without creating national RMs for each chemical compound. Given that the vast majority of chemical compounds subject to strengthened regulation in recent years are organic compounds, we developed a universal calibration technology targeting organic compounds.

## 4 An analytical method that achieves our objectives: Quantitative NMR

### 4.1 The required calibration technology

Absolute values for amount-of-substance can be obtained using SI-traceable measurements. This type of measurement is known as the primary method of measurement<sup>Term 6, [2]</sup>. Table 1 shows a list of analytical methods certified as primary methods of measurement, divided into primary direct methods and primary ratio methods. The primary direct methods, also called the absolute measurement methods, are defined as “the methods for measuring the value of an unknown without reference to a standard of the same quantity.” Examples of primary direct methods are coulometry<sup>Term 7</sup>, gravimetry<sup>Term 8</sup>, and the freezing point depression method<sup>Term 9</sup>. Because these analytical methods yield absolute values for amount-of-substance, they are appropriate for valuing the national RMs. However, in general, they tend to be slow and their application are limited to short list of substances, and they are not suitable candidates as universal calibration technology that is the objective of this study. Primary ratio methods, on the other hand, are already in practical use. They are defined as “methods for measuring the value of a ratio of an unknown to a standard of the same quantity; its operation must be completely described by a measurement equation.” They include titrimetry<sup>Term 10</sup> and isotope dilution mass spectrometry<sup>Term 11</sup>. Another analytical approach that qualifies as a primary ratio method, though not well established as an analytical technology, is the quantitative nuclear magnetic resonance (quantitative NMR).

A measurement method that can be applied to the calibration of a wide range of working RMs must satisfy the following conditions:

- 1) It must satisfy market demands regarding uncertainty, while also provide speed and simplicity of use.
- 2) It must be highly versatile and applicable to a wide variety of chemical compounds (general organic compounds for the purposes of this study).

Quantitative NMR is the most feasible candidate that can satisfy both conditions 1) and 2), although the answer is not yet fully established. Accordingly, in this study, we endeavored to establish quantitative NMR as a universal calibration technology for working RMs in organic compounds.

#### 4.2 Principles of quantitative NMR

NMR is one of the main methods for determining the molecular structure of a chemical compound. It has an extensive track record in unraveling molecular structures, including the analysis of complex molecules such as proteins. Information obtained using NMR, such as chemical shift (the resonance peak position dependent on atomic bonding and the ambient environment) and spin-spin coupling (a split of the peak due to bonded nearby nuclei), provide hints about the chemical species and ambient environment of a molecule. In addition, the area ratio of various peaks, which resonates according to different chemical shifts, generally indicates the ratio of the number of atomic nuclei contributing to the peaks. As Figure 2 shows, the area ratio of  $^1\text{H}$  NMR signals can easily be used to confirm the relative number of protons for the resonances, which is vital for the qualitative analysis

of organic compounds.

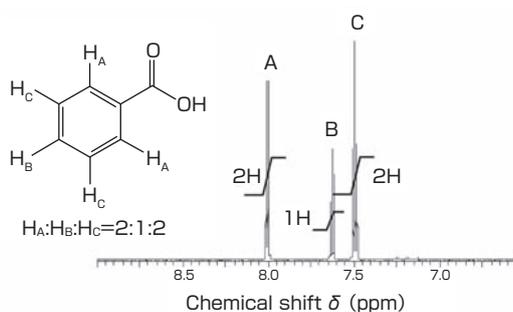
Conventionally, this aspect of NMR was used exclusively to determine the chemical structure, solely by expressing the number of protons as a ratio in a molecule. However, the concept can be applied differently. If the molecular structure of an organic compound is already known and assignments of its  $^1\text{H}$  NMR spectrum has been set, the number of protons contributing to each resonance peak is known, and this information can be applied to the quantitative analysis of chemical compounds. Thus, when the  $^1\text{H}$  NMR measurement is performed by adding a reference chemical compound to a sample solution separately in an analyte (substance to be analyzed) solution, the spectra of the two chemical compounds overlay each other, as shown in Fig. 3. At this point, if the mass (weight), molecular weight, and purity of the added reference chemical compound (hereinafter, will be called the Primary Standard: PS) are known, the amount-of-substance (number of molecules) corresponding to peak I in Fig. 3 will also be known, and can be used as the criterion for finding the number of molecules in the analyte. To illustrate with a specific example, if the number of protons in PS (I) is the same as the number of protons in analyte (D) (the number is 6 for both), the ratio of the areas for peak I and peak D indicates the relative number of molecules. As such, the relationship can be expressed as follows:

$$(\text{Peak area I})/(\text{Number of molecules of PS}) = (\text{Peak area of D})/(\text{Number of molecules in analyte})$$

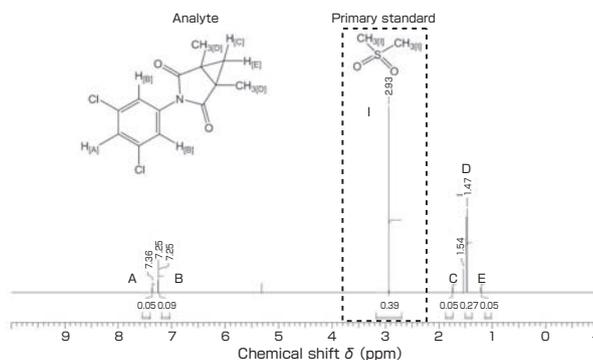
Since the number of molecules in PS is already known, the

**Table 1** Types of primary methods of measurement and their characteristics.

Analytical method	Primary direct method			Primary ratio method		
	Coulometry	Gravimetry	Freezing point depression method	Titrimetry	Isotope dilution mass spectrometry	Quantitative NMR
Outline of analytical method	Amount of electricity used in electrolysis of specified substances is measured.	Settling quantity of specified substances in solution is measured.	Relationship between fraction melted and temperature around the melting point is measured.	The specified substance is measured using chemical reactions.	Mass spectrometry is performed using a stable isotope.	The ratio of areas of $^1\text{H}$ peaks with different chemical shifts is measured.
Main target substance	Metallic elements	Inorganic salts	High purity organic compounds	Acid, base, elements	Trace metals trace organic compounds	Organic compounds
Reference standard	Not required	Not required	Not required	Reference standards based on the principles of titration are required.	Required for each analyte	A reference standard for $^1\text{H}$ is required.
Uncertainty (less than 1 %)	○	○	○	○	○	△(Unknown value)
Rapid analysis	×	×	×	×	○	○
General applicability	×	×	×	×	×	○



**Fig. 2** Qualitative analysis of chemical compounds using  $^1\text{H}$  NMR.



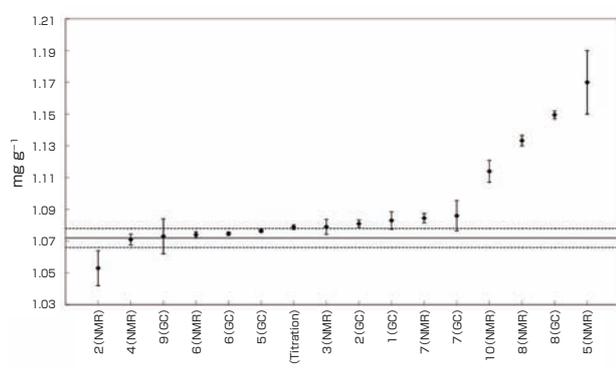
**Fig. 3** Quantitative analysis of chemical compounds using  $^1\text{H}$  NMR.

number of molecules in the analyte can be obtained. The mass (weight) and molecular weight of the target substance can then be used to determine the purity of the analyte<sup>[3]</sup>. Therefore, quantitative NMR is, in principle, a primary ratio method which can be used to obtain traceable measurement values for the number of protons — that is, amounts of substance in a sample.

In the example in Fig. 3, both the analyte and the PS are pure substances. After weighing the two substances individually, they are dissolved in a deuterated solvent, and quantitative NMR is used to measure the purity of the analyte using the mass ratio of the two substances. Working RMs, in contrast, are often supplied in the form of solution. If supplied at a certain concentration (about 0.1 %), quantitative NMR can be applied by dissolving the working RM in an appropriate deuterated solvent. The concentration of working RM can be found from the number of molecules obtained for the analyte, the mass of sample solution added, and the number of molecules in the analyte.

#### 4.3 Feasibility of quantitative NMR

National metrology institutes in several countries (including AIST), which are members of the Consultative Committee for Amount of Substance (CCQM)<sup>Term 12</sup>, have shown interest in the possibility of applying quantitative NMR as a primary ratio method, which was first suggested by Germany's Federal Institute for Material Research and Testing (BAM). In 2001, the Laboratory of the Government Chemist (LGC) in the United Kingdom and BAM served as pilot laboratories to conduct an international comparison<sup>Term 13</sup> for the quantitative analysis of ethanol in aqueous solution, with the participation by 10 institutes in key countries. On this occasion, measurements were conducted on the same sample using conventional analytical approaches such as gas chromatography (GC) as well as quantitative NMR<sup>[4]</sup>. The sample was precisely



**Fig. 4 Results of international comparison on quantitative analysis of ethanol in aqueous solution.**

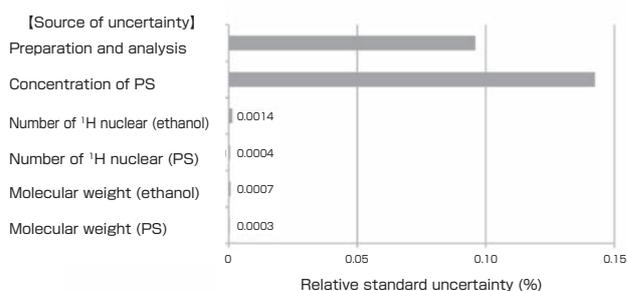
The solid line indicates the preparation value; the dotted line indicates uncertainty for the preparation value. No. 6 is the result for NMIJ/AIST. Participants: BAM (Germany), KRISS (Korea), LGC (UK), LNE (France), NIST (USA), NMI (Netherlands), NMIJ (Japan), NRC (Canada), NRCCRM (China), and VNIM(Russia).

produced by LGC, one of the pilot laboratories. The ethanol concentration was  $1.072 \text{ mg/g} \pm 0.006 \text{ mg/g}$ , but this value was not disclosed to the participants. Also, BAM separately supplied a deuterated water solution of PS (3-trimethylsilyl sodium propionate- $d_4$ ) of known concentration to the participating institutions that declared to conduct the quantitative NMR measurement.

The measurement results were reported individually to the pilot laboratory. Figure 4 is a summary of the results. Each data point represents a reported result. The adjacent error bar is the measurement uncertainty estimated by each participating institution (95 % confidence interval). The uncertainty of the quantitative NMR results from most institutions was in the range that could be described as percentage, and some of the results deviated significantly from the preparation values. In short, it was found that the quantitative NMR lacked accuracy compared to the conventional analytical methods such as GC. From the result of this international comparison, it was determined that the quantitative NMR did not offer sufficient technical accuracy. This view remains essentially unchallenged in the international scientific community today.

At the same time, Fig. 4 shows that the value reported by AIST closely matched the preparation value and its uncertainty was considerably smaller than the quantitative NMR findings of other participating institutions. This is why AIST takes a different stance on quantitative NMR. The uncertainty AIST reported to the pilot laboratory for quantitative NMR in the international comparison is illustrated in Fig. 5. Upon evaluating the relative standard uncertainties of each component, we found that the greatest factor was the uncertainty of the concentration of  $^1\text{H}$  PS supplied by the pilot laboratory. Because the uncertainty of AIST's quantitative NMR measurement was much smaller, it became clear that a much smaller measurement uncertainty would have resulted if AIST had supplied its own more accurate PS.

It should be emphasized that the quantitative NMR offers a major advance in versatility. Whereas GC and other



**Fig. 5 Uncertainty for  $^1\text{H}$  NMR in the international comparison on quantitative analysis of ethanol in aqueous solution.**

conventional analytical calibration technologies applied in the international comparison can only be used to compare the concentrations of like chemical compounds (PS must be the same chemical compound as the measured substance), quantitative NMR can compare quantities of chemical compounds of different types (that is, PS does not have to be the same type of chemical compound as the measured substance). As such, although quantitative NMR requires at least one substance including  $^1\text{H}$ , it can be used to measure any organic compound that includes proton, and a wide range of applications can be expected accordingly. The Authors believe that quantitative NMR can be applied in the calibration of working RMs by developing and integrating certain elemental technologies. These are discussed below.

## 5 Development and integration of elemental technologies to realize the quantitative NMR

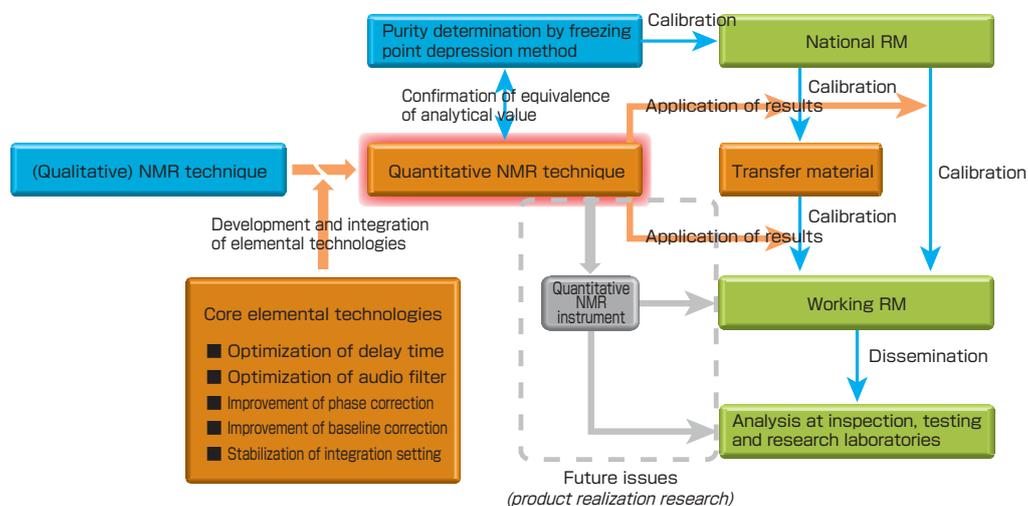
### 5.1 Core elemental technologies

Figure 6 illustrates the elemental technologies developed by the authors, and the combination necessary to realize the potential of quantitative NMR as a universal calibration technology for working RMs. The features required of NMR differ greatly depending on whether the technology is optimized for qualitative analysis or for quantitative analysis, as in our case. With quantitative NMR, the highest priority is to observe the signal in accurate proportion to the number of atomic nuclei in the analysis, rather than improving measurement speed or improving the signal-to-noise ratio (S/N). We therefore revised the conditions for selecting the core elemental technologies.

The first elemental technology corrects a signal amplification issue. Generally speaking, NMR signals relax throughout its lifetime called the spin lattice relaxation time ( $T_1$ ), which is the time taken for the atomic nuclei to settle from their excited state to their ground state. This period varies according to the

environment of protons (such as bonding with other atoms). When NMR is performed for qualitative analysis, the sample is irradiated with microwave pulses with short cycle to increase the signal and to improve S/N. In such case, the delay time may be shorter than  $T_1$ , where excitation pulse is applied before all protons settled to their ground state. As result, differences in  $T_1$  among the protons of analyte and PS make it impossible to obtain the peak area in correct proportion for the number of protons in each proton. We resolved this problem by measuring the relationship between repetition time and peak area. By taking delay time six times or greater than  $T_1$  for the analyzed protons, it was demonstrated by experiment that 99.9 % or more of original signal intensity could be obtained, providing a stable peak-area ratio<sup>[5]</sup>. By ensuring that the delay time was sufficiently longer than the longest  $T_1$  for all protons in the analyte, it was possible to obtain accurate peak-area ratio that was unaffected by the  $T_1$  of the protons (though the measurement time increased several times longer than the conventional method).

The second elemental technology also concerns the S/N. Normally, S/N in the NMR signal is further improved by using an audio filter to narrow the bandwidth. However, this filter is not “flat” in sensitivity throughout the bandwidth, but exhibits severe loss of sensitivity at both ends of the filter bandwidth. Depending on the chemical shift, this loss of sensitivity can be in the range of several percents. Greater the chemical shift in the protons observed in the analyte and PS, more difficult it is to obtain an accurate peak-area ratio. To obtain flat sensitivity, we set the audio filter to cover 60 %~70 % of bandwidth and also widened the spectral width for data acquisition to 100 ppm, compared to less than 20 ppm in the conventional setting. This setting allowed the resulting spectrum to remain unaffected by sensitivity loss caused by filter for all chemical shifts. While such filter settings are not practical for ordinary NMR that involves handling of large volume data, we were able to solve several issues by taking an unconventional



**Fig. 6 Development of elemental technologies for the construction of universal calibration technology and the process of integration.**

approach with priority on measurement accuracy<sup>[5]</sup>.

In addition to the two elemental technologies described above, the Authors found that to improve the reproducibility of measurement results, phase correction, baseline correction, and peak area integration setting (range) were more important compared to other minor factors.

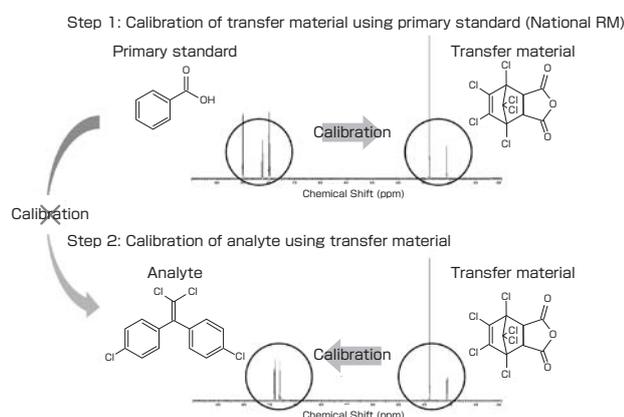
### 5.2 Use of transfer materials

Although quantitative NMR requires  $^1\text{H}$  as the PS, the analyte does not have to be the same substance. The PS (limited to pure substances in this discussion) must satisfy the following conditions:

- 1) It must have as little impurities as possible, to keep the uncertainty for its purity value small.
- 2) It must dissolve easily in wide range of solvents, and must be stable in solution.
- 3) It must have low volatility (sublimability) and absorbency, so its mass (weight) can be measured easily.
- 4) Its chemical shift must not overlap with that of the target substance.

Although some national RMs satisfy these conditions for PS, many national RMs do not satisfy requirement 2), because a suitable solvent for dissolving both the PS and the analyte has not been found. Also, some national RMs do not satisfy 4), as the PS used depends on the analyte, and different PSs must be used with certain analytes.

The number of national RMs cannot be reduced if different PSs must be prepared according to various analytes. The Authors solved this problem using the calibration methods illustrated in Fig. 7, marshaling the advantages of quantitative NMR. We achieved this by selecting the transfer materials or chemical compounds whose chemical shifts do not overlap with either the PSs or the analytes. In Step 1, the PS (national RM) is used to calibrate the characteristic peak of the transfer material using quantitative NMR. In Step 2, the characteristic peak of the calibrated transfer material



**Fig. 7 Use of transfer material in quantitative NMR.**

is adopted as the standard for calibration of the analyte. By adopting this two-step calibration method, the number of national RMs, which anchor the traceability system, can be minimized. Moreover, the transfer material does not need to be homogeneous or long-term stable like the RMs, so a wide range of materials is available for selection according to their match with a given analyte. The introduction of transfer materials to quantitative NMR was an important technological development in the process of synthesizing the elemental technologies.

### 5.3 Evaluating the integrated technologies

In sections 5.1 and 5.2, we described how several elemental technologies were integrated to construct a calibration technology using quantitative NMR. Next, we demonstrated the reliability of the technologies by comparing them with long-established techniques. To do this, we first selected several target substances from commercially available, high-purity compounds. Their purity values were determined using the freezing point depression method, a well-established primary direct method that AIST has been using for the valuation of national RMs (see Table 1). Then we measured the same samples with the newly developed quantitative NMR to find the purity value, and checked whether the two values matched in the range of their respective uncertainties.

As the PS for measurements using quantitative NMR, we used benzoic acid (NIST SRM 350a,  $99.9958\% \pm 0.0027\%$ ), a national RM distributed by the National Institute of Standards and Technology (NIST) of the United States. We performed the two-step calibration process described above using dimethyl sulfoxide or 1,4-bis(trimethylsilyl)benzene- $d_4$  (1,4-BTMSB- $d_4$ ) as the transfer material, as the peak of the chemical shift for several substances overlaps the peak for benzoic acid. To dissolve the PS and the analyte, solvents were selected from a number of deuterated solvents, to minimize skewing of results from the protons of any impurities in the solvent. The solubility and other characteristics of the PS and analyte were also taken into consideration, and a solution with a concentration of about 1000 mg/L was prepared.

The analytical results are summarized in Table 2. Although in many cases the uncertainty was larger for the purity values by quantitative NMR compared to freezing point depression method, the values for the two methods matched within the uncertainty ranges, demonstrating that our calibration technology using quantitative NMR was sufficiently reliable<sup>[6]</sup>. The uncertainty for quantitative NMR was between 0.3 % and 1.2 % ( $k=2$ , 95 % confidence interval). Although this accuracy as a purity measurement technology is somewhat inferior to the freezing point depression method, quantitative NMR can be used to calibrate substances to which the freezing point depression method cannot be applied, including a wide range of organic compounds, and

it satisfies the market demand for the uncertainty levels in working RMs.

## 6 Issues for further study

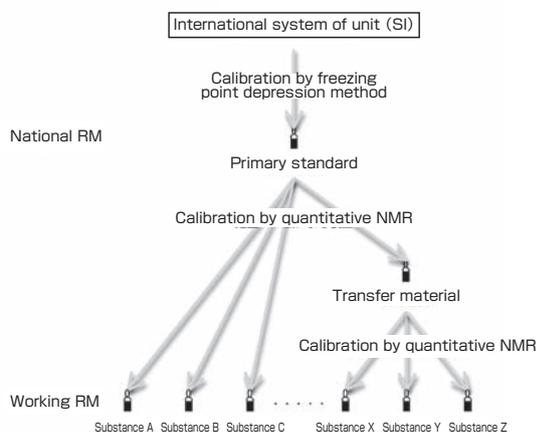
We envision a transfer from the current one-to-one traceability system based on separate national RMs for each substance, to one-to-many traceability system in which several substances can be traced to just a few national RMs. So far, we made advancement for the development of universal calibration technology, a core technology applicable to numerous organic compounds. After establishing an ideal scenario for this project, we began by developing elemental technologies, using irradiation pulse delay time and optimization of audio filters. We then demonstrated that these calibration technologies could satisfy market

requirements for uncertainty. We learned that the transfer materials could be used to minimize the number of national RMs required as standards for amount-of-substance. Finally, we plotted a roadmap toward an efficient traceability system, as illustrated in Fig. 8.

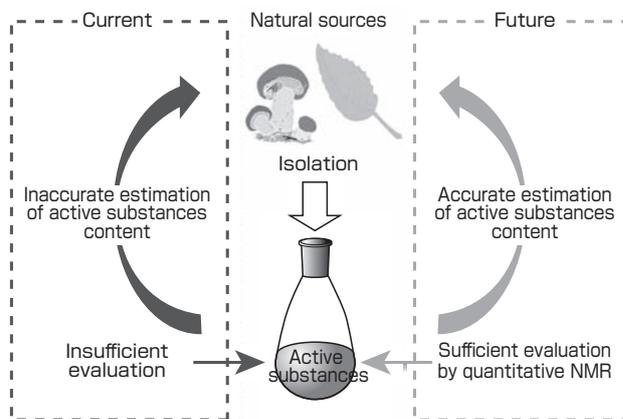
The system we outlined represents a quantum leap in the efficiency of traceability systems, since it removes the need to maintain one-to-one traceability chain from national RMs to working RMs for individual substances. It is an entirely new approach to RMs, unseen elsewhere in the world. The novelty of this technology, however, means that it is necessary to conduct numerous proving tests and to publish the results. The quantitative NMR technique must be standardized as an analytical method, and new international comparisons will be required at national metrology institutes

**Table 2 Purity analysis results for organic compounds using quantitative NMR.**

Target substance	Freezing point depression method		Quantitative NMR				
	Reference value (%)	Uncertainty (% , $k=2$ )	Analytical value (%)	Uncertainty (% , $k=2$ )	Primary standard	Transfer material	Solvent
<i>trans</i> -Nonachlor	99.6	0.2	99.5	0.6	Benzoic acid	----	Acetone- $d_6$
<i>cis</i> -Nonachlor	99.8	0.2	99.9	0.5	Benzoic acid	----	Dichloromethane- $d_2$
Oxychlorodane	99.9	0.1	99.3	0.5	Benzoic acid	----	Dichloromethane- $d_2$
Endrin	99.7	0.2	99.2	0.8	Benzoic acid	----	Dichloromethane- $d_2$
<i>trans</i> -Chlordane	99.8	0.3	99.5	0.6	Benzoic acid	----	Dichloromethane- $d_2$
<i>cis</i> -Chlordane	99.7	0.4	99.1	0.5	Benzoic acid	----	Dichloromethane- $d_2$
Trichlorfon (DEP)	99.7	0.3	99.6	0.5	Benzoic acid	----	Dichloromethane- $d_2$
Heptachlor	99.7	0.3	99.3	0.3	Benzoic acid	----	Dichloromethane- $d_2$
4,4'-DDT	99.6	0.3	99.9	1.2	Benzoic acid	Dimethyl sulfone	Acetonitrile- $d_3$
4,4'-DDE	99.7	0.3	99.8	0.7	Benzoic acid	Dimethyl sulfone	Acetonitrile- $d_3$
4,4'-DDD	99.8	0.2	99.9	0.6	Benzoic acid	Dimethyl sulfone	Acetonitrile- $d_3$
Procymidone	99.9	0.2	99.3	0.5	Benzoic acid	Dimethyl sulfone	Dichloromethane- $d_2$
Fenobucarb (BPMC)	99.8	0.2	99.8	0.7	Benzoic acid	1,4-BTMSB- $d_4$	Dichloromethane- $d_2$
Fenitrothion (MEP)	99.8	0.3	99.6	0.6	Benzoic acid	1,4-BTMSB- $d_4$	Dichloromethane- $d_2$
$\alpha$ -HCH	99.6	0.3	99.2	0.6	Benzoic acid	----	Dichloromethane- $d_2$
$\beta$ -HCH	Inapplicable (thermal decomposition)		99.5	0.3	Benzoic acid	----	Dichloromethane- $d_2$
Atrazine	Inapplicable (thermal decomposition)		99.7	0.7	Benzoic acid	1,4-BTMSB- $d_4$	Dichloromethane- $d_2$
EPN	Inapplicable (Uncrystallized)		99.4	0.7	Benzoic acid	1,4-BTMSB- $d_4$	Dichloromethane- $d_2$
Diazinon	Inapplicable (Uncrystallized)		99.8	0.7	Benzoic acid	1,4-BTMSB- $d_4$	Dichloromethane- $d_2$
Malathion	Inapplicable (Uncrystallized)		99.5	0.7	Benzoic acid	----	Dichloromethane- $d_2$
Etofenprox	Inapplicable (Uncrystallized)		99.5	0.5	Benzoic acid	Dimethyl sulfone	Dichloromethane- $d_2$



**Fig. 8 Efficient traceability system with quantitative NMR.**



**Fig. 9 Quantitative evaluation of active substances in natural sources using quantitative NMR.**

around the world. More work must be done before one-to-many traceability can be firmly established.

At the same time, it is necessary to build the infrastructure that allows the industrial community to perform calibration of the wide range of working RMs that are in demand by the society. For this purpose, national RMs that are easy to use with quantitative NMR must be supplied along with sample applications. Automation tools are also necessary, covering all processes from measurement parameter sets using quantitative NMR to data analysis.

## 7 Future directions

Quantitative NMR has great potential marketability, as the necessary analytical equipment are commercialized (Fig. 6: Future issues). As reasonably priced, easy-to-use equipment, which are optimized for quantitative NMR, become available, and applications for nuclei other than  $^1\text{H}$  are developed, they will find use not only in calibration technologies for working RMs, but also in quantitative analysis of several organic compounds occurring in numerous fields conducted at a wide variety of proving, testing, and research laboratories.

Many de facto commercial calibration standards are in use today, even though evaluation of their purity or concentration remains inadequate. For example, for active substances in natural sources, such as bioactive constituents and herbal medicines, quantitative analysis often depends on the samples of isolated constituents or the commercially available reagents. Quantitative NMR can offer highly reliable and effective quantitative analysis in such cases (see Fig. 9)<sup>7)</sup>, where the discovery of appropriate standard would normally be difficult.

Perhaps most exciting of all, an efficient traceability system based on this calibration technology for organic compounds may provide an effective scheme for responding flexibly to today's proliferating demand for RMs. Although core technologies other than quantitative NMR have not yet been demonstrated, universal calibration technologies that can be used similarly in the construction of a rational traceability system may be developed. The Authors hope that this paper will serve as a starting point for the development of such universal calibration technology.

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Finally, Dr. Shinichi Kinugasa (AIST) provided valuable assistance in writing this paper, for which we thank him sincerely.

## Terminology

- Term 1. Positive List System: Established in 2006 based on a revision of Japan's Food Sanitation Law, this system prohibits the sales of foods that contain agricultural chemical residues above a certain quantity. In cases where the safe (not harmful to human) quantity has been specified (called the residue level), the agricultural chemical must be below that quantity. In case where the safe quantity has not been specified, a uniform limit of 0.01 ppm is applied.
- Term 2. Official Method of Analysis: A set of analytical procedures officially published and recognized in accordance with laws governing chemical compounds, to enable comparison of analytical results among different testing laboratories and samples. An official method of analysis must be robust and universally applicable. Examples used in Japan are Japanese Industrial Standard (JIS), Japanese Agricultural Standard (JAS), and Japanese Pharmacopoeia (JP).
- Term 3. Certified reference material (CRM): In ISO Guide 35, which provides the international guidelines for RMs, this is defined as "reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability."
- Term 4. Traceability: The characteristic of a measurement result, where the result can be linked to a known reference standard (usually a national standard) through an unbroken chain. In the 3<sup>rd</sup> version of

the *International Vocabulary of Metrology* (VIM), this term is amended to “metrological traceability” to distinguish from the term used to manage the shipping histories of foods and other goods.

- Term 5. National metrology institute: A research institute that sets a country’s official measurement standards. In Japan, it is the National Metrology Institute of Japan within the National Institute of Advanced Industrial Science and Technology.
- Term 6. Primary method of measurement: The method used to define national RMs. It is defined as follows: “primary method of measurement is a method having the highest metrological qualities, whose operation can be completely described and understood, for which a complete uncertainty statement can be expressed in terms of SI units.”
- Term 7. Coulometry: The method of measuring the amount-of-substance of an analyte from measurements of current and time when electrolysis is applied to a specific substance based on Faraday’s Law. It is used in the analyses of inorganic ions of metallic elements as well as of trace amounts of moisture.
- Term 8. Gravimetry: An analytical technique in which the quantity of an analyte in a sample is found by separating the analyte from the rest of sample using a reagent that reacts specifically to that component. The resulting mass is used to determine the quantity of the analyte. Generally, mass is found by precipitating the selected component out of the solution, but it can also be found by separating the selected component from the sample as gas, adsorbing the component using an adsorbent, and then calculating the mass from the amount adsorbed.
- Term 9. Freezing point depression method: An analytical technique that finds the amount-of-substance fraction of impurities in a sample as a proportion of its amount-of-substance by measuring the temperature and enthalpy of impurities in a sample, as its freezing point decreases. It is generally used to determine the purity of high-purity organic compounds.
- Term 10. Titrimetry: This is volumetric measurement in a limited sense. A solution that includes an RM that reacts with the sample is dropped into a sample solution, and the quantity of RM consumed before the equilibrium is reached is measured to find the quantity of the analyte in the solution. Depending on the chemical reaction used, the method includes neutralization (acid-base) titration, oxidation-reduction titration, complex formation titration, or precipitation titration.
- Term 11. Isotope dilution mass spectrometry: A method of finding the quantity of an analyte in a sample using substance labeled with a stable isotope. The labeled substance is added to the sample, and the signal ratio of the mass spectrums of the analyte and

labeled substance are obtained. Because the chemical properties of the analyte and the labeled substance are roughly identical, the effect of the process of sample preparations with significant impurities can be cancelled (the signal ratio of the analyte and its labeled substance is maintained). In this technique, the concentration of the labeled substance for the RM must be known in advance.

