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Synthesiology

English edition

Development of automatic cell culture system for cell therapy and regenerative medicine

Selection of next-generation low global-warming-potential refrigerants by using a risk trade-off framework

Industrial safety and application of the chemical accidents database

Capacitor devices for rapid charge/discharge storage

Physical separation technology to support the strategic development of urban mining

Synthesiology editorial board

2013 ④

Synthesiology-English edition ④ 2013

National Institute of Advanced Industrial Science and Technology (AIST)

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, this stage 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 actively try to bridge the gap.

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
(written in January, 2008)

Note 1 : The period was named "nightmare stage" by Hiroyuki Yoshikawa, the then President of AIST, and historical scientist Joseph Hatvany. The "valley of death" was used by Vernon Ehlers in 1998 when he was Vice Chairman of US Congress, Science and Technology Committee. Lewis Branscomb, Professor emeritus of Harvard University, called this gap as "Darwinian sea" where natural selection takes place.
Note 2 : *Type 2 Basic Research*
This is a research type where various known and new knowledge is combined and integrated in order to achieve the specific goal that has social value. It also includes research activities that develop common theories or principles in technology integration.
Note 3 : *Full Research*
This is a research type where the theme is placed within the scenario toward the future society, and where framework is developed in which researchers from wide range of research fields can participate in studying actual issues. This research is done continuously and concurrently from *Type 1 Basic Research* (Note 4) to *Product Realization Research* (Note 5), centered by *Type 2 Basic Research* (Note 2).
Note 4 : *Type 1 Basic Research*
This is an analytical research type where unknown phenomena are analyzed, by observation, experimentation, and theoretical calculation, to establish universal principles and theories.
Note 5 : *Product Realization Research*
This is a research where the results and knowledge from *Type 1 Basic Research* and *Type 2 Basic Research* are applied to embody use of a new technology in the society.

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Contents

Development of automatic cell culture system for cell therapy and regenerative medicine

— Robotized system for high quality cell product preparation —

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[Translation from *Synthesiology*, Vol.6, No.4, p.198-208 (2013)]

We carried out R&D in order to dramatically facilitate cell culture for clinical use, the difficulty of which had been a major hurdle in adapting basic research to clinical applications of cell therapy and regenerative medicine. The world's first robotized cell culture system (MDX) was developed by Kawasaki Heavy Industries, Ltd., and the systems were installed in Shinshu University and AIST. Based on the technologies of the MDX system, we developed a novel cell culture system R-CPX (Robotized-Cell Processing eXpert system) which can produce high quality medical cell products. This system does not need to be placed in a CPC (cell processing center), which is expensive to construct and difficult to manage. We aimed to realize rapid progress of various cell therapies and production of medical cell products of global standard quality.

Keywords **:** Tissue engineering, cell engineering, auto culture system

1 Introduction

1.1 Why is it necessary to develop an automatic cell culture device now?

As low birth rate and aging progress, we have reached the limit of symptomatic therapy using alternative materials such as artifacts and drug administration that were done conventionally against adult-onset diseases such as cancer, diabetes, and dementia, and the development of new medical technology is expected. To fulfill this expectation, it is necessary to apply the diverse elemental technologies and research results of the fast-evolving medical fields to drug discovery, as well as the development of the analysis tools, diagnostic technology and medical equipment that support such discovery. It is important for the private companies and clinical research institutes to unite and engage in R&D to achieve quick and practical application.

In place of conventional medicine, regenerative medicine and genetic/cell therapy are expected to be the next-generation medicine. They are medical fields whose objective is to utilize the cell functions such as growth and differentiation. The patient or donor cells are harvested, grown or differentiated *in vitro* or maneuvered by gene transfer, and then transplanted to the diseased area of a patient to treat a certain disease. This field is currently expanding rapidly and many good results are being accumulated. In Japan, skin grafting using autologous cultured epidermis tissues has been put into practical use (has been commercialized).

Although the operation of cells harvested from the body is a technological development at the basic research level where the growth and differentiation of the cells are controlled, translational research (TR) from basic research is necessary for clinical application and commercialization.[1] The cultured tissues obtained from (autologous) cells harvested from the patient or (homologous) cells harvested from the donor must be handled as products, and it is necessary to guarantee their safety, and to present the efficacy of these products to the physicians and patients who are the customers. In the process of cell culture, the succession of cells in the processes of harvesting and growing, and the cell processing such as induction of differentiation are necessary. Presently, such complex cell culture operations are done by skilled technicians at the cell processing center (CPC) that are specifically set up in the hospital or company (Fig. 1A).

For the cell culture operation at CPC, the maintenance of a sterile environment is necessary since the cells and tissues cannot be sterilized. Also in the cell culture process, cross-contamination (contamination by mixing with cells of other people) and human error are not tolerated. From such a

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perspective, the therapy follows the Medical Practitioners Act in Japan, while CPC and cells and tissues used for therapy must satisfy the Good Manufacturing Practice (GMP) that is the rule for quality control, process control, and facility for the manufacture of drugs. The three principles of GMP that must be satisfied by the CPC are: ① prevention of contamination and deterioration of quality, ② minimization of human error, and ③ system to guarantee high quality.[1][2] Therefore, (1) aseptic control, biohazard countermeasure, and cross-contamination prevention, (2) mix-up prevention, and (3) documentation and recording of the operation status are essential. Currently, many CPCs are in operation in Japan, and R&D for regenerative medicine is being done, but there are limits to the medical system that uses the conventional CPC due to the maintenance cost necessary to satisfy the aforementioned high level requirements, as well as the demand to respond to various new medical technologies. Therefore, the development of improved systems and devices that are in compliance with GMP are awaited, keeping in mind the commercialization of regenerative medicine and cell therapy. For items ② and ③ of the three principles, an automatic culture system that replaces the manual operation is important, and for ①, the development is under way for an isolator system where the sterile environment of CPC that is expensive to maintain can be achieved in a small device and the operation can be done through the glove box (Fig. 1A). The culture by manual operation using the isolator is expected to become more prevalent in the future.

In this R&D, to advance the automatic culture system, the culture system is incorporated inside the isolator, with the objective of developing a robotized cell processing expert system (R-CPX) that can be used for various usages and does not require a CPC. With the development of this system, the next generation R-CPX that does not require a CPC is created to fulfill the demand of the small to medium businesses. The specialized device can be provided at low cost to satisfy the demand of medium to large companies in the diffusion phase of regenerative medicine. This is expected to help spread low-cost and safe regenerative medicine.

1.2 Objective, execution, and outline of the R&D

In this R&D, the goal was to dramatically simplify the preparation of clinical cells that is one of the major barriers in the translational research from basic research to clinical application of regenerative medicine and cell therapy technologies. Figure 1B shows the technological items and their configuration of this project. Kawasaki Heavy Industries, Ltd. (hereinafter will be called Kawasaki), Shinshu University (SU), and the National Institute of Advanced Industrial Science and Technology (AIST) have already created the Medical Device Project X (MDX, Figs. 2 and 3), a cell culture robot system, for the first time in the world. The system installed at SU was called Evaluation Unit 1 and the system at AIST was called Evaluation Unit 2. SU has abundant experience and know-how in cell culture technology for regenerative medicine in CPC, while AIST has the knowledge of cell culture used for drug discovery and development. Kawasaki's cell culture robot was designed under the concept of replacing the movement of a skilled technician conducting manual cell culture with the movement of a robot (mainly a robot arm). The culture techniques of SU and AIST were incorporated in Evaluation Units 1 and 2, and tests were done for verification. The research was conducted with the goal of developing the culture system R-CPX based on the results obtained.

Regenerative medicine and cell therapy are highly novel therapies for which aggressive R&D is being done presently, and the quality standard and required functions are changing

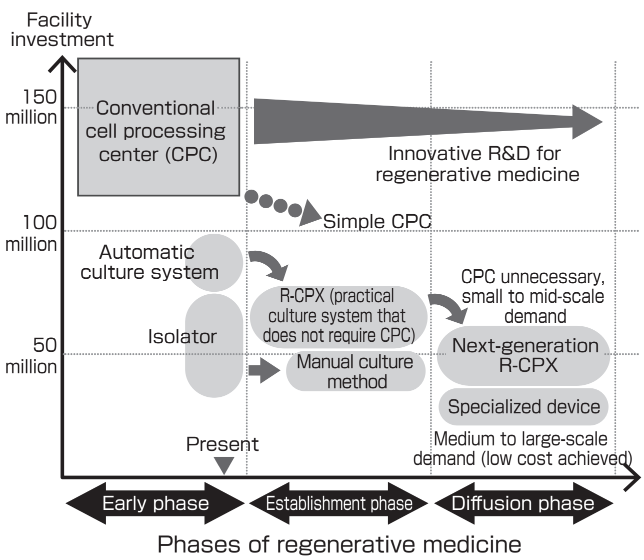


Fig. 1A Roadmap of the cell preparation system

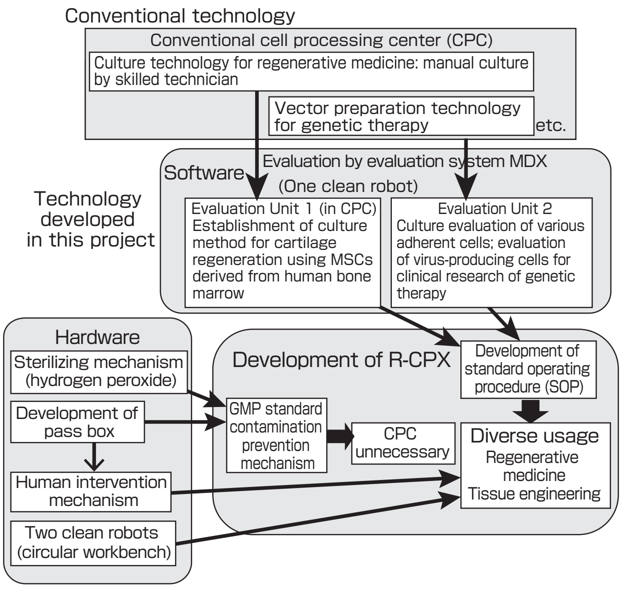


Fig. 1B Technological items in this project and the configuration diagram

daily. Also, since the method can be applied to wide-ranging diseases, the cells and tissues used as raw materials as well as the final products (cells) that are being prepared are varied. Therefore, it is insufficient to merely transplant to a robot system the cell culture technique that was already established for manual operation in one of the protocols. Therefore, development was done by selecting two different, specific projects that contained representative procedures of diverse operations, and concentrated on the improvement of these procedures. The regenerative medicine and cell therapy projects selected were "Establishment of culture method for cartilage regeneration using human mesenchymal stem cells from bone marrow" (Evaluation Unit 1) and "Evaluation of virus-producing cells for clinical genetic therapy" (Evaluation Unit 2). Since the researchers of these projects were highly experienced, the standard operating procedures (SOP) were established for the manual operation in the existing CPC for the cell reagents used in clinical trials. The actual reagents were prepared according to the SOP and the quality of the product was verified. Concurrently with these researches, the following main technical items were incorporated, to construct the R-CPX hardware that smoothly operates independently without using the CPC:

(i) Sterilizing mechanism for the interior of the R-CPX by hydrogen peroxide,
(ii) Incorporation of a human intervention mechanism by developing the pass box, without robotizing the entire process to enable diverse usages, and
(iii) Achievement of efficiency by two clean robots, which could not be achieved with one clean robot.

Particularly for the robotization process, verification tests were conducted using the existing MDX, and the aim was to automate most of the manual operation in the future.

According to the above objectives, the following five research items were set for the R&D:

① Develop the R-CPX that meets the GMP standard
② Establish and evaluate the regenerative medicine using R-CPX
③ Investigate the vector production method for genetic therapy using R-CPX
④ Develop the SOP
⑤ Evaluate the culture by evaluation equipment

Of the above items, ①, ④, and ⑤ that are directly related to the device development will be explained in detail.

2 Development of R-CPX that meets the GMP standard

2.1 Basic concept of the R-CPX design

The contamination prevention function and human intervention mechanism that were needed for achieving R-CPX were developed, and based on these the total configuration of the R-CPX was developed. For the contamination prevention, the ventilation function where the interior could be maintained at positive/negative pressure to be adaptable to P2 was verified using a prototype and its performance was confirmed. For the sterilization function, sterilization by hydrogen peroxide steam was employed after comparative study. Various tests were conducted to check the sterilizing performance, and basic data needed for the R-CPX design was obtained. For the human intervention mechanism, interlock mechanism was designed, as it had to be cooperative with the robot. Also, the fitting mechanism for gloves was designed to prevent decrease of operability when the interior of the device was at negative pressure, and this was verified in the prototype.

From the results of Evaluation Unit 1, and Unit 2 that was developed for drug discovery and installed at AIST, the total configuration of R-CPX was considered, the specifications were determined, and the design diagram was completed. Prototypes were used for items that required verification and confirmation of performance, such as pipette insertion tests, improvement of operability of the culture instruments, and attachment/removal of the pipetter. The configuration was kept simple to ensure the sterilization performance by hydrogen peroxide steam and to improve the ease of maintenance. The environmental recognition technology by

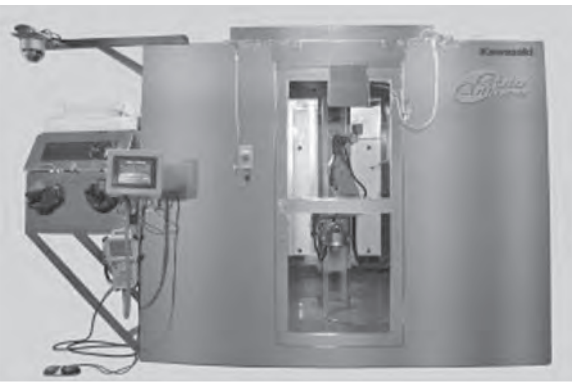


Fig. 2 MDX Evaluation Unit 1 (installed in Shinshu University) (for regenerative medicine)

Fig. 3 MDX Evaluation Unit 2 (installed in AIST) (for drug discovery)

image processing was also investigated.

The detailed design of R-CPX was done, and the prototype was completed after reviewing the generation mechanism for hydrogen peroxide steam. The sterilization of the interior and pass box by hydrogen peroxide, and the culture operation using two clean robots that were not present in Evaluation Units 1 and 2 were created (Fig. 4), and a performance test was conducted for confirmation. For Unit 1, the issues in the hardware that arose during the culture tests at SU were improved, and after revising the automatic culture SOP, the culture evaluation was conducted concurrently with manual culture using the same donors and the same period of time.

2.2 Development of the contamination prevention method that meets the GMP standard

For contamination prevention, the following four functions were required:

(a) Interior of the device is not contaminated from the exterior

(b) Interior of the device is not contaminated when loading/unloading from the exterior

(c) Cross-contamination does not occur when handling different samples within the device

(d) Exterior is not contaminated from the interior of the device, in handling the cultures for genetic therapy

To realize these four functions, the R-CPX was equipped with a ventilation function where the interior could be maintained at either negative or positive pressure, as well as the sterilization function of the device including the pass box. For the sterilization function, all the areas with the possibility of contamination must be sterilized. In the R-CPX, hydrogen peroxide steam sterilization was employed since there was little damage to the interior equipment and the sterilization time was relatively short. The hydrogen peroxide steam sterilization is employed for the sterilization of the isolator used in pharmaceutical and medical research, and sufficient sterilization performance could be expected if appropriate conditions were set.

In the hydrogen peroxide steam sterilization, the surface that comes into contact with the hydrogen peroxide steam is sterilized. Therefore, the issue was whether the steam reached the target surface sufficiently. Since there was a concern that the steam may not sufficiently reach the interior of complex structures or narrow spaces, the structure was kept simple. Since the presence of gaps and screws could not be avoided, sterility of those parts was checked. After the sterilization process, the degree of sterility was tested using the bio-indicator, and the results indicated high sterilization capacity.

One of the characteristics of R-CPX that was not present in the previous devices (Evaluation Units 1 and 2) is the human intervention mechanism, and this was accomplished using the glove box (Fig. 5). The gloves replaced part of the culture operation done by the robot. Therefore, among the motion range of the robot engaging in culture operation, the locations where human intervention by use of gloves occurred were allotted to the areas that could be reached by the robot, and the areas that could be accessed by the person facing the front side of the device. The material for the gloves was limited and the operability was poor because they were exposed to hydrogen peroxide steam and there would be pressure difference (approximately 150 Pa to −50 Pa) with the external environment. Particularly, when the interior of the device was kept at negative pressure, the gloves expanded and would not fit the operator's hands. Therefore, we devised a way to have the gloves fit closely to the operator's hands and thereby improving the operability. The configuration is as seen in Fig. 6. The airtight ring was placed at the upper arm area of the operator, air was pumped into the ring for sealing, and then air was drawn from the space beyond the airtight ring to fit the gloves closely to the operator's hands.

2.3 Basic configuration of R-CPX

The automation mechanism was considered by reducing the number of places that may be contaminated, and by simplifying and making the mechanism as close to hand culture as possible, in addition to the contamination

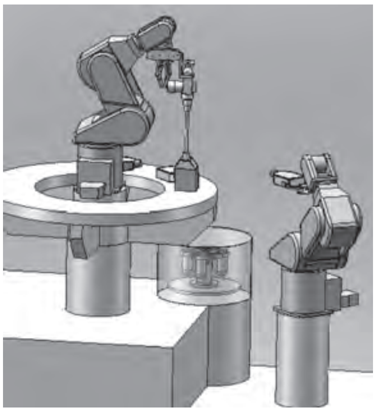


Fig. 4 Arrangement of the robot and rotating workbench

Fig. 5 Gloves that can be treated by hydrogen peroxide steam sterilization

prevention and human intervention mechanism that were considered above. The operability of Evaluation Unit 1 installed at SU and Unit 2 at AIST were compared, and the following basic configurations were determined.

(a) The use of automated machine with complicated structure was minimized. The main bodies were two clean robots, where one mainly engaged in transportation (a transport robot) and the other mainly engaged in culture operation (an operation robot).

(b) The one-touch cap was used so the capper would not be used to open/close the screw cap.

(c) For the pipetter, the method of joining the syringe pump and tube was not employed, and an independent pipette similar to the one used by an operator was used. The pipette was exchanged for each operation, and it would be removed and sterilized after each series of culture operation.

(d) Since the multiple use of sensors made the structure complex, the processed image from the TV camera was used as the sensor for identification in areas that could be replaced by remote visual inspection.

(e) Hip flask that is often used in hand culture operation was used as the culture container.

(f) The doors of the incubator and refrigerator were opened/closed by a robot rather than by cylinder.

(g) The workbench for the culture operation was arranged in a circle with the robot in the center, and the rotation of the workbench was controlled. The movement of the rotary workbench reduced the range of culture operation to be done by the pipette attached to the robot.

(h) The centrifuge tubes were used as common containers for the medium or reagent, and the empty containers were used as liquid waste containers.

(i) The hand mechanisms were installed on the robot, and the robot operated the pipette attached to it and also held the container.

(j) Storages other than the incubator (such as room-temperature and refrigerated storages) were concave without much depth, considering the ease of sterilization.

The R-CPX system was constructed based on these basic configurations. The overall diagram and the main components of the completed device are shown in Figs. 7 and 8.

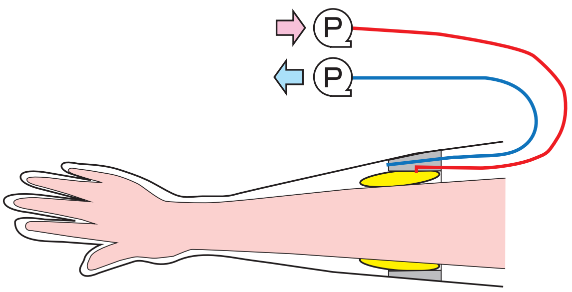


Fig. 6 Glove fitting mechanism

3 Development of standard operation procedure (SOP)

In the case of culture by manual operation, SOP serves as a standard manual, and if an operator with a certain degree of skill reads the manual and does the operation, he/she should be able to obtain the same results. When this is replaced by the automatic culture, it is composed of four parts.

(a) Operations that are needed by both manual and automatic culture operation: Preparation of culture, seeding on collagen, etc.

(b) Operations not needed in manual but necessary in automatic culture: Packing of disposable items, etc.

(c) Operations of the automatic culture device: Loading of disposable items, unloading of test samples, etc.

(d) Motion of the automatic culture device

The most important item here is (d). The motion of the automatic culture device will not be entirely the same as the movement of a human operator. For example, in changing the media immediately after the primary culture, the blood components from the bone marrow will remain, and the dish must be shaken before the medium change to allow the blood components to rise into the supernatant as much as possible before disposal. The operator visibly checks the amount of shaking, but the robot is incapable of doing this. The manner of shaking must be determined beforehand. Therefore, the strength and frequency of the shaking motion were experimentally compared and determined. In Fig. 9 (left),

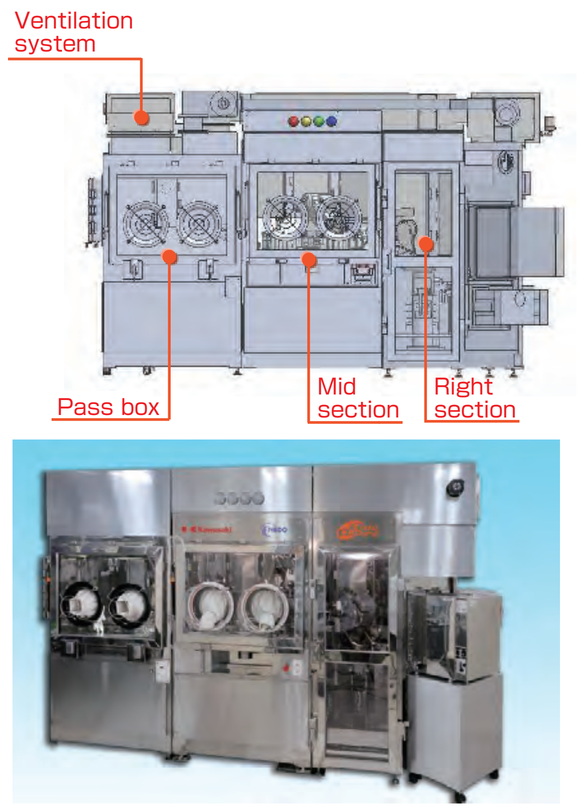


Fig. 7 Overall diagram of the R-CPX (top) and photograph (bottom)

the dish after the medium change at initial shaking condition had a reddish color, indicating that there were residual blood cells. As a result of correcting the shaking condition, the red color could no longer be visibly seen in the dishes after medium change. As shown in Fig. 9 (center, right), the blood components were hardly seen in the microscopic observation.

Based on the above basic concept, the SOP was developed for the automatic culture for cartilage regeneration and automatic culture for genetic therapy.

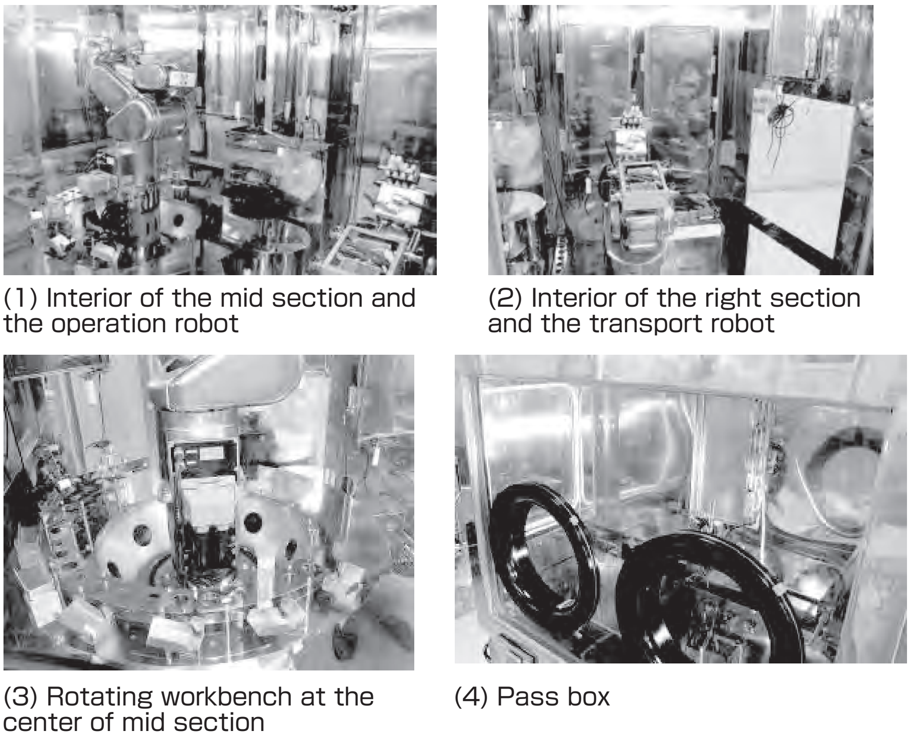
The SOP for culture by manual operation has the following issues: methods are different by different operators even at the same facility; records are not kept accurately; transfer to other operators is difficult; and the quality of the product is not stable. Assuming the development of SOP for automatic culture, the SOP for manual culture was reviewed, and the points that were ambiguous or lacking in scientific evidence were investigated and clarified. Moreover, the thinking for the transfer of the SOP from manual culture to automatic culture was organized. Through such studies, the ways to achieve the SOP for manual and automatic cultures became clear.

4 Culture evaluation by evaluation equipment

The cultured subjects of R-CPX include not only the mesenchymal stem cells (MSCs) for regenerative medicine, but also various cells such as the virus-producing cells for genetic therapy and other clinical research. The evaluation of MSC culture was done in Evaluation Unit 1. Adherent cells other than MSCs were evaluated using Evaluation Unit 2.

4.1 Outline of Evaluation Unit 1 installed at Shinshu University

Evaluation Unit 1 was installed in the CPC of Shinshu University Hospital for the purpose of culturing MSCs for regenerative medicine in clinical research. For use in clinical



(1) Interior of the mid section and the operation robot

(2) Interior of the right section and the transport robot

(3) Rotating workbench at the center of mid section

(4) Pass box

Fig. 8 Photographs of the main sections of R-CPX

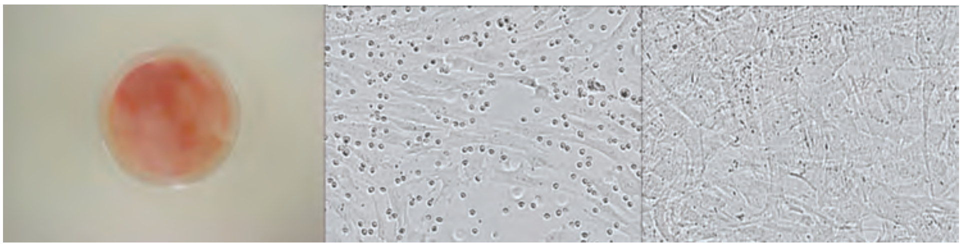


Fig. 9 Dish immediately after the primary culture (reddish color also seen after medium change) (left). Microscope photograph comparison of the effect of improving the shaking method (middle: before improvement, right: after improvement).

research, it was necessary to obtain approval based on the "Guidelines on clinical research using human stem cells" of the Ministry of Health, Labour and Welfare, and we conducted culture evaluation at the level applicable to clinical research.

Unit 1 has the following characteristics:

(a) The culture is started from bone marrow, the amount of MSC necessary for cartilage regeneration is cultured, and then it is obtained as cell suspension.

(b) The device is placed in the managed area with cleanliness level 100,000, and the interior of the device is maintained as sterilized space of cleanliness level 100.

(c) The interior contamination is prevented by using a glove box when loading/unloading the disposable items or cells, and by using sterilized packages.

(d) Primary culture, medium change, successive culture, cell recovery, and cell observation can be done automatically within the device. The main body of culture operation is done by a clean robot. Also, samples for testing can be made.

(e) The culture operation procedure is managed by a computer. Not only can scheduling be done freely, but also all movements are logged.

(f) There is a storage space within the device, and disposable items are stored in the room-temperature storage, reagents in the refrigerator. Complete automatic culture operation is possible.

(g) There is a remote monitoring function that enables monitoring the same information as the terminal in the CPC, and the image inside the device can also be viewed.

4.2 Outline of the cell culture method and evaluation method by Evaluation Unit 1

Concurrently with the dry run (culture in which the cultured cells are not transplanted to the donor) of manual culture, the culture of the bone marrow cells of the same donor was conducted in the dry run of the automatic culture. The culture medium was the same as the one used in the manual dry run, and was prepared from the donor's autologous serum. For evaluation, the sterility test and quality tests were done for endotoxin and mycoplasma during succession and cell recovery. Cell count was conducted and surface antigens were analyzed, to calculate the percentage of cells considered to be MSCs within the obtained cells. The standards for cell reagents, converted to 9 ml of bone marrow from the donor, were a total number of cultured cells of 10^7 or more within 3 weeks of culture period, and cells with 90 % or higher MSC marker positive recovered at 80 % or higher purity.

Through the five dry runs of automatic culture, we were able to achieve culture that reached the qualifying level. The marrow supernatant during the primary culture was sterility test negative (2 week culture) and endotoxin of less than 0.1 EU/ml. In the quality test for successive and cell recovery by automatic culture, sterility test negative (2 week culture), endotoxin of less than 0.1 EU/ml, and mycoplasma negative were confirmed, and pathogenic contamination was not observed in the culture process. After the improvements in the automatic culture SOP and the device, the product quality standard was demonstrated in the fifth dry run, and an MSC reagent with high quality in both purity and specificity was created. Since the quality guaranteed MSC was created, the adequacy of the automatic culture SOP was verified.

4.3 Outline of Evaluation Unit 2 installed at AIST

The Evaluation Unit 2 is an automatic cell culture device that was created for the purpose of usage in non-clinical research such as drug discovery, and has the following characteristics:

(a) Direct automation of manual culture operation: The series of procedures that were done by hand, from changing the culture medium, succession, cell recovery, and cell observation are automated.

(b) Capacity to handle various cells: The general culture operations are programmed, and the user can set various parameters such as the peeling time during succession, and quantity and discharge speed of the reagents.

(c) Culture support by image identification: It is equipped with image processing unit that enables observation of the cells inside the device and automatic recording. The cell occupancy rate can be displayed and automatically recorded.

(d) Culture scheduling function: Each culture operation can be freely scheduled.

(e) Stability and uniformity of cell quality: Stability and uniformity of performance and culture quality can be achieved through automatic culture operation.

(f) Contamination prevention: The cleanliness level inside the device is 100. Since the operations are done by a clean robot, the contamination of the cultured cells can be prevented. It is equipped with a decontamination function by automatic alcohol spray to prevent cross-contamination.

(g) Compact size: Approximate dimensions of the device are width of 3 m, depth of 1 m, and height of 2 m.

4.4 Outline of the cell culture method and evaluation method by Evaluation Unit 2

The subjects of culture by R-CPX are not only the MSCs for regenerative medicine, but also include virus-producing cells for genetic therapy and various cells used for various studies of clinical research. In Evaluation Unit 2, the target was cells other than MSCs, and the evaluations were done for a wide range of cell types as possible. The evaluation was done for the adherent cells. For virus-producing cells for genetic therapy, the cytokine-producing cells that excrete protein components into the culture supernatant, much like the virus, was used as the evaluation cells.

4.4.1 Culture evaluation of a wide range of adherent cells

Although the main objective of this system is the automatic culture of adherent cells, there are wide variations in the adhesiveness of the cell types. There were 13 types of cell lines such as HeLa and NIH3T3. Good results were obtained for the culture parameters by preliminary determining the initial cell count, frequency of succession, and dilution rate where stable hand culture was possible and by fine-tuning using Unit 2 based on the results. In the cells with weak adhesiveness such as 293 gp/mIL2, the discharge speed of the PBS and culture medium (from the pipette) was studied. Figure 10 shows the situations of cell peeling at discharge rate 3, 1, 0.3, and 0.1 ml/sec. The optimal discharge speed was 0.3~1 ml/sec. In the case of cells that were hard to peel such as PC-12, the peeling time was increased compared to the initial setting, and the number of tappings was increased to improve the peeling rate. By setting the culture parameter with consideration for the cell characteristics enabled the automatic culture of a wide range of cells.