- Term 12. Consultative Committee for Amount of Substance (Comité Consultatif pour la Quantité de Matière: CCQM): One of the consultative committees formed under the aegis of the International Committee of Weights and Measures (Bureau International des Poids et Mesures: BIPM) that consists of the Meter Convention member institutions. Established in 1993, this consultative committee discusses issues on metrology in chemistry.
- Term 13. International comparison (CCQM inter-comparison): Comparison among calibration laboratories to confirm the degree of equivalence in the calibration and measurement capabilities and values assigned to RMs between various national metrology institutes. Normally, this process begins with an international comparison for research purposes, called a pilot study. After the technical groundwork has been established to a certain degree, an official international comparison, called a key comparison, is performed.

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## Authors

### Toshihide Ihara

Completed the doctoral course in engineering at Tokyo Metropolitan University in 1994. In 1996, he joined the National Institute of Materials and Chemical Research of the Agency of Industrial Science and Technology, where he worked on the development of RMs for volatile organic compounds and other organic compounds. At the National Institute of Standards and Technology in the United States from 2002 to 2003, he pursued development of RMs related to health foods. Moving to BIPM from 2005 to 2006, he worked on purity evaluation techniques for organic compounds. In 2006, he was assigned to his current position at the RMs Systems Division of the National Metrology Institute of Japan of AIST (now the Measurement Standards Systems Division), where he conducts research on standards dissemination systems in the fields of environmental science, foods, and clinical testing. In this paper, he conceived the idea for a new traceability system in chemical metrology and designed specific approaches.

### Takeshi Saito

Joined the National Institute of Materials and Chemical Research of the Agency of Industrial Science and Technology, where he engaged in research in advancing Spectral Database (SDBS) for Organic Compounds, which is now publicly available on the Internet. He is now in charge of this project. Since joining the Institute, he has made extensive use of NMR in research. In a contract work with the New Energy and Industrial Technology Development Organization (NEDO), he worked on a platform for measurement at nanoscale, focusing on the measurement of particle diameter in liquid using NMR. Currently he is working to improve the precision and accuracy of quantitative analytical techniques using NMR. He also works on the general application of quantitative analytical methods. In this paper, he constructed the basic technology for quantitative NMR.

### Naoki Sugimoto

After completing the doctoral course in Natural Sciences and Technology at Kanazawa University in 1997, he joined the National Institute of Health Sciences (NIHS) in the same year. There, he worked on setting standards for food additives and other substances. From 2005 to 2006, at the Food and Drug Administration (FDA) and Center for Food Safety and Applied Nutrition (CFSAN) in the United States, he developed methods for analyzing food additives, to promote international standardization. Since 2008, he became the chief of 3rd Section, Division of Environmental Chemistry at NIHS, where he currently works on setting criteria and developing guidelines of analytical methods for chemical substances related to water quality. In this paper, he contributed to the application technologies for quantitative NMR and to the proposal of automation tools to make the technology accessible to the general public.

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## Discussion with Reviewers

### 1 General evaluation

#### Comment (Akira Ono)

Today the society is facing difficulties as the development of techniques for accurate analysis of harmful organic compounds in

foods and environment cannot keep up with the ever-diversifying demands. The quantitative NMR developed in this research project, along with the new, more efficient traceability system, strike at the heart of this problem. They hold the potential for a revolution in the metrological traceability.

I believe your approach represents the first use of NMR equipment for quantitative analysis that was originally developed for qualitative analysis. What makes this project a particularly outstanding *Type 2 Basic Research* is that you returned to the development of elemental technologies to complete the core technology of quantitative NMR.

#### Comment (Hisao Ichijo)

Your writing shows clearly how you steadily pursued your program of research and development, by drawing scenarios along the way toward the ambitious goal of switching to a new, more efficient traceability system based on calibration technology.

### 2 Focus on specific descriptions

#### Question and comment (Akira Ono)

You advocate a new traceability system using quantitative NMR. Since that alone is a remarkable accomplishment, I think you should describe this system in a more understandable way. Perhaps you could provide a simple description of the freezing point depression method and how it is used to measure the purity of pure substances.

#### Question and comment (Hisao Ichijo)

Your paper clearly describes the objectives, how they relate to the demands of society, the elements of technology, and so forth. You determined that the quantitative NMR is appropriate (because it can be applied to a wide range of substances within the uncertainty range the market demands), and that the freezing point depression method is inappropriate (because of crystallization problems). I think your paper will be easier to understand if you explain more fully the research processes by which you came to your conclusions (crystallization is difficult, number of applicable substances is limited, and so on).

#### Answer (Toshihide Ihara)

We rewrote the paper to change the rationale behind the comparison with freezing point depression method and to focus more closely on the technical structure of quantitative NMR. The freezing point depression method is a well-established technique. We described it only to demonstrate the appropriateness of quantitative NMR.

### 3 Illustration of research scenarios and integration of elemental technologies

#### Question and comment (Akira Ono)

Please add some figures illustrating your research scenarios for *Type 2 Basic Research* and the integration of elemental technologies, to make your paper more accessible to a general readership.

#### Answer (Toshihide Ihara)

We added Fig. 6 to illustrate the process of integrating the elemental technologies to construct the universal calibration technology.

### 4 Selection of primary standards

#### Question and comment (Akira Ono)

In the purity determinations of organic compounds in Table 2, benzoic acid, a national RM from NIST of the United States, is used as a primary standard for quantitative NMR. Why didn't you use one of the national RMs as high-purity organic compounds available from AIST?

#### Answer (Toshihide Ihara)

Benzoic acid (NIST SRM 350a), the NIST national RM used in our study, satisfies the conditions 1) to 3) as outlined in section

5.2. We therefore determined that it is the ideal RM among the national RMs currently available for quantitative NMR. Certain national RMs at AIST, such as potassium hydrogen phthalate (NMIJ CRM 3001-a) and 1,4-dichlorobenzene (NMIJ CRM 4039-a), qualify for condition 1), but potassium hydrogen phthalate does not dissolve easily in organic solvents, and therefore, fails to satisfy condition 2) in our view. Similarly, 1,4-dichlorobenzene is highly sublimable and does not meet condition 3). At present, no national RMs have been developed specifically for quantitative NMR. We are currently in the process of developing the AIST national RMs that satisfy condition 4) as well as 1) to 3).

## 5 Final status of primary standards

### Question and comment (Akira Ono)

You assert that, in principle, the ideal outcome of the application of quantitative NMR would be the development of a single primary standard that serves as the national RM for all organic compounds. Realistically, how many national RMs do you expect are required when this future traceability system is completed? Do you have any specific candidates in mind as organic compounds for the national RMs?

### Answer (Toshihide Ihara)

In this study, our priority was to minimize the number of national RMs required, thus reducing development time and expense. That is why we proposed the use of transfer materials in the multi-stage calibration process. Benzoic acid has served as the primary standard for all organic compounds we have measured so far. This success gives us confidence that a traceability system based on a single national RM can be constructed for all organic compounds for which <sup>1</sup>H NMR measurement can be performed.

On the other hand, such a traceability system has its disadvantages. Multi-stage calibration is time-consuming and increases uncertainty. If the accuracy or swiftness of analysis becomes more important for users, it is necessary to develop multiple national RMs with different polarities and chemical shifts. We are looking at ways of restricting calibration to single stage. To handle organic compounds that do not have protons, it is necessary to develop quantitative NMR for other nuclei, such as phosphorus and fluorine, along with the corresponding national RMs.

## 6 Preparation and use of transfer materials

### Question and comment (Akira Ono)

I ask about how the transfer materials are used. When this new, efficient traceability system is completed in the future, will AIST produce, store, and disseminate these transfer materials as needed? Or can the reagent manufacturers that produce working RMs make the transfer material when needed, and dispose it when they are done?

### Answer (Toshihide Ihara)

In our paper, we envisioned the transfer material to be prepared by the developers or suppliers of the working RMs (RM producers) according to their objectives. To ensure appropriate evaluations, the transfer materials will not be prepared for each batch, but the RM producers will be responsible for producing and storing them for a certain period.

Also, as described in chapter 7, if quantitative NMR becomes widely used as a quantitative analytical method for organic compounds, prepared transfer materials can be used. Moreover, AIST or RM producers may supply easy-to-use transfer materials as RMs.

## 7 Comparison of quantitative NMR and freezing point depression method

### Question and comment (Akira Ono)

My question concerns the analytical results in Table 2. In

the freezing point depression method, uncertainty for purity determinations rarely exceeds the upper limit of 100 %, whereas in many cases using quantitative NMR, the upper limit for analytical result exceeds 100 %. Such results are unreasonable. Since the freezing point depression method directly measures impurities in pure substance, the upper limit for analytical result over 100 % is rare. Using quantitative NMR, on the other hand, measurement of the main components is performed when the concentration of the pure substance is diluted to about 1000 mg/L. Isn't this one reason why the upper limit for analytical result can rise above 100 %? Isn't this the case where quantitative NMR is fine for measuring components in a solution but is inappropriate for measuring the purity of pure substances? If so, quantitative NMR seems to be most promising for *Product Realization Research* surrounded by the dotted line in Fig. 6. I'd like to hear the authors' views on this.

### Answer (Toshihide Ihara)

Although the factors contributing to the uncertainty of quantitative NMR are not separated in Fig. 5 between preparation uncertainty and measurement uncertainty, preparation uncertainty is not relatively small. Thus, when applied to purity determination, quantitative NMR is undeniably inferior to the freezing point depression method in terms of uncertainty for preparation of solutions, and purity determination higher than the upper limit for analytical result exceeding 100 % is obtained as a result, as you pointed out (however, this does not indicate any bias in the purity determinations).

The freezing point depression method cannot be applied to measure concentrations of components in solution, but there are many examples where the characteristics of quantitative NMR can be applied, as you also pointed out. Because many organic solvents contain hydrogen, we must find ways of reducing these effects so NMR can be applied to protons. In *Product Realization Research*, including the development of quantitative NMR equipment, solving the issue of protons in solution and enabling measurement of concentrations of components in solution are keys to establishing the use of quantitative NMR.

## 8 Other candidates for universal calibration technologies

### Question and comment (Akira Ono)

In chapter 7, "Future Directions," you raised the possibility that universal calibration technologies other than quantitative NMR may be found in the future. Are there any candidate calibration technologies at this time?

### Answer (Toshihide Ihara)

In section 4.1, we stated that a universal calibration technology should theoretically be an analytical method qualified as a primary ratio method (measures the value of a ratio of an unknown to a standard of the same quantity; its operation must be completely described by a measurement equation).

Although not yet established as an analytical technique, one candidate the Authors are examining is a combination of chromatography and atomic emission spectrometry. In this process, the analytes are separated from the sample by chromatography. Then each analyte is introduced into high-temperature plasma and atomized into constituent carbon, hydrogen, oxygen, and other atoms. These atoms can then be measured to find the emission of spectrally separated (for example) carbon atoms. By adding a primary standard containing a known quantity of carbon to the sample, the quantity can be combined with the emission of carbon to find the quantity of analyte, as the primary standard itself is also atomized. The point here is that the efficiency of atomization is not dependent on the molecular species. Currently, the combination of gas chromatography and helium-plasma atomic emission spectrometry can obtain uncertainty of 5 % (95 % confidence interval). Further

improvements are needed for the commercialization of this technique.

### 9 Reason for using deuterated solvents

#### Question and comment (Akira Ono)

You noted in section 4.2 that you used a deuterated solvent. Can you explain why you used deuterated solvents for quantitative NMR? Should we infer that using  $^1\text{H}$  (proton) solvents disable quantitative NMR?

#### Answer (Toshihide Ihara)

In our study,  $^1\text{H}$  was used as the measurement nucleus. When solvents contain  $^1\text{H}$  or protonated solvents are used, the  $^1\text{H}$  signals from the solvents become much stronger than those from the compounds intended to be observed. As a result, the dynamic range of an instrument may prevent the accurate measurement of the analyte signal. Deuterated solvents are used to minimize the  $^1\text{H}$  from the solvents to resolve this problem. This is, in general, not just for quantitative NMR, but is also for conventional  $^1\text{H}$  NMR measurements.

On the other hand, in the international comparison of ethanol, aqueous solution was used, and the solvent in this case

was protonated water ( $\text{H}_2\text{O}$ ) rather than deuterated water ( $\text{D}_2\text{O}$ ). Therefore, the problem of dynamic range may occur. In such case, the resonance frequency of the solvent (water) signal is irradiated selectively with low power radio frequency pulse to saturate this signal. This saturation pulse is immediately followed by a normal pulse. This approach, called the pre-saturation method, cancels the interference of a strong  $\text{H}_2\text{O}$  peak. Although power applied to this saturation pulse is low, peaks resonating at nearby frequencies are influenced by the pulse. This may compromise the accuracy of the analytical value obtained in this method. In other cases, irradiation strength, duration, and other factors must be set correctly to obtain the accurate analytical values. For these reasons, it is simple and safe to use a deuterated solvent.

Additionally, to maintain the stability of the magnetic field, resonance frequency of the deuterium signal from the solvent is monitored to adjust the strength of the magnetic field from time to time to maintain constancy of the signal frequency. This process is called a "deuterium lock." Since NMR measurements, including quantitative NMR, tend to take relatively long time, deuterium lock is indispensable to obtain spectra of high resolution. If the sample solvent is not deuterated, deuterated solvent must be added.

# Modeling the social acceptance of industrial technologies

## — Development of an eco-product diffusion analysis model that incorporates three existing models —

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[Translation from *Synthesiology*, Vol.2, No.1, p.23-31 (2009)]

In order to bring change to society through technological developments, analysis of the social acceptance of a given technology is indispensable. In this research, we developed a model that includes the effects of the diffusion of environmentally conscious products. To analyze the long term diffusions and to analyze the effects of various diffusion promoting measures, we have incorporated three existing models: the Bass diffusion model, the consumer preference model, and the learning curve model. These models have been argued for individually to date. The paper describes the research objective, existing models, the developed model, the related developed tools, and an analysis example.

**Keywords :** Social acceptance of technologies, eco-products, product diffusion model, Bass model, consumer preference

## 1 Introduction

Technology evolves through interactions with the society. There are periods of nightmare of technologies when new technologies are not accepted readily by the society<sup>[1]</sup>. To bring in changes on society through technological research and development, it is necessary to understand and formulate a model for the interaction between technology and society. This study is an attempt to create a model for the relationship between them. Needless to say, there are several phases and diverse facets in the relationship of technology and society. We aim to tackle related topics and to build a comprehensive and multi-faceted model by building up corresponding models one at a time.

This paper describes the research on building a model for the social diffusion of environmentally- conscious products or “eco-products” that we position as part of building up a corresponding model. This research was conducted as part of Global Warming Countermeasure Survey of the Japan Ministry of Economy, Trade and Industry (METI)<sup>[2][3]</sup>.

The research processes were as follows:

1. Clarification of research goal (chapter 2)
2. Survey of existing models (chapter 3)
3. Formulation of Model (chapter 4)
4. Data collection (chapter 5)
5. Tool development (chapter 6)
6. Analysis (chapter 7)

In this research, three existing models were integrated to achieve the research goal. One of the models was Bass model that was a representative product diffusion model, second

was conjoint analysis that was related to consumer preference model, and third was learning curve model that describes the cost reduction in the course of technological advancement. The foundation was the Bass model. The above processes will be described in the following chapters. Chapter 2 explains the objectives of the research, and chapters 3 outlines the existing studies on product diffusion analysis. Chapter 4 introduces the model that we developed in this research. Chapter 5 presents the collected data, and chapter 6 demonstrates the tool that we created to enable easy use of the model and data. Chapter 7 shows the example in which the model was applied to the assessment of diffusion of energy-saving air conditioners, and the final chapter states the conclusion and future issues.

In the course of research, the above six processes did not necessarily progress in one direction. Particularly, the discussions to and from 1 and 3 were repeated several times. In considering the model, the research goal was reviewed and the model was rebuilt and reviewed several times. The details of this process are described in Section 4.

## 2 Clarification of research objective

This study was conducted as part of Global Warming Countermeasure Survey of the METI. Some of the goals of the research were clear from the beginning, while others took shape during the process of the research. Both will be described as follows.

The goal of the survey was projection and analysis of diffusion of eco-products. The subjects of the diffusion analysis were following products:

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(1) Products that contributed to countering global warming (reduction of CO<sub>2</sub> emission)

(2) Products purchased by general consumers.

Specifically, they included energy-saving vehicles (hybrid cars etc.), energy-saving appliances (air conditioners, refrigerators, etc.), high-efficiency water heater, high-efficiency lighting, solar power generation system for home, and others.

In terms of whose viewpoint the analysis should take, it was

(3) Diffusion analysis useful to policymakers.

The objectives of the survey were to answer the following questions.

– To what level would the target eco-products diffuse at what speed?

– What would be the effect on diffusion when subsidy is granted to the eco-product?

– What would be the effect on diffusion if the energy-saving performance of the eco-product improves further in the future?

We call the first question as basic analysis, and the following two questions as factor-change-effect or sensitivity analysis.

(4) We develop a model that enables basic and sensitivity analyses.

(5) We create an analysis tool so that analysis could be conducted readily.

Finally, the period of diffusion analysis was set as follows:

(6) Analysis would involve the long-term spanning several decades.

While the first two points (target products) were determined at the beginning of the research, the following four points were unclear. It became apparent that clarifying the remaining four points was necessary in determining the appropriate model for the analysis. This will be addressed in chapter 4.

### 3 Survey of existing models

The models for diffusion analysis of products can be roughly divided into two categories. One is logistic curve model (Bass model) and the other is consumer preference model. Their characteristics are described below. Also, learning curve model that describes the long-term price reduction of new technology is often used as model of technological and production innovations. The three models are described below.

#### 3.1 Bass model [4]-[6]

Diffusion curve of a product often presents S-shape. Figure 1 shows the diffusion curves of major products in Japan. Frank Bass formulated the diffusion model by applying the logistic curve model, which was originally employed in physics and biology, to the dynamics of product diffusions<sup>[4]</sup>.

Mathematical formulation is as follows. When  $X_t$  is number of new purchases during period  $t$ ,  $N$  is final number of diffusion,

and  $n_t$  is diffusion rate during period  $t$  (percentage against  $N$ ), the equation will be as follows:

$$X_t = (p+r \cdot n_t) \cdot (1 - n_t) \cdot N \quad (1)$$

$p$  is called coefficient of innovation and  $r$  is called the coefficient of imitation. In Fig. 1,  $N \cdot n_t$  is the vertical axis while  $X_t$  is the incline of the curve. Equation (1) can also be expressed as follows:

$$\frac{dn_t}{dt} = (p+r \cdot n_t) \cdot (1 - n_t) \quad (2)$$

When the boundary condition is set at  $n_{t=0}=0$ ,  $n_t$  can be expressed as follows<sup>[2][6]</sup>:

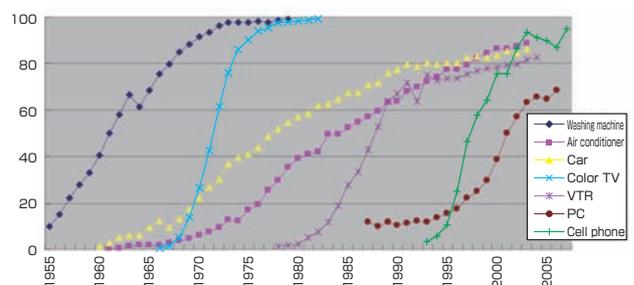
$$n_t = \frac{1 - e^{-(p+r)t}}{1 + \frac{r}{p} \cdot e^{-(p+r)t}} \quad (3)$$

When the three parameters  $p$ ,  $r$ , and  $N$  are determined, the temporal transitions of  $X_t$  and  $n_t$  are determined.

In applying the diffusion analysis to eco-products, in the 1980s, International Institute for Applied Systems Analysis (IIASA) of Europe used it for diffusion projection of renewable energy. While the Bass model could approximate the long-term temporal transition of diffusion, it was unable to analyze the effect on diffusion in case there were changes in the factors. For example, it was difficult to analyze the effect of product price changes due to subsidy policy on the diffusion, or the effect of change in consumer preferences on the diffusion. While attempts were made to incorporate the effects of price changes and advertisements to the model by extending the Bass model<sup>[5][6]</sup>, it was only possible under assumption that sufficient statistical data were available.

#### 3.2 Consumer preference model

There exists an approach of analyzing diffusion by constructing a model of consumers' product preferences<sup>Note 1)</sup>. In the simple consumer preference model, hypothesis is set that



**Fig. 1 Diffusion transition curve for past major products.**

Vertical axis represents the household diffusion rate. Source: For items other than cell phones, *Trend of Household Consumption – Annual Report of Consumption Trend Survey*, Economic and Social Research Institute, Cabinet Office, Government of Japan. For cell phones, *Report on Communication Usage Trend Survey for Households*, Japan Ministry of Internal Affairs and Communication.

consumers select the most economically rational technologies and products. There are finer models of consumer preference and decision-making, and conjoint analysis is often used for fine modeling<sup>[7][8]</sup>. Since this approach allows fine analysis of effects on consumer preference brought on by changes in price or product performances, it enables analysis of effect of the factor changes on diffusion. However, since this model basically has no temporal dimension, it is unable to analyze temporal transition of diffusion, particularly for long-term.

### 3.3 Learning curve model

The learning curve model is used to analyze the cost reduction of industrial products<sup>[9][10]</sup>. New products tend to decrease in cost with mass production. Learning curve model describes this trend. Figure 2 shows the transition of production volume and price of solar cell. From past data, there is empirical rule “when the cumulative production doubles, the production cost and time required for production decreases by certain percentage.” The observed percentage of reduction is 15~30 % in semiconductor industry and 5~20 % in machine assemblies<sup>[10]</sup>.

### 3.4 Characteristics of existing models

The characteristics of the above models are summarized in Table 1.

## 4 Model formulation

### 4.1 Process of model determination

Three existing models were described in the previous chapter. Long period of trial and error was necessary in figuring out how to utilize (or not utilize) and to integrate the models. The research goal was clarified at this point, and the model was created based on whether it was persuasive or not. There were three types of persuasiveness selected for this research: (1) persuasiveness of result, (2) persuasiveness of logic, and (3) persuasiveness of analogy. (1) is the persuasiveness gained from the match between the result of modeling and the reality, and it is naturally the most convincing item. However, in many cases, the actual result of a projection is not available (for example, we do not know the “diffusion 20 years from now”), and this standard cannot be applied. However, it can be used as counter-evidence when the model fails to explain the state of diffusion, or the non-adequacy of the model. (2)

is persuasion through the adequacies of assumption and logic of the model, and (3) is persuasion through referencing the similar cases in the real world.

Based on these points, Fig. 3 shows the process of determining the model for this research. Initially, we thought understanding consumer preference was primary concern, and tried to build the diffusion model based on consumer preference model. However, we were unable to draw the diffusion curve that matched reality (failure of (1)). We attempted to create something that resembled reality through numerous revisions, but were unable to obtain sufficient level of persuasion in the logic of the revisions (failure of (2)). At this point we reconsidered the model. The key of reconsideration was whether the subject of diffusion analysis was long-term (several decades) or short-term (few years). We realized that consumer preference model was effective in short-term while Bass model was good for long-term. This point was not indicated in existing literature. Confirming that our study was for long-term, we set Bass model as the foundation of our model. In the Bass model, it was possible to reference the diffusion coefficients of similar products (section 3.1). For example, it could be seen that 40 to 50 years would be required for diffusion of hybrid cars in reference to past automobile products (such as automatic transmission cars), and similar number of years would be necessary for diffusion of energy-saving appliances in reference to similar appliances. This is (3) persuasiveness of analogy.

Next, to enable sensitivity analysis that was difficult to accomplish using the Bass model, we attempted to incorporate the consumer preference model. The integration method will be described in the following section. We determined that it was most convincing among considered integrated models (superior in (2)). However, we do believe that there is room for more discussion for this integrated model.

### 4.2 Formulation of model

In this research, the original equation (1) for the Bass model was modified, and the model was formulated as follows:

$$X_t = (p + r \cdot n_t) \cdot (1 - n_t) \cdot N \cdot \frac{H_t}{H^0} \tag{4}$$

$H_t/H^0$  is multiplied to equation (1).  $H_t$  and  $H^0$  are values

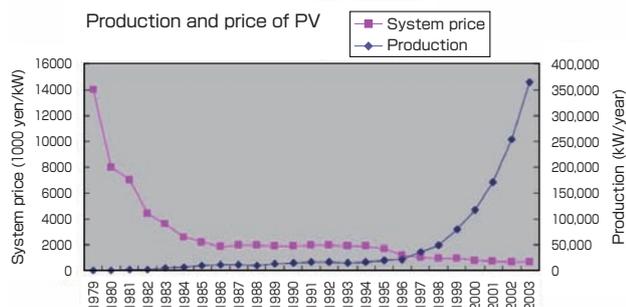


Fig. 2 Production and price of photo voltaic (PV) in Japan.

Table 1 Characteristics of current models.

Model	Characteristic
Bass model	Macro-model where diffusion transition is seen as a whole. Appropriate for long-term diffusion transition analysis. Sensitivity analysis is difficult.
Consumer preference model	Micro-model for looking at diffusion by consumer preference. Appropriate for short-term diffusion transition analysis and sensitivity analysis. Long-term diffusion analysis is difficult.
Learning curve model	Model for transition of cost reduction of industrial products.

calculated in reflection of the consumer preference model, and have the following definition. Consumers are assumed to have two choices: eco-product (EC) and traditional or “trad-product” (TR). The distribution of difference of consumer’s preference for eco-product and trad-product ( $U_{i,EC} - U_{i,TR}$ ) is calculated. Definition of  $U$  will be given in section 4.4.  $H$  is the percentage of consumers who prefers eco-products to trad-products (percentage of consumer  $i$  that satisfies  $U_{i,EC} - U_{i,TR} > 0$ ). The value of  $H$  calculated according to current level (current  $s$  value) is  $H^0$ , and  $H$  value during period  $t$  is  $H_t$ . Since the  $H$  value changes according to policies (e.g. subsidy) and technological advances (e.g. increased performance), in equation (4), when percentage  $H_t$  of consumers who prefer eco-product changes during period  $t$ , the new purchases  $X_t$  during period  $t$  changes in proportion to the percentage of the change. If  $H_t$  is same value as  $H^0$  throughout  $t$ , the curve will be same as the one for the Bass model.

**4.3 Setting the diffusion coefficient ( $p$ ,  $r$ , and  $N$  of equation (4))**

The diffusion coefficients ( $p$ ,  $r$ , and  $N$ ) for products targeted for analysis are set as follows according to the status of diffusion of the products<sup>[6]</sup>. (1) If the product is already diffused to some level,  $p$ ,  $r$ , and  $N$  are estimated from past diffusion transitions (actual past values of  $X_t$  and  $n_t$ ). (2) If the product is newly launched on market or has not been launched yet,  $p$ ,  $r$ , and  $N$  values for diffusion of past similar products are applied.

In principle, for this research, we use the latter method.

**4.4 Setting the consumer preference model ( $H$  of equation (4))**

Consumer  $i$ 's preference to product  $k$ , that is  $U_{ik}$ , is defined as sum of item of preference factor  $j$  as follows:

$$U_{ik} = \sum_j w_{ij} \cdot s_{kj} \tag{5}$$

$j$  is preference factor (attribute), and  $s_{kj}$  is value (level) of attribute  $j$  of product  $k$ . In the example of energy-saving air conditioner described in chapter 7:

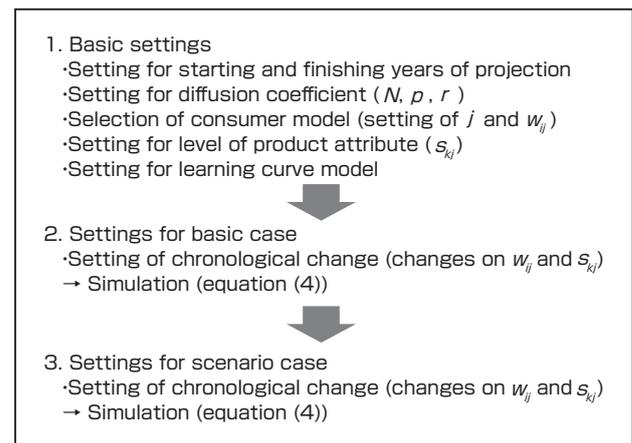
$k = \{\text{conventional air conditioner, energy-saving air conditioner}\}$

$j = \{\text{initial price, annual electricity bill, eco-image, others}\}$

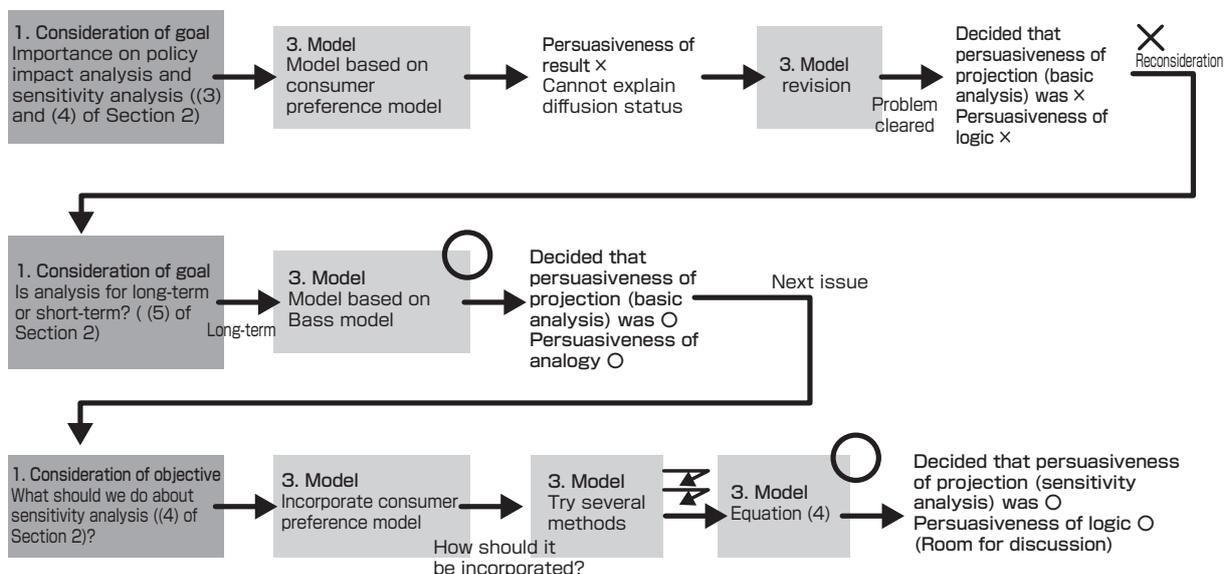
This is one example of the setting.  $w_{ij}$  is weight of preference of each factor, and conjoint analysis is used for quantification.  $U_{ik}$  is quantified, and  $H$  value of equation (4) is calculated based on these values. Examples will be shown in sections 5.2 and 7.2.

**4.5 Flow of analysis**

Figure 4 shows the flow of the analysis. First, basic settings were determined. The years in which the diffusion analysis would be started and completed were set. Next diffusion coefficients  $p$ ,  $r$ , and  $N$  of the subject product were set (method shown in section 4.3). Next, consumer preference model was set. Using equation (5) as format of consumer preference model, attribute  $j$  of the equation was determined, and



**Fig. 4 Flow of analysis.**



**Fig. 3 Process of model construction.**

coefficient of preference weight  $w_{ij}$  was set based on the result of conjoint analysis. Level  $s_{kj}$  of product attribute was set. Also, learning curve model was set to set the price reduction transition of eco-product in the basic case. The change of level of attribute in basic case was set. Other price change factors (such as subsidy), if any, were set. Based on the above settings combined with basic setting, the diffusion was simulated by equation (4). This was the diffusion projection of basic case.

Next, the scenario case was set to conduct the scenario analysis. Change of levels of attributes that were different from basic case was set. For example, future changes of attribute levels due to technological advances or government policies such as subsidy and carbon tax were set as scenario. As in basic case, diffusion was simulated by equation (4).