4.4.2 Culture evaluation of the virus-producing cell assuming clinical research for genetic therapy

Since the retrovirus used in genetic therapy requires the P2 level dispersal prevention device, it is necessary to seal the device and to enclose the virus inside by maintaining negative pressure against the exterior of the device. However, in the evaluation stage, the investigation using the cell line that released secreted protein was sufficient because the operation procedures were the same as the recombinant retrovirus, and the evaluation was done for whether the virus supernatant could be actually recovered. The cell line used was NIH3T3/mIL2. This is a cell made to release mIL2 into the culture supernatant through genetic transfer. To evaluate the recovery performance of automatic culture, the culture supernatant was recovered at 34 h, 58 h, and 82 h after cell seeding, and the results were compared to the manual culture. The mIL2 concentration in the supernatant was quantified, and we were able to obtain the supernatants with the same concentration for automatic and manual cultures. From the results of the conducted evaluation tests, it was found that the automatic culture device could perform stable cell culture almost at the same level as manual culture, and the cells that required specific conditions could be cultured by setting fine-tuned culture parameters.

5 From manual culture to automatic culture

This system was developed on the concept that the operation conducted smoothly by manual operation of a skilled technician could be replaced by the movements of a robot arm. A skilled technician conducts each maneuver based on experience, under optimal condition for the cell while observing through the culture microscope. There is a SOP and the work of the machine is programmed accordingly. However, it is difficult to incorporate the unconscious operation nurtured through experience to the machine unconditionally. The cells that readily peal are injected from the pipette to the culture medium softly. The cells that do not peel readily are injected vigorously onto the medium, and sometimes tapping is done. Even for the same cell, the adhesiveness and reproducibility differ slightly according to slight conditional differences. To conduct one operation completely (peeling the cell or changing the medium without cells peeling off) regardless of the differences, it is necessary to employ conditions that do not cause problems, yet be stricter than the optimal conditions of the SOP. This is the difficulty of determining the SOP. A novice is instructed to not leave the door of the CO_2 incubator open for a long time. A skilled technician does that unconsciously. If the SOP is made disregarding the unconscious, the door may be left open too long, the CO_2 concentration inside the incubator changes and this affects the culture. First, we were unaware of this, and got worse results than manual culture, but this was improved by adjusting the timing of open/close of the door. How to reflect the unconscious operation that is not written in the operation protocols done by humans in the SOP was one of the challenges of automation.

6 Summary

We developed a practical culture system R-CPX (robotized cell processing expert system) where high quality cell reagents could be prepared without a CPC. The characteristic of the R-CPX is the flexible structure that can handle various usages, including the GMP-standard contamination prevention mechanism and operation by two clean robots.

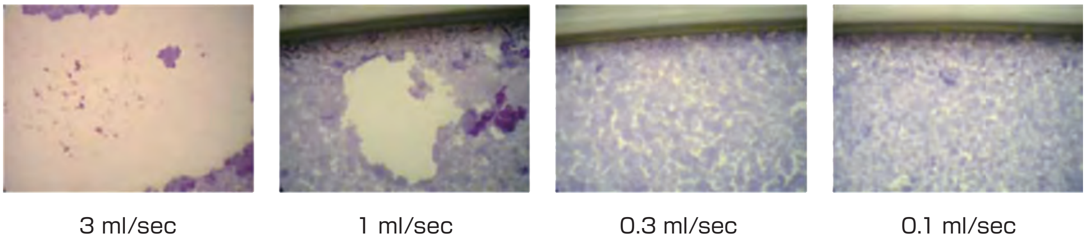


Fig. 10 Relationship between the discharge speed and cell peeling (293 gp/mIL2 cell)

7 Desired research stance and issues for the future

Through this research, we aimed for the swift achievement of diverse regenerative medicine and cell therapy, as well as the development of a device. The diseases that were the subjects of the study were the regenerative medicine of joint cartilages, for which one of the authors has abundant research experience and over 50 cases of clinical research, and the regenerative medicine of periodontal tissues including jaw bone regeneration using the MSCs, for which there are about 40 cases in Japan. If the R-CPX system can be applied to such diseases, the exploratory clinical tests for regenerative medicine and cell therapy for "refractory diseases derived from adult-onset diseases" involving cranial nerves, heart muscles, or marrow that use the same cell source, and the execution of clinical trials for the following commercialization can be facilitated dramatically.

This R&D was conducted to realize the vision of "R-CPX System Development Center" as shown in Fig. 11, to break through the adverse effect of individual research institutions conducting research separately for individual diseases.

Through the advancement of this R&D, the network with leading researchers of Japan was built. Also, collaboration with industry is essential for commercialization and practical use. In realizing regenerative medicine and cell therapy, the role of the cell preparation companies is large, and the participation of the major companies with ample resource of specialists in various fields and abundant financing is necessary. On this point, collaborations are being built along with the advancement of this R&D.

Also, it is clear that commercialization cannot be done if the cell preparation companies depended on manual culture for preparing the cells, and many companies are awaiting the development of the automatic culture device. Therefore, it is necessary to form a consortium of companies that possess various technologies that comprise the device.

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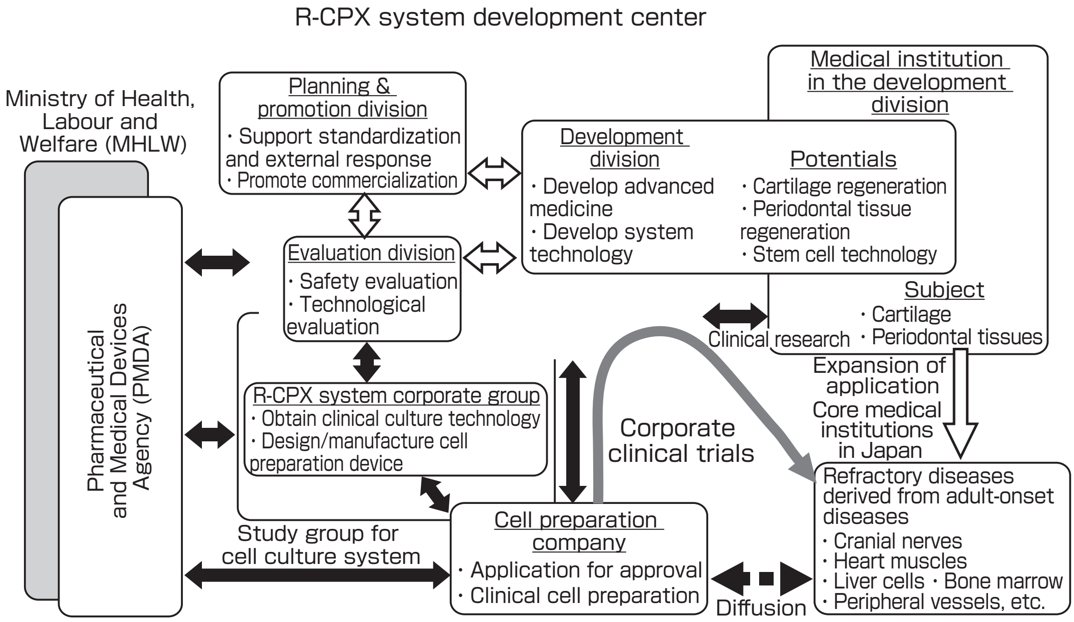

Fig. 11 Scheme for achieving regenerative medicine and tissue engineering by innovative cell preparation system

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Discussions with Reviewers

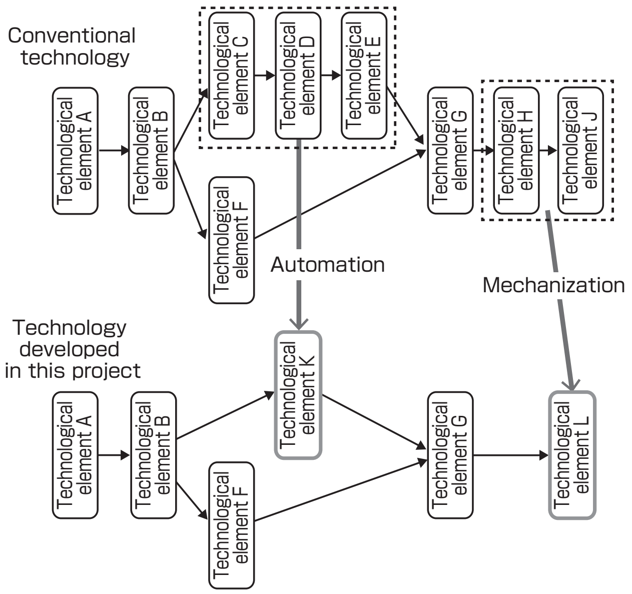
1 Motivation for development, research objective, technical elements, etc.

Question and comment (Tai Kubo, Molecular Profiling Research Center for Drug Discovery, AIST)

Please rewrite to emphasize the necessity of the automatic culture device and your motivation for its development, such as how CPC requires high level of safety, hygiene, and quality control, how expensive it is to build and maintain such a facility, as well as the requirement for solid skills and the need to satisfy the demand for "quantity" that will be necessary for the clinical application in the future. Also, as the descriptions of the experiment and results for Evaluation Unit 2 are too detailed, please narrow down the content appropriately.

Question and comment (Toshimi Shimizu, AIST)

The research objective of this project is to develop the R-CPX culture system that allows the preparation of high quality cell reagents without setting up a specialized CPC. To gain understanding of the readers who are not experts in the field, I recommend you draw a configuration diagram that allows immediate grasp of what technical items and components (procedures) there are, to what extent they are completed, how technological elements were modified to enable the automation, mechanization, and human intervention. Moreover, the large framework and detailed technologies are mixed throughout the paper, and this makes it difficult reading. Particularly, I recommend you keep to a minimum the descriptions of cell culture and evaluation methods by Unit 1, and the evaluation of adherent cell culture by Unit 2.



Answer (Toshimasa Uemura)

Since this project was an integration of the technological developments from many fields, it was difficult to maintain uniformity of the description, and perhaps it had become rather difficult for the readers to understand. First, I greatly revised "1 Introduction," "1.1 Why is it necessary to develop an automatic cell culture device now?" and "1.2 Objective, execution, and outline of the R&D." Also, based on the development roadmap for the cell preparation system, the configuration diagram of the technological items that show the correlation of the conventional and new technologies was added as Fig. 1B.

2 GMP, the rules for facility, procedure control, and quality control for drug manufacture

Question and comment (Tai Kubo)

For GMP, you need an explanation to enable the readers to understand the incredibly high hygiene and quality levels required for the approval of this machine.

Answer (Toshimasa Uemura)

I added the explanation of the GMP required particularly for CPC in chapter 1.

3 Examples of failure and trial-and-error in the development process

Question and comment (Tai Kubo)

It is in the scope of the *Synthesiology* paper for you to describe the failures, trial-and-errors, and requests for improvement you heard from the companies and clinical practices, in the process of the device development. Please include them in the paper, if any.

Answer (Toshimasa Uemura)

I added a story of hardship as chapter 5 "From manual culture to automatic culture."

4 Contribution of the multiple authors and various research institutions

Question and comment (Toshimi Shimizu)

Please introduce briefly in the paper the roles and contributions to the individual technology elements by the listed multiple authors.

Answer (Toshimasa Uemura)

There seems to be quite many authors, but there are five times more people who contributed to this project, and the authors are the central figures amongst them. In this project, Kawasaki Heavy Industries, Ltd. participated in creating the device as part of their corporate mission. For other institutions, the individuals rather than the organizations were important. The roles and missions of the organizations were not so important, but the roles and missions of the people with experiences or technologies that no one else possessed were important. I explained the chapters penned by the authors in their profiles, and I think that will help in understanding which part of the project the authors contributed.

5 Technological contribution by AIST; its role, characteristic, and superiority

Question and comment (Toshimi Shimizu)

Please explain clearly the content and characteristic of the core technology of AIST in this project. Particularly, the Evaluation Units 1 and 2 were installed at Shinshu University and AIST, respectively. Please explain the technological contribution, role, characteristic, and superiority of AIST pertaining to these units.

Answer (Toshimasa Uemura)

I think the technological contribution by AIST can be summed up by its experience in cell culture. The automatic culture system was designed with the concept of a robot, namely a robot arm, conducting the same movements carried out by a skilled technician engaging in manual operation. The necessary human movements were programmed into the Evaluation Unit 2 installed at AIST. The movements could be checked progressively, and I think this led to perfection. Although this did not involve intellectual property, this was an extremely important contribution.

Selection of next-generation low global-warming-potential refrigerants by using a risk trade-off framework

— Risk trade-off assessment for R-1234yf —

Hideo KAJIHARA

[Translation from *Synthesiology*, Vol.6, No.4, p.209-218 (2013)]

Because the refrigerants currently used in air-conditioners have high global-warming-potential (GWP), substances with lower GWP, such as R-1234yf, are being sought as candidate next-generation refrigerants. However, low-GWP substances often have comparatively high chemical reactivity and may carry increased risks of combustibility, toxicity, generation of degraded products, and CO_2 emission increase caused by poor energy-saving performance. It is therefore possible that there is a risk trade-off between currently used refrigerants and low-GWP ones. In this research, I proposed a framework for evaluating this risk trade-off in the following five categories: (1) environmental characteristics; (2) combustion characteristics; (3) toxicity; (4) volume of greenhouse gas emissions; and (5) applicability to air-conditioning equipment. I then selected substances well suited as next-generation refrigerants in accordance with a specific screening process. I showed the importance of clearly specifying the combination of a number of end points and assessment criteria in the process of decision-making based on risk trade-off. This yields a rapid understanding of the necessary data, as well as flexible decision-making that is relevant to the social conditions.

Keywords **:** Refrigerant, global warming, energy saving, flammability, toxicity

1 Development of refrigerant materials and next-generation refrigerants

The materials used to date as refrigerants for air-conditioners can be roughly categorized into four generations.[1]

In the first generation (from 1830 to the 1930s), the most important consideration was the development of functioning refrigeration systems. For this reason, even materials with toxicity, flammability, and corrosive properties were used as refrigerants owing to their superior properties as refrigerants. In the second generation (from 1931 to the 1990s), safety and chemical stability were pursued and materials such as chlorofluorocarbons (CFCs) and hydrochlorofluorocarbons (HCFCs) were introduced. In the third generation (from the 1990s to the 2010s), hydrofluorocarbons (HFCs), which do not contain chlorine, were introduced to prevent depletion of the ozone layer. In the fourth generation (from 2010 onwards), a search for refrigerants that have lower global-warming-potential (GWP)[Term 1] than materials such as HFCs and unlike CFCs do not contribute to depletion of the ozone layer has begun. We are currently in a period of transition from the third to the fourth generation of refrigerants. For the purpose of this paper, refrigerants that belong to the fourth generation will be called “next-generation refrigerants.”

2 Risk trade-off relationship among requirements for the next-generation refrigerants

A risk trade-off occurs when a reduction in a certain type of risk leads to an increase in a different type of risk. Next-generation refrigerants are required to have lower GWPs than today’s refrigerants, but in most cases such refrigerant materials have comparatively high chemical reactivity. In other words, to reduce GWP either a low infrared absorption coefficient or a short atmospheric lifetime is needed, but the latter implies high atmospheric reactivity. It is therefore possible that there is a risk trade-off between materials that have low GWPs and those that do not, because the former choice may lead to higher risks in terms of flammability, toxicity, generation of degradation products, and energy-saving performance (i.e. more energy may be needed to operate the air-conditioning equipment).

Presently, the requirements for next-generation refrigerants can be summarized into the following five categories:

1. Do not contribute to ozone layer depletion (ozone depletion potential = 0) and have sufficiently low GWPs. [Environmental characteristics]
2. Have low flammability that falls within the range of risk management, or are nonflammable. [Combustion characteristics]
3. Are intrinsically of low toxicity. [Toxicity]
4. Have good heat-cycle performance (energy-saving performance) as refrigerants. [Energy-saving performance]
5. Cause no problems when they are being charged into, and used in, air-conditioning equipment. [Applicability to air

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conditioning equipment]

In light of all of these requirements, my aim here was to use a risk-trade-off framework to assess refrigerant materials in the above five categories, which are highly important to the introduction of low-GWP next-generation refrigerants that can replace HFCs.

3 Status of development of next-generation refrigerants

Examination of the impacts of refrigeration and air-conditioning equipment on global warming has given a total estimated refrigerant emission (values for FY 2010, carbon dioxide (CO_2) converted volume) of 17.1 million t CO_2. The breakdown was 11.3 million t CO_2 from business-use refrigerators and air-conditioning equipment (66 %), 2.9 million t CO_2 from home-use air-conditioning equipment (17 %), 2.5 million t CO_2 from automotive air-conditioning equipment (15 %), and 400,000 t CO_2 from home-use refrigerators (2 %).[2]

The analysis of low-GWP refrigerants is more advanced in the case of automotive air-conditioning than for other types of air-conditioning. 2,3,3,3-Tetrafluoropropene ($CH_2=CFCF_3$), an olefin compound with the number R-1234yf, has a GWP of 4 and is one of the most promising next-generation refrigerant candidates.[3] (For more on refrigerant numbers see Note 2 at the end of this paper.)

Although R-1234yf is likely a highly viable replacement candidate for R-134a (the current refrigerant used for automotive air-conditioning), particularly high refrigerant performance is expected of the next-generation refrigerants used in stationary air-conditioning. This is because refrigerants such as R-410A used in stationary equipment have greater refrigerant performance than R-134a (i.e. their energy consumption rates while the air-conditioning equipment is in use are low). What this means is that an increase in energy consumption during the operation of air-conditioning equipment can become a greater problem in the replacement of refrigerants for stationary air-conditioners than for automobile air-conditioners.

In addition, because home-use stationary equipment has a shorter life than its business-use counterpart, greenhouse gas (GHG) emission reductions due to replacement with low-GWP refrigerants are expected to appear fairly quickly. Therefore, the results achieved by studying home-use equipment should benefit changes in business-use equipment. From this perspective, I chose to use a risk trade-off framework in my evaluation and selection of next-generation refrigerants for home-use air-conditioning, and I paid particular attention to changes in energy consumption during equipment operation.

4 Selection of next-generation refrigerants by using a risk trade-off framework

In choosing an ideal refrigerant material when there are multiple risk assessment categories, such as combustibility, toxicity, and global warming potential, the risks in each category should first be quantified by using a uniform risk measure. The material with the smallest total risk should then be selected. However, a uniform quantification technique applicable to different types of risks is not yet available for practical use.

For this reason, I aligned all risk categories sequentially and chose candidate materials by following a step-by-step screening method. The order of the categories began from the category connected to the property of the candidate material itself and progressed through to the category connected to the property of the candidate material when it was used as a refrigerant.

The assessment framework used in this study and the results of the assessment are shown in Table 1. Appropriate environmental characteristics (does not deplete the ozone layer and has low GWP) were placed at Stage 1 of the assessment. These environmental characteristics have only recently (i.e. since the advent of the third-generation refrigerants) started to be seen as important. Combustibility was placed at Stage 2. This was because choosing materials with high atmospheric chemical reactivity as a way of reducing GWP will directly result in increased combustibility. Toxicity was placed at Stage 3. Although it is possible that toxicity can also increase because of increased chemical reactivity in the atmosphere, it was placed at the third stage of the assessment on the assumption that its change was likely to be smaller than the change in combustibility. Thus assessment categories related to the properties of the candidate material itself were placed at Stages 1 to 3. Placed at Stage 4 was life cycle assessment (LCA), which requires the incorporation of information regarding the use of equipment. At Stage 5 was the assessment of applicability to air-conditioning equipment, which requires the incorporation of information on equipment design. The assessment categories from Stage 4 onward were deeply dependent on the environment in which the refrigerants were to be used. The stages were thus ordered so that increasingly more detailed information was required with each stage.

Tests on burning velocity and flammability limit were especially important in the combustion characteristics assessment, as was toxicity testing in the toxicity assessment.

In Stage 1 of the assessment, likely candidates for next-generation refrigerants were screened against the GWP value of the current refrigerant R-410A. A number of materials,

Table 1. Framework of the risk trade-off assessment and the results of screening of candidate materials for next-generation low-GWP refrigerants

Assessment stage	Description of assessment category	Step-by-step selection of candidate materials
Stage 1	Assessment of environmental characteristics (selection of materials that do not deplete the ozone layer and have low GWP)	R-1234yf, R-32, R-152a, R-290, R-600a, R-717, R-744
	In assessing GWP, the GWP value of 1730 for R-410A, the refrigerant currently used for home-use stationary air-conditioning equipment, was used as a reference value.	
Stage 2	Assessment of combustion characteristics	R-1234yf, R-32, R-717, R-744
	Materials classified by ISO 817 or ASHRAE 34 as Class 3 (higher flammability) or Class 2 (lower flammability) were excluded; only those classified as Class 2L (lower flammability with a maximum burning velocity of ≤ 10 cm/s) or Class 1 (no flame propagation) were left.	
Stage 3	Assessment of toxicity	R-1234yf, R-32, R-744
	An atmospheric exposure assessment was performed on the decomposition products of those refrigerants with short atmospheric lifetimes.	
Stage 4	LCA	See subchapter 5.4.
	The sum of direct (air emissions from refrigerants) and indirect (GHG emissions due to energy use) GHG emissions from air-conditioning equipment using each candidate refrigerant was quantified.	
Stage 5	Assessment of applicability to air-conditioning equipment	See in chapter 6.
	Assessment of the applicability of refrigerants to actual refrigeration and air-conditioning equipment. This included assessment of safety measures for leakage from equipment.	

including R-1234yf, R-32, R-152a, R-290, R-600a, R-717, and R-744, were considered to be candidates. During this process, R-1234ze(E), an isomer of R-1234yf, was not included in the list of materials to be assessed because of its poor data availability. Nevertheless, because R-1234ze(E) is similar to R-1234yf in terms of chemical structure and physical properties (combustion characteristics and GWP), its assessment result would likely be comparable to that of R-1234yf.

In Stage 2 (combustion characteristics), to exclude materials that were clearly flammable, materials classified by ISO 817 and ASHRAE 34 as Class 3 (higher flammability) and Class 2 (lower flammability) were excluded and only those classified as Class 2L (lower flammability with a maximum burning velocity of ≤ 10 cm/s) or Class 1 (no flame propagation) were left. Hydrocarbon refrigerants R-290, R-600a, and R-152a were thus excluded from the list of candidates. R-1234yf and R-32 are classified as Class 2L. The combustion characteristics of these two types of refrigerants will be described in detail in subchapter 5.1.

In Stage 3 (toxicity), R-717 was excluded because of its strong toxicity. Details of the toxicity assessment and the decomposition products of R-1234yf will be given in subchapters 5.3 and 5.4, respectively; in brief, this compound was considered to carry no notable risk in terms of toxicity and decomposition products.

Besides R-1234yf, this leaves R-32 (a conventional refrigerant with slightly increased GWP) and the natural refrigerant R-744 as candidate refrigerants.

In Stage 4 (LCA), reduction of GHG emissions by the candidate materials remaining after the above-described screening had been performed was quantified. Further details on this point are given in subchapter 5.4.

Although evaluation of the applicability to air-conditioning equipment (Stage 5 of the assessment) could not be performed in this study because of a lack of data, it will be considered qualitatively in chapter 6.

5 Detailed assessment of viable candidate materials in each risk category

5.1 Assessment of combustion characteristics

After the screening for environmental characteristics, combustion characteristics, and toxicity, R-1234yf, R-32, and R-744 remained as candidate materials (see Table 1). Because R-744 is nonflammable, it does not require an assessment of combustion characteristics. Both R-1234yf and R-32 are classified as Class 2L by ISO 817 and ASHRAE 34, the international standards for the combustion characteristics of refrigerants. However, according to the relevant Japanese laws and regulations (the High Pressure Gas Safety Act and Refrigeration Safety Regulations), R-1234yf is classified as a combustible gas, whereas R-32 is not. Therefore, whether or not mixed refrigerants comprising these two refrigerants are deemed flammable or nonflammable depends on their mixing ratio.

Therefore, a combustion experiment was performed to see whether or not the measured flammability limits for the mixed refrigerant R-1234yf – R-32 coincided with the values predicted by Le Chatelier’s Principle on the basis of their

Table 2. Flammability limits of mixed refrigerants comprising R-1234yf and R-32

R-1234yf : R-32 (volume ratio)	Lower flammability limit (vol%)		Upper flammability limit (vol%)	
	Measured value	Predicted value	Measured value	Predicted value
100 : 0	5.53 (0.10)	5.53	13.3 (0.5)	13.30
80 : 20	6.22 (0.05)	6.27	14.5 (0.5)	14.80
60 : 40	7.2 (0.1)	7.24	17.0 (0.6)	16.69
50 : 50	7.78 (0.05)	7.85	18.5 (0.5)	17.82
40 : 60	8.53 (0.08)	8.56	19.9 (0.7)	19.12
20 : 80	10.45 (0.05)	10.48	23.6 (0.7)	22.39
0 : 100	13.5 (0.1)	13.50	27.0 (0.5)	27.00

mixing ratios. Measurements were conducted in air at a humidity of 50 % and a temperature of 296.15 K. The results are shown in Table 2. For example, Table 2 shows that a mixed gas with a volume ratio of 50:50 burns when it exists in air at a range of 7.78 % to 18.5 %. The value of the lower flammability limit (LFL) coincided well with the predicted value, and the value of the upper flammability limit (UFL) coincided fairly well with the predicted value.

Next, the dependence of maximum burning velocity ($S_{u0, max}$) on mixture ratio for the mixed refrigerant R-1234yf – R-32 was measured (Fig. 1). The results of measurement of the LFL and GWP values for the mixed refrigerant are also shown for reference. On the one hand, an increase in the ratio of R-32

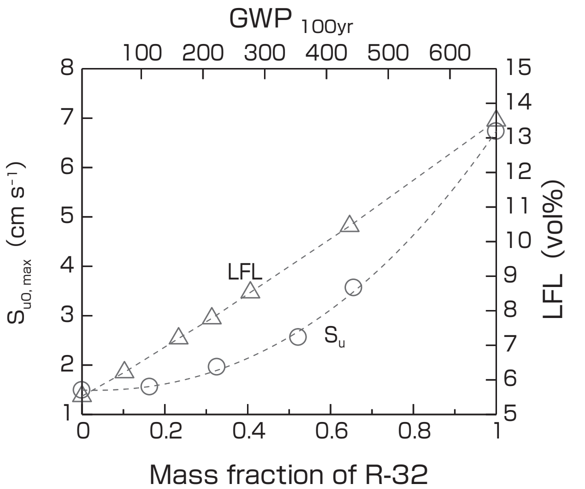

Fig. 1 Dependence of maximum burning velocity on mass fraction of R-32 in the mixed refrigerant R-1234yf – R-32

$S_{u0, max}$: maximum burning velocity; LFL: lower flammability limit

increased the LFL value and made the mixture nonflammable, but on the other hand it also increased the maximum burning velocity and the burning velocity once it started to burn. In addition, the increase in burning velocity increased with the increase in the ratio of R-32.

The related laws and regulations in Japan define a flammable refrigerant gas as follows: either the LFL value is 10 % or less, or the difference between the UFL value and the LFL value is 20 % or more. What this means is that to realize non-flammability in compliance with this definition, the percentage of R-1234yf by volume in the mixture needs to be 36.2 % or less, or 55.4 % or less in terms of weight ratio.[Note] The GWP of the mixed refrigerant based on this mixing ratio (44.6 % R-32 by weight) was estimated to be about 300. In addition (see Figure 1), the burning velocity at this mixing ratio was not dramatically greater than that of pure R-1234yf. Therefore, this mixing ratio was used as one of the many conditions for the LCA (see subchapter 5.4).

5.2 Toxicity assessment

Because R-32 and R-744, but not R-1234yf, are presently used as refrigerants and can be considered to have low toxicity, only R-1234yf was assessed for toxicity. R-32 is a component of R-410A, and R-744 is used as a refrigerant in heat-pump-type water heaters.[Term 2] The results of toxicity testing of R-1234yf are shown in Table 3. An acute toxicity test, repeated exposure test, cardiac sensitization test, and two-generation reproduction study conducted with extremely high concentrations (tens of thousands of ppm) did not result in any particular toxicity. In addition, from the results of the genotoxicity test it was inferred that R-1234yf was not genotoxic in vivo. Among those tests that did reveal adverse effects, the one in which R-1234yf had adverse effects at the lowest concentration was the developmental toxicity test in rabbits. However, the concentration at which death of a pregnant rabbit was observed was high (at 5500 ppm or more). In contrast, in rats, not only were there no recorded deaths of mother rats in the developmental toxicity test and the two-generation reproduction study, but also there were no adverse effects even in repeated exposure testing at a high concentration (50,000 ppm). These findings suggest that rabbits have greater sensitivity than rats to R-1234yf. After a comprehensive examination of the results shown in Table 3, it was judged that R-1234yf was of low toxicity.

Minor[5] states that the toxicity level of R-1234yf is similar to that of the present-day refrigerant R-134a. Rinne,[6] Schuster *et al.*[7] and the Japan Society of Refrigerating and Air Conditioning Engineers[8] also state that the toxicity of R-1234yf is low. However, because there are currently no publicly available data on the details of toxicity testing, published toxicity test reports are awaited in future so that we can ensure objective and transparent toxicity assessment.

Table 3. Summary of toxicity information on R-1234yf

Endpoint	Test content	Test results	References
Acute toxicity	Rats, inhalation, 4 h	No deaths observed until 400,000 ppm	[5],[6],[9]
Repeated inhalation toxicity	Rats, inhalation, 2 weeks	NOEL=50,000 ppm	[9]
	Same as above, 4 weeks	NOAEL=50,000 ppm	[9]
	Same as above, 13 weeks	NOAEL=50,000 ppm	[5],[6],[9]
Cardiac sensitization potential	Dogs, inhalation	No adverse effect until 12 % (120,189 ppm)	[5],[6],[9]
Genomics	13 weeks	No activation until 50,000 ppm	[5],[6]
Developmental toxicity	Rats, inhalation (nasal cavity)	NOAEL=50,000 ppm	[5],[6]
	Rabbits, inhalation (whole body)	NOAEL/LOAEL=4,000/5,500 ppm	[5],[6],[9],[10]
Two-generation toxicity	Rats, inhalation, 6 h/day	NOAEL=5,000 ppm	[5],[6]
Genotoxicity (Ames test)	*S.typhimurium* (TA1535, TA98, TA100)and *E.coli* (WP2uvrA)	Positive at 20 % or more for both TA 100 and WP2uvrA; the remaining results were negative	[9]
Genotoxicity (human cells)	Human lymphocytes, 4 h	Negative at 760,000 ppm	[9]
Genotoxicity (in vivo micronucleus test)	Mice, inhalation, 4 h	Negative (maximum 200,000 ppm)	[9]
	Rats, inhalation, 4 h	Negative (maximum 50,000 ppm)	[9]
Unscheduled DNA synthesis inhibition test	Rats, inhalation, 4 weeks	Negative (maximum 50,000 ppm)	[9]

NOEL: No observed effect level,
NOAEL: No observed adverse effect level,
LOAEL: Lowest observed adverse effect level

5.3 Atmospheric exposure assessment

Because R-1234yf has higher atmospheric reactivity than conventional refrigerants, relatively high concentrations of decomposition products could be generated. For this reason, the volume of R-1234yf emitted into the atmosphere was estimated for the case in which the refrigerants used in all types of air-conditioning equipment (home use, business use, and automotive use) were replaced by pure R-1234yf refrigerant. Studies of the use of R-1234yf as a refrigerant for automotive use are far more advanced than those of its use for home or business use; nevertheless, to calculate maximum rates of emission it was assumed that the use of R-1234yf in all types of air-conditioning equipment. Additionally, although there is a strong possibility that R-1234yf will be used in mixtures because it can be mixed in different ratios, it is assumed that R-1234yf was used as a pure refrigerant so as to determine the maximum emission rates. The atmospheric concentration of R-1234yf after its atmospheric emission and the atmospheric concentrations of the atmospheric decomposition products of ozone, formaldehyde, and trifluoroacetic acid (TFA) were also estimated to study their impact on human health and ecology (aquatic organisms).