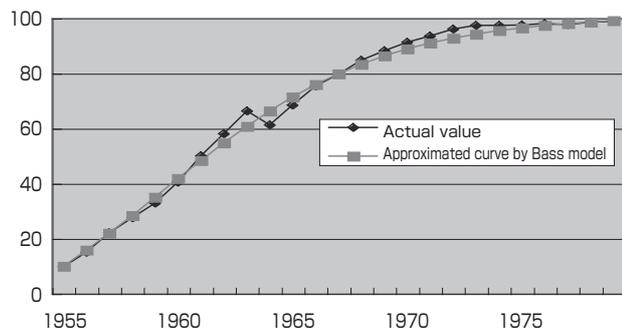
### 5 Data collection

#### 5.1 Diffusion coefficient of past products

To refer to the diffusion coefficients of past products, the diffusion curves of past products were collected and their diffusion coefficients were extracted. Figure 5 shows the diffusion transition of washing machines and the approximated curve by Bass model. In this research, diffusion curves of 28 products were collected. Table 2 shows the diffusion coefficients of 20 products. As guideline of speed of diffusion, the rightmost column of the table shows the years required for the diffusion rate to increase from 10 % to 50 %. It generally took four to five times as long as the years specified in the rightmost column from launch of product to saturation in market. For automobiles, it was 40 to 50 years, while it was about 10 years for home appliances such as television that diffused very fast in the 1960s.

#### 5.2 Conjoint analysis

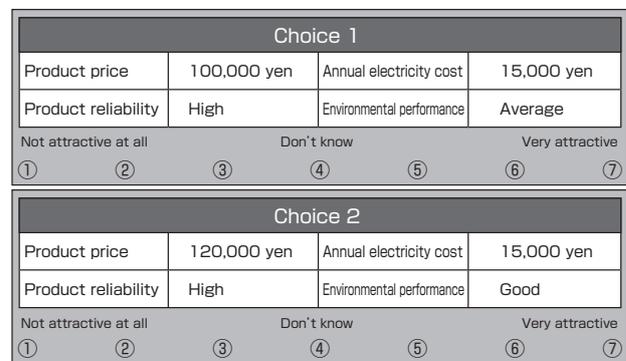
In this research, three conjoint analyses were conducted. They were conducted for 1) home electric appliances about 100,000 yen, 2) home installations about 1 million yen (for home photo voltaic system, in particular), and 3) automobiles. The methods and results of conjoint analysis for 1) home electric appliances at around 100,000 yen will be presented here.



**Fig. 5 Transition (actual) of household diffusion of washing machine and approximated curve by Bass model ( $p = 0.044$ ,  $r = 0.165$ ,  $N = 101.2$ ).**

The analysis was conducted for 1,112 respondents who were sampled and selected statistically on the web. Attribute  $j$  was set as four attributes including initial price, annual electricity cost, product reliability, and environmental performance. Figure 6 is an example of the profile. The two profiles in the figure have different levels of “product price” and “environmental performance.” Twelve profiles were shown to each respondent who were asked to indicate his/her preference of each profile according to seven-step scale. Based on the responses, coefficient of preference weight ( $w_{ij}$  of equation (5)) for each attribute  $j$  of each respondent  $i$  was calculated. Each attribute was calculated as having the following values as average of respondents when converted to product price:

- Annual electricity cost is 1,000 yen less → Same value as product price being 5,500 yen less
- Product reliability is high → Same value as product price being 10,000 yen less



**Fig. 6 Example of profile by conjoint analysis.**

**Table 2 Diffusion coefficient values of past products.**

Product	Period	$N$	$p$	$r$	Speed
Flushing toilet	1964-2003	118.1	0.12	0.133	17
AT car (excluding light car)	1958-2005	87.8	0.00042	0.182	14
AT car (light car)	1959-2005	87.8	0.00053	0.182	13
Microwave oven	1970-2004	100.5	0.0059	0.151	13
PC	1987-2006	76.5	0.011	0.190	13
Fluorescent lamp	1953-2005	76	0.021	0.099	13
Air conditioner	1961-2003	92.3	0.0069	0.148	12
Stereo	1961-2004	65.9	0.041	0.145	12
Washing toilet seat	1992-2006	112.2	0.023	0.067	12
Automobile	1960-2003	90	0.011	0.120	11
Facsimile	1964-2006	118.1	0.0095	0.142	10
Automatic washing machine	1983-2004	77.8	0.00014	0.313	9
Gas water heater	1966-1981	80	0.038	0.260	8
CD player	1987-2004	62.3	0.012	0.530	6
Washing machine	1955-1979	101.2	0.044	0.165	6
VTR	1978-2004	84	0.0042	0.410	5
Refrigerator	1955-1982	98.1	$3.6 \times 10^{-7}$	0.429	5
Black & white TV	1955-1968	95.9	0.013	0.681	4
Color TV	1967-1982	99.2	0.00023	0.638	3
Cell phone	1993-2007	92	0.00042	0.709	3

The source of diffusion transition data is taken mostly from *Trend of Household Consumption – Annual Report of Consumption Trend Survey (for FY2004 and FY2006)*, Economic and Social Research Institute, Cabinet Office, Government of Japan. Rightmost column shows the years required for the diffusion to increase from 10 % to 50 %.

• Environmental performance is good → Same value as product price being 32,900 yen less  
 Preference function ( $U_{ik}$  of equation (5)) was formulated from this result ( $w_{ij}$ ) and product specification ( $s_{kj}$ ) to calculate the H value of equation (4), and this was used in diffusion analysis. Specific example will be presented in section 7.2.

**6 Tool creation**

A tool that allows the analysis to be done easily was created based on the above model and data. Figure 7 shows the screen of the tool. Basic setting and Bass model setting are done on the upper left section of the screen. The diffusion coefficient is set by directly entering the figures or by selecting the past products. The settings for consumer preference model and scenario case are done in the right part. Result is displayed in center left and lower left.

**7 Analysis**

Using the tools and methods shown in the above section, diffusion analyses of energy-saving air conditioner, energy-saving refrigerator, hybrid car, high-efficiency water heater, compact (bulb-type) fluorescent lamp, and solar power generation system were conducted. This section will describe the diffusion analysis of energy-saving air conditioner.

Air conditioners consume about 25 % of total power consumption at home<sup>Note 2)</sup>, and as their energy-saving performance has improved over the past 10 years or so<sup>Note 3)</sup>, diffusion of energy-saving air conditioner is expected to be effective countermeasure for global warming.

**7.1 Settings**

In the analysis, it was assumed that there were two types of air conditioners, traditional (TAC) and energy-saving (EAC).

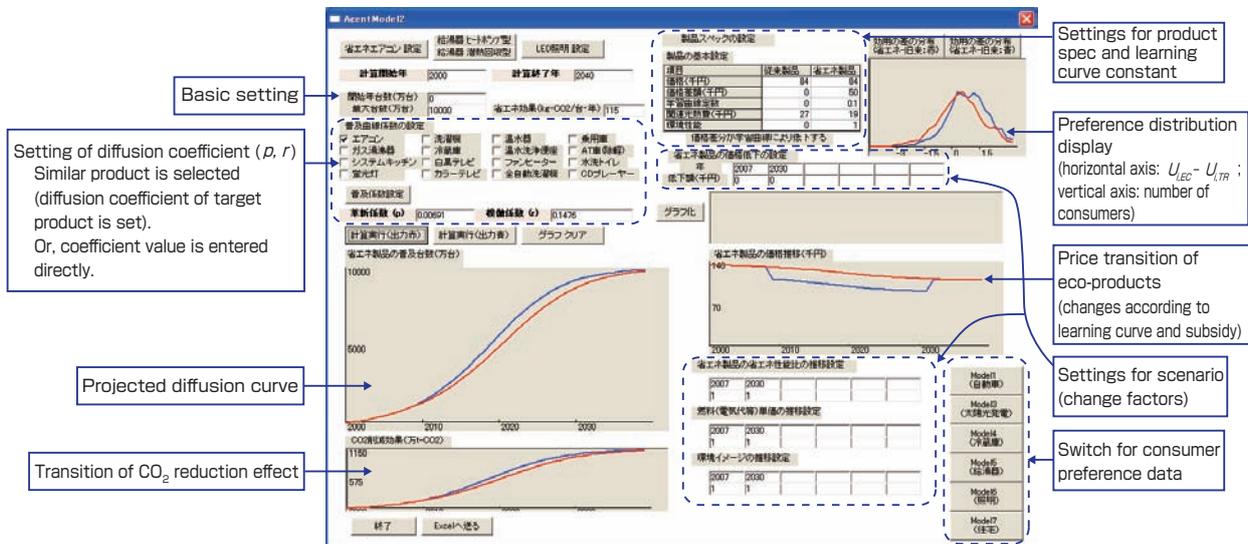
Consumers selected one or the other. Assuming that energy-saving air conditioner started diffusion from year 2000, the analysis period was set from 2000 to 2040. The consumer preference function was set up as follows:

$$\begin{aligned}
 U_{i, EAC} &= W_{i, \text{initial price}} \cdot t_{EAC, \text{initial price}} \\
 &+ W_{i, \text{annual electricity cost}} \cdot t_{EAC, \text{annual electricity cost}} \\
 &+ W_{i, \text{eco image}} \cdot t_{EAC, \text{eco image}} \\
 &+ W_{i, \text{others}} \cdot t_{EAC, \text{others}} \\
 U_{i, TAC} &= W_{i, \text{initial price}} \cdot t_{TAC, \text{initial price}} \\
 &+ W_{i, \text{annual electricity cost}} \cdot t_{TAC, \text{annual electricity cost}} \\
 &+ W_{i, \text{eco image}} \cdot t_{TAC, \text{eco image}} \\
 &+ W_{i, \text{others}} \cdot t_{TAC, \text{others}}
 \end{aligned}
 \tag{6}$$

The product specifications of energy-saving air conditioner and traditional air conditioner were set according to the model case shown in the homepage of the Energy Conservation Center, Japan<sup>Note 4)</sup>. They are shown in Table 3.

**Table 3 Settings for diffusion analysis of energy-conserving air conditioner.**

Item	Setting
Start of projection	2000
End of projection	2040
Final number of diffusion	130 million (current diffusion)
Innovation coefficient ( $\rho$ )	0.0069 ( $\rho$ value of air conditioner)
Imitation coefficient ( $r$ )	0.148 ( $r$ value of air conditioner)
Initial price	Trad-product: 84,000 yen Eco-product: 134,000 yen
Price segment that is affected by the learning curve	50,000 yen
Learning curve constant	0.1
Annual electricity cost	Trad-product: 27,000 yen/year Eco-product: 19,000 yen/year
Eco-image	Trad-product: 0 Eco-product: 1
CO <sub>2</sub> reduction effect	115 kg-CO <sub>2</sub> /conditioner · year



**Fig. 7 Screen of diffusion analysis tool.**

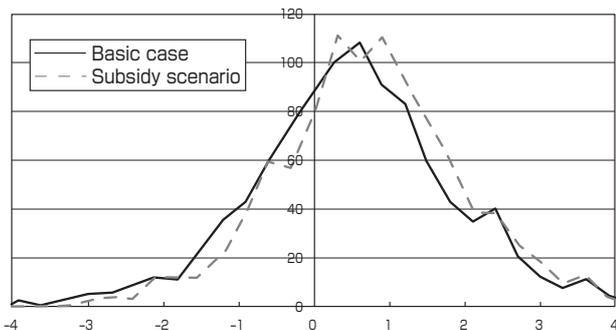
The maximum number of diffusion of energy-saving air conditioner was set at approximately 130 million, which was the number of current diffusion of home-use air conditioners<sup>Note 5)</sup>. For innovation coefficient and imitation coefficient, coefficient values (Table 2) extracted from past diffusion curves of air conditioners were used. We applied the learning curve model, and assumed that the 50,000 yen price difference between eco-products and traditional products contracts by learning curve constant 0.1. The effect of CO<sub>2</sub> reduction per diffusion of one eco-product was 115 kg-CO<sub>2</sub>/year by converting 8,000 yen difference in electricity cost. These are summarized in Table 3.

Three scenarios of granting subsidy money to energy-saving air conditioner were set. We assumed subsidy of 20,000 yen per conditioner. First scenario was provision of subsidy from FY 2008 to 2030, and this was compared with basic case to investigate the effect of the subsidy. Second and third scenarios were subsidy provision period from FY 2008 to 2013 and FY 2015 to 2020, and the effects of periods of subsidy provision were compared.

### 7.2 Results

Figure 8 shows the distribution of consumer preference in basic case and subsidy provision case. In the basic case, of the 1,112 sample consumers (conjoint analysis respondents), there were 675 consumers who preferred energy-saving air conditioner to traditional air conditions (consumer *i* that satisfied  $U_{i,EAC} - U_{i,TAC} > 0$ ) ( $H^0 = 675/1112 = 0.61$ ). About 60 % of the consumers preferred energy-saving air conditioner (Fig. 8). The preference distribution when the product price decreased 20,000 yen due to subsidy was  $H_i = 751/1112 = 0.68$  (Fig. 8).

Using these data in equation (4), the diffusion transition of energy-saving air conditioner was simulated. The result is shown in Fig. 9. In the basic case, eco-product reached 49 % (64 million conditioners) in year 2020, 87 % (110 million conditioners) in 2030, and reached saturation in 2040. The effect of CO<sub>2</sub> reduction by diffusion was 7.4 million ton-CO<sub>2</sub> in 2020, and 14 million ton-CO<sub>2</sub> in 2040. In the subsidy scenario (2008-2030), diffusion was 57 % (74 million conditioners) in 2020 and reached 92 % (120 million



**Fig. 8 Distribution of consumer preference.**  
Horizontal axis:  $U_{i,EAC} - U_{i,TAC}$ ; vertical axis: number of people (total 1,112 people).

conditioners) in 2030.

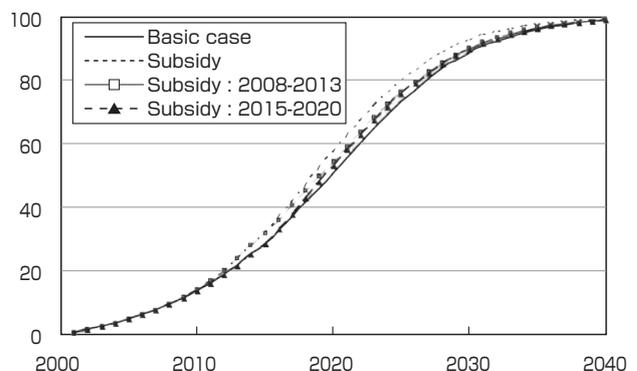
In case the subsidy period was 2008-2013 and 2015-2020, diffusion reached almost same number for both cases after 2020. However, since diffusion occurred earlier in the former case, the number of subsidized air conditioners would be less than the latter case. The total number of subsidies in former case would be about 2/3 of the latter case, and the burden of cost was also 2/3. The result indicated that the provision of subsidy was more efficient when started in the early stage of diffusion.

## 8 Result and issues

A model of social acceptance of eco-products that contribute to global warming countermeasure was constructed. We aim to develop this research further, and to use this model as a component of the larger model of interaction of technology and society.

One of the issues of this research is the investigation of adequacy of the integration method (equation (4)) of the Bass model and consumer preference model that was hypothesized in this research. It is necessary to consider the method to verify the adequacy of the integration method from the perspective of projection accuracy. Second, since the objective of this study was long-term diffusion analysis, the model was created based on the Bass model, and setting of diffusion coefficients (*p*, *r*, and *N* of equation (4)) were done in reference to the diffusion coefficients of past similar products. In this research, the person conducting the analysis selected the similar products, but it is desirable to have a standard for similarity. We shall consider some guideline for selecting products to be references of coefficient values.

In the future, we aim to develop the model of interaction of technology and society by including corporate decision-making, results of government policy on industrial technology, and social impact assessment of public research institutes<sup>[11]</sup> that were not included in this model.



**Fig. 9 Result of diffusion analysis for energy-saving air conditioner.**

Vertical axis: % (100 % is 130 million conditioners, and CO<sub>2</sub> reduction effect at that moment is about 15 million t-CO<sub>2</sub> (over 1 % of total CO<sub>2</sub> of Japan)).

## Acknowledgement

This research was based on the “Survey on the technology selection model for global warming countermeasure” of Survey for Global Warming Countermeasure Survey 2006 of the Japan Ministry of Economy, Trade and Industry. We thank the people whom collaborated with in this research: Professor Jun Fujimoto of The University of Tokyo, Professor Yasushi Umeda of Osaka University, Director Haruki Tsuchiya of System Technology Research Institute Inc, and .Dr. Keiji Masui of AIST.

## Note

**Note 1)** Examples include AIM end-use model by Morita *et al.*

**Note 2)** Source: Sources after “Outline of Electricity Demand FY 2004,” Agency for Natural Resources and Energy is taken from the homepage of The Energy Conservation Center, Japan (<http://www.eccj.or.jp/catalog/2006s/memo/3.html>).

**Note 3)** Simple average value of annual electricity consumption of major home air conditioners in Japan decreased almost to half, from 412 kWh in 1994 to 227 kWh in 2005. Source: *EDMC Handbook of Energy & Economic Statistics in Japan 2006*, The Institute of Energy Economics, Japan, p. 101.

**Note 4)** Homepage of The Energy Conservation Center, Japan (<http://www.eccj.or.jp/catalog/2006s/memo/13.html>).

**Note 5)** Number of diffusion was estimated to be approximately 130 million air conditioners from number of ownership per 100 households = 255.5 (as of March 2007; source: *Consumer Behavior Forecasting Survey*, Cabinet Office, Government of Japan) and number of households in Japan = 51.71 million (as of March 2007; source: *Basic Resident Register*, Japan Ministry of Internal Affairs and Communications).

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## Authors

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## Discussion with Reviewers

### 1 Clarification of research objective and explanation of process of consideration of the model

#### Question and comment (Masaaki Mochimaru)

Reading the work as “*Synthesiology*,” I realized that the uniqueness of this paper was the integration of three technologies (particularly Bass model and consumer preference model). It can be considered aufheben type synthesiology (Fig. a). (Kobayashi: *Synthesiology - English edition*, 1(2), 134 (2008))

This paper contains *Synthesiology* information not only on the integration of the two (or three) technologies, but in the process of repeating the revision of research goal and model. The objective of *Synthesiology* is “to archive knowledge system on technological integration to solve problems that are socially significant issues.” The process described in the final paragraph of chapter 1 is worth inclusion in the knowledge archive of *Synthesiology*. Rather than writing simply “it was repeated several times,” I want you to specifically describe the “process of considering the technological integration (or synthesis)” including what objectives were set, which models were considered accordingly, why some were discarded upon evaluating the results, and how the following

goals were set. Although it may be too much to explain all of the considerations, by selecting the major consideration processes, I think you will be able to clarify “why the models were selected and combined” and “what are the (current) technological limits of the combined model.”

In this case, it becomes difficult to arrange the chapters of the paper. As written in the end of chapter 2 (Clarification of research objectives), you had both clearly decided goals and those with degree of freedom. How about stating how setting goals with freedom was involved in the integration of model in chapter 3, and how you settled the objectives and models after what kind of consideration processes and evaluations in the beginning or the end of chapter 4?

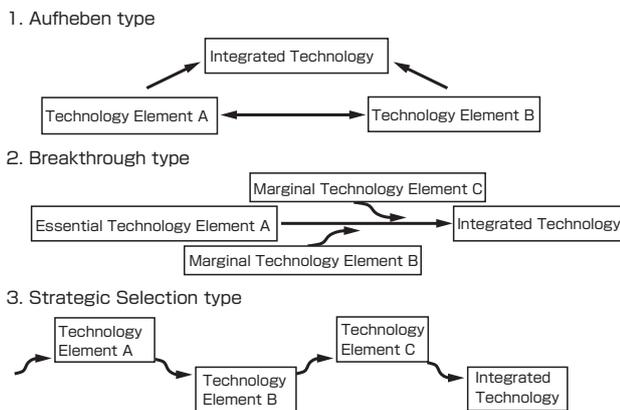
**Answer (Mitsutaka Matsumoto)**

In modeling a phenomenon, particularly when modeling human and social phenomena rather than natural phenomenon, it is impossible to model every single aspect, so it is important to consider the model by clarifying “which aspect of phenomenon you want to focus (= setting the objective)” at all times. The standard to determine the success or failure of the model in the process is ultimately “persuasiveness.” In case of natural phenomenon, the power of persuasion of a model or a theory is how accurately it can explain and recreate the phenomenon. However, it is often impossible to use reproducibility as point of persuasion because experiment cannot be done in human and social phenomena. In that case, it is necessary to consider what should be the scale of persuasiveness of the model. According to your advice, we newly added section 4.1 to describe the processes of objective setting and model consideration (Fig. 3) and added discussion on persuasiveness on which our research depends. For objective, “whether the subject of diffusion projection was short-term (several year span) or long-term (several decade span)” became the key criteria for model selection. For persuasion, we emphasized “persuasion by analogy.” In this case, when we are asked, “Why did you get this projection?” in assessing the diffusion speed of eco-products, we made sure we had logical ground to reply, “Because the diffusion speed of the past similar products showed those figures.”

**2 Ultimate goal (dream) of the research**

**Question and comment (Masaaki Mochimaru)**

I understand that the subject of research was the process of acceptance of industrial technology by the society, and I think it is significant that you have constructed a computational model. Here, you took up the survey for METI as specific example, but please indicate the destination of this social acceptance model (researcher’s dream and social acceptance) in the beginning. For example, like what you mention in the end of the paper. In



**Fig. a Different types of synthesis.**

an ordinary academic paper, significance and difficulty of the specific issues to be solved are described in the beginning, and then future developments and views in the end. In *Synthesiology*, we recommend presentation of researcher’s dream (image of what one wishes to realize in future although it is not totally solved in the paper) in the beginning, and then describe why the subject presented in the paper was selected as a way to realize that dream. This is because we believe the way of thinking (knowledge system) where large dream is realized step by step is part of “*Synthesiology*.”

**Answer (Mitsutaka Matsumoto)**

As dream, I wish to deeply understand the interaction of technology and society. Recently, companies speak of “management of technology” and “management of innovation,” and policymakers talk of “science of science policy.” Both are pursuit of understanding of relationship of technology and society. Our research is related closely to these. Our research deals with the part close to the market. As approach in pursuing the dream, I think the ideal will be to study the research theme one by one and to accumulate the results toward the large goal. I added the description of the goal in the beginning of the paper.

**3 Age dependence of consumer preference model**

**Question and comment (Masaaki Mochimaru)**

I understand that the expression of consumer preference model and the ways to obtain the parameter are effective. I ask the following question with this knowledge. This consumer preference model is age dependent (affected by social consensus). For example, wouldn’t changes in society such as “increased environmental consciousness” influence the  $H_i$  value?

**Answer (Mitsutaka Matsumoto)**

As you indicate, there is age dependency in consumer preference. The model selection in Discussion 1 was closely related. The reason why the basic model was changed from consumer preference model to Bass model was because we decided it was difficult to set consumer preference model as base since consumer preference do change with time. In this study, age dependency of consumer preference was handled as scenario. For example, with the rise of environmental consciousness, the importance of consumer’s environmental image of a product (in the model, “ $w_{i, \text{eco-image}}$ ” of equation (6)) would increase, and it was evaluated in similar manner as the subsidy scenario of the paper. It is very interesting to see how much the consumer’s environmental consciousness has changed in the real world.

**4 Verification of the model**

**Question and comment (Masaaki Mochimaru)**

Since the model deals with human group behavior in the real world, I understand verification is difficult. Isn’t confirmation of parameter sensitivity a possible verification method at this point? In the integrated model, the necessary parameters are determined by similar phenomena and experimental data, but I think simulation analysis can be done to determine which parameter will strongly influence the projection or what level of care is needed to identify the parameter.

As another method, there is verification of to what level reproduction is possible using this model for the social policy intervention and technological diffusion that were actually conducted in the real world. For example, we can see the level of reproducibility of this model for how much the right-of-way priority for hybrid cars, which was conducted in California, affected the technological diffusion, with comparison with nearby states. Although it seems that actual verification is difficult (to obtain data), it will be useful for you to indicate what the actual

difficulties are.

**Answer (Mitsutaka Matsumoto)**

Verification is a problem. We attempted statistically extracting product price and changes in diffusion rate using diffusion transition of past product and price change data obtained from price statistics, but failed to obtain statistically significant results. In the point of parameter sensitivity, we worked on seeking influences on product diffusion of shifts in product price, running cost (electricity or gasoline costs), improved environmental performance, and environmental consciousness. Relative sensitivity basically is dependent on the result of conjoint analysis. As result of conducting sensitivity analysis in expected range of change, we obtained result that improvement of environmental

performance was effective in promoting diffusion. In terms of absolute sensitivity, our model may be dull in sensitivity. The result (Fig. 9) shows that there isn't much change in diffusions in different scenarios. For the other method that you indicated, consideration of the policy in California is very interesting. Currently, we are conducting survey of policy assessments. As verification material, since the amounts of subsidy differ by local governments for home-use solar power generation system, we can see the relationship between subsidy and diffusion. Powerful diffusion promotion has been conducted for the electronic toll collection (ETC) system for vehicles, though not an eco-product, through discount on expressway costs. It is an interesting case in observing the effect of diffusion promotion policy. Verification is an issue that we are currently working from various perspectives.

# How Grid enables E-Science?

## — Design and implementation of the GEO Grid —

Yoshio Tanaka

[Translation from *Synthesiology*, Vol.2, No.1, p.32-41 (2009)]

In this paper, we report on the design and implementation of the GEO (Global Earth Observation) Grid IT infrastructure as an example of E-Science. Using Grid technologies, the GEO Grid provides an IT infrastructure that integrates wide varieties of data sets and computing services for the Earth science community. This paper presents an example of Grid-based E-Science and its application to a wide range of scientific communities. A methodology for system development based on many different software components is also discussed.

**Keywords :** Grid, GEO Grid, E-Science, middleware, software design

### 1 Introduction

Recently, with the advancement of network technology and the diffusion of network infrastructure, there is active research in E-Science, which is a research methodology enabling science and technology to promote new discoveries and new fields in transdisciplinary research, by using various resources such as high-performance computer connected to high-speed networks, databases, large-scale storage devices, and various kinds of experimental devices. The grid<sup>[1]</sup> is a technology in which various resources that are connected by high-speed networks are combined safely, actively, and flexibly. It is expected to become the infrastructure technology that supports E-Science. About 10 years have passed since the term “grid” was first used, and the R&D in the elemental technology acquired for the grid has been rapidly progressing. The grid is now in the transition phase from demonstration experiment to practical use.

In addition, there is increased focus on earth observation for environmental issues, including global warming, forecast of and countermeasures for disasters such as earthquakes and floods, and exploration for natural resources. In these fields, it is necessary to conduct data analysis and simulation by referencing various data, including satellite data, sensor data, and geological maps, owned by several different organizations. It is not easy to conduct analysis by sorting through multiple databases while adhering to the different policies of the organizations that own the data. Development of a system that enables this easily has been greatly anticipated. The solution to this problem could certainly be realized using the grid, and therefore, the R&D for the GEO (Global Earth Observation) Grid was set into action.

GEO Grid<sup>[2]-[4]</sup> is a system and a concept that enables users to handle integrated processing and analysis of geographical information system data as well as various observation data located in distributed environments, by large-scale archiving and high-speed processing of earth observation satellite data using grid technology. Its objective is to provide an environment where research communities and companies can safely and securely use diverse data and make the acquired computation for earth observation. The plan is to promote information integration of geological and satellite information owned by AIST, to promote further integration of this data with a broad range of earth observation information, and also to promote active international cooperation, particularly focusing on advanced use of these resources in Asia. Considering the trend for international standardization, the aim is to maintain international interoperability of all of the information systems and data.

GEO Grid is an example of E-Science. There are many other areas where technological development may be greatly accelerated through E-Science, such as the bio information field for promoting efficient drug discovery using bio information databases, or the medical field for developing next-generation medical diagnosis systems utilizing medical databases and systems to support cancer diagnosis through the use of large-scale medical image databases.

Although most of the basic technologies of the grid have achieved the level of practical use, they have not yet been put to wide use due to the following reasons.

- The grid was originally born in the field of high-performance computation, and is thus seen as “technology for conducting large-scale computation using

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supercomputers.” There are several issues that must be solved for the computation grid, such as: performance issues, since the performance of the Internet relies on “best effort” and there is no actual guarantee for performance; the current parallel programming method is not suitable for grid use due to problems of fault tolerance and simultaneous securing of computers; and technological issues where the scheduling technology for selecting optimal computing resources is only in the research phase.

- There are very few case study reports that can say, “we were able to do this using the grid,” and the application community’s views are, “we would like to use it but don’t know how;” “it won’t work anyways;” or “I have gotten no idea what to use it for.”

Not all the basic technologies required for the grid have achieved a practical level, but it is possible to provide novel and realistic research methodologies for various science and technology fields by combining the technologies that have been developed so far. The objective of our research is to build an E-Science infrastructure using the grid as the basis of the GEO Grid, and thus to provide a research environment for earth science researchers, as well as to clarify and solve issues standing in the way of full realization of use of the grid in wide-ranging science and technology fields. The aim is to contribute to the creation of innovations in science and technology fields. To achieve this goal, the required specifications for an information infrastructure based on the scenarios of the case studies of GEO Grid were analyzed, and the system was designed and implemented. The strategy taken was to actually build a system for distributing satellite data to provide a research environment to earth science researchers using the grid. Issues were identified as they arose from the findings and feedback of this implementation, and a strategy for realization was planned.

In this paper, the tasks undertaken to achieve system construction, the security issues in E-Science, and the problems that still need to be solved will be explained using the GEO Grid as an example. The main objective of this paper is, for researchers in application fields, to promote diffusion of the grid by demonstrating the feasibility of the case study, and to enhance understanding of the grid by clarifying “what can be done and what cannot be done.” Also, for researchers in IT fields, I will explain the methodology used for constructing a system by combining multiple software components.

GEO Grid is composed of applications, content, and an information infrastructure, and this paper will report on the design and implementation of the information infrastructure. First, the methodology of system construction in the IT field will be discussed. Then, the requirements of the GEO Grid information infrastructure and a design policy based on these

requirements will be presented, and finally I will explain the implementation method as well as the findings and results obtained through the construction of the actual system.

## 2 Requirements of the information infrastructure

The requirements of the GEO Grid information infrastructure are summarized as follows.

- (1) Provision of large-scale data  
Satellite observation data accumulates to several hundred terabytes to petabytes in size throughout its operation period, and high scalability that enables a quick search for the data needed by the user from such large-scale data is required.
- (2) Handling of diverse data  
The ability to handle diverse data stored in diverse formats provided by diverse organizations is required, including climate data obtained for different physical quantities, and different time-space resolutions for temperature, humidity, and cloud cover.
- (3) Observation of data provision policy  
While there are free data sets with no limitation on use, in general, the data owner has the right to license, as well as the right to set and change the conditions, such as authorized range of data access or data format, under which such data can be provided. Thus, it is necessary to achieve flexible access control based on the disclosure policy of the data owner.
- (4) Integration of data and computation  
It is necessary to provide integration of computation and data, such as large-scale simulation of areas affected by pyroclastic flow based on data, and easily done computations, such as format change, and preliminary processing of data.
- (5) Support for a diverse community  
It is necessary to set up a mechanism that allows sharing data, computation, tools, and process flow in the form of templates that can be altered flexibly to support diverse communities and various earth science projects, such as environmental watch, disaster watch, and resource exploration.
- (6) Ease-of-use  
It is necessary to provide tools and interfaces that can be “easily used” by all participants, including users, data providers, and project administrators. Also, the system must allow easy management of tens of thousands of users.

## 3 Design

Based on the requirements mentioned in the previous

chapter, the basic design policy and the usage model were decided before the selection and implementation of specific basic technology. In this chapter, I will explain the design policy and the usage model of the GEO Grid information infrastructure.

### 3.1 Design policy

In order to share and integrate diverse data and computations as mentioned in Requirement (2), and as described in Requirements (3), (4), and (5), and to provide the results to the research community, the concept of a virtual organization (VO)<sup>[5]</sup>, where the provided data and computations are abstracted as a “service” provided through standard protocols and interfaces, and the usage environment is built by actively combining such services, will be introduced in the design of GEO Grid information infrastructure. A VO is a research environment composed of ideal information infrastructures achieved by combining the services needed by the research community from among the diverse data service and computation services available.

### 3.2 Usage model

As shown in Fig. 1, there are four roles in the GEO Grid information infrastructure, including service provider, VO administrator, end user, and GEO Grid administrator. The service provider is the owner of data and computation, and provides them as a service to the end user. The VO administrator can be considered the administrator of a community and a project, and engages in construction of the VO, management of users that participate in the VO, and construction of a user portal. The GEO Grid administrator

manages the registry where the available services are registered, and manages access control for that registry. The end user basically participates in one or more VOs, and conducts research and surveys by using the services offered.