Table 4. Atmospheric concentrations of R-1234yf and its decomposition products with the use of R-1234yf as a refrigerant (annual average, Kanto region)

	R-1234yf [ppb]	Ozone [ppb]		Formaldehyde [ppb]	
		–	Increase*1	–	Increase*1
Max. value	0.28	44	+0.13	2.9	+0.012
Min. value	0.0068	11	−0.03	1.1	−0.005
Average	0.050	34	+0.03	2.0	+0.002

*1 : Increase compared with the control case (no replacement of refrigerants)

To estimate emissions from the refrigerants, the refrigerants used in all newly produced air-conditioning equipment, beginning in 2011, were assumed to be switched to R-1234yf, and emissions from the refrigerants after 40 years of use were estimated for each type of equipment and for each stage of its lifecycle. The estimated parameters, including the number of items of equipment manufactured, the emission factors, and the recycling rates at the time of disposal, were assumed to be the same as those for current-day equipment. The purpose of this assumption was not to forecast the future, but to estimate emissions under the hypothetical scenario in which all refrigerants used in today's air-conditioning equipment were completely replaced by R-1234yf. The estimated total annual emission rate was 15,172 t. Breakdown of the emissions by type of equipment revealed that the majority was from home use (6,366 t/year) and business use (6,734 t/year); in terms of equipment lifecycle stage, the largest source of emissions was the disposal stage (8,744 t/year).

The atmospheric model used for this purpose was ADMER-PRO,[11]-[13] in which are embedded the reaction processes of nitrogen oxides (NOx), volatile organic compounds (VOCs), and ozone and the dry deposition process. The reaction process beginning with the reaction of R-1234yf and OH radicals and proceeding to the generation of the intermediate product trifluoroacetyl fluoride [$CF_3C(O)F$] and of the final product, TFA, as well as the process of wet deposition of TFA, was added to ADMER-PRO for the purpose of computation. The overall reaction rate constant for the process, in which TFA was generated as a result of hydrolysis of the intermediate product $CF_3C(O)F$ in cloud water, was measured by using an experimental method (two-phase flow method).

The concentrations of R-1234yf, ozone, and formaldehyde computed by the atmospheric model are shown in Table 4.

The maximum concentration of R-1234yf was estimated to be 0.28 ppb; because this was 10 million times lower than the lowest NOAEL (4,000 ppm in rabbit developmental toxicity testing; see Table 3) in the toxicity assessment, the chronic impact on humans of inhalation exposure to R-1234yf in the ambient air is likely to be negligible. Moreover, the increase in the average concentration of ozone or formaldehyde compared with the control cases (i.e. no replacement of refrigerants) was only about 0.1 %. Because these values are sufficiently small, the impact of R-1234yf on the generation of oxidants can be presumed to be extremely small.

In addition, the annual maximum average concentration of TFA in rainwater was estimated at 3.4 μg/L. The NOEC (no observed effect concentration) of TFA in aquatic organisms was 100 μg/L[14] for *Selenastrum capricornutum*, which was the most sensitive alga among various aquatic organisms (fish, crustaceans, and algae). Because the estimated maximum concentration was well below this NOEC, the possibility of TFA in rainwater having any impact on aquatic organisms is extremely small.

5.4 LCA

5.4.1 Scope of the assessment

GHG emissions throughout product life cycles were estimated by using the LCA method on the basis of the assumption that each candidate material was used as a refrigerant for home-use air-conditioning. GHG emissions were roughly divided into two categories: emissions from energy and emissions from refrigerants. Emissions from energy are estimates of the CO_2 generated from electricity consumption while air-conditioning equipment was in use, as well as from the energy consumed to manufacture air-conditioning equipment. Emissions from refrigerants are estimates of the greenhouse effect of leakage of refrigerant. If refrigerants were replaced by low-GWP materials, refrigerant-related GHG emissions would be reduced because of the reduction in GWP, but GHG emissions from energy would be increased if the performance of the refrigerant were to be lower. To verify whether or not the net GHG emissions were reduced, it is needed to check the reduction in total GHG emissions from energy and refrigerants.

After the screening described in chapter 4, three materials—R-1234yf, R-32, and R-744—remained as candidates. However, because the data required to conduct an LCA on R-744 as a refrigerant for home-use stationary air-conditioning equipment could not be found, it is deemed impossible to sufficiently examine the possibility of using R-744 as a next-generation refrigerant. Therefore R-744 is excluded from the assessment. However, if data showing an increase in CO_2 emissions due to poorer energy-saving performance when R-744 is used as a refrigerant in home-use stationary air-conditioning equipment become available in future, it is likely that R-744 will achieve an LCA result similar to that for R-1234yf; moreover, its suitability as a refrigerant is likely to be judged similar to those of others described later in this section.

In addition to the two pure refrigerants R-1234yf and R-32, a mixture of the two is assessed. The mixing ratio was R-1234yf : R-32 = 55.4 : 44.6 (by weight); this mixture would be deemed a nonflammable gas according to the relevant Japanese laws and regulations in Japan. (See subchapter 5.1 on the assessment of combustion characteristics.)

The scope of the assessment covered the entire product life cycle, and GHG emissions due to energy and refrigerants were estimated separately for each stage of manufacture of a refrigerant, manufacture of equipment, use of equipment, and disposal of equipment. The place of manufacture, use, and disposal of air-conditioning equipment was assumed to be Japan. CO_2, nitrous oxide (N_2O), and methane (CH_4) were included as GHGs in the estimate in addition to the refrigerant materials and were converted to CO_2 equivalents on the basis of GWP.

5.4.2 Questionnaire survey on status of use of air-conditioning equipment

The amount of GHGs generated in the use stage of air-conditioning equipment is equivalent to the consumption of electrical power, but power consumption depends greatly on the actual status of use of the air-conditioning equipment. To compute a power consumption rate that closely reflects the actual status of use of the air-conditioning equipment, a nationwide survey consisting of detailed items (household attributes, housing attributes, specifications of air-conditioning equipment, use of the equipment, hours of equipment use, etc.) was conducted. The questionnaire survey was conducted on the internet twice—the first time in February 2010 and the second in December 2010. In the first survey, 4,000 households nationwide (10 regions with 400 households in each region) were surveyed. In the second survey, in addition to the follow-up survey of the households subjected to the first survey, another 4,000 households nationwide (10 regions with 400 households in each region) were included. Valid responses were collected from 7,090 households. On the basis of the data collected in the survey, the average annual hours of use of each air-conditioner are calculated. The average annual hours of use for each region are shown in Fig. 2. According to the survey results, the reason why regions with low outdoor temperatures, such as Hokkaido and northern Tohoku, had comparatively fewer hours of use of heating was because more than half of the households in these regions mainly used equipment other than air-conditioners for heating.

In addition, on the basis of the survey results, the schedule of use of air-conditioning equipment was computed over each 24 h for 365 days; by taking the outdoor temperature and the hours of continuous operation into consideration, the average annual power consumption was calculated per item of equipment for each region.

5.4.3 Results of assessment of candidate refrigerant materials

An LCA was performed on a total of four types of refrigerant: the present-day refrigerant R-410A, the pure refrigerants R-1234yf and R-32, and the mixed refrigerant R-1234yf – R-32. The characteristics of the refrigerants subjected to the LCA are shown in Table 5. The numbers ①, ②, and ③ below the columns indicate different types of power consumption assumptions made to estimate GHG emissions from energy. Because the performance of the refrigerant R-1234yf is poorer than that of R-410A,[15] a positive value was assumed for increases in power consumption with pure R-1234yf and its mixed refrigerant; a zero or a negative value was assumed in the case of R-32, because its performance as a refrigerant is superior to that of R-410A.

The GHG emissions from each next-generation refrigerant per home-use air-conditioner are shown in Fig. 3. When viewed in terms of their contributions to GHG emissions in each life cycle stage, for every refrigerant the contributions from the refrigerant in the manufacture stage (manufacture and equipment) and from energy in the disposal stage were very small. For refrigerants with large GWPs the contributions from refrigerant in the disposal stage were large, and for those with small GWPs the contributions from energy in the manufacture and use stages were large. As a general trend, it was evident that a decrease in GWP of a refrigerant correspondingly reduced GHG emissions. However, when R-32 was used, the GHG emission was approximately 1,100 kg CO_2 for all energy-saving performances; this is about 50 % of 2,300 kg CO_2, the estimated emission with R-410A. In comparison, the GHG emission with mixed refrigerant was approximately 920 kg CO_2—not much different from that with a pure R-32. For this reason, the advantage of using mixed refrigerant compared with R-32 in terms of reduction in GHG emission was not large. In contrast, with pure R-1234yf the emission came to between about 670 and 740 kg CO_2, thus reducing GHG emission to about 40 % of that with conventional refrigerant.

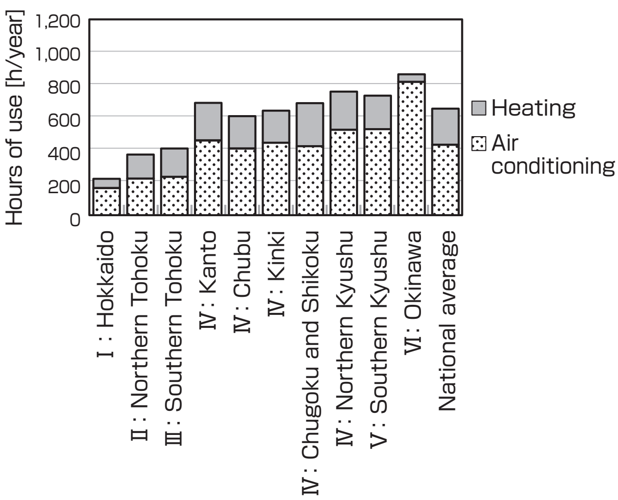

Fig. 2 Average annual hours of use per air-conditioner in each region (I through VI indicate the category of each region, in accordance with the Act on the Rational Use of Energy.)

Table 5. Characteristics of refrigerants subjected to LCA

Refrigerant	GWP	Refrigerant used per item of equipment [kg]	Increase in power consumption due to use of equipment [%]*2
R-410A	1730	1.2	
R-32	650	1.0	①-2.5 %, ②0 %
R-1234yf/ R-32*1	300	1.1	①+2.5 %, ②+5 %
R-1234yf	4	1.1	①+5 %, ②+10 %, ③+20 %

*1) R-1234yf : R-32=55.4 : 44.6 (weight ratio)
*2) R-410A values were used as a baseline.
The numbers ①, ②, and ③ indicate different types of assumption made regarding increases in power consumption. For R-1234yf and its mixed refrigerant, the data of Endo *et al.*[15] were used for the adjustment.

6 Discussion and conclusions: selection of next-generation refrigerants

In this chapter, I discuss the results of the assessment and

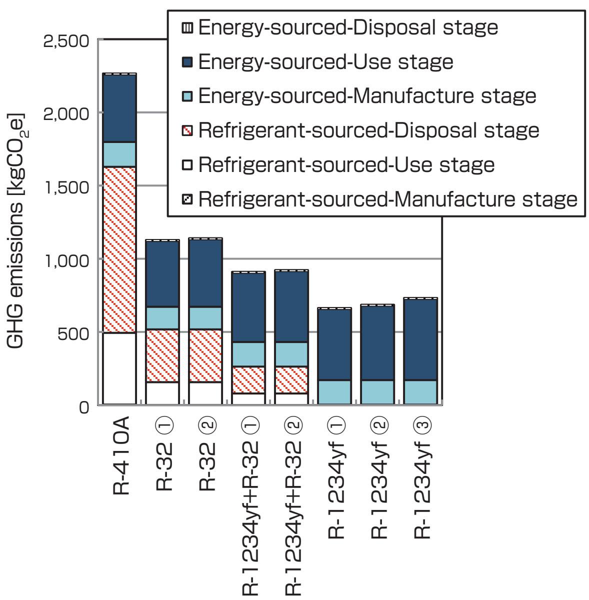

Fig. 3 Results of estimation of GHG emissions throughout the life cycles of home-use air-conditioning equipment when the refrigerants used were replaced (for information on each type of refrigerant on the horizontal axis, see Table 5)

the challenges faced by this study. Qualitative references to Stage 5 of the assessment, namely the applicability of refrigerants to air-conditioning equipment, are made.

The reduction in GHG emissions that could be achieved by introducing pure R-1234yf refrigerant was so huge that an even larger reduction can be expected in comparison with the emissions with the two other refrigerants (pure R-32 and mixed refrigerant) compared here. However, the price of R-1234yf is high, and the challenge for the future is to reduce this price. In addition, if R-1234yf is to be introduced, the technical problems regarding its use in stationary air-conditioning equipment must be solved: for example, the size of the compressor is likely to increase because of changes in the design of bent pipes.

If pure R-32 were to be introduced, although it would result in a smaller reduction in GHG emissions than that produced by using R-1234yf, the reduction would not be negligible. Because R-32 is a component of present-day refrigerants, there would be few problems in relation to its use in air-conditioning equipment. This refrigerant is also cheap and thus can be considered a candidate next-generation refrigerant. However, even though R-32 is classified as a Class 2L (lower flammability with a maximum burning velocity of ≤ 10 cm/s) refrigerant, it has a greater burning velocity than that of R-1234yf (in dry ambient air); therefore, measures to ensure its safe use are necessary.

The mixture of R-1234yf and R-32 can qualify as a candidate next-generation refrigerant, because its reduction of GHG emissions, its price, and its flammability all fall into a range mid-way between the values for the two pure refrigerants. Its only likely flaw is the difficulty in handling the refrigerant when charging it into the equipment; this is characteristic of non-azeotropic refrigerant mixtures.

For these reasons, it is important that Stage 5 of the assessment—applicability to air conditioning equipment—is conducted quantitatively on the three refrigerants examined here after measures are taken to correct the defects and problems described above. Also, because the results in Stage 5 depend strongly on the design of the equipment and are affected by the price of the refrigerant, the assessment needs to be conducted in close cooperation with equipment manufacturers, researchers, and government.

In addition, as was pointed out in the details on Stage 3 (toxicity assessment), the details of toxicity tests have not yet been made publicly available. Therefore, to ensure an objective and transparent assessment, we await the future publication of toxicity test reports by the manufacturers of refrigerants. In Stage 4 of the assessment, LCA could not be performed on R-744 because there were insufficient data. It is therefore clear that publication of data by the manufacturers of home-use air-conditioning equipment on CO_2 emission increases due to reduced energy-saving performance of equipment using R-744, as well as assessments based on such data, remain as problems for the future.

The results of my assessment must be viewed with caution, as in their current state they cannot necessarily be applied to air-conditioning equipment other than that used at home. This is because, among the five stages of assessment shown in Table 1, Stage 4 (LCA) and 5 (applicability assessment) are strongly affected by such factors as the form of equipment used and the relationship with present refrigerants.

Although here I used the risk trade-off framework to propose a decision-making method for choosing next-generation refrigerants, the method is likely applicable not only to the selection of next-generation refrigerants but also to decision-making processes in general that use risk trade-off frameworks, for the following reasons. The method clearly defines multiple assessment categories and indicates clear assessment standards. The method combines a step-by-step screening process and a detailed assessment, making it possible to point out the types of data that are required or are insufficient at each step. These characteristics of the method should enable easy reassessment that is reasonably consistent with previous assessments, even when new assessment categories are added or changes in assessment standards are required. Moreover, because the connection between the necessary data and decision-making can be easily grasped, use of the method should help to promote the establishment of cooperative relationships that encourage the exchange of data with other research organizations.

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Note) The flammability limit values[4] of the following pure substances, measured in accordance with the ASTM International’s Standard Test Method (ASTM E681-01), were used to calculate the flammability limit value of the mixed substance: R-1234yf, LFL = 6.2 and UFL = 12.3; R-32, LFL = 14.4 and UFL = 29.3 (all units are in vol%).

Terminologies

Term 1. Global-warming-potential (GWP). The GWP expresses the strength of the greenhouse effect of a particular gas in the atmosphere relative to the same concentration of CO_2. If not otherwise stated, all GWP values are taken from the *IPCC Second Assessment Report: Climate Change 1995.*

Term 2. Refrigerant numbers and chemical formulas

Refrigerant number	Chemical formula	GWP
R-1234yf	CH_2=$CFCF_3$	4
R-1234ze(E)	CHF=$CHCF_3$	6
R-134a	CH_2FCF_3	1300
R-410A	1:1 (weight ratio) mixture of CH_2F_2(R-32) and CHF_2CF_3(R-125)	1730
R-32	CH_2F_2	650
R-152a	CH_3CHF_2	140
R-290	$CH_3CH_2CH_3$	6[a)]
R-600a	$CH_3CH(CH_3)_2$	7[a)]
R-717	NH_3	1300
R-744	CO_2	1

a) Indirect GWP values are from IPCC/TEAP *Safeguarding the Ozone Layer and the Global Climate System: Issues Related to Hydrofluorocarbons and Perfluorocarbons* (2005). However, the value for R-600a (isobutane) is the value for an isomer of butane.

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Discussions with Reviewers

1 Selection of refrigerants for the assessment

Comment (Hiroshi Tateishi: AIST Tsukuba)

Though I am not sure since the terms used are inconsistent, judging from the content, the argument of this paper seems to be focused on refrigerants for home-use air-conditioning equipment. However, the world is no doubt filled with business-use air-conditioning equipment, mobile air-conditioning equipment for automobiles, etc., and with much other equipment such as home-use and business-use refrigerators, freezers, etc. that use similar refrigerants. Therefore, a comprehensive discussion that considers all these factors should be needed from the perspective of preventing global warming. Considering the purpose of this paper, a comprehensive survey is not necessary, but I think that at least some remarks should be made on the following points:

・The position of home-use air-conditioning equipment relative to other uses as seen from the amount of refrigerants used.

・Relationship between home-use and business-use air-conditioning equipment.

・Whether or not the limiting of the discussion to home-use air-conditioning equipment has an impact on the risk trade-off assessment framework.

Response (Hideo Kajihara)

From the perspective of preventing global warming, I think it is important to indicate the share of home-use air-conditioning equipment in the total refrigeration and air-conditioning equipment. In chapter 3, the amount of refrigerant emission was used to explain the ratio of refrigerants used in business-use, home-use, and automotive-use equipment in the total refrigeration and air-conditioning equipment. As for the relationship between home-use and business-use air-conditioning equipment, I stated that "because home-use stationary equipment has a shorter life than its business-use counterpart, greenhouse gas (GHG) emission reductions due to replacement with low-GWP refrigerants are expected to appear fairly quickly. Therefore, the results achieved by studying home-use equipment should benefit changes in business-use equipment."

As for the question on whether or not the limiting of use to home-use air-conditioning equipment has an impact on the risk trade-off assessment framework, I believe that limiting to home-use air-conditioning equipment should not have much impact on the assessment results of environmental characteristics (ozone layer depletion and the GWP values), combustion characteristics, toxicity, and generation of degraded products. However, the result of the LCA is thought to be greatly influenced by the energy-saving performance and the GWP of the present refrigerants, the length of time equipment is in use, operating conditions, etc. and this point was added to chapter 6.

2 Concept of the assessment scheme

Question (Hiroshi Tateishi)

The framework of the risk trade-off assessment as shown in Table 1 is at the very basis of the entire paper and it must be the reason why this paper deserves to be a paper for *Synthesiology*, but it is used a priori without any clear explanation on how this framework was formed and therefore gives a sense of incongruity. Only obvious assessment categories are listed here, so where is the ingenuity of the author and why was the content of each of these assessment categories defined as such and placed in this order? Moreover, explanations on the techniques needed to assess these categories were also missing here, though they were later given in a different place. For example, why were refrigerants with "lower flammability with a maximum burning velocity of ≤ 10 cm/s" not excluded in Stage 1 of the assessment?

Answer (Hideo Kajihara)

I added an explanation at the beginning of chapter 4 in response to the remark pointing out that the reasoning behind the framework of the risk trade-off assessment shown in Table 1 was missing. The gist of the added explanation is as follows: "ideally, a uniform indicator should be used for comparison purposes, but since such an assessment technique is yet to be established, I aligned all risk categories sequentially and chose candidate materials by following a step-by-step screening method." The explanations on the techniques needed to assess each category were also added.

As for the handling of refrigerants with "lower flammability with a maximum burning velocity of ≤ 10 cm/s" in the combustion characteristics, the explanation was revised to stress that materials classified into Classes 2 and 3 were excluded because the combustibility classification by ISO 817 and ASHRAE 34 goes as Class 1 (no flame propagation), Class 2L (lower flammability with a maximum burning velocity of ≤ 10 cm/s), Class 2 (lower flammability), and Class 3 (higher flammability) and the objective of the step-by-step screening method was to exclude materials with clear combustibility.

Question (Hiroaki Tao: Research Institute for Environmental Management Technology, AIST)

This paper proposes a method for selecting next-generation refrigerants by using a risk trade-off framework. However, I think it is highly important for the paper to include information on various assessment methods proposed to this day and the novelty and the ingenuity of this proposed assessment method in comparison to existing methods. To make this point clear, I think it necessary to include information on assessments done in the past, problems identified, and the ideas introduced into this method so as to overcome such problems. Since this paper states that "R-1234yf is likely a highly viable replacement candidate for … the current refrigerant used for automotive air-conditioning," and thus can be assumed that some assessments have already been done until now, could you not include information on the things that have been improved compared with these past assessments?

Answer (Hideo Kajihara)

The existing methods that assessed R-1234yf as a refrigerant for automotive air-conditioning equipment checked whether or not the candidate material subjected to the assessment posed a problem or not by itself or in contrast to the current refrigerant materials for each of the assessment categories of toxicity, combustibility, refrigerant property, etc. (for example, see reference [4]). However, as explained in chapter 1, the materials used as refrigerants have historically gone through many changes. Since this can be said to be the result of shifts and additions made to the assessment categories in each era, there is always the possibility of further evolution of refrigerant materials in the future. Under such circumstances, the most important thing to do seems to be to clearly state the assessment criteria used in decision-making in each era. In this research, after showing each assessment category and the assessment criterion in the form of a list (Table 1 Framework of the risk trade-off assessment), the candidate materials were gradually selected from the many possible materials following a step-by-step screening method. By doing it this way, I think it offers the advantage of placing the decision-making of this time in the history of refrigerant selection. I added such a view to the end of chapter 6 and the Abstract.

The differences between past assessments on refrigerants for automotive air-conditioning equipment and the assessment on refrigerants for home-use air-conditioning equipment, which was the subject of this research, were added to chapter 3. The main difference between the two assessments is the difference in the performance level expected of the refrigerants, because current refrigerants used for each equipment are different.

3 Appropriateness of excluding certain materials from the assessment

Question (Hiroshi Tateishi)

In section 5.4.1, you (the author) said that “because the data required to conduct an LCA on R-744 … could not be found … I therefore excluded R-744 from the assessment.” But would it be permissible to allow such an exclusion that can be deemed arbitrary in this way? You should at least identify the type of data that was unavailable and the reason why the lack of such data can make the assessment meaningless, as well as remark on the possibility of R-744 being reconsidered as a candidate material depending on future examination.

Answer (Hideo Kajihara)

Since the description stating that R-744 was excluded from the assessment due to insufficient data could be interpreted as an arbitrary decision, I added the following explanation to section 5.4.1 so as to show that R-744 still remains a candidate material: “However, if data showing an increase in CO_2 emissions due to poorer energy-saving performance when R-744 is used as a refrigerant in home-use stationary air-conditioning equipment become available in future, it is likely that R-744 will achieve an LCA result similar to that for R-1234yf; moreover, its suitability as a refrigerant is likely to be judged similar to those of others described later in this section.” In addition, the following description was also added to Chapter 6 so as to clarify the problems left for the future: “In Stage 4 of the assessment, LCA could not be performed on R-744 because there were insufficient data. It is therefore clear that publication of data by the manufacturers of home-use air-conditioning equipment on CO_2 emission increases due to reduced energy-saving performance of equipment using R-744, as well as assessments based on such data, remain as problems for the future.”

Comment (Hiroaki Tao)

If a certain material is to be excluded from being a candidate material because of insufficient data for the assessment, it may raise questions on the reliability of such an assessment. If it is a viable candidate material, missing data should be collected and used for the assessment. Instead of simply stating that the assessment was not done because of insufficient data, if there are other facts that support the rationality of the decision, then it is advisable to state these facts in the paper. If not, then maybe the collection and assessment of such data should be stated as issues for the future. As said in the comment 2 above, making others aware of the existence of currently unavailable data and of the importance of conducting experiments for acquiring such data are also an important role of the assessment.

Response (Hideo Kajihara)

Since identification of insufficient data and clarification of additionally required studies and experiments within the overall assessment framework are highly important, I revised the description in the paper accordingly. To be more precise, I added the following to section 5.4.1: “However, if data showing an increase in CO_2 emissions due to poorer energy-saving performance when R-744 is used as a refrigerant in home-use stationary air-conditioning equipment become available in future, it is likely that R-744 will achieve an LCA result similar to that for R-1234yf; moreover, its suitability as a refrigerant is likely to be judged similar to those of others described later in this section.” In addition, I also added in chapter 6 that the collection and assessment of such data were problems for the future.

4 Generalization of the assessment scheme

Comment (Hiroaki Tao)

I believe the method proposed in this paper can be generalized so as to deal not only with individual problems such as the selection of next-generation refrigerants, but also with cases where decisions are needed to be made using a risk trade-off framework. I believe the techniques needed would be a combination of a screening method and a detailed examination, the means needed to collect assessment data would be data mining for existing data and experiments and/or questionnaires for non-existent data. In the case of this paper, the author himself seemed to have collected data by conducting experiments and questionnaires, but another effective way to do this might be to publicize the type of data that is needed so as to encourage universities, research institutes, corporations, etc. to voluntarily provide such data. By generalizing the application of the method from the selection of a refrigerant to a more general decision-making using a risk trade-off framework, I believe this paper would be able to propose a new assessment method for the future.

Response (Hideo Kajihara)

I believe it can be said that the significance of this paper is that it illustrates, through an actual example, the importance of the provision of a step-by-step decision-making process, various assessment categories, and assessment criteria for each assessment category in decision-making using a risk trade-off framework. It also shows that it is important to identify the type of data that is needed for the assessment and the type of assessments that can be done using such data. This significance of this paper was also added to chapter 6 and the Abstract.

5 Intention of the assessment experiment

Question (Hiroaki Tao)

It says in the footnote that the literature data [4] for the following flammability limit value, measured in accordance with the ASTM International’s Standard Test Method (ASTM E681-01), were used in the calculation. Does this mean that the value of 55.4 % was not obtained from the experiment result (Figure 1), but can be computed from the literature data? If so, for what purpose was this experiment conducted? Was the LFL experiment done to confirm the accuracy of the literature value? Could it be that the meaning of this experiment was in finding out the maximum burning velocity not included in the document? It may be because of my lack of understanding, but I would think it better to clearly state the purpose of the experiment.

Answer (Hideo Kajihara)

The description of the purpose of the experiment, which was done to assess combustion characteristics, was not clearly written. The main purpose of the experiment was to confirm that the experimental values for the mixed substance between R-1234yf and R-32 agreed with the LFL and UFL values for the mixed substance as estimated from the LFL and UFL values of the pure substances. The paper and the footnote were revised to clarify this point. In the second paragraph in subchapter 5.1, I added, “I therefore performed a combustion experiment to see whether or not the measured flammability limits for the mixed refrigerant R-1234yf – R-32 coincided with the values predicted by Le Chatelier’s Principle on the basis of their mixing ratios.” In the footnote, the word “pure substances” was added.

6 Toxicity assessment

Question (Hiroaki Tao)

Was a toxicity assessment conducted on R-32 and R-744? I think a toxicity assessment should especially be conducted on R-32. If it was not, I think it advisable to include the reason (may be because it was already done somewhere else?) in the paper. Since R-1234yf and R-32 were examined in subchapters 5.1, 5.3, and 5.4 of chapter 5, I think it would be better to include some description in subchapter 5.2 as well.

Answer (Hideo Kajihara)

A toxicity assessment was not conducted on either R-32 or R-744 because both are presently used as refrigerants. The following description was added to the beginning of subchapter 5.2: “Because R-32 and R-744, but not R-1234yf, are presently used as refrigerants and can be considered to have low toxicity, only R-1234yf was assessed for toxicity. R-32 is a component of R-410A, and R-744 is used as a refrigerant in heat-pump-type water heaters (see Term 2).” In the column for R-410A in the table in Term 2, I added the refrigerant number (R-32, etc.) to the chemical formula of the components of R-410A. Also, there was a typing error in the table in Term 2 where R-744 was mistakenly typed as R-747, so the error was corrected.

Industrial safety and application of the chemical accidents database

— Relational Information System for Chemical Accidents Database and Progress Flow Analysis —

Yuji WADA

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The Relational Information System for Chemical Accidents Database (RISCAD) was developed and operates using data collected from the aftermath of fire, explosion, and leakage accidents related to chemical substances, chemical processes, high-pressure gas, and explosives. In RISCAD, some of the accident data are linked to the "Accident Progress FlowChart" (APFC), which shows the timeline and the cause analysis of each accident. In order to create these APFCs, an accident analysis called "Progress Flow Analysis" (PFA) is conducted. This analysis method is also useful for increasing company safety awareness. In this paper, the outline and development process of RISCAD are introduced, and the procedures and application related to PFA industrial safety are reported.

Keywords : Database, chemical accidents, industrial safety, conceptual model for causes, Progress Flow Analysis (PFA)

1 Introduction

Major chemical accidents have recently increased in number, and although each accident may have its own set of causes, the declining number of experienced engineers is often cited as the fundamental underlying factor. This is because most of the skilled engineers who supported operations on site through to the 1970s, and who became experienced in resolving various operational anomalies and accidents, have since retired, and they have been replaced by a generation of engineers with little or no experience in handling these problems. This new generation of engineers tends to regard stable operation as a matter of course, and finds it difficult to respond effectively when unexpected events occur. In an effort to alleviate this problem, hands-on programs in safety education and training have become widespread, but their results still leave much to be desired.

"Learn from accidents" is a common suggestion, but it would be irrational to actually cause accidents for this purpose. Therefore, it is essential to find more practical ways to "learn from past accidents."

The Relational Information System for Chemical Accidents Database (RISCAD) was developed in this light and is designed to enable the virtual experiencing of accidents by learning from actual accident cases, and thereby prevent their recurrence. Herein, I will describe the RISCAD framework and its development, together with the results of our investigation on the procedures and methods used for implementation and utilization of the Progress Flow Analysis (PFA)[1] system for company industrial safety. The PFA was developed to facilitate the construction of "Accident Progress FlowCharts" (APFCs), which are recorded in some of the accident cases covered in RISCAD, and has been found to be effective for heightening organizational safety awareness.

2 RISCAD

2.1 Significance of accident database

The occurrence of an accident at a chemical plant can result in severe censure if a similar accident had occurred previously at the same plant, but criticism can also be harsh if information on such an accident occurring at another company or plant had not been effectively considered and utilized. "Learn from accidents" is a common suggestion, and emphasizes the point that past accidents can serve as instructors that help prevent future accidents. When contemplating or planning an operation, questions arise such as regarding the types of risks present and accidents that may occur. In many instances, this can only be accomplished by actual implementation. However, since gaining first-hand accident experience is problematic, if records related to failure cases that resulted in accidents exist, they can serve as teaching materials that should be learned from. This is the starting point for compiling accident cases.

That being said, when actually collecting cases, it soon becomes evident that it is difficult to search through such reports in order to find accidents that occurred when objectives matching one's own were pursued. First, as many accident cases as possible must be gathered, after which one must attempt to extract cases that match the objective in question. This is an elementary approach to case collection and utilization, and illustrates the need for an accident case database.

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Although this may be an elementary approach at present, it may actually be the best available method, providing that the bare minimum data collection has been accomplished beforehand. However, even if a case matching one's own objectives is found this way, it may not yield useful information. As it currently stands, the actual benefits of this approach may be limited to finding potential countermeasures for preventing recurrence of the identified accidents, contrasting them with the countermeasures emplaced at one's own company, and thereby gaining a degree of peace of mind.