The service provider registers the information on the services provided in the registry managed by the GEO Grid administrator. The VO administrator searches for the data and computation resources available in the registry, and if there is a service that he/she wishes to use, the administrator negotiates individually with the provider. When the service provider authorizes the provision of service to the VO, the service provider changes the appropriate system setting to allow access to the VO. As mentioned earlier, access control can be set by each VO, each user, or by free access, based on the policy of the service provider.

## 4 Selection and implementation of the basic technology

Based on the design policy described in the previous chapter, the GEO Grid information infrastructure was implemented using grid technology. Considering the fact that the service must be linked among several organizations, implementation of security in accordance to a standard is mandatory. Also, it is important to effectively utilize the existing tools and software to reduce the cost of implementation and to increase interoperability of the systems. In this chapter, I will explain the selection of the basic technologies and their combination for the implementation of the GEO Grid information infrastructure.

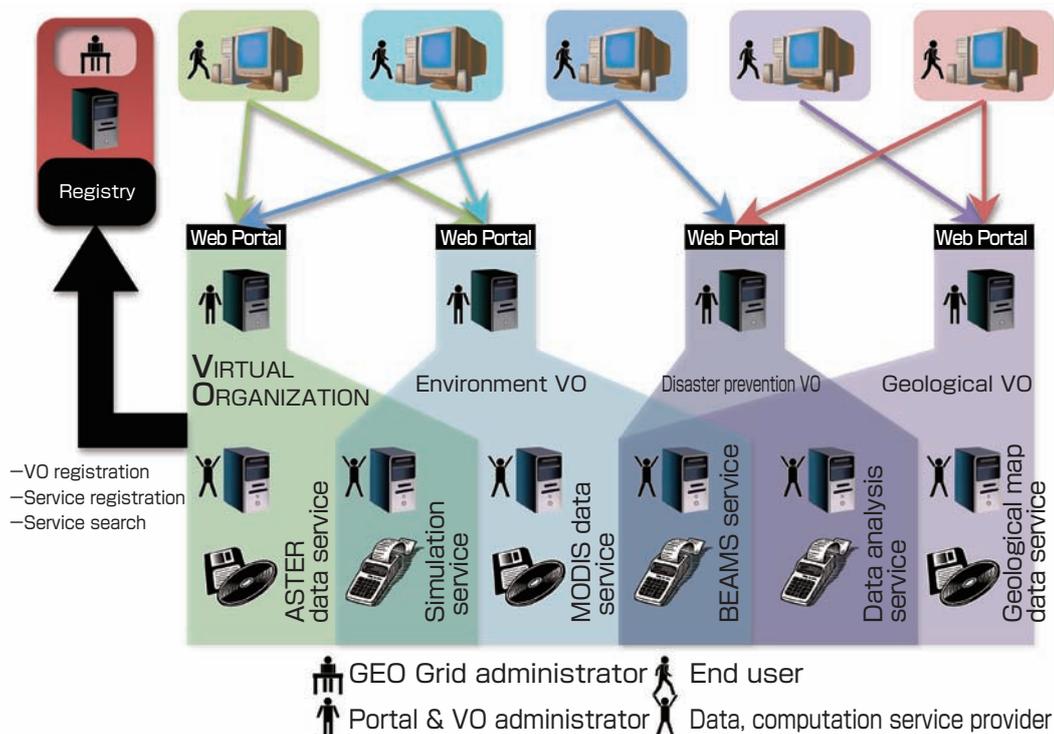


Fig. 1 Usage model of the GEO Grid infrastructure

#### 4.1 Security

The security for the GEO Grid is based on the Grid Security Infrastructure (GSI)<sup>[6]</sup> and an authorization mechanism at VO level. GSI is a standard authorization infrastructure using the Public Key Infrastructure (PKI) and an X.509 certificate<sup>[7]</sup>, and allows single sign-on and authority transfer through the proxy certificate. GSI is a standard technology for grid security, and considering its compatibility with other systems, and the fact that many grid middleware suits already support GSI, the decision was made to employ GSI for security.

For composition of the virtual organization and access control based on a VO, we used the Virtual Organization Membership Service (VOMS)<sup>[8]</sup>. VOMS is software developed by the Enabling Grid for E-Science in Europe (EGEE), and it manages the members participating in a VO, as well as member registration, formation of groups, and assignment of roles to users. Also, it issues a VOMS proxy certificate, which is the VO user's proxy certificate embedded with attribute information (name of VO, group name, assigned role, etc.) upon a request by the user. The service provider can adjust various access controls according to its own policy.

The authorized user is normally mapped to the UNIX account at the service provider side, and access control is managed by the authority of the UNIX account. However, in this method, all user entries must be managed by the service provider, and this may increase the management cost for the service provider, and it is not scalable to the number of users. Therefore, an authorization mechanism at VO level is introduced to achieve flexible access control to reduce the burden on the service provider and to allow scalability for the number of users, through authorization at the VO, or group to which the user belongs in the VO, or through approval according to authorization already given.

Other than VOMS, PERMIS<sup>[9]</sup> and CAS<sup>[10]</sup> were also available as middleware that provides access control at VOM level, but VOMS was employed for the following reasons: the implementation where attribute information is embedded in the proxy certificate is compatible with the account management system that will be explained in section 4.5; there are several tools included, such as an interface for user management, and high quality software can be expected since it is more widely diffused, compared to other systems.

#### 4.2 Service provision of data and computation resources

To abstract and provide the data and computations as a usable service via standard protocols, middleware that wraps the data and computations, and provides them as a service is used. For servicing data, OGSA-DAI (Open Grid Service Architecture - Data Access Integration)<sup>[11]</sup> that was developed

by the UK-eScience project, and its successor project, the Open Middleware Initiative-UK, is used. For servicing computations, Grid Resource Allocation Administrator (GRAM) of the Globus Toolkit<sup>[12]</sup>, developed by the Globus Alliance of the USA, is used. These are compatible with certification using GSI and VOMS. Other methods for providing computation as a service include implementation as a Java service on Apache Axis, but taking its good compatibility with GSI into consideration, the computation service is provided using GRAM.

Both OGSA-DAI and Globus Toolkit are widely used as grid middleware compatible with GSI, and it is currently thought that there are no other more appropriate choices.

Search results of satellite data and map information are generally provided through web service regulated by the Open Geospatial Consortium (OGC)<sup>[13]</sup>, such as Web Map Service (WMS), Web Feature Service (WFS), or Web Coverage Service (WCS). Software that provides access control using VOMS is available for Apache<sup>[14]</sup>, and is compatible with the security scheme of the GEO Grid.

#### 4.3 Heterogeneous database linkage technology

It is possible to provide an abstracted database as a service using OGSA-DAI via appropriate authorization and approval, but that alone will not enable integration of multiple heterogeneous databases. The function needed by the user is one that allows him/her "to conduct batch query and distributed combination for multiple heterogeneous databases," and therefore, Extended OGSA-DAI-DQP (Distributed Query Processing)<sup>[15][16]</sup>, developed by AIST, is used as middleware.

#### 4.4 Large-scale storage system

It is necessary to consider a storage system for storing large-scale data of several hundred terabytes to petabytes. In most current systems, satellite data is stored on tape, but considering the real-time demand of data search, and the decreased price of hard disks in recent years, use of tape devices or a commercial Storage Area Network (SAN) is not appropriate. Therefore, we decided to use a cluster file system that enables large-scale storage by connecting nodes equipped with hard disks of multiple terabyte capacities via a network. Cluster file system is a technology in which multiple distributed disks are provided as a virtual file system. Although both commercial and free software are available, we employed the Grid Data Farm (Gfarm)<sup>[17]</sup>, developed at AIST, to achieve high throughput using parallel IO, and highly reliable performance with flexible replica allocation.

#### 4.5 Account Management

GSI is an authorization technology based on PKI, where users are required to manage a secret key and a user certificate. However, installing special software to obtain the certificate

and appropriate management of the secret key are burdens for the user, and the provision of a simple interface was felt necessary. Therefore, we created a mechanism for managing the user's account and certificate on the server side using the GAMA (Grid Account Management Architecture)<sup>[18]</sup>, developed by the San Diego Supercomputer Center. GAMA is software where functions such as a request from a user for opening an account, and login and account administrator functions for user management are provided as a portlet. The user account is managed by the GAMA server, and the GAMA server has functions such as an authorization station to issue certificates to the user. By using GAMA, the user can access the GEO Grid information infrastructure via authorization by user name and password, without obtaining or managing the secret key or certificate by him/herself.

GridSphere<sup>[19]</sup> is used as a portal for users. GridSphere is a framework for constructing a portal based on JSR168<sup>[20]</sup>, that has been standardized by the Java Community Process as an API for creating small web components called "portlet," used for portal applications. It provides the authorization module needed to create the proxy certificate from the GAMA server and the portlet for the portal administrator. The original GAMA authorization module only obtains the proxy certificate from the GAMA server and does not include an interface with VOMS. Therefore, we modified the GAMA authorization module so the VOMS proxy certificate is created by a query to the VOMS server after the proxy certificate is obtained from the GAMA server.

#### 4.6 Integration of elemental technology

The basic technologies described in this chapter are compatible with all security requirements based on GSI, and in addition to the implementation of the interface for

VOMS in the account management system, integration through interfaces provided by each middleware suite is possible. In constructing a large-scale system like the GEO Grid, it is not realistic to develop everything on our own, and it is important to reduce the development cost by actively utilizing available technologies, while maintaining the core competence.

### 5 Construction of the actual system

Based on the proposed architecture, we implemented a system in which the main target was ASTER (Advanced Spaceborne Thermal Emission and Reflection Radiometer)<sup>[21]</sup>, a collection of satellite data (Fig. 2). This system is composed of a gateway server that provides access to the GEO Grid cluster through GRAM and Grid FTP server, a server to provide metadata and a catalog of ASTER data, a map server to provide image data as WMS, a GIS server to provide high-grade data such as WFS and WCS, and GAMA and VOMS servers that conduct account management. In this system, three VO for environment, disaster prevention, and information, currently exist, and each is currently in actual operation, where users are actually using them. ASTER consists of sensors loaded on a satellite called Terra, launched by NASA. There are two sensors loaded, and an elevation model of the earth's surface can be calculated from the results of these observations. ASTER data has been stored in a tape library managed by the Earth Remote Sensing Data Analysis Center (ERSDAC) since the launch of Terra, and is provided to users as fee-based data. Since last year, the data has been supplied to AIST, and at AIST, the ASTER data is stored in a cluster file system rather than as a tape library. The cluster (a GEO Grid cluster) used is composed of 36 dual Xeon nodes connected by Gigabit Ethernet, and its capacity is 264 TB, in total. The cluster

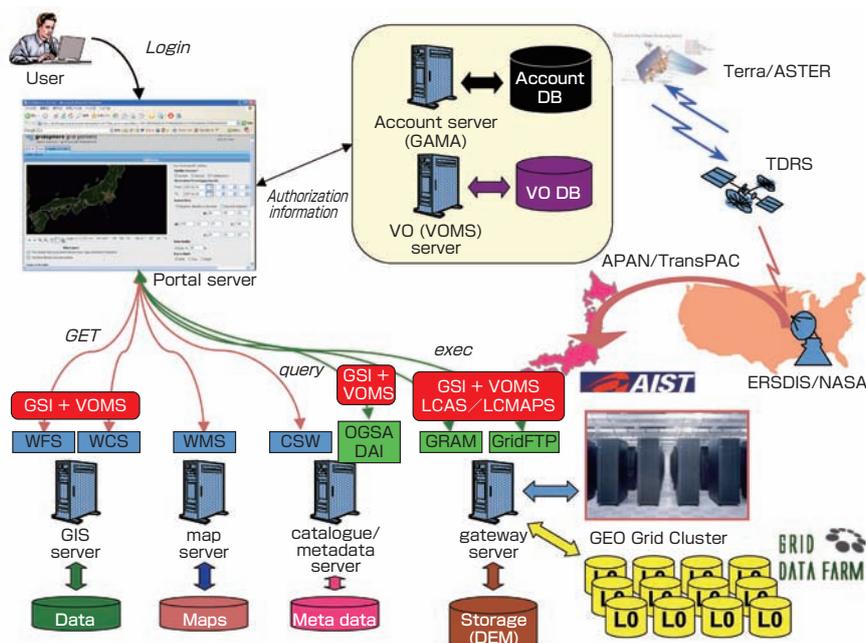


Fig. 2 Architecture of the GEO Grid system

file system used is Gfarm v1.4. At this point, all ASTER data (about 140 TB) is stored, and about 70~100 GB of data are transmitted from NASA daily to be stored in the GEO Grid cluster. For management of metadata, PostGIS, expanded for GIS for PostgreSQL, is used, and the metadata is provided as a data service by OGSA-DAI. For data processing, an F32 cluster composed of 256 nodes of dual Xeon processors connected by Giga-bit Ethernet is used. The GEO Grid cluster and the F32 cluster are connected by a 10 Giga-bit Ethernet.

A demonstration experiment was conducted for the GEO Grid that integrated multiple databases managed by multiple organizations, by constructing a “DB Collaboration Application” that enabled simultaneous search of AIST’s ASTER data, MODIS (Moderate Resolution Imaging Spectroradiometer)<sup>[22]</sup> data, and Formosat2 data owned by the National Space Organization (NSPO) of Taiwan. It was confirmed that “data search,” “conversion to digital geographic model,” and “transfer of result,” could be implemented as individual services. These were provided as high level services by linkages based on authorization provided by GSI and VOMS, a VO was constructed through integration, and the research environment was then provided to the application community. Also, through applications that allow linkage of ASTER data and free sensor data, and an application that returns the search results in WFS, it was confirmed that the proposed security architecture was able to provide appropriate access control based on the requirements of application and service providers.

## 6 Discussion

Here, I will discuss the findings obtained through the construction of the system and its subsequent operation.

Through the preliminary assessment of each software component and the development and testing of the ASTER Grid system, we were able to verify the adequacy of both the design and the implementation of the GEO Grid information infrastructure. Using the security framework utilizing GAMA and VOMS, it was confirmed that the system provided an easy-to-use interface to users, and flexible access control in compliance with the policies of the service providers. Also, through access control at the VO level using VOMS, a security system scalable to the number of users could be achieved. By using existing software and tools such as GAMA, VOMS, OGSA-DAI, and the Globus Toolkit, we were able to construct the system with low development costs. Other than the portlet used for applications, the development done by the information infrastructure side was an incorporation of VOMS and GAMA interfaces into the GridSphere. By designing and implementing all basic technologies based on a standard protocol and a standard interface, we were able to easily construct a high-grade system by linking multiple, independent basic technologies.

For the construction of an actual grid system, this may require development and use of giant middleware packages such as the data analysis system for the large-scale accelerator experiment in high-energy physics using the gLite Grid Middleware<sup>[23]</sup> suite developed by EGEE of Europe, or the Cyber Science Infrastructure project where a large-scale research grid has been constructed over university and research institutes using the NAREGI middleware<sup>[24]</sup> suite developed by the National Research Grid Initiative of Japan. The Earth System Grid<sup>[25]</sup> and GEON<sup>[26]</sup> of the USA also intend to construct a research environment with integrated earth observation data as in the GEO Grid. All of these use authorization and approval based on grid security in some part, but most are composed of non-grid technology based on web services. A case like GEO Grid is highly original, where the research environment is constructed with flexible access control based on grid security by creating a VO through the combination of data and computation provided as a service using various grid middleware suites. Therefore, this research is significant because it demonstrated that a large-scale system could be readily built by linking the grid middleware, as long as all elements were implemented according to standard security and protocols, as described in this paper.

Through building this system, it has been confirmed that the basic technologies can be utilized without any significant problems. As issues that must be solved toward full realization, the following five can be pointed out.

### (1) Creation of a tool kit

Many of the grid middleware suites used had complex installation and configuration requirements, and cannot be readily installed and used by everyone. Although the user is provided with a simple interface that can be used with only a user name and password, it is necessary to provide a tool kit where the required middleware set can be easily designed and installed for the benefit of all participants, including service providers and VO administrators, in order to promote further development in various application fields.

### (2) Realization of a more flexible authorization function

Some of the existing application communities already employ their own authorization function, such as OpenID currently used in some bio information fields. To achieve seamless transfer from the existing research environment to an E-Science environment, it is necessary to implement a more flexible authorization function that produces grid authorization information from the authorization mechanism that is already being used, such as those of OpenID, Shibboleth, or Kerberos.

### (3) Construction of workflows

Many of the application researchers use certain preset

procedures (process flows) for a large quantity of data. To obtain required data quickly when conducting multiple simulations, such as in seismic vibration analysis and liquefaction projection during the occurrence of earthquake, or in flood projection as water levels rise, it is desirable to construct a workflow for the procedures. The preceding workflow studies have already been done for the grid, and the introduction and construction of workflows is necessary for the GEO Grid.

#### (4) High performance processing

Large-scale image data processing requires large-scale computation resource, and existing software may consume several minutes to several tens of minutes for image processing. Considering interactive data transmission, it is desirable that image production takes only a couple of minutes, at most. Recently, multi-core architecture suitable for image processing, like CELL/B.E.TM is beginning to be used, and high speed capacity for image processing and simulation, utilizing the latest architecture, can be expected in the GEO Grid.

#### (5) Development of a metascheduler

In the system constructed in this research, the computation services for simulation and image processing are provided from a single site. In the future, when the same services are provided from multiple sites, it is necessary to develop a registry that manages where data is located and what kind of services are available, i.e., a monitoring system that checks the usage status of the computation server that provides the system, and a metascheduler that selects “seemingly best” services based on that information.

Research is being done on all five issues, and issues (1) to (3) can be addressed in about one or two years. For issue (4), it is necessary to increase the speed capability of the software, and in many cases, the source program is not provided due to licensing conventions for commercial software. However, preliminary assessments have been conducted for increasing the speed of image processing software on CELL/B.E.TM, and there is a possibility for significant improvement. Issue (5) is the biggest issue for the grid. To realize the concept of the grid – a world “where service can be available without thinking about which resource is used when the computer is connected to the network,” a metascheduler function is mandatory. But it is extremely difficult to select the “optimal” resource in a complex environment where the decision of what is “optimal” is based on the characteristics of the computation (such as the ratio of quantities of communication to computation) and where the resources (network and compute server) that compose the grid changes dynamically in structure and efficacy. Research will continue to try to solve this issue by setting a limit on the range of criteria that will not interfere with the user in the scenario of the GEO Grid.

## 7 How to proceed with subsequent R&D

In this study, the implementation of the system was considered by studying the demands and ideas from the Institute of Geology and Geoinformation, the Geological Survey of Japan, the Research Institute for Environmental Management Technology, and the Grid Technology Research Center (currently, a part of the Information Technology Research Institute), as a transdisciplinary research project of AIST. The Grid Technology Research Center strengthened the organization to help advance the R&D effort for the GEO Grid by shifting personnel from the GSJ to the Center; by employing researchers in application fields of the National Research Institute for Earth Science and Disaster Prevention, the Japan Aerospace Exploration Agency, and the National Institute for Environmental Studies; and by close discussions between the researchers in the information and application fields.

GEO Grid management meetings were held regularly to discuss the policy of the GEO Grid, relationships with external organizations, the clarification of pressing issues and measures, as well as for progress management. To ensure the smooth operation of a large-scale project with total of about 20 people from the application and information fields from the Grid Center alone, the application and information fields regularly held meetings for progress management, to pinpoint problems and to discuss the solutions, and great effort was made to share information on the issues among the research team members. It was important for the researchers of both fields to work at the same location, and to be in an environment where frequent discussions and brain-stormings were possible, other than just at the regular meetings.

For this research, several middleware suites, developed not just by AIST but also by overseas institutions, were used. Basically each middleware suite is implemented through the employment of a standard protocol and interface, but there were some problems due to defective implementation and a lack of function in the middleware when actual tests were conducted. Since there was close collaboration among the developers of each middleware suite through the Open Grid Forum<sup>[27]</sup>, a grid standardization organization, and through international conferences, it was possible to ask the developers to take immediate measures when issues arose. Also, it was possible to have them incorporate new functions in the next version by communicating the required specifications, and they, in turn, provided advice for specific implementation methods. In many cases, a grid system is realized by linking an extremely large number of middleware suites, and it is not practical in terms of development cost to implement everything on our own, and therefore it is important to engage in daily communication with other developers to create a system where R&D can be conducted with cooperation from overseas organizations, while

maintaining the core competence.

## 8 Summary and future issues

This paper reported on the findings obtained through the design, implementation, and actual operation of the GEO Grid information infrastructure. The way of thinking about VOs in E-Science and methods to realize management, authorization, and approval of user accounts were discussed. In the GEO Grid information infrastructure, all computation and data resources are provided as usable services via a standard protocol. The research community forms a VO, and the required services are combined and provided to users within the VO. A security infrastructure that is scalable to the number of users is implemented through approval at VO level, as is flexible access control based on the policy of the service provider, through an authorization mechanism using the VOMS attribute.

The plan is to evaluate and brush up the system through ongoing operations while continuing to work on R&D for the issues mentioned in chapter 6. About a year and half had passed since the start of system development of the GEO Grid, and it was possible to construct a system suitable for practical use, surpassing the prototype stage. However, about a two to three year period of R&D is still necessary for the full realization of the system by solving the remaining issues.

## Acknowledgements

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## Author

### Yoshio Tanaka

Received doctor's degree from Keio University in 1995. Doctor of Engineering. Joined the Real World Computing Project in April 1996. Joined the Electrotechnical Laboratory, Agency of Industrial Science and Technology in April 2000, which became the National Institute of Advanced Industrial Science and Technology (AIST) in April 2001. Joined the Grid Technology Research Center, AIST in January 2002. Became senior researcher of the Information Technology Research Institute, AIST in April 2008. Interested in grid programming and grid security. Chairman of the Asia Pacific Grid Policy Management Authority (APGrid PMA), and co-chairman of the Open Grid Forum Certificate Operations Working Group.

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## Discussion with Reviewers

### 1 Readers of the paper

#### Question and comment (Kazuhito Ohmaki)

I think the objective of the paper, or who (what kind of people) you wish would read the paper, is unclear. Do you wish to say, "This is an age where the world is full of software with excellent function rolling around like PDS, and if we pick them up and combine them, we can make incredible things, and fairly high performance can be obtained by presenting core competence?" And then, do you want to present grid technology as an example to a wide range of software engineers to give them assurance, or do you want to say that although the application is now for geology, the range must widen to astronomy and the environment? Or do you want to emphasize that it is an age where software or data should be presented as a "service?" Or is it all of the above? I think you should explain the objectives more clearly with more words in the "introduction" or the "discussion" and "conclusion" sections.

#### Answer (Yoshio Tanaka)

The main purpose of this paper is to contribute to the creation of innovation in science and technology by promoting the diffusion of grid technology and E-Science infrastructure by using that technology, and to demonstrate the construction of an E-Science infrastructure using grid technology, with GEO Grid as an example, and finally, to make all of this available to researchers in wide-ranging fields of science and technology. Also, I wish to show that a large-scale system can be realized easily if the basic technologies are implemented according to standard protocols and APIs. I wish to emphasize the importance of standardization and collaboration with overseas institutions in developing each basic technology. I also wish to point out that in constructing a large-scale system, it is not realistic to development everything on your own, and it is important to reduce the development cost by actively using available technology, while maintaining the core competence.

I added some explanation in chapter 1 to clarify these themes. I also modified the abstract.

### 2 "Distributed computing"

#### Question and comment (Kazuhito Ohmaki)

Although I think the idea of grid technology for connecting high-speed computers is important and interesting, from a layman's point of view, I don't feel that the concept of grid has become any more familiar than it was 10 years ago, when it was first proposed. Or, do you think it is correct to say, "No, that is

a lack of knowledge on the part of the reviewer, and it's totally different from what it was before, and it is now within reach?"

#### Answer (Yoshio Tanaka)

While many of the basic technologies of the grid are maturing, I think the reason it does not feel quite familiar is because there are some outstanding technological issues, particularly in the computation grid, and there are very few case studies or success stories using the grid. However, the grid is at the level where it can accomplish a lot with currently available technologies, and in fact, the GEO Grid is capable of responding to the demands of the earth science researchers by combining current technologies. I added this point to chapter 1. The objective of this study, as mentioned in the Answer for Discussion 1, conforms to this explanation.

### 3 Security

#### Question and comment (Kazuhito Ohmaki)

I think the issue of security is always a problem, whether past or present, in the VO concept. Is that the only remaining issue, and if this is solved will it become sort of operational? Or, is there some other factor? Or will it be solved if a *de jure* standard is employed? I would like to see some mention of the "issues," particularly those pertaining to grid technology.

#### Answer (Yoshio Tanaka)

For security, I think the technology that can be put to practical operation is already established for most science and technology fields. I think there are three factors or problems in grid technology: many of the grid middleware suite cannot be easily installed or set. They are not user friendly in terms of important issues such as handling of user certificates, etc. And the key technology, a metascheduler, is still in the research phase. Detailed explanations of these problems were added to "Issues to be solved" in chapter 6.

### 4 Strategy and scenario

#### Question and comment (Naoto Kobayashi)

GEO Grid, as an application of grid technology, is an extremely effective technology that may help solve many issues of the 21st century, where society must become sustainable through prevention of global warming, resource conservation, disaster projection and prevention, and efficient land use.

Based on the above viewpoint, the papers of *Synthesiology* emphasize the relationship of the research objective and society, as well as the importance of this scenario. In this paper, I see the greater objective concept, but I think the specific research objective is unclear. I understand ultimately that the essence of the grid technology is for everyone to be able to conduct information processing freely, utilizing CPU resources and databases that are distributed in several different places, as if they exist in one's own computer or in the close proximity, without being conscious of the existence of the grid technology. If that is true, I think you should have an explanation of what is the final objective of the GEO Grid in this research project, and to what phase you wanted to attain in this paper amongst the greater objectives. I expect also to see some explanation of the strategy and scenario for that purpose.

#### Answer (Yoshio Tanaka)

As you pointed out, the final objective of the GEO Grid and the current level of achievement were not clear, so I added the final goal in chapter 1, as follows: "The objective of this research is to build an E-Science infrastructure using the grid as the basis of the GEO Grid, to provide a research environment for earth science researchers, and to clarify and to solve the issues in the way of a full realization of its potential in wide-ranging science and technology fields. The aim is thus to contribute to the creation of innovation in the science and technology fields."

Also, I explained the issues that need to be solved that became clear in the process of system construction in chapter 6, and added some further explanation in chapter 8. I also added an explanation of the strategy for achievement of the final goal in chapter 1.

## **5 Synthesis of basic technology and an explanation of technical terms**

### **Question and comment (Naoto Kobayashi)**

The individual basic technologies and the reason for their selection are described very understandably. However, there are many technical terms, and they must be explained in the text. On the other hand, the issue is a synthesis of the basic technologies. It is described that basic technology is designed and implemented, based on standard protocols and standard interfaces, but please explain the uniqueness, innovativeness, and superiority of such a synthesis. Of course, the ease of system construction is an

advantage having both uniqueness and superiority. I think it would be good if you can address whether the quality of security and service obtained from this synthesis is sufficient from the view point of GEO Grid, or whether it requires more improvement.

### **Answer (Yoshio Tanaka)**

I think the superiority and importance of this research and the main theme of this paper is to show that a large-scale system can be realized easily if the basic technologies are implemented according to standard protocols and APIs, and to state that for the development of each basic technology, standardization and collaboration with overseas institutions are important. And also, that it is not realistic to develop everything on our own when constructing a large-scale system, but it is necessary to reduce the development cost by actively using available technologies while maintaining the core competence. These caveats are mentioned in chapter 6, and I also added some descriptions in chapter 1.

# Basic materials research for the development of ubiquitous-energy devices

— Applications to positive electrode materials of Li-ion batteries, electrode catalysts of proton-exchange fuel cells and gold catalysts —

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Koji Tanaka<sup>1</sup>, Kazuyuki Okazaki<sup>2</sup> and Jun Kikkawa<sup>3</sup>

[Translation from *Synthesiology*, Vol.2, No.1, p.42-50 (2009)]

For ubiquitous-energy devices, the development of well-performing functional materials is the key issue. Effective collaboration between development researchers and researchers carrying out basic materials analysis using electron microscopy observations, surface-science observations and theoretical calculations is of great importance. We have previously discussed the role of basic materials research in our discussion of *full research* and have made efforts to carry out a successful collaboration. To this end, we have attained valuable contributions to materials development as well as high-level scientific achievements as substantiated by numerous awards through the development of original observational and calculation techniques relating to the positive electrode material of Li-ion batteries, the electrode catalysts of proton-exchange fuel cells and gold/oxide catalysts.

**Keywords :** Materials for energy and environmental problems, basic materials research, electron microscope observation, first-principles calculation, lithium-ion battery, fuel-cell electrode, gold catalyst

## 1 Introduction

With the advent of the ubiquitous information society, lithium ion (Li-ion) batteries and fuel cells are drawing attention as portable power source for cell phones and mobile PC. Portable power sources, which are lightweight, high output, high capacity, highly durable, and environment-friendly, are important for use in robots, various medical devices, and small transportation device such as electric wheelchair, to serve the society with advanced medical welfare. By achieving higher output, they can be applied further as power sources for electric vehicles and hybrid cars, and are expected to have great impact on the environment. Energy storage and hydrogen gas refinement technologies are important to support the power source devices. The development of excellent functional materials for electrode, catalyst, and storage of hydrogen and ions is positioned at the center of the development of such ubiquitous energy device. Since they must clear high hurdles of output/weight ratio, safety, and environmental compatibility, the role of functional material development is extremely significant. In our research institute, R&D is mainly focused on the development of functional materials<sup>[1][2]</sup>. The Authors have been conducting research on basic material analysis combining nano-structure analysis using transmission electron microscope (TEM) observation and scanning probe microscope (SPM) and theoretical computations such as first-principles calculation<sup>[3]-[5]</sup>. We can

expect major results by ingeniously combining *Type 1 Basic Research* and material R&D.

However, effective collaboration between material development and basic material analysis is not generally easy, and much effort and trial and error are required. This is a common issue for R&D in other fields also. Our group engaged in discussions to shape our direction, and was able to achieve some success through collaboration between the development and basic analysis. We shall introduce our experience and results in this paper, and share some of the lessons we learned. Particularly, we shall discuss the role and significance of basic material analysis (*Type 1 Basic Research*) in material development.

## 2 Importance of basic analysis for energy and environmental materials

Many ubiquitous energy devices such as fuel cells, Li-ion batteries, hydrogen storage devices, and devices for production and refinement of hydrogen gases utilize exchange of electrons during the reaction of molecules and absorption/desorption of ions at the electrode, as well as various reactions and absorption/desorption of energy media. While it is believed that unique properties and phenomena of nanoparticles, nanostructures, and surface/interface dominate the function, details of the mechanism have not been clarified.

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From the perspective of material development, it is extremely important to experimentally and theoretically clarify structure, function, and various phenomena of such energy and environment materials using TEM observation and first-principles calculation<sup>[3]-[5]</sup>. For example, when a material with excellent function is discovered, further improvement, discovery, and development do not follow unless we understand why such excellent function manifests. Particularly, when the correlation between the structure and function of nanostructure is clarified, the possibility of developing excellent materials through design and control of nanostructures broadens dramatically. Also, the performance of functional materials deteriorate after they are used for some time, but measures against deterioration and plans for improvements cannot be made unless we understand what is occurring on the microscopic level. Rather than searching blindly for materials from experience and inspiration, it is much more efficient to search systematically upon understanding the crystal, electronic, and nano structures of the materials. Of course, there are ample examples of serendipity in material development. However, to run into serendipity efficiently or to not miss serendipity, it is essential to simultaneously conduct microscopic analyses.

On the other hand, basic analysis of energy and environment materials has its unique problems. Manifestation of function involves complex reaction process and material transfer of hydrogen (proton) and Li-ions, such as absorption and reaction, electron transfer, oxidation/reduction, and valence fluctuation under gas atmosphere or in electric field. TEM observation is normally conducted under ultrahigh vacuum, and TEM observation of light element such as hydrogen and lithium is not generally easy. First-principles calculation at this point cannot readily handle large-scale reaction system or material and electron transfer. To advance the basic analysis of energy and environment materials, improvements and innovations of the basic analysis method itself is necessary. These are the factors that have delayed the application of basic analysis compared to other materials (such as semiconductor devices).