On a visit to the U.S. Chemical Safety Board (CSB) in 2001, we were informed that the board had collected approximately 10,000,000 accident cases in a project spanning the past three years, and had succeeded in narrowing them down to approximately 600,000 cases, but had ultimately been unable to find any information that would be useful for effective accident analysis. They proved, in short, that simply collecting cases had little or no significance. With this in mind, the CSB revised their database operational approach to one of selecting just a few cases each year and forming a team of two to five investigators to perform a detailed investigation of each selected case, including interviews of the related workers and managers, and then to analyze the results and issue a report on the case investigation.

The status of the CSB, however, differs substantially from that of similar organizations in Japan. It is an independent governmental organization with the authority to issue recommendations to the chemical and peripheral industries, as well as to the government itself, and is, therefore, vested with specific authority for direct accident investigations. No such organization with similar authority to conduct accident investigations in the chemical industry exists in Japan, and it would, accordingly, be difficult at best to find any chemical accident investigation reports about domestic incidents that have the in-depth content found in CSB accident investigation reports.

This leaves it up to individual organizations to perform accident analyses in Japan. However, to learn more from accident examples, rather than simply determine that a previous case matches one's objectives and then ascertain the relevant recurrence prevention measures, it is necessary to expand the range of cases collected, analyze those collected cases, and extract information, such as lessons learned, that will prove useful to the organization. This constitutes an additional accident case collection goal.

2.2 Details of RISCAD development

In the latter half of the 1990s, the Materials Safety Workshop established under the leadership of Prof. Terushige Ogawa of Yokohama National University (currently Professor Emeritus, research consultant Research Institute of Science for Safety and Sustainability, AIST) and others, conducted a program aimed at the development of an expert system for chemical plant safety diagnosis.[2]-[4] Through an effort at systemization of "chemical company safety expert" thought patterns, they found that safety experts mentally organize and store their knowledge of past chemical accident cases together, as well as their expertise in chemical engineering and chemical process safety. This led to the clear recognition of the need to incorporate an accident database into the expert system. At the time, however, the available databases on Japanese domestic accident cases consisted largely of text information, with each case limited to a few lines serving as a case overview, which did not facilitate the extraction of knowledge and lessons based on those cases.

In the light of these findings, the National Institute of Advanced Industrial Science and Technology (AIST) led the planning that resulted in the development of an accident case database specializing in chemical accidents. Development was carried out over a period of three years beginning in October 1999 with support from the database development program of the Japan Science and Technology Agency (JST). During its development, it was known as the Chemical Accident Database linked with Substance Physicality (which was the project name of RISCAD at the development stage). That database was launched publicly as RISCAD in October 2002.

A key consideration in its development was the question of how to incorporate information that would be beneficial to its users in their efforts to prevent similar accidents in advance. Thus, the goal was the construction of a database that records links between accident cases along with hazard information on the chemical substances involved in the accident, performs accident classification based on hierarchized keywords, and includes non-text information and case analysis results that would enable the users involved in the handling of chemical substances to search for matching accidents in terms of the chemicals and conditions of their use, obtain information on the hazards associated with the chemical substance, and ultimately gain a deeper understanding of the circumstances in which the relevant accident occurred.

2.3 RISCAD overview

RISCAD in profile, as of the end of August 2012:

・Mode of presentation: Provided by AIST and released free of charge via the Internet as a research-information database (RIO-DB) that is open to the public
URL: http://riscad.db.aist.go.jp/
・Cases recorded: 5,840
・Case period: October 28, 1949 to September 10, 2011
・Substances recorded: 5,544
・Accident Process FlowCharts (APFCs): 159

The database development began with the entry of existing information on accidents involving high-pressure gas and explosives listed in the Hazard and Accident Database, a

Table 1. Typical keyword hierarchy for processes

Layer 1	Layer 2	Layer 3
Production, Manufacturing	Chemical reaction	Batch Continuous Other
	Separation	Distillation Filtering Centrifugation Other
	Transport, Transfer	Powder Gas Liquid Other
	Drying	
	Pulverization	
	Recovery, Extraction, Elimination	Absorption Adsorption Washing Neutralization Dust colle
	Operations	Subdivision Mixing Washing Concentration Loading, Unloading Startup, Shutdown Trial operation Other
	Others	Pyrotechnics Fireworks Heating, Cooling
Testing and research	Testing, Analysis	Pretreatment Testing, Analysis
	Experiment	Lab-scale Other scale

Layer 1	Layer 2	Layer 3
Storage	Liquid storage	Tanks (fixed) Cans, Bottles Cylinders (liquid)
	Gas storage	Tanks (gas) Cylinders (gas)
	Solids storage	Pellets Powders Bulk Packaged products Other solids
	Other storage	
Transport	Transfer	Air
		Ship (sea, river)
		Train
		Truck
	Loading, Unloading	
	Pipelines	Liquid Gas Other
Maintenance	Examination Inspection Cleaning Repair Modification	
Disposal, Recycling	Incineration Intermediate process Final disposal Recycling Collection, Transport	
	Retention	Open-air Container
	Other disposal and recycling	
Consumption	Sale, Installation Use	
	Explosives consumption	Blasting Fireworks
	Other consumption	
Others, Unknown		

previous RIO-DB operated by AIST, together with relatively detailed information on accidents at chemical plants personally held by the development group members. The database now includes daily collection and registrations of accident information relating to chemical substances by the RISCAD management group.

Chemical hazards information is focused on specific gravity, melting point, boiling point, and particularly on thermal hazards. It also includes registration of data on ignition point, flash point, explosion limit, and other such physical data. Thermal analysis data are also recorded and the database includes a function that enables the user to perform dynamic analysis on the Web browser screen in situations where it is appropriate to the user objectives.

In chemical searches, a constant problem is the large number of names used for a given chemical. It is essential that searches under different names for the same chemical, such as ethanol and ethyl alcohol, lead to the same chemical. Therefore, the RISCAD system includes an alias dictionary consisting of the differing names of compounds, thus leading to the same results regardless of which registered compound name used in the search.

It was determined that creating search keywords associated with the accident case categories would facilitate search and retrieval of information relevant to the objectives of the user's investigation, including particular processes and process equipment. As a result, keywords were hierarchized to facilitate expansion of the search range to other similar accident cases in response to a small hit number. The keyword hierarchy was constructed by experts and includes the final events, involved processes and equipment, inferred causes, and damage events of the accident cases, together with a search function based on keywords in each of these levels. The keywords were created with reference to well-known chemical accident databases operated by other countries at the time of development, together with keywords that characteristically emerge in actual accident analyses. Table 1 shows a typical keyword hierarchy for processes. For example, in processes, since there were many accidents in the disposal and recycling categories, keywords were added that related to aspects of disposal and recycling but were not found in other databases.

Similarly, the keyword hierarchy for equipment includes safety equipment keywords.

In terms of non-text information, the database includes reaction-process flowcharts, device and equipment drawings, schematic drawings of accident-causing equipment, reaction formulas, and other such entries from accident investigation reports, together with other types of graphical information.

The display functions for accident analyses results include, for macro statistical analysis, a graphical display function for accident search results and a function that enables dynamic changes in display mode and other aspects on Web browser screens.

From the results of various accident analyses, experts produce timelines of accident events, and APFCs are constructed and linked to those cases. These APFCs extract deviations from normal operations that could be the triggers of accidents from the analysis results. APFCs will be described in greater detail below.

As requested by JST, in order to meet the rapidly growing trend of internationalization, it was decided that the entire database would be translated into English and that equivalent functions would be made available for use in the English version.

Actual application of the database begins with the collection of daily accident information. This is performed via an extensive search of Internet newspapers, news agencies, and other news media websites in order to identify accident occurrences using multiple keywords based on experience and expertise. Many people tend to assume that the growth of the Internet and advent of an age of easy searching has made gathering such information a simple matter. In reality, a keyword input such as “explosion” may yield outputs like “batting-order explosion” or “exploded in anger,” while the response to the keyword entry “fire” may well miss relevant reports on “an outbreak” or “small fires.” Even with multiple, well-selected keywords, the final assessment and confirmation step can only be performed by human beings.

Once a search reveals information on the occurrence of an accident, the next step is to seek more accurate detailed information by searching the websites of the company involved in the accident and/or those of the local government in the region where it occurred. For major accidents, in particular, continued follow-up is essential, since detailed investigative reports may not be publicly issued for several months (or in some cases for more than a year) after the accident.

When producing accident overviews, it is not possible to incorporate media news reports verbatim because of potential problems in copyright and reliability; therefore, the text of the overview is composed using extractions from multiple media reports, limited to objectively factual content, and written in accordance with specified rules, as will be described in more detail below. The classification of cases, in terms of the abovementioned hierarchized keywords, is performed by specialists with a deep knowledge of chemistry and chemical plants, since it would be most difficult for others.

Using this process, approximately 250 new cases are added to RISCAD each year.

3 PFA method of accident analysis

3.1 Details of PFA development

In RISCAD, the PFA method for accident flow analysis has been designed and developed as a means to facilitate immediate user understanding of complex accident details. It has grown into a technique for construction of the APFCs that are each linked to several accident cases.

The production of each APFC is initiated by a member of the RISCAD management group, who extracts a timeline of events from the accident investigation reports and other materials associated with the case, considers the causes, and produces a draft APFC. The draft is then assessed, discussed, and finalized by the RISCAD management group members.

The RISCAD management group includes not only researchers in safety engineering and chemical safety, but also former chemical company employees, not only those with chemistry backgrounds but also those with non-technical backgrounds. The researchers are proficient in interpreting accident investigation reports but often do not have a clear understanding of the actual site. The fact that it is common sense for certain countermeasures to be in place on site for certain facilities is something that the researchers can learn for the first time by listening to the words of career veterans based on their own experiences. It also happens that seemingly naïve questions posed by those members who are bound by neither on-site nor chemistry “common sense” can sometimes penetrate to the true core of the matter. In short, it was found that through discussion on the APFCs, their respective backgrounds complement one another, thus enabling the sharing of knowledge and experience. The experience-based observations provided by the chemical company veterans would otherwise be particularly difficult for researchers who have no experience in working at chemical plants to obtain, and have proved highly useful for extracting accident causes that cannot be pinpointed simply by reading accident investigation reports. This is definitely an effective means of countering the continuing decline in the transmission of expertise and experience of veteran personnel to juniors, and the corresponding weakening in organizational safety awareness, factors that are proving problematic in the frontlines of today’s companies.

In the knowledge that on-site implementation of this procedure for sharing expertise and experience at chemical plants would generally be difficult or impossible, it was decided to compile a “procedure for the creation of Accident Progress Flowcharts,” in the form of a PFA flowchart. In the time since then, the PFA has come to be regarded as not only a means for APFC production and accident analysis, but also a means of transmitting organizational safety culture and increasing safety awareness through accident analysis.

3.2 APFC structure

Previously, the only way to gain a clear understanding of an accident was by individual reading and interpretation of the difficult text of an accident investigation report, which usually ran to several tens of pages in length, making them particularly difficult to use on site. This led to the decision to link an organized and succinct description to the accident case as a means of facilitating ready understanding of the accident and its probable causes, without even reading the difficult accident investigation report. This was realized as the APFC.

As shown in Fig. 1, the five main sections of the APFC form are the “Accident overview,” “Background,” ”Progress flow,” “Permanent counter-measures,” and “Lessons learned.”

The “Accident overview” field is used for the entry of the date and time, location, and capsule description of the accident. In RISCAD, certain rules apply to the entries in this section. Specifically, the date and time of occurrence entries are entered according to the Western calendar; the location entry extends to the metropolitan name; the descriptive overview begins with “where” (plant name) and “what” (explosion, fire, leak, or toxicity) occurred, and continues through the spread of damage, firefighting actions and other salient aspects, and the final damage comprises both material damage and personal injury, all in this order. Next, the inferred causes of the accident are entered, with “possible cause” entered for those that remain unclear to avoid definitive assertion. The final entry consists of post-accident measures, administrative dispositions, and other such aspects.

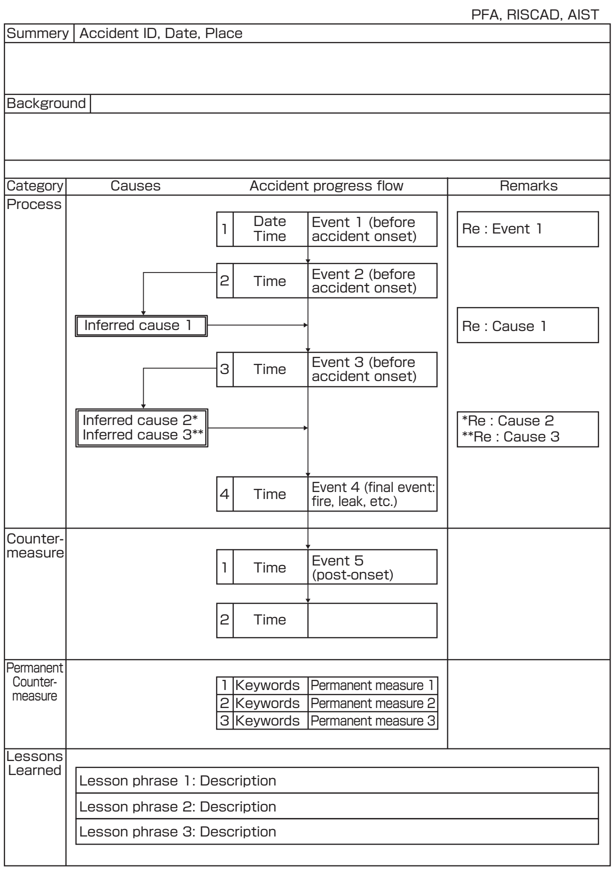

Fig. 1 Accident Progress FlowChart (APFC) form

Next, the “Background” field is completed to describe relevant background matters and supplementary information on the context leading to the accident. Any further information deemed useful for understanding the accident, even if not necessarily about directly related matters, is entered as well. This may include information such as the era and course of the facility establishment where the accident occurred, social trends, the state of the premises at the time of the accident, and, in the case of a chemical process accident, the attendant risks and hazards of related chemical substances, process flow, and other aspects.

The accident sequence flow forms the main constituent of the APFC and provides the base for implementation of the PFA. It occupies three columns in the “Progress flow” section. Events are arranged in time series in the center column, and examined for the presence of a relevant problem. If an event is deemed problematic, its cause is extracted to the column to the left. The events leading up to the final fire, explosion, leakage, or other outcome are entered as the progress of the accident. The events following the onset of the accident, such as damage expansion and firefighting are entered in the “Countermeasure” section. The “Remarks” fields in the far-right column are for entry of any supplementary information and observations on the events and inferred causes, together with an explanation of the reasons and course leading to these inferences.

The “Permanent countermeasures” section is for consideration and entry of countermeasures to each of the inferred causes entered under “Accident progress flow”. These permanent countermeasures, following their generalization, are entered as “Lessons learned” in that section. In RISCAD, the lessons learned are to be expressed in phrasing that is simple, concise, and likely to draw reader interest, and are described in a manner of wording such that the reader can comprehend the parts associated with the analyzed case accident to which the general meaning and the lessons apply.

The APFC is a time-series-based system of analysis, and is therefore relatively easy to construct even for beginners. Its construction is preferably performed when access to detailed information on the accident is available, but causes can, nevertheless, be appropriately extracted and responses examined with little available information. For non-analyst third parties, the progress and cause of an accident are far easier to understand from the completed APFC than from the difficult accident reports, and the time-series-based confirmation of the progress of the accident is expected to provide a vicarious experience of the accident by a reader following the timeline.

Well-known methods of accident analysis include fault tree analysis (FTA), event tree analysis (ETA), why-why analysis (WWA), and variation tree analysis (VTA), but their use requires a certain degree of analyst experience and a volume of accident-related information. The PFA method is superior because of its simplicity and its amenability to implementation with a relatively small volume of available information.

3.3 Cause extraction: cause systematization model

In early implementations of accident analysis with the APFC, several problems became apparent. One was the difficulty of immediately distinguishing related events from causes. For example, in a leakage case, a mistaken opening of a valve might be regarded either as the cause of the contents release or as nothing more than a related event, in which case it can be assumed that the cause or causes of the valve opening would lie elsewhere.

The PFA method of accident analysis alleviates this difficulty. Operator and organizational actions, the situation, equipment and devices, the chemicals and their manuals, and any other relevant elements are all defined as events, providing that their actual occurrence is clear or they can be inferred with a substantial degree of accuracy. This mode of definition effectively simplifies the APFC construction and enabling the analyst to organize the flow of events by placing them on a single timeline. In terms of the above example, the leak actually occurred and the valve was certainly opened. Therefore, these can be regarded as events.