### 3 Issues in the collaboration between material development and basic material analysis

There is a mountain of issues that must be clarified through application of basic analysis in the actual practice of R&D of ubiquitous energy device and its functional materials. However, there are several issues and difficulties to realize an efficient and useful collaboration. First, the pace and phase of material development and basic analysis are not necessary in synch. Since basic analysis involves the development of analysis method, it is often necessary to study one topic over long period. Naturally, the topics are studied separately, and flexible collaboration is inhibited. Second, since the actual materials and phenomena are often too complex, application

of basic analysis is not easy. Therefore it becomes necessary to deal with the model material rather than the actual material, and close communication between the people involved in material development and those in basic analysis becomes necessary. Third, the gap in objectives and values, the difference in knowledge and understanding of the issue, and the lack of understanding of each other's research occur between the researchers of material development and basic analysis, and this inhibits close collaboration.

In the Research Institute for Ubiquitous Energy Devices (established in 2004) of AIST Kansai, a group was formed by researchers who were involved in TEM, SPM, and first-principles calculation since the inception of the Special Division of Green Life Technology in 2001. The group has engaged in discussion of where to position the basic material analysis in the system of *Full Research* and ways to contribute to material development. The reasons are: first, as mentioned earlier, energy and environment materials have potential for dramatic development through design and control provided by basic analysis since nanostructure itself is key to phenomena and functions; and second, we believe there is a creative value in the research methodology for the collaborative effort between basic analysis and development. Of course, as third reason, such collaborative effort is advantageous in obtaining research fund to maintain large apparatus.

Figure 1 is an outline of the collaborative effort from the standpoint of basic analysis. First, for research unit management, we promoted (1) the sharing of objectives between development and basic analysis, and (2) the construction of system where flexible sharing and close communication were possible. These were promoted by holding colloquiums for the whole unit and working groups as well as discussion between unit leaders and groups, and budgetary allowances were provided to promote such activities. The Authors' basic analysis group discussed the role of basic analysis as part of *Full Research*, and defined (1) the clarification and search to overcome the valley of death, and (2) the discovery and generalization/systematization of the potentials. It can be said that both aspects are necessary including the promotion of specific collaboration with development and the continuous effort for systemization by basic analysis. For the latter, we set the objectives of construction and systemization of theories of "metal/inorganic nano-hetero interfaces" that often held the key of function in ubiquitous energy devices<sup>[3]</sup>. In the metal-oxide hetero catalyst, exemplified by gold catalysts that will be mentioned later, and the Pt/C catalysts of proton-exchange fuel cells, hetero effect of the interface and the nano-size effect of metal particles are greatly involved in excellent function, but the details are unclear, and there is potential for building generalized design theory and guideline through the construction and systemization of theories. While tackling various topics flexibly from the perspective of (1), the findings

are accumulated and systematized in long-term from the stance of (2). The latter findings must be shared by everyone including the members of the material development group.

As tasks to be achieved by the basic analysis group, we conducted the specification and clarification of issues through collaboration with development group, as well as the establishment of observation technology of the actual materials and system. This involved pioneering the original TEM observation method for the fuel cells and the Li-ion batteries that will be described later. Second, we worked on the review and establishment of first-principles calculation technique of complex structure. Also, we worked on the collaborative analysis technology of theoretical calculation and TEM observation and surface science methods. Such pioneering of the basic analysis technology for energy and environment materials is not easy, but must be tackled simultaneously to solve the issues of various phenomena and functions of the materials.

The three issues described in the beginning of this chapter could not be solved easily. However, when efforts spent while the researchers were fully aware of the issues, improvements and solutions did progress. Specific results will be described in the next chapter, and the lessons learnt from the effort will be discussed in chapter 5.

## 4 Some examples of significant results

In this research, we obtained several significant results that

were utilized in the development of functional materials, and were highly evaluated academically as demonstrated by reception of various awards. Some examples are explained herein. The example of positive electrode materials for Li-ion batteries was a result that leads directly to new material development, while the examples of Pt/C electrode catalysts for fuel cells and gold/oxide catalysts had great impact on the construction and systematization of theories for metal/inorganic nano-hetero interfaces as well as the improvement and development of materials. Both helped advance the basic analysis technology.

### 4.1 Mechanism for increasing capacity of positive-electrode materials for Li-ion batteries

A Li-ion battery is a storage cell that uses transition metal oxides including Li for its positive electrode, and carbon or Li metal or alloy for its negative electrode. The capacity and power density in comparison to weight are outstanding compared to conventional storage cells. It is expected to be used widely in automobiles as well as mobile devices, and further increase in capacity and power density, and improvement in durability and safety are necessary. In the charge process, Li ions move from the positive to negative electrodes through electrolytes, and return from the negative to positive electrodes in the discharge process. The development of excellent positive electrode materials that can absorb and release high density of Li ions repeatedly is the most important. Currently,  $\text{LiCoO}_2$  is commonly used as the positive electrode material, but a material that is capable of achieving high capacity and high power density without using

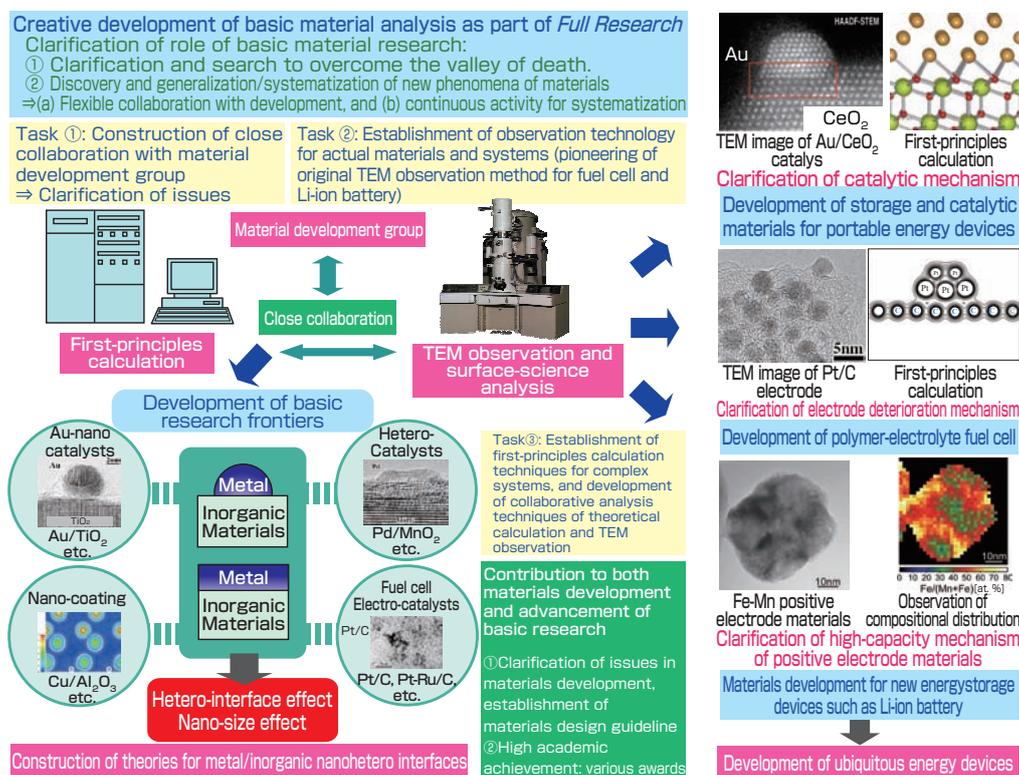
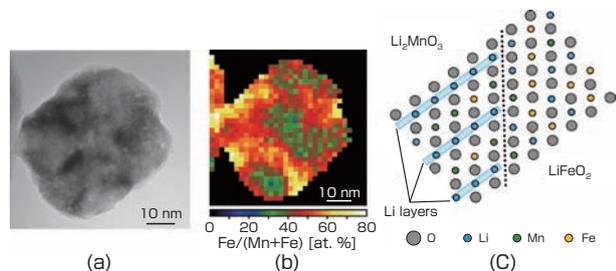


Fig. 1 Outline of research activities of basic material analysis for the development of ubiquitous energy devices.

rare metal Co is desired. Tabuchi *et al* of AIST developed the high-capacity complex oxide  $\text{Li}_2\text{MnO}_3\text{-LiFeO}_2$  ( $x\text{Li}_2\text{MnO}_3\text{-(1-x)LiFeO}_2$ ) (capacity > 200 mAh/g) containing Fe and Mn<sup>[6]</sup>.  $\text{Li}_2\text{MnO}_3$  and  $\text{LiFeO}_2$  that comprise this material are inactive materials that do not absorb or release the Li ions in individual bulk. Superior materials may be developed by clarifying the mechanism of how they are activated to achieve high capacity when they are in complex form.

Therefore, we began working on this material using TEM observation under close collaboration with the development group. First, we discovered that each particle of the material had structure with Fe-rich ( $\text{LiFeO}_2$ -like) and Mn-rich ( $\text{Li}_2\text{MnO}_3$ -like) chemical nano-domain under common oxygen lattice, using the STEM-EELS (scanning transmission electron microscope - electron energy loss spectroscopy) spectrum imaging method (method of quantifying and imaging the element concentration distribution by accumulating EELS data at every scan position of the electron beam<sup>[7]</sup>) and the nano-beam analysis method (Fig. 2)<sup>[8][9]</sup>. The nano-scale domain structure without clear grain boundaries or interfaces was a new discovery. It is thought that the difference of lattice constants was small between the two phases and there was mixing at the atomic level in the interface region. In conventional x-ray diffraction observations, it was estimated from average information that the  $\text{LiFeO}_2$ -like and  $\text{Li}_2\text{MnO}_3$ -like phases might exist, but the existence in the form of chemical nano-domain structure was finding far beyond expectation.

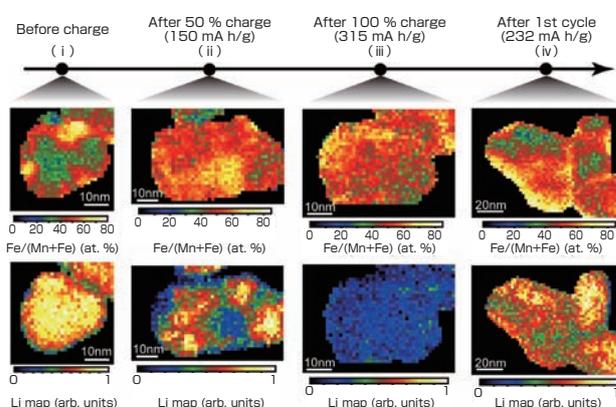
To investigate the mechanism whereby chemical nano-domain structure produces high capacity, it is necessary to investigate the absorption and release of Li ions in each phase by charge and discharge. Therefore, we developed a new method to visualize the concentration distribution of Li ions in real space using the STEM-EELS spectrum imaging method. Conventionally, analysis of EELS data for Li was not easy, and quantitative analysis of Li concentration distribution was in fact impossible. If the thickness of the sample was sufficiently thin, the strength of the secondary differential peak strength of the EELS spectrum was deemed



**Fig. 2** (a) Transmission EM image of a  $\text{Li}_2\text{MnO}_3\text{-LiFeO}_2$  particle as positive electrode materials for high-capacity Li-ion batteries. (b) Concentration distribution of transition-metal elements observed by the STEM-EELS spectrum imaging method. (c) Conceptual diagram of the chemical nano-domain structure.

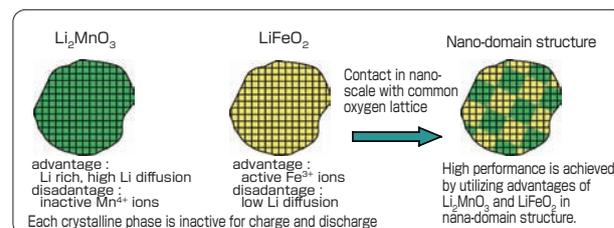
to be in proportion with concentration, and therefore, we succeeded in quantitative visualization of Li concentration distribution by devising a data analysis method<sup>[10]</sup>. This method was first in the world to investigate the real space distribution of Li ions.

As shown in Fig. 3, by applying the new method to the positive electrode material in the processes of charge and discharge in a battery cell, it was found that the Li ions are extracted first from the Fe-rich domain in the charge process and then extracted from the Mn-rich domain. Li returned after discharge, but there were unevenness in recovered concentration in certain places in correspondence to decreased capacity<sup>[10]</sup>. As shown in Fig. 4, it is clear that in nano-domain structure, Fe-rich domain that is inactive



**Fig. 3** Concentration distributions of transition-metal elements (upper) and of Li (lower) in  $\text{Li}_2\text{MnO}_3\text{-LiFeO}_2$  particles as positive electrode materials for high-capacity Li-ion batteries, observed during the charge and discharge processes.

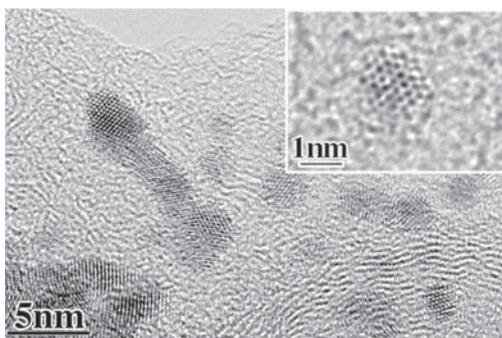
- (i) In a sample before charging, each particle reveals chemical nano-domain structure consisting of  $\text{Li}_2\text{MnO}_3$ -like (green, blue) and  $\text{LiFeO}_2$ -like (yellow) domains (upper figure), where Li ions are distributed throughout the particle (lower figure).
- (ii) In a 50 %-charged sample, there is a match between the blue domains for the concentration distribution of Li (lower figure) and the yellow domains for the concentration distribution of transition metal elements (upper figure), which clearly indicates the preferential Li-ion extraction from the  $\text{LiFeO}_2$ -like domains in the early stage of charging.
- (iii) In a 100 %-charged sample, Li ions are desorbed from the entire region of each particle (lower figure).
- (iv) In a sample after discharge, Li ions are recovered throughout the particle (lower figure). However, the recovery does not seem to be perfect, because slight decreases of Li-ion concentration are detected locally.



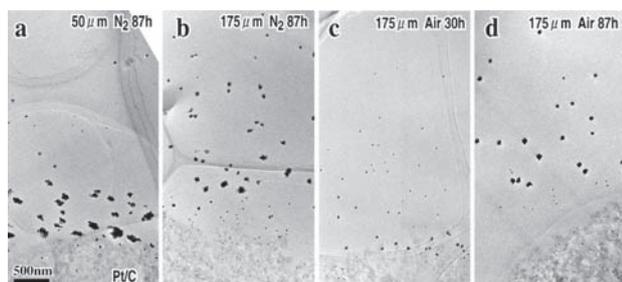
**Fig. 4** Conceptual diagram of the generation of excellent performance in  $\text{Li}_2\text{MnO}_3\text{-LiFeO}_2$  positive electrode material through the chemical nano-domain structure.

in bulk is activated by being surrounded by the layered Mn-rich domain that is advantageous for diffusion of Li ions, and then when Li becomes depleted in the Fe-rich domain, the Li ions are extracted even from the Mn-rich domain. It is thought that oxygen provides charge compensation in Li extraction from the  $\text{Li}_2\text{MnO}_3$  domain composed of tetravalent Mn. Decrease of capacity is thought to occur due to the desorption of neutral oxygen by charge compensation, and the actual reduction in oxygen concentration was observed in the STEM-EELS spectrum imaging.

It was possible to clarify the mechanism of increased capacity where the chemical nano-domain structure activated each component material, by discovering the chemical nano-domain structure utilizing the TEM technology and by developing the visualization technology for quantitative distribution of Li-ion concentration. It is greatly significant to clarify the specific involvement of the nanostructure in the performance of positive electrode materials. Currently, material performance is being improved from the perspective of optimal control of such chemical nano-domain structure. The essential factor that enabled the above results was the



**Fig. 5 High-resolution TEM image of PtRu/C electrode catalysts.**



**Fig. 6 TEM images of the precipitation and growth of Pt particles inside the electrolyte film, caused by Pt dissolution from the Pt/C positive electrode in various testing conditions.**

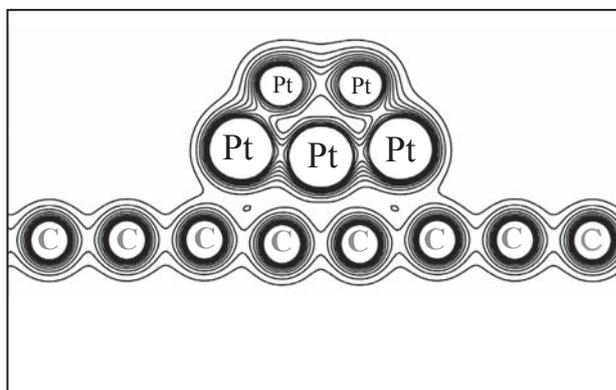
(a) Nitrogen was supplied to the Pt/C electrode with an electrolyte film of thickness 50  $\mu\text{m}$ , under the potential for 87 h. (b) Nitrogen was supplied to the electrode with an electrolyte film of thickness 175  $\mu\text{m}$ , under the potential for 87 h. (c) Air was supplied to the electrode with an electrolyte film of thickness 175  $\mu\text{m}$ , under the potential for 30 h. (d) Air was supplied to the electrode with an electrolyte film of thickness 175  $\mu\text{m}$ , under the potential for 87 h. The features of the precipitation and growth of Pt particles depend on the thickness of the electrolyte film, supplied gasses, and the time of potential charge.

research conducted through daily communication of issues, topics, and experimental observation plan through close collaboration with the  $\text{Li}_2\text{MnO}_3$ - $\text{LiFeO}_2$  development group.

#### 4.2 Microscopic structure and deterioration mechanism of electrode catalysts in fuel cells

In a polymer-electrolyte fuel cell, electrons are extracted by the dissociation and oxidation of a fuel hydrogen molecule at the Pt particle of the negative electrode ( $\text{H}_2 \rightarrow 2\text{H}^+ + 2\text{e}^-$ ) by using the structure in which Pt particles are supported by carbon material (Pt/C electrode) as electrode catalysts, and proton  $\text{H}^+$  transfers to the positive electrode through the polymer electrolyte. Similarly, water is produced by reaction of proton and oxygen on the Pt particle at the positive electrode ( $1/2\text{O}_2 + 2\text{H}^+ + 2\text{e}^- \rightarrow \text{H}_2\text{O}$ ). At this moment, electrons from the negative electrode are used through the carbon and the conductor. Since CO often mixed in the hydrogen gas suppresses the catalytic activity of Pt particles at the negative electrode (CO poisoning), Pt-Ru alloy particles are used. It is important to increase the reaction efficiency while reducing the amount of rare metal Pt by controlling the electrode composition as well as the size and dispersion of Pt particles and Pt alloy particles.

Deterioration through use is an issue for the Pt/C electrode, and the clarification of that mechanism is demanded. Under close collaboration with the group conducting the development of electrode catalysts and deterioration testing, we attempted clarification through TEM observation<sup>[11]-[13]</sup>. The TEM observation of the electrode catalysts of fuel cells was extremely rare. Electrolyte-electrode catalyst assembly was sliced using ultra-microtome to prepare the TEM samples, and optimal observation conditions were sought by trial and error. Figure 5 shows the typical high-resolution transmission electron microscope (HRTEM) image of the PtRu/C electrode catalysts. The lattice image of the fine particles of the catalyst could be seen clearly, indicating that excellent high-resolution observation was possible.



**Fig. 7 First-principles calculation of a  $\text{Pt}_{10}$  cluster/graphene system.**

Valence-electron charge distribution of the relaxed configuration indicates little electron transfer or orbital hybridization at the interface.

The deterioration test was conducted by activating the fuel cell under various conditions. By TEM, the increase of the diameter of the catalyst metal particles was observed, the preference dissolution of Ru from the Pt-Ru particles was detected, and the precipitation and growth of catalyst metal particles within the electrolyte film far from the electrode was observed, depending on the test condition (Fig. 6). The particle diameter distribution and particle space distribution changed by altering the type of gas supplied to the negative and positive electrodes and by changing the thickness of the electrolyte film. It was clarified for the first time, that such dissolution and precipitation behaviors of the catalyst metal particles were factors of the deterioration phenomena, along with oxidation of carbon material. The TEM observation of microscopic structures and deterioration of the electrode catalyst of a polymer-electrolyte fuel cell was done for the first time in the world (Table 1).

On the other hand, first-principles calculation is important in understanding the function and nanostructure of the Pt/C electrode. We are working on first-principles calculations of basic interface reactions for various forms of Pt metals or clusters deposited on carbon (graphene sheet) (Fig. 7)<sup>[14]</sup>. The reactivity of the  $\pi$  bond surface of the graphene sheet is small. The interactive (bonding) energy between Pt-C reaches maximum for single Pt atom, then decreases as the coordination number and size increase for Pt clusters, and reaches minimum for the crystal surface. Using this calculation data, it is possible to simulate the mesoscale structure of the Pt/C electrode. We obtained comparable results in the TEM observation, and this is important as theory of metal/inorganic nano-hetero interfaces<sup>[15]</sup>.

The above results were only possible with daily collaborations and discussions with the group that was actually creating the electrode catalyst for fuel cells and conducting the deterioration test.

#### 4.3 Mechanism of gold/oxide nano-hetero catalysts

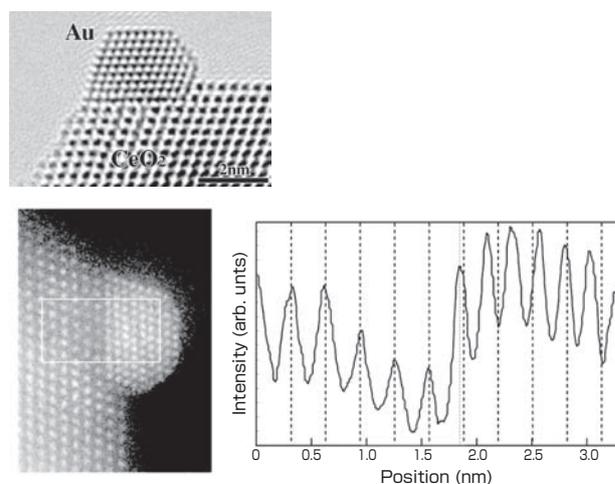
Gold is generally inactive, but shows distinctive catalytic activities such as CO low temperature oxidation and water gas shift reaction (reaction to remove CO from hydrogen gas,

$\text{CO} + \text{H}_2\text{O} \rightarrow \text{CO}_2 + \text{H}_2$ ) when it is supported on the surface of oxides such as  $\text{TiO}_2$  and  $\text{CeO}_2$  in nano-particle form<sup>[16]</sup>. To clarify the mechanism of how inactive gold is activated should contribute to the development of designing technology of novel metal/inorganic nano-hetero catalysts. We have been engaging in the basic analysis combining TEM observation, surface science, and first-principles calculation, under close collaboration with the catalyst development group.

In the Au/ $\text{TiO}_2$  system, the strong interaction between Au and  $\text{TiO}_2$  could be inferred since there is preferred orientation relationship at the interface observed by TEM. From surface science experiments such as SPM observation, it was found that the Au- $\text{TiO}_2$  interaction is stronger in the reduced surface (Ti-rich surface) with oxygen deficiency compared to the normal stoichiometric surface of  $\text{TiO}_2$  (surface with equal amount of anion and cation). On the other hand, it was indicated from the first-principles calculation that the interfacial bond becomes much stronger when the interface is non-stoichiometric as Ti-rich or O-rich, revealing stronger orbital hybridization and electron transfer between Au and  $\text{TiO}_2$ , which would affect the catalyst activities<sup>[17][18]</sup>. For further investigation, we conducted detailed observation of atomic arrangement at the interface using the high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) (a method for obtaining the image of atomic column through high-angle scattered wave from atoms by scanning with focused electron beam), and succeeded for the first time in detailed observation that allowed the identification of the atomic columns. On the other hand, from the first-principles calculation of atomic and electronic structures of the interface based on such observation model, it was clarified that Ti-rich or O-rich interfaces might be stabilized according to the atmosphere, and that Ti-rich or O-rich interfaces have unique electronic states.

**Table 1 Recent awards from academic societies and conferences.**

FY 2004	Satoshi Ichikawa, Japan Institute of Metals 2004 Fall Meeting, Best Poster Award (EM) Tomoki Akita, MRS 2004 Fall Meeting Poster Award (EM) Satoshi Ichikawa, MRS 2004 Fall Meeting Poster Award (EM) Shingo Tanaka, MRS-J 2004 Symposium Encouragement Award (Computation)
FY 2005	Tomoki Akita, Catalysis Society of Japan Poster Award (EM) Shingo Tanaka, MRS-J 2005 Symposium Encouragement Award (Computation)
FY 2006	Tomoki Akita, International Federation of Societies for Microscopy ICM-16 Poster Award (EM) Tomoki Akita, IUMRS-ICA 2006 Best Paper Award (EM)
FY 2007	Koji Tanaka, Japan Institute of Metals, Metallographic Contest in Division B 1st Prize(EM)
FY 2008	Jun Kikkawa, The 63th Annual Meeting of the Japanese Society of Microscopy, Poster Award (EM) Jun Kikkawa, The 14th International Meeting on Lithium Batteries, Most Excellent Poster Paper Award (EM) Tomoki Akita, ICC-14 Pre-Symposium, Best Poster Presentation Award (EM)



**Fig. 8 TEM observation of a Au/ $\text{CeO}_2$  catalyst system.**

Upper: High-resolution TEM image of a Au nano-particle bonded on  $\text{CeO}_2$ . Lower, left: HAADF-STEM observation of the same structure. Lower, Right: Analysis of inter-layer distances by the profile of integrated HAADF-STEM image intensity along each atomic layer.

For the Au/CeO<sub>2</sub> system, we discovered the novel phenomena that (i) Au nano-particles supported on CeO<sub>2</sub> disappeared during TEM observation, as layer-by-layer with only the Au first layer at the interface remained, and that (ii) the Au nano-particles recovered at the same places when the electron beam was stopped and left in the chamber<sup>[19][20]</sup>. Such atmosphere-dependent structural changes should be related to the catalytic property, and the clarification of mechanism is important. It could be inferred that the effect of oxygen deficiency on CeO<sub>2</sub> surfaces is important since the Au particle growth on CeO<sub>2</sub> at high temperature could be controlled in the H<sub>2</sub> atmosphere. We succeeded in obtaining a detailed image of the interface atomic arrangement for the first time using the HAADF-STEM method (Fig. 8)<sup>[21]</sup>. The interface is steep and the distance between the Au and Ce atomic layers can be measured. By comparing this observation with the first-principles calculation, it could be concluded that a Ce-terminated interface is formed. The series of phenomena could be explained from the theoretical analysis including the chemical potential depending on the atmosphere, where the Au-atom trapping by oxygen vacancies in CeO<sub>2</sub> surfaces and bulk and the strong bonding at the Ce-terminate interface are involved.

At this point, the mechanism of the catalytic activity of the Au/TiO<sub>2</sub> and Au/CeO<sub>2</sub> systems are not completely clarified, but there have been no other cases where the interface structures of metal/oxide hetero catalysts are revealed at this resolution, as proved by many awards (Table 1). From the first-principles calculated based on this observation, it is strongly implied that the key of function is held by the stoichiometry of the interface and its control by atmosphere. As next step, the TEM observation in gas atmosphere and the first-principles calculation of molecular absorption and reaction path of the real interface and peripheral models are in progress.

The above results were made possible by effectively setting topics and plans through continuous collaboration and close information exchange with the catalyst production groups inside and outside the unit.

#### 4.4 Recent awards

The above research activities have won several awards. Table 1 shows the recent awards. The results of basic material analysis through close collaboration with the material development have drawn much attention, and our activities have been acclaimed highly as basic science. The reasons for receiving the awards are as follows: (1) the construction of high level basic analysis technologies and new methods, (2) the pioneering work advancing the frontier of the clarification of the energy and environment materials and the metal/inorganic nano-hetero interfaces, and (3) the results of basic analysis highly expected to be used in real material development and improvement. Of course, rather than pure basic research, the awards were probably given to the results and expectations from the developmental viewpoint.

## 5 Discussion and summary

In general, there are still no solid methodology or guideline for the development of new materials, and this is a grave fact. From the perspective of device development (*Type 2 Basic Research*), various findings must be pursued (results of *Type 1 Basic Research* and experience from *Type 2 Basic Research*) and the development and search of the materials must be done by trial and error. However, since the process (of making the material in various ways) deals with nature (matter), we often run into novel mysterious phenomena that no one has experienced before. In seeking novel materials, this cannot be avoided. When that happens, we cannot wait for someone else to solve the issue for us (with *Type 1 Basic Research*). The developer and group of developers must attempt clarification by investigating the phenomena by themselves. Therefore, it is necessary to utilize the *Type 1 Basic Research* available within the same research organization and to closely collaborate with such researchers. This is the way of materials development as *Full Research*. On the other hand, to make such collaborative activity effective, the researchers involved in *Type 1 Basic Research* bear mission to work hard on analysis method and to pioneer and refine the new methods. For dramatic materials development, it is important to strike balance and efficiency of “specialized” and “collaborative” researches between the development (*Type 2 Basic Research*) and the analysis (*Type 1 Basic Research*).

The experience of the Authors is limited, and not all issues are solved. Some areas are dependent on individual ability. The lessons and significance at this point can be summarized as follows. First, it is important to have an organization and management policy where the development and basic analysis groups can collaborate through daily information exchange on the same floor or at close proximity. Second, the priority topic in actual development often deals with new phenomenon or interdisciplinary phenomenon that are valuable in terms of basic science. Basic research in collaboration with actual development raises the level of basic research. Of course, the researchers must spend more effort to establish new analysis technology. Such efforts may lead to the creation of new disciplines (for example, electrochemistry and catalyst chemistry at the atomic and electronic level). Third, the cooperation of development and basic research provides plans and ideas for material design and development from new perspective to the development side. Of course, continuous efforts are necessary for such ideas to be truly utilized in dramatic development. Fourth, we believe the continuous accumulation and systemization of experience and knowledge in the collaboration of such materials development and basic research, as well as the education of human resources that are capable to handle them, is the “core competence” that must be carried on and developed in a research institution.

## Acknowledgements

The case study described in this paper was conducted in cooperation with the researchers of the material development group. For the positive electrode materials in Li-ion batteries, we thank Dr. Mitsuharu Tabuchi, Dr. Masahiro Shikano, and Dr. Kuniaki Tatsumi (Research Institute for Ubiquitous Energy Devices, AIST); for the electrode in fuel cells, Dr. Kazuaki Yasuda (Research Institute for Ubiquitous Energy Devices, AIST); for the gold catalyst, Professor Masatake Haruta (formerly of Research Institute for Green Technology, currently Tokyo Metropolitan University), and Dr. Tadahiro Fujitani (Research Institute for Innovation in Sustainable Chemistry, AIST). We received the support of the New Energy and Industrial Technology Development Organization (NEDO) for the researches of the positive electrode materials in Li-ion batteries and the electrode in fuel cells; the Japan Science and Technology Agency (JST) for the calculation of fuel cell electrodes; and Grant-in-Aid for Scientific Research and JST for the study of gold catalysts. We are grateful to all the people and sections involved.

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## **Discussion with Reviewers**

### **1 Expectation for the management**

#### **Question and comment (Kazuo Igarashi)**

You mentioned in this paper that it is possible to conduct dramatic material development by taking an effective balance of “specialized” and “collaborative” researches by organizing the groups (human resource) that engage in development (*Type 2 Basic Research*) and analysis (*Type 1 Basic Research*) in the same research unit, and I certainly approve of this idea. I ask you one question related to this. I understand that in this paper, the research was conducted through the consensus of the research unit, but I also think the role of the leader who brings the organization together to formulate the consensus is important. Therefore, what kind of management do you expect from a leader of an organization, in general, to reach a consensus?

#### **Answer (Masanori Kohyama)**

In our unit, one of our objectives from its inception was to propagate the research dramatically through effective collaboration of “development” and “basic analysis” and to establish a methodology for that purpose. This is the desire of the research unit leader, and it was understood as a challenging and significant issue through discussions by the members in the course of designing the unit. As discussed in the beginning of chapter 3, there are several inhibitory factors in the collaboration of “development” and “analysis”: (1) pace and phase of the researches of the two groups often are out of synch, (2) consistent effort is necessary since analysis of actual complex materials is not easy, and (3) there are gaps in values and consciousness of the researchers. I think the leader of the organization must understand this situation, listen to the difficulties and complaints of the researchers, patiently provide support, and emphasize the importance of achieving results from the collaboration.

### **2 Organization and system most suitable for developing new materials**

#### **Question and comment (Norimitsu Murayama)**

Can you comment on the ideal organization and system when viewing the process from search of material to module creation? The

paper indicates the effectiveness of conducting research by having the measurement/analysis group and the material development group in the same place. Yet on the other hand, research over distance using the Internet or other communication methods has become practical. Please provide your view on the ideal organization and system, for example, organization within AIST in which the Authors work, as well as collaboration among the universities, public research institutions like AIST, and corporations.

**Answer (Masanori Kohyama)**

In general, it is possible to realize effective collaboration using various communication methods even if the joint research does not take place in the same ground. Also, in case of long-term, deeply involved research, the development and analysis groups can conduct research in different places and occasionally meet for discussion. In fact, we do conduct that type of joint research. However, for working on urgent or concentrated problem solving, and from the perspective of efficiently executing *Full Research* as a research organization, I think there is great advantage for an organization that enables daily exchanges between the development and analysis groups, like us. For example, the inhibitory factors mentioned above can be better moderated through daily discussions within the same unit. Particularly for the basic research group, the desire to challenge new or difficult topics in response to the technological and social demands of the development side is born from the sense of mission of “being part of *Full Research*” by sharing the greater objective as a research organization, without settling into our own little world.

**3 Collaboration with analytical instrument industry**

**Question and comment (Norimitsu Murayama)**

I understood very well from this paper about the great contribution that can be made to materials development by the study of assessment and analysis. I think the study of assessment and analysis will promote development of new measurement technologies and instruments, and contribute to the progress of analytical instrument industry industry. Please comment on this point.

**Answer (Masanori Kohyama)**

The development of measurement technologies and devices can progress further by linking up with actual practice of materials development. In the research of positive electrode materials for Li-ion batteries described in this paper, we originally developed the technology to observe the real space distribution of Li-ion concentration. Also, in various catalyst researches, we are involved in the actual development of technology for “on-site observation under real environment” for catalytic reaction in gas atmosphere. Of course, we ourselves cannot develop the measurement devices, but we are considering joint developments with other research groups and companies.

The companies that develop measurement technologies and devices cannot engage in effective development unless they have thorough knowledge of the complex phenomena of materials and substances handled by the engineers and researchers who would be actually working with the device. This is more substantial as the research becomes more advanced, as in measurement and assessment at atomic and electronic levels. Therefore, the exchanges of researches and human resources between the research groups for basic analysis and measurement assessment and the groups for materials development and energy and environment technology are expected to be extremely useful.

# Innovation in distillation processes

—Process intensification for energy savings through concept of “detuning” from ideal state —

Masaru Nakaiwa\* and Takao Ohmori

[Translation from *Synthesiology*, Vol.2, No.1, p.51-59 (2009)]

A methodology of process intensification was discussed through the concept of “detuning” from the ideal state, especially for the energy-saving continuous distillation processes, which are typical energy consumer in the chemical and petrochemical industries. First, the reversible distillation was shown as the thermodynamically ideal state. Then, it was indicated that several energy efficient modifications of distillation processes can be obtained by “detuning” or simplifying the reversible system. Among these modifications, an internally heat-integrated distillation column (HIDiC) was one of the most promising options. The development of the HIDiC in the national projects was reviewed and the reduction of energy consumption by the HIDiC was estimated to be 60 % of the conventional column from the results of the projects.

**Keywords :** Process intensification, distillation process, energy saving, detuning

## 1 Introduction

“Process intensification (PI)” is discussed as a new paradigm in the field of chemical engineering where chemical processes and/or their components such as reaction apparatuses and separation devices are investigated. However, the definition of PI at present is not particularly clear. As Hirata mentioned<sup>[1]</sup>, there is only a vague understanding of PI that is shared among the researchers. “Successful implementation of PI results in dramatic improvement in performance.” The goal is to achieve a performance improvement of at least tenfold. It is called a “quantum leap.” Performance improvements that can be achieved through advancement of existing technology by modifying processes and equipment can be limited to a few dozen percent at most. The realization of a “quantum leap” is necessary for a fundamental change, starting from the operating principle and the sizes and shapes of the equipment.

Looking back at the history of PI, it can be understood that the term itself is not new. According to Kuroda and Matsumoto<sup>[2]</sup>, the term PI was used over 30 years ago in the United Kingdom within the context of safe design and size reduction of chemical plants and processes. However, the outset of increasing interest toward PI in the United States of America and Japan was marked by an article by Stankiewicz and Moulijn<sup>[3]</sup>. The authors’ perspectives on PI have since been changing slowly<sup>[4][5]</sup>, but a few keywords have remained constant. They are “miniaturization” and “simplification,” represented by efforts to reduce the equipment size and the number of operations in a given process; “increased efficiency,” represented by efforts to boost performance and energy saving; “integration” and “combination,” represented by efforts for simultaneous processing of multiple operations such as distillation and heat transfer, or

reaction and separation, using a single unit of equipment; and “enhanced safety,” represented by efforts to minimize waste. Described as such, it is evident that PI has much in common with the concept of Minimal Manufacturing (MM)<sup>[6]</sup>, which is promoted by National Institute of Advanced Industrial Science and Technology (AIST). The MM concept is to manufacture only as many components and products as required, when required, using only the raw materials and equipment that are truly necessary. Perhaps MM is superior to PI, since PI only deals with chemical processes. However, PI has the same goal as MM. MM attempts to reconcile seemingly conflicting demands, such as energy saving with resource conservation, high efficiency with low cost, and high functionality with new features.

We have developed a heat-integrated distillation column (HIDiC) process where the heat transfer and the distillation operations are integrated, with the goal of energy saving during the distillation process. The process from the basic research to the practical application has not been smooth. Looking back, we can state that it was a R&D called *Full Research*. Also it was not intended from the beginning, but the research can be termed a successful example of PI. What follows is a description of the history, method of conceptualization, and approach to practical application of the HIDiC process in relation to PI. More specifically, we attempt to show that the designing and developing a new process through “detuning” from the thermodynamically ideal state is one method of achieving PI.

## 2 Approach to energy saving – thermodynamically ideal state and “detuning”

To discuss the innovation and energy saving in distillation

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processes in relation to PI, we would first like to explain the concept of “energy saving.” Descriptions like “Energy consumption was reduced by 20 % due to energy-saving efforts” are often encountered. Such statements are not so ambiguous and there is no problem as a daily expression. Thermodynamically, however, a closer inspection of them should be carried out, since according to the First Law of Thermodynamics, energy is something that is conserved, not something that can be consumed. If a person gets a 20 % improvement in rate of fuel consumption from purchasing a compact car, what is reduced is the amount of fuel like gasoline that would have been consumed by traveling a given distance, not the energy itself. In an automobile, the chemical energy of fuel is converted through heat into work that is used for moving with the engine (an Otto cycle heat engine for a gasoline vehicle). Except for electric and hybrid vehicles, the term *fuel-efficient engine* refers to one with high energy-conversion efficiency. The upper limit of the efficiency is theoretically determined with thermodynamics under the conditions such as temperature and so on. In other words, there exists a theoretical efficiency limit of converting fuel into moving for the gasoline engine. Improvement of engine efficiency is an important subject for enhancing the rate of fuel consumption in an automobile, but it is basically impossible to achieve the high efficiency that exceeds the limit determined with thermodynamics. As another example, a refrigerator with a compressor is a heat engine called a reverse Carnot cycle, and there is also a theoretical limit of its efficiency, which corresponds to the amount of heat that can be transferred and dissipated from the inside to outside using a given amount of electrical energy. Its limit is theoretically determined with the temperature inside the refrigerator and the outside (room) temperature. It cannot achieve energy saving exceeding the limit of reverse Carnot cycle.

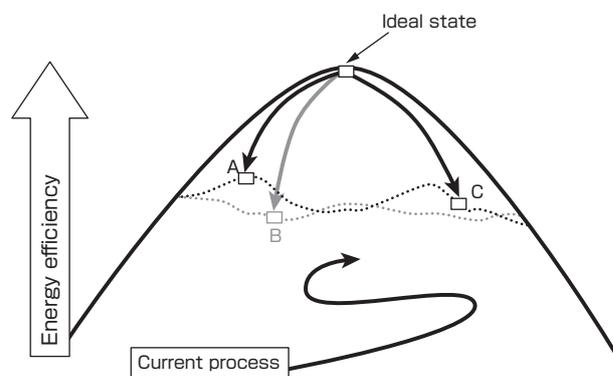
Energy saving can be defined as the reduction of amount of energy required to accomplish a given task. There is a theoretical limit in achievable energy saving, which differs for each task. In other words, energy saving is to realize a given function as close to the theoretical limit as possible. In this paper, we use the term “detuning” to refer to the changing the process from the ideal state to one that is feasible. The term “detuning” is generally used when the engine technology developed for the F1-race vehicles is modified for use of commercial car. Modifications usually include reduced cost, increased durability, and improved usability, while the engine performance is decreased. In the field of energy saving, the term “targeting” is often used. It suggests targeting a high-efficiency process with an energy-saving goal, by starting from a current process. In this paper, we take the opposite direction of strategy for the technology development. First, we determine the ideal state, from which no further energy saving is possible (due to requiring unrealistic initial costs and/or equipment setup), and then sacrifice a little energy efficiency to achieve the feasible

process. To emphasize this point, we use in this paper the uncommon term “detuning” by intention.

It should be noted that the path of “detuning” from an ideal state to a feasible condition is not one-dimensional. Fig. 1 shows a schematic diagram of the paths taken to enhance energy-saving performance in a certain process. Here, a conventional approach for energy saving with process improvement and refinement corresponds to slowly climbing up from the base of a mountain. On the other hand, the “detuning” process is like arriving first at the summit, then descending while considering energy efficiency as well as the other parameters like cost. In this approach, there are multiple paths that lead down the mountain, and therefore multiple possible destinations. Such an approach has two main characteristics. First, fundamentally unattainable goals are not derived, since the path descends from the theoretical upper limit. Second, when faced with various difficulties to a practical application, it is relatively easy to start again from the peak and seek another “detuning” path. One problem with “detuning” is the risk that a detuned process may become far from the current process. This means, however, that achieving PI that requires “rapid and discontinuous dynamic changes” would become possible.

### 3 Strategy for energy saving in distillation process through “detuning”

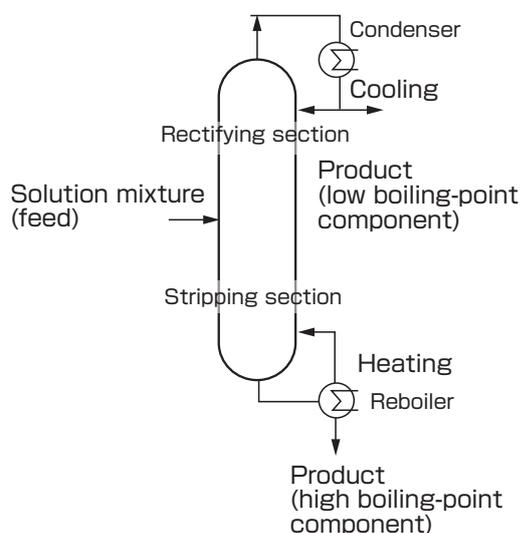
First, we examine the history of energy-saving efforts in the distillation process, while keeping previous discussions in mind. The distillation process is one of the oldest chemical processes: it was actually used to purify perfumes more than two thousand years ago. The principle of distillation is to separate solution components by evaporating them through heating and then condensing them through cooling. Solutions are separated with the difference in the boiling point (BP) of each solution components. The operation involved the heating of the source solution in a container for a given period of time to generate vapor, which was cooled, liquefied, and then collected. This process is known as simple distillation. Subsequently, distillation was used for many applications,



A, B, C: Processes obtained by “detuning” from ideal state  
**Fig. 1 “ Detuning” from ideal state.**

including alcohol and acid productions, and as an important technique during the Italian Renaissance for alchemy (not the occult kind, but utilizing the laws of nature). During the late 18<sup>th</sup> century to early 19<sup>th</sup> century, a discovery was made that heat is a form of energy, and the concept of evaporative latent heat was introduced, leading to an understanding that the thermal energy contained within a vapor can be used for heating liquids. In the late 19<sup>th</sup> century, the foundations of the continuous distillation process were established through various experimentations, stimulated by a need of refining crude oil for use as automobile fuel<sup>[7][8]</sup>. This development of the distillation process from simple to continuous can be regarded as a realization of PI, where “simplification” of the operation as well as “increased efficiency” with high performance and continuous mass processing were achieved. Evaporative latent heat, a major scientific discovery of that time, brought revolutionary changes to the distillation process.

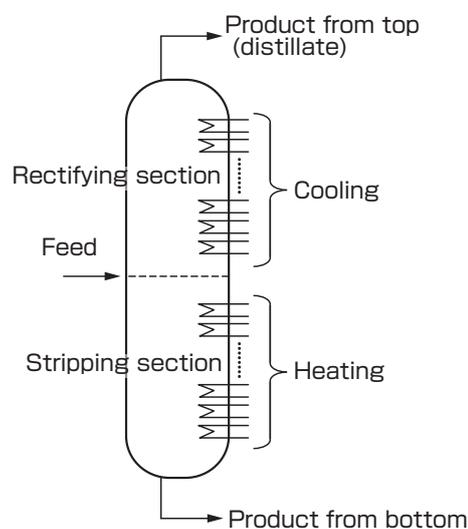
Fig. 2 shows a schematic diagram of a typical continuous distillation column. The parts of the column above and below the feed position are called the rectifying section and the stripping section, respectively. In the rectifying section, the concentration of low boiling point component is higher than in the feed material, while in the stripping section the concentration of the high BP component is higher than in the feed. The interior of the column is designed such that the gas-phase mixture rising from the lower part and the liquid-phase mixture descending from the upper level come into contact. This is accomplished through the shelf-like constructions known as plates or trays with or without the various shapes of packings. Due to this mutual contact, the phase transition occurs via the transfer of evaporative latent heat between the gas and liquid-phase mixtures. In the vapor phase thus generated, there exists a higher concentration of low BP component while in the liquid phase a higher concentration of high BP component. Therefore, the low and high BP components can be concentrated toward the both ends of the



**Fig. 2 Conventional continuous distillation column.**

column, respectively. Based on this principle, the separation of liquid mixture in a distillation column inevitably requires that the liquid solution should be converted into vapor with the supply of heat from a reboiler at the bottom of the column. Also, to allow the contact between liquid and vapor for mass transfer throughout the column, the latent heat of condensation must be removed from the vapor to reconvert it back to the liquid in the condenser at the top of the column.

In a continuous distillation column process, cooling at the top of column and heating at the bottom are carried out simultaneously to achieve gas-liquid contact throughout the column. According to thermodynamic analysis, the most efficient operation of distillation can be theoretically done when the continuous heating in the stripping section and the continuous cooling in the rectifying section are conducted along the bottom-to-top direction of column, as shown in Fig. 3<sup>[9][10]</sup>. This is called an operation of reversible distillation. Specifically, using a distillation column with infinite number of plates, infinitely small amount of heats are used for cooling in each plate of the rectifying section and for heating in each plate of the stripping section, respectively. This is the only thermodynamically ideal and the most efficient operation of continuous distillation, no matter what energy-saving strategies are applied to distillation columns, or whether new energy-saving technologies are developed. As the energy-saving technology becomes more advanced, the operation should approach the reversible distillation. In other words, the effort of energy saving in the distillation process is described as a “detuning” from the reversible distillation process with minimal performance deterioration while achieving economical viability. However, bringing the operation of forced heat transfer such as heating and cooling into mass transfer that is the essence of distillation, would cause significant alterations to the process, and therefore careful consideration of their effects is necessary in developing the desired process. The next step is to consider



**Fig. 3 Reversible distillation operation.**

how to configure the equipment for “detuning” while keeping the effects in mind, and this is one process towards realization of PI.

#### 4 Equipment configurations for achieving “detuning”

Interpretation of reversible distillation, an ideal process, is important for performing “detuning.” The reversible distillation column shown in Fig. 3 can be interpreted as the equipment involving the infinite number of heaters (reboilers) and coolers (condensers). If one column is divided into multiple (infinite) distillation columns of different heights, the configuration is represented in Fig. 4a). Moreover, by “detuning” to simplify the design to only 2 columns instead of an infinite number of columns, we have the configuration shown in Fig. 4b). Petlyuk *et al.* studied on this process in the 1960s, and thus this structure is generally called the Petlyuk column<sup>[11]</sup>. Further simplification along this consideration was carried out, and the resulting distillation process, developed by BASF of Germany, has been commercialized. In Japan, Kyowa Hakko Co., and Sumitomo Heavy Industries, Ltd. have developed this kind of commercial processes<sup>[12]</sup>.

Another example of “detuning” the reversible distillation from a different viewpoint is discussed next. As a typical characteristic, the concentration of low BP component is higher and the temperature is lower in the upper section of a distillation column. Using the principle of reverse Carnot cycle mentioned above, it becomes possible to take heat from the low-temperature source (rectifying section), to elevate the temperature, and then to supply it to the stripping section where heat is required. The strategy for “detuning” in this line is shown in Fig. 5a)<sup>[13]</sup>. In this process, the “integration” of distillation column with heat pump is achieved since the condenser plays the role of heat pump. The figure illustrates that the heat taken from the upper section is supplied to the lower section by elevating the temperature with each condenser. This process is close to that of reversible distillation, excluding the supply of work for condensation.

Then, further “detuning” gives rise to the process shown in Fig. 5b) where the number of condensers is reduced to only one and the heat exchange operations are carried out at a single point each in the rectifying and stripping sections. The process shown in this figure is generally known as a vapor recompression column (VRC). The VRC is advantageous when the temperature difference between the top and bottom of the column is relatively small, and the enrichment of low-concentration ethanol is an example of commercialized use. In the VRC, the heat exchanges are executed only at the top and bottom of the column, where the temperature difference is the greatest in the apparatus. This makes the “simplification” of equipment much more than for the reversible distillation process, but the divergence from the ideal state is considerable, and thus only limited energy saving is achieved.

#### 5 HiDiC aiming toward more ideal condition

Petlyuk column and VRC process described in the preceding sections are two different ideas for energy-saving distillation, and correspond to the points B and C of Fig. 1. The basic structures of these apparatuses are completely different, but they were both derived from a common methodology of “detuning” from the ideal state. So, are there any other possibilities of “detuning”? The key point of “detuning” for the VRC was exchanging heat only at one location in the rectifying section, and another in the stripping section. The process would be able to approach closer to the ideal if the heat exchange were carried out in the multiple locations instead. However, this would call for the multiple condensers, which would make the strategy impractical. Therefore, to investigate a more realistic equipment configuration that allows for the heat exchange at the multiple locations, we once again turn our attention to the characteristics of a typical continuous distillation column (see Fig. 2). The internal temperature decreases with increasing height, due to the change in concentration of the solution in the continuous distillation column. The same characteristic is exhibited in a reversible distillation process: the cooling temperature

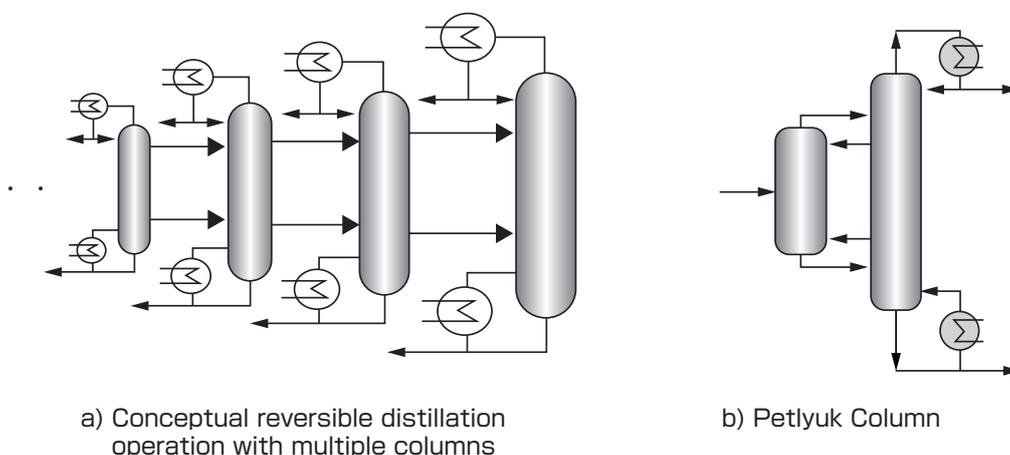
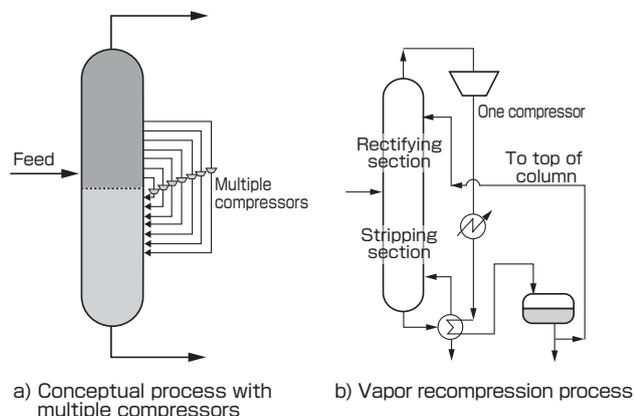


Fig. 4 Approach to reversible distillation operation with multiple columns.

in the rectifying section is always lower than the heating temperature in the stripping section. Therefore, the heat taken from the rectifying section cannot be supplied directly to the stripping section. In Fig. 5, the condenser (heat pump) is used to elevate the temperature to solve this problem.

So, how can we achieve the heat transfer in the multiple locations simply? In Fig. 5a), all the cooling points in the rectifying section have a lower temperature than all the heating points in the stripping section. If the temperature of the rectifying section is higher than that of the stripping section, the heat from the cooling points can be supplied directly to the heating points. Would it then be possible to elevate the temperature of the rectifying section? In the separation via distillation, the equilibrium relation of liquid-gas is used. Increasing the pressure results in a higher equilibrium temperature, and we can achieve it by increasing the pressure in the rectifying section to above that in the stripping section. This requires an equipment configuration that the rectifying and the stripping sections are divided, and the pressure of rectifying section are increased until the heat from each cooling point in the rectifying section can be transferred to the corresponding heating point in the stripping section. Increasing the pressure in the rectifying section can be achieved by pressurizing the steam from the stripping section. Only one compressor is required to accomplish this task.

Once the temperature of the rectifying section exceeds that of the stripping section, various methods can be considered for the heat transfer. The simplest one is to arrange the direct contact between the rectifying and the stripping sections. The HIDiC aims to achieve the high efficiency by closely approximating the reversible distillation process, with the addition of compression<sup>[14]</sup> (see Fig. 6). We consider that this is also a type of “detuning,” and that it corresponds to point A in Fig. 1. The HIDiC also can be regarded as an “integration” process of distillation, heat transfer, and heat pump. A better energy-saving performance can be achieved in the HIDiC for a system of liquid mixture that is difficult to separate in a conventional distillation column because

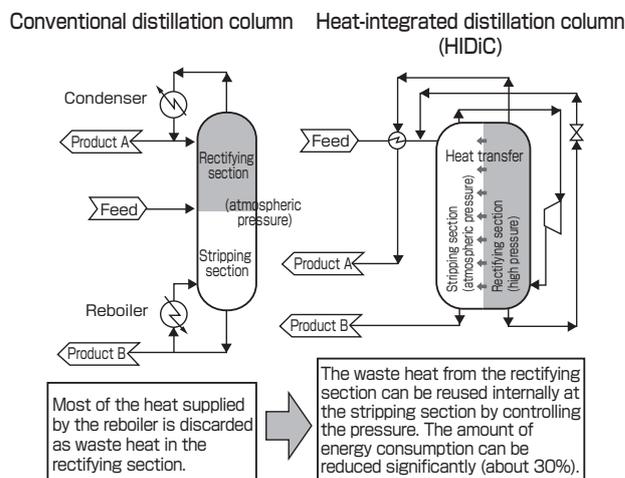


**Fig. 5 Approach to reversible distillation operation with multiple compressors.**

the temperature difference between the top and bottom of the column is small. In the propylene/propane mixture that the difference of BP is small, our evaluation shows that the HIDiC can separate the mixture using only 1/10 of the energy consumption in a conventional distillation column.

Table 1 briefly summarizes the characteristics of the HIDiC, VRC, and Petlyuk column. The “Initial cost” in the table is the construction cost of a distillation column. The difference in total construction cost of distillation process is not as significant as that in construction cost of the column, because additional costs of plumbing and measuring instruments are required. “Applicability” corresponds to the number of industrially relevant solution systems to be processed. The HIDiC is particularly suitable for the solution systems where the temperature gradient in the bottom-to-top direction of column is relatively uniform. The key products for the petrochemical industry such as the mixture solutions of benzene/toluene/xylene and purification of crude cyclopentane are classified in this category. On the other hand, Petlyuk column is suitable for removing impurities of low concentration while VRC is for separating solutions with small BP difference. A conventional distillation column can be applicable in a wider range of solution systems, and the initial cost is generally favourable. The HIDiC realizes the concept of reversible distillation operation more faithfully, and has a wider range of application with achieving higher energy efficiency compared against Petlyuk column. It has also more advantage of energy efficiency since there is great improvement on the problem that the large temperature increase via compression is required in the VRC. In the HIDiC, the increase in energy efficiency of more than 20 % is expected over the Petlyuk column and the VRC, though it would depend on the separation specifications.

Professor Richard Mah of Northwestern University in the USA published the basic concept of the HIDiC in the 1970s for the air separation by cryogenic distillation<sup>[15]</sup>.



**Fig. 6 Internally heat-integrated distillation column (HIDiC).**

He called this system Secondary Reflux and Vaporization (SRV) distillation (see Fig. 7). However, only its theoretical possibility was noted in the paper. It was shown that the energy saving can be achieved for the low-temperature systems that have a small difference in BP, such as air separation; but its potential for practical application was not considered in the paper. Professor Mah himself seemed to think that its practical potential was low. In fact, he submitted no patent application for this idea, and therefore what might be called a ‘master patent’ for the HiDiC does not exist. Professor Mah was not an expert in separation via distillation. Rather, he studied on an optimization of process flow using graph theory. After the first oil crisis of the mid-1970s, it seemed that he started investigating on energy saving of the distillation process, the most energy-consumption process in chemical plants. At the time, it was a common practice to wrap the distillation column with insulation materials to try to minimize any heat transfer from/to the outside except for the top and bottom of the column. (This is still a common practice today.) Thus, it was completely beyond the common sense to deliberately allow heat to enter and exit from the column body. According to Professor Kazuyuki Shimizu of Kyushu Institute of Technology, who worked on the SRV under Professor Mah at the beginning of the 1980s, the response to their investigation presented at the meeting of the American Institute of Chemical Engineers (AIChE) was very cold, and it was labelled as “a research just for publishing a paper” and almost ignored. Thereafter, several proposals on the HiDiC like concept were made in the form of research papers and patents in the U.S.A., but all of them suggested ideas or concepts only, and no realization research has been carried out.

## 6 Road to Practical Applications of HiDiC

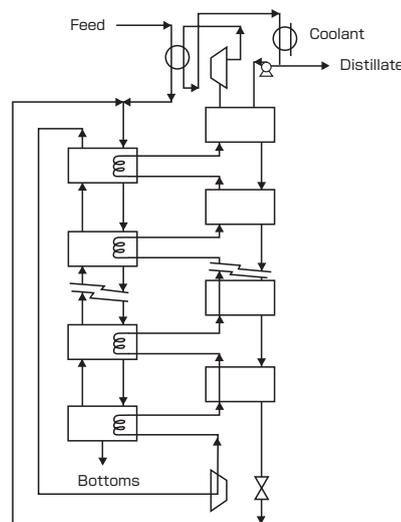
Several years after Professor Mah first published the paper mentioned above, the idea of HiDiC had attracted the attention of Professor Takeichiro Takamatsu of Kyoto University. He began to study on the fundamental characteristics of the process. Professor Takamatsu investigated on exergy analysis and thermodynamic analysis of chemical processes at the time, and he seemed to take notice of the high energy efficiency of HiDiC process. In the mid-1980s, the authors uncovered the characteristics of this process theoretically and experimentally at the National

**Table 1 Comparison between HiDiC and other energy-saving distillation technologies.**

	Energy efficiency	Applicability	Operation range	Initial cost
HiDiC	○	○	○	△
VRC	△	△	△	△
Petyuk	△	×	△	○

Chemical Laboratory for Industry through the collaborative research with Professor Takamatsu. First, we demonstrated theoretically that the column height and number of plates required as well as the heat transfer area, which allows us to prepare the overall column design, can be obtained by specifying the separation conditions and operation pressure. Also we showed that the operation pressure in the high-pressure side should be as low as possible for energy saving; but there is a thermodynamical limit of the value, which can be determined by providing the separation condition. Experimentally, it was proved using the small apparatus that the amount of heat required at the bottom of the column can be reduced via the internal heat-exchange. However, in this experimental apparatus, the size of compressor was larger than the column and its efficiency was low, we were unable to show the overall performance of energy savings considering the electrical power input.

The “Super Heat Pump Energy Accumulation System” project was in progress at the Agency of Industrial Science and Technology in those times, and we anticipated that the HiDiC technology would be positioned as an energy-saving industrial process where the heat pump in the wide sense was used. In the 1990s, a few groups of university researchers in U.K., France, and Hungary started investigating experimentally, but no prospect for realization was obtained. In Japan, on the other hand, the “Broad Area Energy Utilization Network System Technology (Eco-Energy City)” project was carried out from 1993 to 2000 in the New Energy and Industrial Technology Development Organization (NEDO). The research and development of HiDiC was conducted within the project by AIST and three companies (Kimura Chemical Plants Co., Ltd.; Maruzen Petrochemical Co., Ltd.; and Kansai Chemical Engineering Co., Ltd.), based on the findings from the collaborative research with Professor Takamatsu and AIST. In December of 1999, a



Mah R.S.H., *et al.*, AIChE Journal, Vol. 23(5), 651-658 (1977)

**Fig. 7 Concept of Secondary Reflux and Vaporization distillation.**

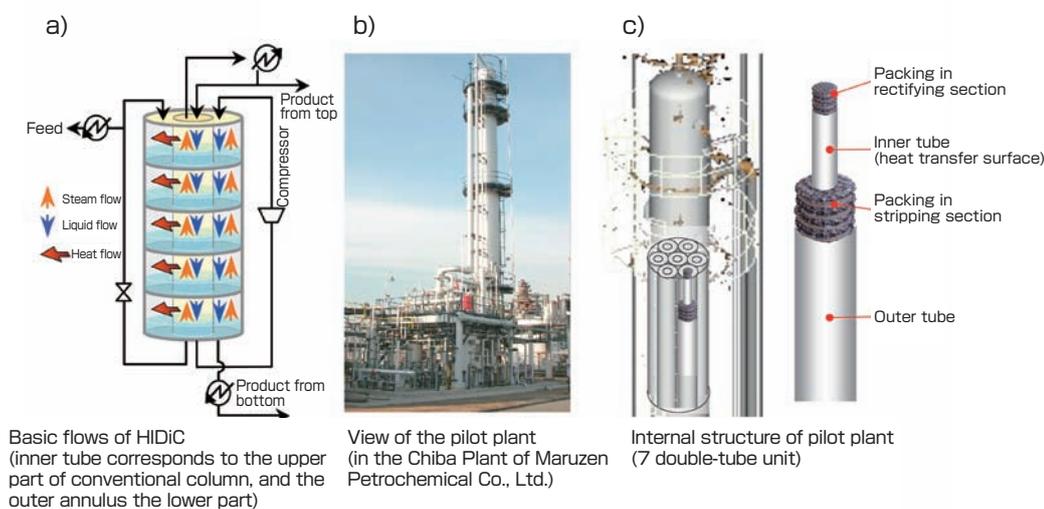
prototype column with diameter of about 300 mm and height of about 25 m was constructed in the Chiba Plant of Maruzen Petrochemical, and the continuous operation of over 100 hours was successfully achieved first in the world although it processed a small throughput of 300 kg/h with benzene/toluene system.

In an effort to further develop this achievement, the Ministry of the Economy, Trade and Industry (METI) and the NEDO launched on September of 2002 the “Development of Energy Saving Distillation Technology through Internal Heat Exchange” project in the New Global Warming Prevention Technology Program<sup>[16]</sup>. One of the authors acted as a leader of this project. The companies participated are Kimura Chemical Plant Co., Ltd., Maruzen Petrochemical Co., Ltd., and Kansai Chemical Engineering Co., Ltd., the target of which is for the petrochemical industries; and two companies that aimed for the air separation market, namely Nippon Sanso Corporation (currently Taiyo Nippon Sanso Corporation) and Kobe Steel Ltd.. The project focused on a double-tube design, in which the stripping section was the outer tube; and the rectifying section was the inner tube with structured packings, as shown in Fig. 8a). At the end of FY 2003, the construction of a pilot plant (see Fig. 8b)) for 12-component mixture system was decided at the Chiba Plant of Maruzen Petrochemical. As illustrated in Fig. 8c), this plant consisted of 7 double-tubes bundled together. Several considerations to realize PI were carried out in the design of plant, such as the inner tubes with 3 settings for diameters according to the gas-liquid load.

Construction of the pilot plant proceeded smoothly, and the first trial operation was conducted in FY 2005. Eventually, the continuous operation of 1000 h was achieved, and the operations under varied conditions and without external heat source were also carried out. In all the conditions, the stable operations demonstrated the energy reduction performance evaluated in the design stage. The amount of energy saving

obtained during the experimental operations was 62 % in primary energy compared with the present distillation column. The reduction in required reboiler heat was 290 to 320 Mcal/h with an input electrical energy of about 30 Mcal/h into the condenser, and thus the ratio between the input electrical energy and the thermal energy gained (Coefficient of performance in heat pump) was approximately 10, which is quite high. After the completion of NEDO project, AIST and three companies in the petrochemical industries mentioned above with two new companies, namely Mitsubishi Chemical Corporation and Toyo Engineering Corporation, established a consortium to investigate on the commercialization of the process and prevailing the technology. The results were taken back to each company and Kimura Chemical Plant opened up the commercial activities on FY 2008. In foreign countries, the research and development of HIDiC has been started from the viewpoint of global environmental issues. Specifically, the research with the aim of commercializing the HIDiC process was begun on January of 2002 in the Netherlands, and currently it is in the second phase of research and development. Many prominent companies in Europe are participating in this project, with Delft University of Technology and Energy Research Centre of the Netherlands.

Why was Japan able to launch commercialization first? The answer to this question is not clear, but we believe it is due to the difference in strategy of realizing the characteristics of HIDiC where the distillation and heat transfer are integrated. The goals of researches in the U.S.A. in the 1980s and Europe in the 1990s were mainly to increase the amount of heat transferred from the rectifying section to the stripping section. Therefore, the consideration of material transfer and distillation performance was presumably insufficient. For example, multiple heat pipes were proposed to use for the heat transfer between the rectifying and stripping sections in a patent submitted in the U.S.A. in 1980<sup>[17]</sup>. This would achieve a sufficient heat transfer, but the realization of equipment would not be possible due to difficulty in



**Fig. 8 Internal structure of HIDiC and pilot plant.**

manufacturing such a design of equipment as well as the obstruction of liquid flow within the column caused by the heat pipes. On the other hand, we studied via simulation technology to prevent decreased distillation performance, and adopted a simple double-tube structure that led more straightforwardly to practical applications. If the amount of heat transfer was not enough, we made the heat transfer area larger by extending the height of column. While the HIDiC process is a realization of PI by “integration” of the distillation and heat transfer, we believe our success was due to the strategy of maintaining distillation performance even in pursuing energy saving through the “integration” of heat transfer into the distillation.

## 7 Conclusion

In this paper, an approach for the development of energy-saving technology for the present process was shown with the concept of “detuning” from the ideal state. We also discussed the development of energy-saving distillation processes, including heat-integrated distillation column (HIDiC). In the case described here, the procedures were: a) to determine the thermodynamically ideal state for the process to be examined; b) to perform “detuning” from the ideal state down to more attainable conditions; c) to evaluate the energy-saving performance, cost, equipment configuration, and other considerations for realistic feasibility after “detuning”; and d) if the evaluation result is not satisfactory, return to b) and explore other “detuning” paths. The course of b) → c) → d) forms a loop, which we consider to be one of the paths to the realization of PI. Actually, we believe that the development of HIDiC followed this path to reach the practical application stage. In summary, we described our thoughts and approaches to practical application of the HIDiC process, which is an energy-saving distillation process, from the perspectives of PI and “detuning.” We hope this paper will help the progress of *Synthesiology*.

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## Discussion with Reviewers

### 1 Comparison with current processes

#### Question and comment (Koichi Mizuno)

I understand that HiDiC is superior to VRC and Petlyuk in terms of energy saving and operability. However, there are some problems in terms of manufacturing cost, performance, and so forth, as referred in the paper. For example, the cost of HiDiC manufacturing might be higher due to its complex structure. What do you think of this point? Also, what are the differences in distillation performance when this process is compared with the other processes?

#### Answer (Masaru Nakaiwa)

In general, a distillation column is entirely custom-made since the specifications of the apparatus are different according to the property of the solution to be separated, the level of product purity required, and the processing volume. Thus, the manufacturing cost depends on the specifications. For the pilot plant of HiDiC (at the Chiba plant of Maruzen Petrochemical Co., LTD.; fractional distillation of gasoline with 12 components at the commercial scale feed of 12,000 ton/year), the cost was 230 million yen. The amount of reduction in annual running cost via the energy saving of HiDiC is about 20 million yen when calculated at the crude oil price of 60 US dollar/barrel. While the manufacturing cost of an ordinary column at the same scale is uncertain, the response of Kimura Chemical Plants Co., Ltd. to user inquiries is: "It is about twice as much as a conventional type." Applying this to the pilot plant, when the reduced annual running cost is subtracted from the cost difference between HiDiC and an ordinary column, the simple payback time is 5.75 years. I think the actual cost would be slightly different since the pilot plant has somewhat special specifications such as the use of temperature measurement system for investigations. The detailed descriptions are summarized in the *Kagaku Kogaku Ronbunshu*, 34(4), 444 (2008). For the distillation performance of HiDiC without the heat transfer, it is about the same as the ordinary process.

### 2 Energy consumption in ideal state and "detuning" process

#### Question and comment (Koichi Mizuno)

Energy saving was achieved considerably in this study. Is it possible to quantitatively describe the difference in energy consumption between the ideal state and HiDiC?

#### Answer (Masaru Nakaiwa)

We have not done such a calculation since the amount of energy consumption depends on the several conditions. HiDiC is a "detuning" process from the reversible distillation operation that is ideal state, but an additional factor of the heat pump effect is involved. The total energy consumption in HiDiC is significantly influenced by the energy efficiency in the compression process. Here, the thermodynamically ideal state of this process is a reverse Carnot cycle, as described in the paper. The energy efficiency of a compression heat pump that is currently used in industries is at most 50 % of the reverse Carnot cycle. Therefore, there is a possibility of reducing the energy use by half at least. If we discuss the minimum energy consumption for the separation of mixture thermodynamically apart from HiDiC, it is possible to achieve a reduction of energy consumption of at least tenfold. Exergy analysis is useful to estimate the value of such a reduction quantitatively.

### 3 Detuning from ideal state

#### Question and comment (Hiroshi Tateishi)

I think Fig. 1 is easy to understand as a concept, yet the meanings of A, B, and C, respectively, are unclear. As I understand that an approximate operation is carried out under some conditions with "detuning" from the ideal state, can you include any explanations from such a viewpoint in the figure?

#### Answer (Masaru Nakaiwa)

We explain a general concept of "detuning" in Fig. 1. Petlyuk column and VRC process do not quantitatively correspond to B and C of Fig. 1. To clarify that Fig.1 illustrates a general concept, we added the explanation to the figure.

### 4 Explaining key points of research on HiDiC

#### Question and comment (Hiroshi Tateishi)

I think the overall structure of paper where the R&D of HiDiC is overviewed from a higher stage of the innovation in distillation process is good. However, I think it is necessary to emphasize the significance of research on HiDiC at AIST using some specific examples. Can you give us more detailed explanation for how the theoretical analysis, numerical simulation and technological developments on HiDiC have been integrated at AIST?

#### Answer (Masaru Nakaiwa)

The description in chapter 6 was revised from the viewpoint of the contributions of AIST.

# Advanced in-silico drug screening to achieve high hit ratio

## — Development of 3D-compound database —

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Every year, several million compounds for drug screening are released by numerous vendors around the world. The information provided on these compounds is in the form of their two-dimensional (2D) structures. We have developed a software system to generate a database of three-dimensional (3D) structures of these compounds and have distributed this database. We have also developed a database of protein-compound docking scores of 180 proteins with respect to these millions of compounds. These databases make it possible to identify new active compounds for many drug targets.

**Keywords** : compound database, myPresto, virtual screening, *in-silico* drug screening, compound library

### 1 Introduction

One of the primary objectives in the post-genome era is the innovation of drug discovery. However, compared with the dramatic advancements in genetic analysis technology, drug discovery processes have been experiencing continuous difficulties and the expected results have not been achieved. In this situation, computational drug screening (*in-silico* or virtual screening (VS)) is considered to be one of the strategies for streamlining the drug discovery process. VS is used to computationally select seed molecules from existing molecules for pharmaceutical applications. Thus, VS requires a computationally accessible database of chemical compounds with 3D molecular structures (hereafter referred to as “compound DB”). Although overseas compound DB products are available, we developed an in-house DB due to the issues of price, quality, and management of results. We developed a compound DB by eliminating duplicated data using a chemical informatics approach, constructing 3D compound structures by a molecular force-field method, and computing atomic charges by quantum chemical calculations. These methods are described in chapter 4. In addition, we also developed a novel DB that predicts the binding energy of large numbers of predefined proteins and compounds. Using these DBs, it is now possible to predict active compounds with respect to target proteins for drug discovery with a high probability of success.

### 2 Objective

Our objective was to develop a compound DB usable for VS

based on several million compounds marketed every year and to make it immediately available to the pharmaceutical industry. Several dozen major reagent vendors in the world distribute electronic files of reagent catalogs listing their 2D molecular structures, but 3D stereoscopic molecular structures rather than 2D chemical structures are necessary for VS. Therefore, the purpose of our study was to construct 3D molecular structures from the 2D molecular structures of millions of compounds in these catalogs and distribute them by compiling a database.

### 3 Benefits

Irrespective of the method used, the development of pharmaceutical compounds begins with a search for candidate compounds that could bind to the target proteins from compound databases. Computational searching in compound databases is a necessity in the modern drug discovery process. However, there are several issues in this process:

(1) Although compound DBs for VS have been developed and marketed for pharmaceutical companies by overseas software developers since the 1980s, license fees are expensive, with a license costing 4–6 million yen per year<sup>[1]</sup>.

(2) Software products for the development of compound DBs are also marketed by overseas software developers<sup>[2]</sup>. Having used costly software to develop compound DBs for VS, we experienced several issues in terms of their quality such as frequent representations of incorrect 3D molecular structures, incorrect appositions of hydrogen atoms, and the generation

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of structures with a low probability of existence.

(3) The distribution of data generated using commercially available software for developing compound DBs is prohibited due to the licensing policy.

As described later in this paper, our objective was to develop and distribute novel DBs for VS using protein-compound affinity matrices based on the compound DBs. However, this cannot be achieved using commercially available software. The development of in-house software that generates compound data and compound DBs will resolve these issues. Upon distribution, the use of VS can be encouraged for users who find it difficult to afford costly licenses such as small- and medium-sized enterprises and academic researchers, and novel and advanced VS methods can be widely disseminated even to large enterprises. Economic and technological benefits will be obtained as a result.

## 4 Processes

### 4.1 Overall perspective

The overall software development process consisted of approximately 10 steps, as follows (Fig. 1). First, we eliminated duplicated compounds listed in 2D SD files provided by reagent vendors (for example, methanol is sold by any vendor). Since hydrogen atoms (protons) are normally omitted in 2D structures, protons were added. Parameters such as distances and bond angles between atoms were assigned to all of the atoms. The 3D structural coordinates, as well as enantiomers if they existed, were reproduced from the 2D coordinates based on this information. Atomic charges were then evaluated by quantum chemical calculations so that equivalent atoms exhibited equivalent charges. The generated 3D data were compiled into a relational database. We developed our software, avoiding violations of the patents on a number of commercially available software products for each step. Each development step is explained in detail below.

### 4.2 Handling of massive data sets

It is difficult to handle massive data sets. If millions of items of compound information are stored in a single file, the file size will exceed the limit that a computer can handle, whereas if one item of compound information is stored in each file, the millions of files produced cannot be contained in a single folder due to the constraints imposed by the computer system. Thus, the information on a single compound was stored in a file and the data for approximately 10,000 compounds were contained in each of several hundred folders prepared in order to handle millions of items of compound information using a hierarchical structure. The developed compound DB could be stored as a single relational database in a system with a 64-bit architecture.

### 4.3 Exclusion of duplicated compounds: Determination of compound identity

It is necessary to determine whether or not two molecules are identical. Since the identification of 4 million compounds requires the square of 4 million comparisons, we developed a high-speed discrimination method that consists of several steps as described later. We prioritized speed over accuracy by sacrificing a certain degree of discrimination accuracy. Since a few percent of commercially available compounds are different from the actual structures due to incorrect structure identifications and insufficient quality control, excessive pursuit of mathematical strictness would be meaningless.

#### 4.3.1 Determination of chemical compositions based on pseudo-molecular mass weight

The chemical composition is a description of the type and number of atoms contained in a molecule; in the case of methanol (CH<sub>3</sub>-OH), for example, it will be C<sub>1</sub>O<sub>1</sub>H<sub>4</sub>. Comparison of chemical compositions is a quick method of discriminating compounds. No further discrimination is necessary if the chemical compositions of two molecules differ from each other. However, the character-string comparison of chemical compositions takes too much time. We therefore evaluated the molecular mass weight using the atomic mass weight with three places after the decimal point for each atom, and obtained a six-digit number for each molecule. This realized an accurate comparison in practical terms of chemical compositions by a single computation of molecular mass weight without comparing their character strings.

#### 4.3.2 Identification of molecular topology based on graph invariants

The structural formulas of two compounds may differ even when their chemical compositions match. Although molecules can be graphically compared by superimposing their graphs, the graphical superposition of molecules is a nondeterministic polynomial time (NP)-complete problem, in which the computation time cannot be described as a polynomial of the number of atoms. In general, high-speed algorithms exist for problems with polynomial computation times; however, no effective algorithm exists in the case of

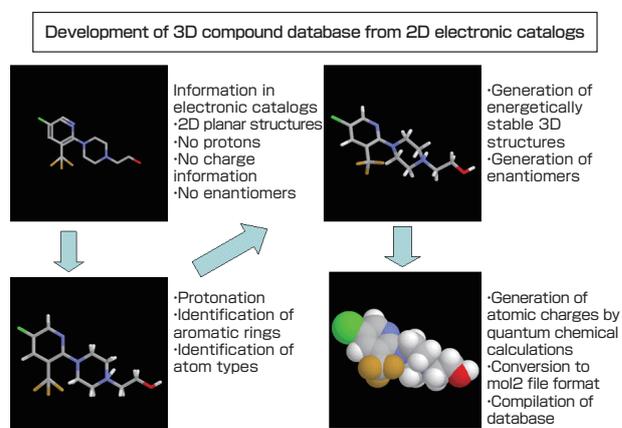


Fig. 1 Process of development of 3D compound structures.

NP-complete problems, which thus require a prolonged period of computation time<sup>[3]</sup>. Hence, we developed a method that compares the topology of molecules using a molecular edge matrix,  $M$ , where  $M(i, j) = 1$  if atoms  $i$  and  $j$  bind to each other and  $M(i, j) = 0$  if not (Fig. 2).

In molecular graphs, the sequence of atomic numbers is meaningless, and graph invariants should thus be evaluated. Here, since the edge matrix is a Hermitian matrix, eigenvalues will be the graph invariants. Although the Hosoya index is known as a method to evaluate graph invariants, it is computationally cumbersome<sup>[4]</sup>. Eigenvalue evaluation is a practical approach because its computation time is  $N^3$  for the number of atoms,  $N$ . Protons were eliminated to reduce the matrix dimensions by half and the atomic number of each atom was substituted in the diagonal terms in order to reflect the type of atom.

#### 4.3.3 Identification of geometric isomers

Although the method described in Section 4.3.2 makes it possible to identify the graphical topology of molecules with reasonable accuracy, it is incapable of discriminating geometric isomers such as cis and trans isomers. Thus, we developed graph invariants that can discriminate geometric isomers. First, for atoms  $i$  and  $j$  bound by a double bond, each graph fragment on the edge of four bonds is sequentially numbered from the maximum eigenvalue of a partial graph matrix as 1, 2 and 1', 2' (Fig. 3). Geometric isomers can thus be identified from the eigenvalues of the whole graph matrix by assigning  $-2$  for the  $i-j$  component if vectors  $1 \rightarrow 2$  and  $1' \rightarrow 2'$  are parallel and  $+2$  if they are anti-parallel.

#### 4.4 Protonation

The number of absent protons in atoms such as C, N, O, and S in 2D structures was predicted from the bond order, and plausible coordinates of these protons were evaluated from the positional relationship with adjacent atoms and appended to the molecules. Although software that appends protons such as babel<sup>[5]</sup> and openbabel<sup>[6]</sup> is available, such software is not necessarily accurate. We investigated the protonated states of various functional groups and devised an algorithm so that it reproduces a molecule with a dominant ion forms under a vacuum and in water (near pH 7.0). Since accurate prediction

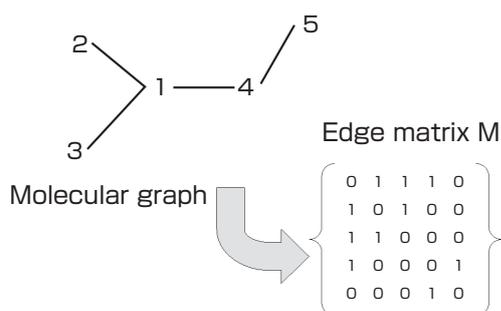


Fig. 2 Construction of a binding matrix,  $M$ , from a molecular graph.

of ionic configuration for a whole molecule is difficult, representative ionic configurations were applied for each functional group. Moreover, since the 2D chemical structures are simply diagrams, the actual atomic distance may be 1 Å or 10 Å. The average distance of the chemical bonds was therefore scaled to 1.5 Å.

#### 4.5 Addition of force field parameters

The generation of 3D molecular structures from their 2D counterparts was conducted using a molecular force field. Our compound DB applied a general amber force field (GAFF)<sup>[7]</sup> to generate 3D structures. Since the parameters of a GAFF are not available for most molecules, molecular structures cannot be determined. We therefore obtained accurate molecular structures by optimization calculations based on ab-initio calculations of quantum mechanics using CSD<sup>[8]</sup>, a crystal structure database, and manually constructed the structures of 660 molecules. We then developed an algorithm that assigns atom types and force field parameters to all of the atoms if the parameters are absent, thereby making it possible to handle more than 99.9 % of molecules. Moreover, in addition to the consolidation of force field parameters, we developed tplgeneL, a software that assigns force field parameters to general compounds. This software is also capable of assigning parameters to the transition states of chemical reactions, which is useful for enzyme research.

#### 4.6 Generation of 3D structures

Once force field parameters have been provided for the molecules, the 3D molecular structures can be generated. We applied cosgene<sup>[9]</sup>, a software that we had previously developed for simulating molecular dynamics, to generate 3D structures by energy optimizations. 3D molecular structures cannot be generated unless a random displacement is applied on the initial coordinates, because a force in the Z-axis direction will not be generated in a 2D structure containing only X and Y coordinates. The structural adequacy of the generated 3D molecular structures (such as atomic distances and binding angles) was assessed by software, and if a distorted structure was generated, the initial coordinates were

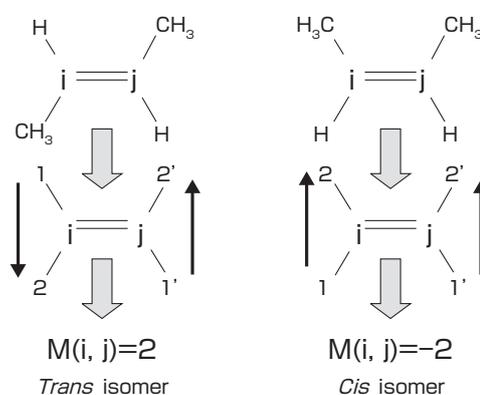


Fig. 3 Identification of geometric isomers. The thin black arrows indicate the sequence of eigenvalues assigned on the partial graphs.

reconstructed and the 3D structure was regenerated.

#### 4.7 Identification of enantiomers and generation of isomers

If each of four chemical bonds of an atom such as carbon binds to different molecular fragments, the central atom will be the chiral center. Hence, discrimination of the four molecular fragments bound to the central atom will be necessary. In the method that we have developed, the bonds to the central atom are cut off and the molecular fragments are identified through comparison using a method similar to the algorithm described in section 3.2. Although the process will be slightly more complex if the central atom is part of a ring structure, a similar discrimination method is used. If only a single chiral center exists in a molecule, the enantiomers can be generated by converting the coordinate of each atom, (X, Y, Z), to (X, Y, -Z). If two or more chiral centers exist in a molecule, the bonds need to be reconnected; we used confgeneC, a newly developed software, for this purpose.

#### 4.8 Computation of atomic charges by quantum chemical calculations

In quantum chemical calculations, electron spins and charges of molecules are necessary in addition to the molecular structures. Molecules used for drug development should not be radicals and also rarely exhibit magnetic properties; hence, the molecules were assumed to be closed-shell with zero spin. We developed an algorithm that automatically computes the molecular charge that stabilizes the system from the information on chemical bonds. The charge of the whole molecule is considered to be the sum of the formal charge of each atom. For example, the formal charge of a carbon atom is considered to be zero if the sum of the chemical bonds is four and +1 if it is three; the charge of nitrogen is +1 if the sum of the chemical bonds is four and zero if it is three; and the charge of oxygen is zero if the sum of the chemical bonds is two and -1 if it is one. The molecular charges were then evaluated by summing the formal charges obtained in this manner from the whole molecule.

There are several methods of computing atomic charges. The Gasteiger method<sup>[10]</sup> assigns electron affinity to each atom and evaluates the equilibrium electron distribution where atoms pull their electrons with each other based on the organic electron theory. A rough estimation requires less than a second for most molecules. In semi-empirical quantum chemical calculations, the AM1 and PM3 models (recently, PM7) of MOPAC<sup>[11]</sup> are well-known. The PM3 model is an excellent method in which an effective Hamiltonian is derived by fitting parameters so that the heat of formation can be represented; however, structures commonly observed in pharmaceuticals such as an amide bond cannot be accurately computed. The AM1 model also evaluates an effective Hamiltonian by fitting parameters; although it is inaccurate in predicting heat of formation, most structures such as

an amide bond can be calculated correctly. However, this method occasionally fails to accurately predict the atomic charges of ring structures that contain nitrogen atoms. If the molecular structure is defined, the computation time will normally be several to several dozen seconds and is approximately proportional to  $N^3$  for the size of an atom, N. The computational accuracy of the charge is very high. In ab-initio calculations of quantum chemistry, wave functions and partial atomic charges are generally computed by the RHF/6-31G\* and restrained electrostatic potential (RESP) methods<sup>[12]</sup>, respectively. Although this approach evaluates charges extremely accurately, the computation time will normally be several to several dozen minutes if the molecular structure is defined and is proportional to  $N^4$  for the size of an atom, N.

Atomic charges will be meaningless unless protein-compound bindings are accurately computed. Thus, docking calculations of 132 protein-compound complexes were performed by sievgen<sup>[13]</sup>, our protein-compound docking simulation software<sup>\*term1</sup>. As a result, accurate structures were obtained with a probability of 56 % by RHF/6-31G\* (with an accuracy of 2 Å), with 2–3 % lower probability by MOPAC AM1, and with about 5 % lower probability by the Gasteiger method. A small-scale drug screening experiment using approximately 10,000 compounds was also performed targeting several proteins such as cyclooxygenase-2 (COX-2) and thermolysin. It was found that the hit rate was higher if the molecular charges were more accurate, and the hit rate was only a few percent lower even when the Gasteiger method was applied.

Since the atomic charges of several million molecules will be calculated, the computation time should be prioritized. In addition, it was found to be unnecessary to use a method that is as accurate as RHF/6-31G\*. Hence, we decided to employ the MOPAC AM1 method for the computation of charges because the compound DB will be the overall foundation. Although MOPAC generally requires a MOPAC-specific input format, we modified it so that we can input and output the mol2 file format, which is a standard format to represent compounds in the field of drug discovery. For this purpose, we are distributing a patch file to modify MOPAC free of charge.

#### 4.9 Determination of equivalent atoms

The charge of three protons in a methyl group should be configured to be chemically equivalent. The determination of atomic equivalency is necessary for computing atomic charges.

The equivalency of arbitrary atoms *i* and *j* is considered to be as follows: If  $i = j$ , the atoms are obviously equivalent. However, if this is not the case, and if atoms *i* and *j* do not directly bind to each other, all of the atoms binding to atom *i* should be equivalent to those binding to atom *j*, whereas if atoms *i* and *j* do bind, all of the other binding atoms should be equivalent to each other.

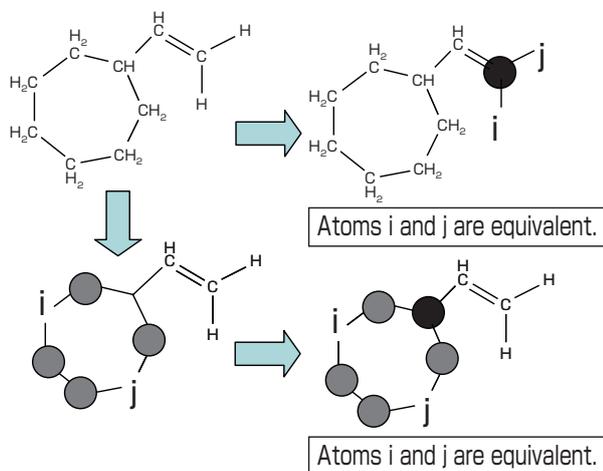
The method of discriminating equivalent atoms is as follows: Arbitrary atoms  $i$  and  $j$  are selected for marking as “already checked.” If the atoms are equivalent, they are marked as “already checked.” If  $i = j$ , the atoms are equivalent and, in this case, no further validation is necessary. If atoms  $i$  and  $j$  are bound by a single bond, both  $i$  and  $j$  bind to the “already checked” atoms, and their atomic symbols are the same, then  $i$  and  $j$  are considered to be equivalent.

All of atoms  $m_i$  and  $m_j$  binding to  $i$  and  $j$ , respectively, are temporarily marked as “already checked” and their equivalency is tested by the abovementioned procedure. Subsequently, if  $m_i$  and  $m_j$  are not equivalent, the “already checked” mark is removed. However, if all of  $m_i$  and  $m_j$  are determined to be equivalent, atoms  $i$  and  $j$  are considered to be equivalent.

When equivalency is tested from atoms  $i$  and  $j$ , the atoms that are to be tested are indicated as gray-filled circles and the atoms that will finally be tested are indicated as black-filled circles in Fig. 4. The equivalency test is necessary up to the point where the routes from  $i$  and  $j$  meet each other (black-filled circles), and the whole graph is not necessarily tested.

#### 4.10 Compilation of database and downloading of files

The compound DB is structured as a relational database. The schema includes the information on compound mol2 files (atomic names, 3D coordinates, atomic charges, chemical bond orders, etc.) in addition to the molecular weight, HOMO/LUMO energy in the MOPAC AM1 model, and solvation free energy per molecule and per atom calculated by the GBSA model. The solvation free energy per atom is useful for identifying the location of a compound in the chemical space of compounds (compound space), and is thus used as a parameter that indicates its diversity (the degree of diversity in the collected compounds) in a DB<sup>[14]</sup>. Compound information can be downloaded in the form of mol2 files from the compound DB.



**Fig. 4 Determination of equivalent atoms.**

“●” indicates “already checked” atoms.

#### 4.11 Computation of protein-compound affinity matrix

We selected a large number of proteins other than the target proteins, performed combinatorial docking calculations against the compound library in the compound DB, constructed a protein-compound affinity matrix, and compiled it into a database. This is the basic DB for the drug screening methods we developed, the multiple target screening (MTS) method<sup>[15]</sup> and docking score index (DSI) method<sup>[14]</sup>, which will be described later, and is a crucial resource for our VS (Fig. 5).

If the compounds that bind to the target proteins are selected in the order of the higher docking scores<sup>\*term2</sup> (scores) calculated by general VS, the hit rate is low. A compound that exhibits a high score against a target protein occasionally also exhibits high scores against other proteins, which indicates that the associativity of the compound with respect to the target protein is not specific. In contrast, only one compound is focused on in the MTS method; the proteins that bind to the compound are searched for and the compounds that bind to the target proteins with the highest score are selected as candidate hit compounds.

The accuracy of the score can also be improved by using the protein-compound affinity matrix. The free energies of binding for a particular compound to bind to analogous proteins are considered to be close in value. Errors in the score can be reduced by averaging the weighted scores depending on the similarity of the proteins; the details are reported elsewhere<sup>[16]</sup>. In particular, the scores were corrected by the following equation:

$$s_a^{new\ i} = \frac{\sum_b s_b^i R_a^b}{\sum_b R_a^b} \quad (1)$$

where  $s_a^{new\ i}$ ,  $s_b^i$ , and  $R_a^b$  are the newly defined score between protein  $a$  and compound  $i$ , the score between protein  $b$  and compound  $i$ , and the correlation coefficient of protein  $a$  and protein  $b$ , respectively.

In addition, if known active compounds exist in the compound list, the scores can also be corrected so that the known active compounds will be preferentially predicted. As shown in the following equation, the corrected scores are described as a linear combination of the scores and the coefficient  $M_a^b$  was evaluated so that the database enrichment<sup>\*term3</sup> was maximized:

$$s_a^{new\ i} = \sum_b s_b^i M_a^b \quad (2)$$

As a result of applying the MTS method to 12 target proteins including COX-2 and HIV-1 protease and selecting the top 1 % of compounds predicted from the compound library, the discovery rate was improved approximately 40-fold

compared with random screening<sup>[16]</sup>.

The DSI method searches for compounds analogous to known active compounds using the protein-compound interaction matrix. Even different compounds that bind to the same protein are considered analogous (Fig. 5). The DSI method does not require the 3D structure of target proteins and can thus be applied to target proteins with unknown 3D structures such as G protein-coupled receptors (GPCRs). In addition, similarly to the MTS method, the DSI method can be combined with methods that correct scores to maximize the discovery rate of known compounds. As a result of applying the DSI method to a total of 14 target proteins including the proteins mentioned above and GPCRs and selecting the top 1 % of compounds predicted from the compound library, the discovery rate was improved approximately 70-fold on average compared with random screening<sup>[17]</sup>.

## 5 Degree of achievement

We have currently achieved more than 90 % of the initial objective. Our first compound DB was released in 2004 and immediately used for compound screening against TNF- $\alpha$  converting enzyme. The MTS and DSI methods were applied using a protein-compound affinity matrix containing 182 proteins and 1 million compounds. Among 900 compounds subsequently purchased, 35 were found to be active compounds. The discovery rate was approximately 500-fold higher than the previously conducted screenings in which seven active compounds were obtained by randomly screening 100,000 compounds. In addition, no active compound was found after purchasing 700 compounds following screening by Glide, a commercially available software; hence, the discovery rate was dramatically improved by our methods. Since then, the compound DB has been annually renewed and the 2007 version is the latest. We have conducted direct screenings with respect to 10

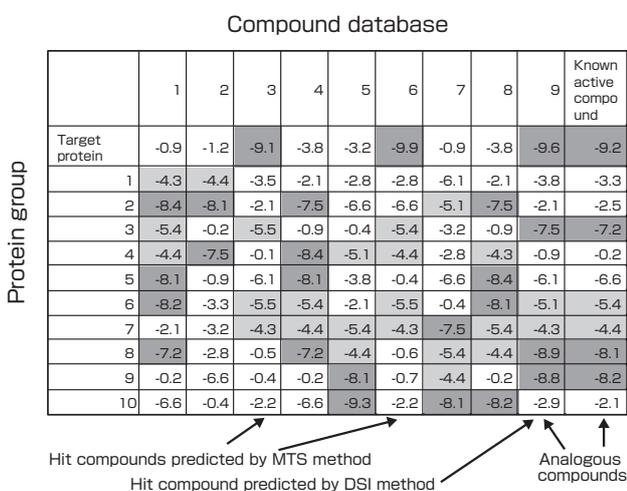
target proteins over a period of six years and obtained active compounds with a probability range of a few to 20 %. This rate is several hundred to one thousand times higher than that achieved by random screening. Moreover, every year the compound DB and the protein-compound affinity matrix have been distributed to 10 to 20 institutions, primarily pharmaceutical companies, in Japan and overseas. The software and the compound DB have been partially released as myPresto<sup>[18]</sup> and LigandBox<sup>[19]</sup>, respectively.

## 6 Future work

Firstly, our compound DB is not suited to screening of inhibitors of metalloproteinases containing metals such as zinc. The ion form of the molecules exhibits a predominant configuration under water; however, it will be different when the molecule binds to metals. For example, while a thiol (-SH) is normally configured as -SH under water, it is deprotonated and becomes -S<sup>-</sup> in the case of coordination with a metal. Changes in the ion form of molecules due to coordination with metals are observed in various functional groups. We found that the discovery rate strongly depends on the ion form of compounds through the VS of metalloproteinases. Accordingly, we plan to develop a compound DB for metalloproteinases.

Secondly, our compound DB does not include inorganic compounds. Inorganic compounds such as metal complexes are considered to be unsuitable for drugs and are generally excluded from the compound DB. However, zinc complex was recently discovered to be an active compound with respect to insulin receptor protein, for which no active compound has previously been known except peptides, and this has attracted attention to inorganic compounds as novel therapeutic agents. The development of a DB for inorganic compounds is therefore necessary in order to examine the possible applications of inorganic compounds.

Thirdly, distribution of our compound DB has depended solely on word-of-mouth publicity and it has not gained recognition by means of journal articles or websites. This is because our compound DB depends on catalog data provided by commercial firms. Catalog distribution is restricted to the marketing of reagents and advertisements of reagent vendors should be posted. For example, the free downloading of ZINC<sup>[20]</sup> was realized by posting advertisements of reagent vendors on university websites as a result of direct negotiations with reagent vendors. However, the advertising of private companies is prohibited at the National Institute of Advanced Industrial Science and Technology (AIST), and free downloading therefore cannot be realized. We are consequently distributing our compound DB on the assumption that AIST has compiled a database from catalogs that the users have independently obtained. It is also possible for incorporated associations, our collaborators who support



**Fig. 5 Diagram of MTS and DSI methods.**

The numbers in the table indicate the scores. Higher scores are indicated by a deeper color.

our research, to distribute our package, but not to negotiate with reagent vendors. Collaboration with private corporations is being promoted through the encouragement of industry-government-academia coordination, however, and this issue is therefore also considered to be a future task.

## Acknowledgement

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## Terminology

Term 1. Protein-compound docking software: Software that computationally predicts the most feasible and energetically stable structure of protein-compound complexes by allocating a compound adjacent to the surface of a 3D protein structure. The docking simulation takes several seconds to a minute in drug screening. Typical software includes DOCK, AutoDock, and myPresto.

Term 2. Docking scores: Values that represent the strength of a protein-compound interaction estimated by docking software, and generally correspond to the free energy of binding.

Term 3. Enrichment: The ratio of the number of correct hit compounds to the number of candidate compounds predicted by computations in drug screening. In general, one out of 10,000 compounds hit in a random screening; thus, if one out of 100 compounds predicted by computational analysis was found to be a hit compound, the enrichment with respect to the random experiment would be 100-fold.

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## Discussion with Reviewers

### 1 Significance of developing the compound database

#### Question and comment (Akira Ono)

The authors stated a clear research aim and comprehensively portrayed a scenario to select elemental technologies as shown in Fig. 1, which were then integrated into a practically operational database. This is a typical *Type 2 Basic Research* and is also an excellent example of *Product Realization Research*. It is expected that the database developed in this study will be highly valued through its applications to drug screening for target proteins.

#### Answer (Yoshifumi Fukunishi)

A compound database is a repository of knowledge regarding the “synthetic easiness” of compounds synthesized in the past. We expect that the database will not only be directly used for drug discovery but also function as a basis to understand easily synthesizable compounds and even previously inconceivable compounds, which may lead to establish a new research field.

### 2 Design of unknown active compounds

#### Question and comment (Akira Ono)

The compound database is intended for efficiently examining the strength of chemical bonds between a particular target protein and numerous predefined compounds, thereby dramatically improved a hit ratio of drugs. Now, is it possible for the users to predict unknown compounds that could bind with a particular target protein even more strongly by using the database?

#### Answer (Yoshifumi Fukunishi)

There is a possibility that the users can predict previously unknown active compounds that are not included in the compound database. There was a trend that active compounds were classified into several clusters according to their chemical properties as a

result of screening compounds that potentially bind to a particular target protein. Therefore, it is considered feasible to synthetically design an unknown active compound that exhibits the properties of a particular active compound group.

### 3 Possible improvement of the database

#### Question and comment (Akira Ono)

As mentioned in section 4.3, it is important to recognize that excessive pursuit of mathematical strictness is meaningless in developing a compound database. In this regard, is there still a room for optimizing the database according to needs by reassessing its development process?

#### Answer (Yoshifumi Fukunishi)

Redesigning of the database according to needs, *i.e.*, ad-hoc database, is considered possible. For example, we adopted a dominant configuration of compounds in water (regarding the protonation state of a carboxylic acid, for example,  $-\text{COO}^-$  was adopted instead of  $-\text{COOH}$ ) for the current version of the database; however, the molecular configuration could be changed when the compounds bind with proteins. Recently, it is often discussed that a docking simulation of a compound targeting a highly-charged protein pocket is extremely difficult. A dominant ion form of carboxylic acid could occasionally be  $-\text{COOH}$  inside the negatively-charged protein pocket. Hence, it will be important to develop a target-oriented compound database in future.

### 4 Comparison with existing overseas databases

#### Question and comment (Akira Ono)

It is mentioned in section 4.11 that when the current database was employed, the enrichment factor was improved approximately 40- or 70-fold compared with random screening. In contrast, how superior is the developed database over the precedent overseas compound databases in terms of enrichment or enrichment factors?

#### Answer (Yoshifumi Fukunishi)

In general, unsuccessful predictions of computationally screened compounds are not published as research articles; thus, it is difficult to compare databases in detail. In our case, the hit ratio was 3–30 % when computationally predicted 100–300 compounds were purchased. So far, only one out of five cases showed 0 % hit ratio. Hit ratios reported on other literatures are mostly 10 % at best and 50 % of targets show 0 % hit ratio. Therefore, the developed database combined with our prediction method is considered more effective than the existing overseas databases.

### 5 Consideration of tautomers and ion forms

#### Question and comment (Takatsugu Hirokawa)

While commercially-produced overseas databases and software are acquiring the major share in the field, it is noteworthy that such a high-quality compound database and an unprecedentedly unique protein-compound affinity matrix were released by Japanese researchers. Various issues involved in digitally processing compound data were fully addressed in each development process discussed in the article, and this ensures that the database can be used reliably by researchers. This work should also be highly acclaimed as *Product Realization Research*.

Regarding the protonation of compounds, how are the tautomers and ion forms considered (such as whether pH7.0 is assumed) besides the statement, “We investigated the protonation states of various functional groups...under a vacuum and in water (near pH7.0)” of section 4.4.

#### Answer (Yoshifumi Fukunishi)

Protonation status is based on the assumption of pH7.0. However, since it is difficult to predict accurate pKa, a dominant configuration of each functional group contained in a molecule at pH7.0, rather than the pKa of the whole molecule, was adopted.

We applied the same scheme on tautomers. Accordingly, although the compound configurations are still not chemically strict, the ion forms of our compound database are more reliable than typical open software such as babel and openbabel, which frequently generate high-energy tautomers.

## 6 Prediction of non-selective compounds

### Question and comment (Takatsugu Hirokawa)

As application examples of protein-compound affinity matrix discussed in section 4.11, non-selective or low-selective compounds (or highly selective compounds), which nonselectively bind to many target proteins, may possibly be predicted by using the database. If so, this may realize highly unique annotations such as *in-silico* frequent hitters or *in-silico* chemical alerts for target selectivity. Please discuss about the possibility of predicting non-selective compounds based on the database, although this might have been conducted already.

### Answer (Yoshifumi Fukunishi)

It is an insightful question. Frequent hitters account for several tens of percent in VS and thus increase the cost and are the bottleneck of screening processes. Approximately 20 % of the predicted compounds are frequent hitters in our screenings. Recently, we are collecting several dozens of compounds that are considered the frequent hitters from literatures (*J. Med. Chem.* 2003, vol. 46, page 4477-4486, *J. Med. Chem.* 2002, vol. 45, page 137-142) and developing their 3D structures. Once the data have been prepared and included in the computation of protein-compound affinity matrix, we may be able to find a property that contributes to a high score against any target protein. However, there is a report that most frequent hitters form micelle colloids when observed under an electron microscope, and thus, the adsorption of the micelle to proteins could be a cause of the "frequent hit" (*J. Med. Chem.* 2002, vol. 45, page 1712-1722). If the frequent hitters exhibit non-selectivity against target proteins as unimolecular compounds, it will be possible to distinguish frequent hitters by docking simulations. However, if the micelle formation is the cause of the "frequent hit," docking simulations,

which assume infinite dilution condition, will not be able to discriminate frequent hitters. Thus far, as a result of applying a solubility prediction based on molecular descriptors to analyze the aqueous solubility of frequent hitters, it was found that highly hydrophobic molecules tended to be frequent hitters and thus could be distinguished from drug molecules that are not frequent hitters (P1-06 at the Chem-Bio Informatics Society (CBI) Annual Meeting 2008 International Symposium). If the water solubility of a compound determines its likeliness to be a frequent hitter, the micelle formation should be the primary cause of "frequent hit." Nevertheless, there remains a possibility that docking simulations could be more effective to predict frequent hitters. Although it will take time, we will continue to characterize frequent hitters.

Although we analyzed the side effects caused by the non-selectivity of compounds by MTS and DSI methods, thus far, no clear association between the side effects and non-selectivity of compounds was found. COX2, a typical target of nonsteroid anti-inflammatory drug (NSAID), and COX1, functioning as a gastric mucosal protector, are the enzymes with 60 % homology in their amino acid sequences; thus, it was an issue of concern that NSAID could cause gastric ulcers by inhibiting not only COX2 but also COX1. Recently, COX2 selective NSAIDs (e.g. coxibs) have been developed. Even though we then examined whether selective and non-selective NSAIDs can be distinguished by using protein-compound affinity matrix, it was not successful. In fact, the COX2 selectivity of coxibs is relatively low; at a concentration of 80 % inhibition of COX2, selective and non-selective NSAIDs inhibited approximately 20 % and 80 %, respectively, of COX1 activity (*Proc. Natl. Acad. Sci. USA.* 1999, vol. 96, page 7563-7568). Hence, the drug selectivity, in this case, is not a black-and-white property but a matter of degree. We consider it possible to distinguish highly selective and non-selective compounds by using protein-compound affinity matrix and currently prepare the structures of approximately 1500 proteins for docking simulations. Although an actual analysis cannot be performed due to the limitation of computational capacity, it will be possible anytime soon.

# One-year anniversary of *Synthesiology*

[Translation from *Synthesiology*, Vol.2, No.1, p.75-80 (2009)]

One year has passed since the launch of *Synthesiology*. In its first year, four issues containing 24 research papers were published. We have attempted to present original research papers with a new style of expression that differ from those of conventional journals. We have received positive reactions from a wide cross section of readers engaged in a variety of fields, as well as from the authors and reviewers. On the one-year anniversary of the journal, the editors got together for a roundtable discussion to reflect on the first year and to speculate on the future of *Synthesiology*.

## *Synthesiology* Editorial Board



### Participants of the round-table talk

Dr. Hiroyuki Yoshikawa	AIST President
Dr. Akira Ono	Editor in Chief
Dr. Naoto Kobayashi	Senior Executive Editor
Dr. Akira Yabe	Senior Executive Editor
Dr. Motoyuki Akamatsu	Executive Editor
Dr. Koh Naito	Executive Editor

### (Ono)

It has been one year since the launch of *Synthesiology*, and I would like to hear your impressions on the activities so far.

### Importance of evolving through “metamorphosis”

#### (Kobayashi)

I am very glad that we were able to publish a new type of academic journal. I have puzzled for a long time over the question “What is synthesis?” . When I interviewed Prof. Richard K. Lester of MIT in March 2008 (see the interview article in Vol. 1 No. 2), we discussed three types of synthesis methods for inclusion in *Synthesiology* and realized at that time it was necessary to further refine the emphasis on synthesis. It is important not simply to gather and combine elemental technologies, but to discern the changes caused by the combination and to document how *Type 1 Basic Research* is transformed into *Type 2 Basic Research*. During this transformation, the research content must also undergo “metamorphosis.” This “metamorphosis” is critical for the transformation of *Type 2 Basic Research* into *Product Realization Research*.

Another point I feel happy about is to have published both English and the Japanese editions. Initially, we discussed whether the journal should be published in English or in Japanese, but we created both because we thought it would be insufficient to have one but not the other. Although, it

requires a lot of effort, I would like to continue the bilingual editions in the future.

### *Synthesiology* was born from the enthusiasm of AIST

#### (Naito)

I was involved in discussions of *Type 2 Basic Research* and *Full Research* from even before the answer to the question “What is *Type 2 Basic Research*?” was widely known within AIST. Therefore my honest feelings are: “Finally, we got the journal started!”

About two years ago, interest in publishing a new journal rose rapidly in AIST, and staff members were united. It was finally launched in January 2008. I am deeply moved by the fact that it was actually launched.



Dr. Naoto Kobayashi

## Re-appreciation of the “importance of writing”

### (Akamatsu)

We created a journal from zero, and I think it was good opportunity to carefully consider, “What is a paper?” and “What is discipline?” In a conventional journal, there is a set writing style, but we suffered because we did not have one. On the other hand, because we did not have a style, we were able to rethink what “writing,” style was most appropriate and were thus able to more deeply appreciate the “importance of writing.”

We often engage in verbal discussions about *Type 2 Basic Research*, but it is important “to write them down properly” in prose. “To write down properly” here means to express the important points without insufficiency or excess, and only by writing, can one see what is insufficient and what is excessive. As I review papers, I am beginning to gradually see what are the insufficiencies and excesses.

## “Visualizing” research to overcome the valley of death at AIST

### (Yabe)

I have always told the people outside AIST, including those from companies and the mass media, “We can overcome the valley of death through *Type 2 Basic Research*,” and I think now we are able to allow people to “visualize” this process through the journal. For the first time, I was able to demonstrate *Type 2 Basic Research* and *Full Research* to people outside AIST.

There is substantial impact whenever I visit companies with the results. I tell industry-academia-government collaboration coordinators in various organizations who are working to revitalize small and medium businesses, “To overcome the valley of death, development in this area of technology is necessary.” They respond surprised, “I thought the valley of death could be overcome if we put in enough money in.” Last year, I was able to present the process convincingly. It was quite significant.

## Reviewing is reading the logic

### (Ono)

I totally share the opinions of the four of you, and I am reminded that we’ve been working toward certain goals. Personally, I have been thinking: “What is science?” “What is research?” “What is a researcher?” Since we became AIST, I have been thinking “What is *Full Research*?” I feel that *Synthesiology* provides significant answers to those questions, and I think it has been very successful.

I also encountered something unexpected, I surprised myself at being able to “read and understand” research papers of

different fields. Of course, I do read books and articles on research conducted in other fields, but I have never read the original research papers written by researchers of other fields. Even at academic meetings in my own field, I didn’t understand anything presented in a different divisions, and even in the same division, I could scarcely understand what was being presented if I walked into a different session. This time, I was surprised “I could understand” the research papers of other fields, and was even more surprised “I could make comments as a reviewer.” This surprise also lead to joy. I discovered this accidentally through working on *Synthesiology*, but I feel it was inevitable.

### (Kobayashi)

It was also a great surprise for me that I could read and review papers from different fields. It was possible only because we discussed, shared, and accumulated what we have been trying to achieve. On the other hand, I can see the authors are struggling with great effort as they try to follow the submission guidelines. Rather than putting *Type 2 Basic Research* as the final goal, I would like authors to reflect carefully on the originality of the synthesis process and what is different from *Type 1 Basic Research*, or upon “What is synthesis in *Type 2 Basic Research*?”

### (Akamatsu)

The ability to review papers is the ability to understand the underlying logic. Assuming that the details of the experimental method had been reviewed somewhere else in the context of a paper on *Type 1 Basic Research*, then, I just have to read and understand the logical threads and their combinations to reach the conclusion. Logic is the root of science. The age when modern science started and when René Descartes was alive almost coincided. Descartes pondered on how to understand the truth. I think this lies at the foundation of scientific methodology. In current *Type 1 Basic Research*, the logic to prove correctness is established, but in *Synthesiology*, the form of logic to be used must be considered carefully and the writer must think of how to build up the logic. Science-oriented people are good at logical thinking, and that enables reviewing.

Writing the logic of synthesis rather than the logic of a proof



Dr. Motoyuki Akamatsu

is the means to motivate the reader. By presenting the logical correctness of the synthesis procedure, readers may be moved to try it for themselves.

### **Synthesis can be written up as a scientific paper**

#### **(Yoshikawa)**

Logic that moves people is a fascinating subject. Reflecting upon historical precedent, synthesis is more old than new. It was in the 1960s that I transferred from a research institute to a university, where I was initially engaged in the teaching of design. At the time, I was surprised at the poor situation in the teaching of design. Although the university claimed, “Design was the most important component in the curriculum, and it formed the core of the engineering department,” the jist of the course involved simply bringing in things designed by companies and copying them. The act of manufacturing is concentrated in the development of the product, but the professors could not teach anything about that. That was my starting point. Although the words “analysis” and “synthesis” existed then, I started developing my design course by thinking about how I could teach the process of synthesis. Because I took upon the study of design as a theme I became isolated in academic society and couldn’t get my papers accepted for five years. I maintained my interest in synthesis, and worked hard on devising a way to write a paper on the study of design.

When I first presented my studies on design at an international conference in 1985, I found that it was well accepted, unlike the situation in Japan. An academic society of dedicated to the study of design was subsequently started, and it became clear that synthesis was not compatible with the conventional style of writing papers.

Of course, companies are engaged in synthesis, but the process and results are not published as documents. I said, “The results of the intellectual activities carried out in companies may remain in the form of products, but the processes leading to their development are ‘scattered like clouds and have disappeared like mist,’ and will not be handed down to the next generation. This is a great loss to humankind.” When I came to AIST, I found that there were people working on this issue! That was a great surprise and made a deep impression on me. I can write papers on synthesis here. On the other hand, I realized that I couldn’t do it alone, and it must be a collaborative effort. In the first year I came to, AIST, I became convinced that synthesis could be developed into a scientific papers through decisive action.

One year later, I invented the word “*Full Research*.” The composition of the research units was indeed *Full Research*. Looking back, it was one of the actions that paved the way to *Synthesiology*.

### **“Place” to logically express the passion of researchers**

#### **(Ono)**

What are your impressions of reading the *Synthesiology* papers?

#### **(Yabe)**

In *Synthesiology*, we ask the authors, “Please emphasize why your research went well. That is the point that appeals to people, and leads to a common methodology.” The authors understood this point and wrote appropriately. For example, they decided to write about meetings with people because discussions with certain people can lead to an innovation. Inclusion of such details helps to systematize the ways to overcome the valley of death. It is wonderful that the authors can write enthusiastically with our encouragement.

#### **(Ono)**

As Dr. Akamatsu says, logic is important and one should write as logically as possible. However, as Dr. Yabe says, there are challenging aspects, and some aspects slightly differ from logic. I call it “passion.” I think conventional scientific research only partially represents the intellectual activities of researchers. We engage in our research with “will,” “intent,” “passion,” and “hope,” but we remove all of these aspects from our research papers. I wanted to create a forum in which researchers are able to express and communicate the “whole picture” of their intellectual activities.

#### **(Akamatsu)**

I don’t think passion is necessarily removed from logic. Rather, the fun in the papers of *Synthesiology* is the fun of reading a story of how the logic is set up toward a certain goal, and I think that is the “importance of writing.”

#### **(Yoshikawa)**

Even the analytical papers are not entirely composed of logic. Sir Isaac Newton described the three laws - uniform motion, acceleration, and action-reaction - in the first three pages of *Principia*, but it doesn’t contain the description of how Newton arrived at the three laws. This is synthesis itself. One sets up a hypothesis, calls the hypothesis an axiom,



**Dr. Hiroyuki Yoshikawa**

and a good match with the observed facts can be achieved derived from that axiom. This is, therefore, a verification, and is a scientific thesis. The creation of the initial axiom or hypothesis is an abduction or a synthesis, but the structure of the scientific thesis does not allow it to be mentioned.

However, in the actual practice of manufacturing, a certain hypothesis may appear, but the verification is done not by logic, but by synthesis in society. The order is changed. In the editorial policy of the journal, it says, “Describe your research goal.” This is very important for human behavior. However, conventional scientific papers have removed that. I feel strongly that science expresses only part of the process in the human thought.

### **No room for failure in the age of sustainability**

#### **(Akamatsu)**

Technological development in terms of engineering advances because of failures. One makes something, it fails, therefore one realizes that a particular method doesn’t work, and one is forced to think how it can be made to work. However, enormous amount of time and social resources are necessary. Now, the demand is on how to minimize the failures.

#### **(Yoshikawa)**

In the era of sustainability, the room for failure is getting extremely small. Human activities and the consequences of their results, or the revenge against mankind, have been accelerated. Mistakes cannot be tolerated. Although re-evaluation must be done, there isn’t much time. We are in an era where the human ideal and the changing situation are in competition. Therefore, along with solving the extremely big problem of “*Synthesiology*” in an academic sense, it also must meet the demand of modern society.

#### **(Akamatsu)**

Perhaps it may be an exaggeration, but a person who can write such a paper is truly a wise person. I am certain that the wise people needed by society can be found in *Synthesiology*.

### **How can we help solve the social issues through *synthesiology*?**

#### **(Kobayashi)**

There are data that indicate that recently Japan’s R&D efficiency (the ratio of the amount invested in R&D to the total additional value five years later in the relevant segment of industry) is lower than that of Europe and the USA. Japanese manufacturing has been considered great, but is now struggling. We hope we can contribute to Japanese manufacturing, but this is a social issue.

#### **(Yoshikawa)**

*Type 2 Basic Research* must be done, but even after *Full*

*Research* and *Product Realization Research*, the product may not get used. The process of “socialization” or “incorporation of knowledge into the society” is necessary, and this is beyond the framework of *Full Research*. The philosophy of *Synthesiology* helped demonstrate this issue.

What are the problems that impedes investment efficiency? Even if we work hard on scientific research, why isn’t it reflected in the economy? According to some studies, Japan has poor investment efficiency, but we can say it’s because the behavior of companies in “socialization” is poor. Product realization up to the finished product is done well. The rest is socialization. I call this “societal technology”, and I think there the main problem is that the “societal technology” of Japanese industry is immature.

### **Clarification of the logic of synthesis and methodology to overcome the valley of death**

#### **(Naito)**

These words –“mass preparation,” “accessible design,” “low-cost production,” “risk assessment strategy,” “design and retail support,” and “improving reliability.” – are from the title of the papers of the first edition, and they are keywords that are not seen in ordinary papers. In 10 or 20 years, when the papers of this journal become a subject of study, I think one can see how the strategy of research will have shifted by analyzing these keywords. In the future, with the increasing importance of issues such as the environment and sustainability, the use of such keywords may increase, and the discussions on the underlying issues will become more clarified and focused.

As you are all saying, I think a journal structure where the reviewers and the authors collaborate with each other is important.

#### **(Akamatsu)**

Certainly. Reading the papers cultivates a keen sense of what one should do in the future. The word “connoisseur” appeared when I interviewed Mr. Umeyama of Toyota Motor. I think there are many points one must be learned before becoming a “connoisseur,” such as the different points of view of a the element being synthesized and the elements that



**Dr. Koh Naito**

can be combined.

**(Kobayashi)**

On the other hand, I feel that some people may misunderstand that one must have gone all the way to product realization in order to write the paper in *Synthesiology*. I think we should provide a place where people can write papers on their work at different stages of synthesis.

**(Yabe)**

Yet, I think the company people respond better to success stories. I think they become very encouraged when they read about some methodology on how to overcome the valley of death, or stories of “we succeeded because...” I feel that the journal can deliver a positive message to such people, and it will be accepted readily into society from this perspective.

**(Yoshikawa)**

I think the main readers of the journal are those who wish to read success stories, but I think it is extremely valuable for people who study “What is synthesis?” if there are papers written with no prominent results. When the discipline of synthesis is established, it will be a subject onto itself, so we should always keep this in mind and be keenly aware of what Dr. Yabe has mentioned.

**(Ono)**

The points of this journal are scenario writing and synthesis. Most of the authors can recall the scenario made and can even revise it. But I have found that sometimes they have trouble with writing about synthesis. Personally speaking, I can scarcely recall why I made certain decisions or took a certain process of synthesis.

**(Yoshikawa)**

I’ve been studying that process. I’ve studied the thought process of design, but I have failed entirely. I have totally forgotten what I’ve been thinking. The abduction does not remain in memory. The greatness of the editors of *Synthesiology* is that they started by asking the authors to write objectively what happened to them, regardless of the logical synthesis. I think that this is the correct way, and one can only write what he/she remembers. The process of ideation is very difficult.

**(Ono)**

Ideation occurs not only by one person thinking, but from ideas arising during discussions with others or when visiting someone else’s laboratory. Good research groups, I think, provide such places. I believe there are many creations of synthesis, or highly productive research groups at AIST.

**(Yabe)**

I think how to analyze and incorporate the writing in *Synthesiology* is an issue challenging us. I think the process

of analyzing and proposing the common methodologies for overcoming the “valley of death” will become very important, including topics such as why I did this for what purpose, for example to improve economy, to maintain environmental acceptance, or to reduce societal risks.

**(Akamatsu)**

In conventional *Type 1 Basic Research*, simply writing a paper is contribution to science, whereas the paper of *Synthesiology* must show the necessary capabilities in actually utilizing technology in society. By writing such papers within the company, one can appeal that he/she is a connoisseur or a human resource capable of integration, and should be able to move up to a better position. It should be used in such way.

Getting a patent only proves the capability of creating elemental technology. One should not just file patents or write papers on elemental technology, but should write papers that show he/she has the capability to integrate. The person should then be treated with respect in society for this capability as a result of writing such papers. We must create a science and technology society that allows that. I think creating such a social system is lacking in the science and technology policies.

**(Yoshikawa)**

In the old days, there was a sort of harmonic hypothesis in that if one wrote a research paper on *Type 1 Basic Research*, it could lead to a patent in some cases, and the society will absorb and use the new ideas which were presented randomly. That was innovation as stated by Joseph Schumpeter, but modern innovation won’t be realized unless we act swiftly. If we do not reduce carbon dioxide levels, global warming will progress and the humankind may become extinct. We must have a keen objective of how we can create the new technology to overcome the situation.

Therefore, company people should read this journal keeping in mind innovations are urgent issues on which they must work. The journal can serve as a guideline that shows how something like basic research, which seems to be floating in the air, can travel all the way to socialization. Researchers must realize that the motivation for writing papers in



**Dr. Akira Yabe**

*Synthesiology* is that we must change our mind by noting that science should be used eventually for solving problems. I think it is necessary to take this position.

**(Ono)**

Thank you very much. I hope there will be submissions to *Synthesiology* from companies and universities, and from abroad. I believe there is much to be gained by writing *Synthesiology* papers.

(December 19, 2008)



**Dr. Akira Ono**

# 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

## 1 Types of contributions

Research papers or editorials 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*, however, 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

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 in. 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.

2) The manuscript shall be prepared using word processors or similar devices, and printed on A4-size portrait (vertical) sheets of paper. The category of article (research paper or editorial) shall be stated clearly on the cover sheet.

### 3.2 Structure

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).

2) Title, abstract, name of author(s), and institution/contact shall be provided.

3) The length of the manuscript shall be, about 6 printed pages including figures, tables, and photographs.

4) 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.

5) 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 the society.

6) The abstract should be 300 Japanese characters or less (125 English words). The Japanese abstract may be omitted in the English edition.

7) The main text should be about 9,000 Japanese characters (3,400 English words).

8) 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 contribution to the paper are included.

9) 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 a part of the article.

10) If there are reprinted figures, graphs or citations from other papers, permission for citation, if needed, should be clearly stated and the sources should be listed in the reference list. All verbatim quotations should be placed in quotation marks or marked clearly within the paper.

### 3.3 Format

1) The text should be in formal style. Chapters and sections should be enumerated. There should be one line space at the start of paragraph.

2) Figures, tables, and photographs should be enumerated. They should have a title and an explanation (about 20-40 Japanese characters or 10-20 English words), and the position in the text should be clearly indicated.

3) 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 x 15 cm or smaller, in black and white.

4) 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 x 7.2 cm or smaller, in black and white.

5) References should be listed in order of citation in the main text.

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

Book – [No.] Author(s): *Title of book*, 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](mailto: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

One year has passed since the launch of *Synthesiology*. We are now venturing into the second year with cooperation and support from many people. We are grateful to all people involved. To reflect on the past year, the core members who participated in the start up of *Synthesiology* gathered to exchange thoughts, and this roundtable talk became one of the articles in this issue. Although the discussion may be too abstract, I hope you perceive the passion of the members, and find interest in the background and the process of launching this academic journal. We also received a letter of comment from Dr. Gaynor, Fellow of The Institute of Electrical and Electronics Engineers, Inc. (IEEE). He read the English edition of *Synthesiology*, and his letter is reprinted in this issue. We set up a section called the Reader's Forum, and I hope the readers will send their comments and impressions, as well as introduce books related to *Synthesiology*.

The papers in *Synthesiology* can be downloaded from the AIST homepage. There have been over 20,000 accesses in one year. It is clear that the electronic version is widely used. The Reader's Questionnaire was included in the printed version of the journal, and about 70 % of the questionnaires returned were from

corporate people. Looking at their business category, almost 40 % were involved in R&D, and about 40 % were managers, sales, and planning. It is delighted to see that our journal is being read from the perspective of technological management as well as technological development. Initially, we sent the journal only to organizations such as companies, universities, and libraries, but dozens of people applied for subscription after they saw the content of the published journal. While it is hard to visualize the readers when the journals are sent to organizations, we can see our readers when we receive individual subscriptions, and the work of editors becomes a pleasure.

This issue includes a roundtable talk with Professors Tanishita and Hishida of the Department of System Design Engineering, Keio University. In the second year, we wish to strengthen alliance with the people of industry, academia, government, mass media, or any sectors in Japan and abroad, who share the goals of *Synthesiology*. If you have any information about people who may be interested, please contact the Editorial Board.

Executive Editors  
Motoyuki Akamatsu

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## Messages from the editorial board

### Research papers

Predictive modeling of everyday behavior from large-scale data

-*Learning and inference from Bayesian networks based on actual services*-  
Y.Motomura

Expansion of organic reference materials for the analysis of hazardous substances in food and the environment

-*Realization of an efficient metrological traceability using the quantitative NMR method*-  
T.Ihara, T.Saito and N.Sugimoto

Modeling the social acceptance of industrial technologies

-*Development of an eco-product diffusion analysis model that incorporates three existing models*-  
M.Matsumoto and S.Kondoh

How Grid enables E-Science?

-*Design and implementation of the GEO Grid*-  
Y.Tanaka

Basic materials research for the development of ubiquitous-energy devices

-*Applications to positive electrode materials of Li-ion batteries, electrode catalysts of proton-exchange fuel cell and gold catalysts*-  
M.Kohyama, T.Akita, S.Tanaka, Y.Maeda, K.Tanaka, K.Okazaki and J.Kikkawa

Innovation in distillation processes

-*Process intensification for energy savings through concept of "detuning" from ideal state*-  
M.Nakaiwa and T.Ohmori

Advanced in-silico drug screening to achieve high hit ratio

-*Development of 3D-compound database*-  
Y.Fukunishi, Y.Sugihara, Y.Mikami, K.Sakai, H.Kusudo and H.Nakamura

### Round-table talk

Reviewing the first year of *Synthesiology*

### Editorial policy

#### Instructions for authors

*"Synthesiology-English edition" is a translated version of "Synthesiology" which is published quarterly, ISSN 1882-6229, by AIST. Papers or articles published in "Synthesiology-English edition" appear approximately four months after the publication of the original "Synthesiology".*