A second problem was uncertainty about the method used for cause extraction and the differences between analysts in their approach to extraction. For example, one analyst might tend to emphasize operator responsibility heavily, whereas another may tend to focus on management responsibility, each reflecting their differing perceptions of cause.

A method of cause extraction that can be considered using the “Cause Systematization Model” (CSM) was developed, as shown in Fig. 2.[5] The CSM was created by adding “chemicals” as an element to a lesson systematization model,[6] which was developed based on the Hawkins “Software,” “Hardware,” “Environment,” and “Liveware” (SHELL) model. In cause extraction with the CSM, the “Organization,” “Human,” “Equipment and devices,” and “Chemicals” directly involved in an accident, together with non-involved or indirectly involved “Organizations,” “Human,” and “Society” (representing their social milieu) are all regarded as elements for clarification, with due consideration given to which of these elements relate to a given event, as well as examinations for relevant inter-element problems. This method of cause extraction can effectively reduce differences in causal inferences arising from differences in analyst experience, and also prevent omissions due to oversights.

Figure 3 shows an example of causes extracted by this CSM-based method.

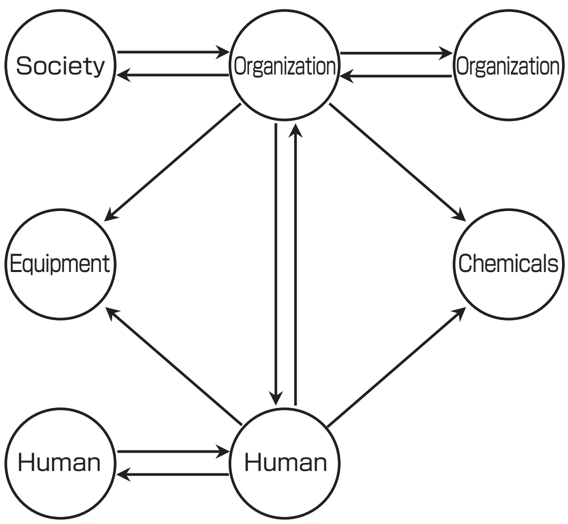

Fig. 2 Cause systemization model

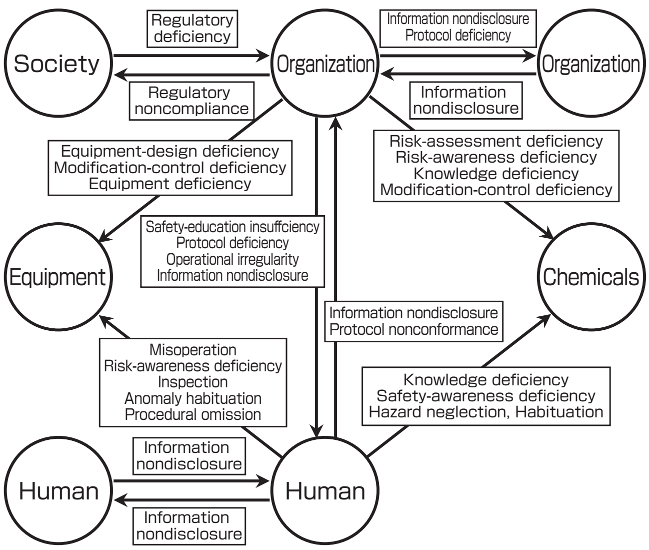

Fig. 3 Typical cause extraction with the cause systemization model

3.4 PFA implementation procedure

The PFA method of accident analysis proceeds along the following steps.
(1) Arrangement of events timeline
(2) Extraction of causes
(3) Examination of permanent countermeasures
(4) Formulation of lessons learned
(5) Finalization of overview description
(6) Group discussion
For details on the procedures, see below.

3.4.1 Arrangement of events timeline

Prior to the actual accident analyses, it is generally necessary to carefully read related accident investigation reports and other sources of information that are relevant to the subject of analysis, and to gain a good understanding of their content. Although accident investigation reports and other relevant sources are generally difficult to follow, they become easier to understand when they are summarized in construction of a timeline of events.

As previously noted, the events arranged in this timeline include relevant activities of operators and organizations, the situation and state of the equipment, devices, chemicals, and manuals, and other elements.

3.4.2 Extraction of causes

The events that caused the accident are presumably somewhere on the timeline. Therefore, each event is examined for the presence of a problem, and those found to potentially harbor problems are then subjected to cause extraction. Unfortunately, even though primary causes are usually already somewhere among the events described in the accident investigation reports and other information sources, those reports do not always cite all relevant causes. Therefore, it is desirable to extract as many tentative causes as possible through application of the expertise and experience of the analysts. This reflects a key difference between accident investigations and accident analyses. In relative terms, accident analysis places greater importance on learning as much as possible from the accident rather than on determining a true cause.

3.4.3 Examination of permanent countermeasures

Since, ideally, a permanent countermeasure is extracted for each extracted cause, causes and measures are usually equal in number.

3.4.4 Formulation of lessons learned

Lessons learned are formulated as generalizations of permanent countermeasures, and it is generally desirable that their number be limited to between two and four as a means of gaining and maintaining widespread interest in the accident and its lessons. Accordingly, before considering individual lessons, it is necessary to examine and identify the essential points illustrated by the accident case, i.e., the points in particular that should be conveyed to those who will consider its occurrence and descriptions. Through this examination, it is possible to present the case in a way that leaves a stronger impression and is more readily retained in the memories of the readers. It also contributes to the development of a better way to focus in on the salient aspects of accidents, determine the points that require attention, and formulate the measures that warrant priority action for the purpose of preventing future recurrence.

3.4.5 Overview description formulation

In the final step prior to group discussion, the analysis results are put in order and the overview description is formulated from the summary. The entry method of this description is described above, in subchapter 3.2.

3.4.6 Group discussion

Creation of the APFC is tentatively completed using the PFA method of accident analysis as described above. However, its formulation essentially includes only the content of the accident investigation reports and the knowledge and expertise of the individual analyst. To fully present the knowledge derived from the accident case in a form conducive to effective utilization, the case is then jointly discussed by a group consisting of several members and the flowchart is completed. In short, for the APFC draft produced by a given analyst, the accident case is discussed by a group of four or five members, including the analyst and others with different career backgrounds, who then finalize the APFC on this basis.

3.5 Utilization of the PFA method for accident analysis

In the group discussion on the APFC, the following results are addressed:
(1) Intra-group sharing of information representing knowledge of the accident,
(2) Compensation for any oversights in formulating the sequence of the accident, and extraction of causes from different perspectives,
(3) Capability of group members to share their respective areas of expertise, knowledge, and experience with other participants, as applied to extraction of the causes and the permanent measures,
(4) Commitment of all members to finding the accident causes and raising overall organizational safety awareness.

Various venues may be used for the discussion, including, for example, the utilization of chemical plants as sites for short meetings.

The range of the completed APFC can be horizontally expanded to cover the entire premises or company, which can prove useful in accident information sharing, education, and safety.

4 Conclusion

This paper provides a basic description of the RISCAD and PFA method of accident case analysis.

At present the utilization of PFA is centered on post-accident analysis of accident investigation reports. Ideally, however, its utilization for accident investigation immediately following its occurrence is also desirable. Specifically, APFC has, been used for immediate analysis of an explosives accident. On one occasion, the PFA has also been directly utilized for analysis of an accident at the request of the company in which it occurred, with demonstrated effectiveness. Tasks that lie ahead include examining the methods of its investigation implementation, which will enable its application to accident investigations, and gaining wider recognition of its effectiveness, and thereby expanding its utilization.

Internationalization of chemical accident databases has shown little progress. One basic reason is the lack of a uniform definition of the term “accident” among countries and regions. High-pressure gas provides one example. Upon hearing Japanese statistics on domestic accidents for high-pressure gas mentioned at international conferences, people from other countries often respond with amazement and disbelief at the high number. However, the number only seems huge to many people because it includes cases of theft. Yet, it remains large even if thefts are excluded because it includes very slight leaks, which are still reported and counted as accidents. These and other such inclusions are seldom seen in other parts of the world.

A second example is provided by the Major Accident Reporting System (MARS), which is managed by the EC’s Major Accident Hazards Bureau (MAHB) as an international chemical-product database and is maintained with the cooperation of countries participating in the Organisation for Economic Co-operation and Development (OECD) Working Group on Chemical Accidents. MARS calls for the reporting of major accidents involving gas leakages that result in designated levels of personal injury or relocation (e.g., number of injuries, fatalities, or evacuees) and chemical inventories.

In Japan, in contrast, accident registration can be defined in terms of the number of fatalities but information on the level of leakage in proportion to number of evacuees or inventory is not necessarily reported or collected, thus making it difficult to judge whether an accident needs to be reported.

Finally, a scenario of RISCAD construction and utilization is shown in Fig. 4. The constituent elements include collected information based on the facts of the accident case, extending from the time and date of onset to the equipment involved, prior information on substance hazards, and causes inferred from the results of accident analysis; also included are responses, lessons to be learned, and the APFC. These elements constitute the basic structure of the database and form the basis for its heightened reliability and ease of use, its value as an educational and training material, and its generation of PFAs.

The underlying goals for RISCAD include its positioning and establishment as a database specialized for chemical accidents, together with an expanding scope of utilization. This scope includes, in particular, its use as an effective contributor to accident prevention and to safety education and training. This will require learning about various accident cases that represent a wide spectrum of accident causes and yield important lessons, as well as detailed analysis of these cases, by which we may communicate the importance of deriving lessons from chemical accidents. For the PFA accident analysis method developed as a key part of RISCAD, the basic goals are to contribute to the development and dissemination of safety technology, further organizational safety awareness, and, ultimately, to enhanced industrial safety and security, through group discussion.

Acknowledgement

RISCAD was jointly developed with the Japan Science and Technology Agency in conjunction with its database development program. RISCAD operation is supported by a Grant-in-Aid for Scientific Research from the Japan Society for Promotion of Science. I am also deeply grateful to the many persons from inside and outside AIST who have provided cooperation and guidance in the development and operation of RISCAD.

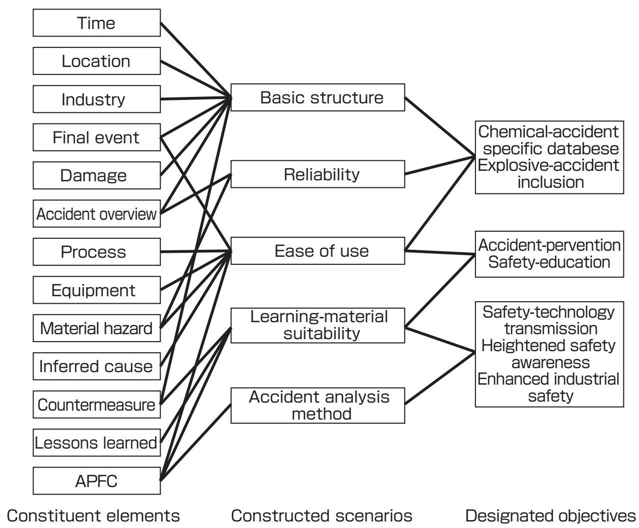

Fig. 4 Scenario of RISCAD construction and use

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Discussions with Reviewers

1 Overall observations

Comment (Koh Naito, AIST)

This paper deals with the development of an accident case database. It may be safely regarded as a scientific paper that will have a large and beneficial impact on “big data” analysis, which is characterized by complex structures and has become the subject of very strong interest by society in recent years. In this paper, the basic aim is transformation of information into a database by incorporating structural methodologies that combine definition of keywords (technical terms), data analysis methods (e.g., PFA), and systematization techniques (SHELL models). A particular value of this paper is its observations that simple technological integration is not enough to create a useful and beneficial database, together with its description of the methodological importance of techniques for information collection and of multifaceted discussion and consideration by experts of differing specializations and backgrounds.

2 Positioning of this research in comparison with previous research

Question (Hiroaki Tao, Research Institute for Environmental Management Technology)

It would be helpful if, in addition to the RISCAD system developed in this research, the main existing databases in Japan and the rest of the world, together with their particular characteristics, were presented in tabular form, as it would undoubtedly help to clarify the direction of research in this field and the distinguishing characteristics of this database. The paper notes the U.S. CSB as an example, but a related question arises as to whether similar research is being performed in the EU and other regions.

Answer (Yuji Wada)

We receive requests for consultation on the existence of databases that could be used for investigating chemical accident information abroad, but at present none exist that would be suitable. The information provided by the U.S. Chemical Safety Board (CSB), is in the form of detailed reports and a reproduced computer graphics library, rather than a database, and cannot readily be used to search for accident cases or to obtain statistical data. In the EU, they have the Major Accident Reporting System (MARS), but this is also limited to major accidents, and is hampered by insufficient cooperation between the EU countries and the Organisation for Economic Co-operation and Development (OECD), resulting in a small number of accident cases (just 14 registered in and after 2010), which is not sufficient for its comparison as a database. In the U.S. since the Sept. 11, 2001 terror attack, the movement has been toward closing the formerly open database of the EPA. In the countries of Europe, individual countries tend to operate their own databases, but whether these are open or closed to the public, they are generally in their own languages (e.g., German). Given these circumstances, it would be quite difficult to provide a comparison in table form at this time.

3 Database content

Question (Koh Naito)

This paper points out the importance of digging deeply into a relatively small number of accidents rather than trying to analyze a huge volume of data, which means focusing on variety and detail rather than on the averages frequently provided by statistical analysis. Further description of this in the final summary would increase the value of this paper.

Answer (Yuji Wada)

As you have noted, further description is desirable, and I have therefore added the following passage in the Conclusion.

“This will require learning about various accident cases that represent a wide spectrum of accident causes and yield important lessons, as well as detailed analysis of these cases, by which we may communicate the importance of deriving lessons from chemical accidents.”

Question (Koh Naito)

The importance of narrowing the generalization of an accident to 2 to 4 is noted; please provide clarification on the grounds for the preferability of narrowing the number.

Answer (Yuji Wada)

As you have indicated, the related grounds were not clearly stated, and I have, accordingly, added the following passage:

“Through this examination, it is possible to present the case in a way that leaves a stronger impression and is more readily retained in the memories of the readers. It also contributes to the development of a better way to focus in on the salient aspects of accidents, determine the points that require attention, and formulate the measures that warrant priority action for the purpose of preventing future recurrence."

4 International standardization

Question (Hiroaki Tao)

You note that you have produced an English version of the database in response to the trend toward internationalization. I believe that various international standardizations have also been performed in regard to safety by ISO and other organizations, but I wonder about the level of progress in the trend of international standardization by researchers performing similar studies. As a reader, I feel this to be an interesting question and believe it would be beneficial to add a description from this perspective, if possible.

Answer (Yuji Wada)

In the Conclusion (chapter 4), I have added the description quoted in the paragraph below. A movement seems to be emerging in the chemical industry for unification of accident databases, but the discussion has just begun and at present there is something of a tug-of-war between Europe and the U.S., with no decision on an appropriate framework. I therefore did not touch on that state of progress.

"A second example is provided by the Major Accident Reporting System (MARS), which is managed by the EC's Major Accident Hazards Bureau (MAHB) as an international chemical-product database and is maintained with the cooperation of countries participating in the Organisation for Economic Co-operation and Development (OECD) Working Group on Chemical Accidents. MARS calls for the reporting of major accidents involving gas leakages that result in designated levels of personal injury or relocation (e.g., number of injuries, fatalities, or evacuees) and chemical inventories.

In Japan, in contrast, accident registration can be defined in terms of the number of fatalities but information on the level of leakage in proportion to number of evacuees or inventory is not necessarily reported or collected, thus making it difficult to judge whether an accident needs to be reported."

5 Outlook for social implementation of this research

Question (Hiroaki Tao)

As described in this paper, the researchers analyze accident investigation reports after they have been produced by parties involved in the accident, and on that basis produce the APFC and the cause systemization model. Ideally, it would seem highly effective for the elucidation of causes and derivation of lessons learned to incorporate the APFC and the cause systemization model produced here into the report beginning at the stage in which the parties involved in the accident produce the accident investigation report. Does any move exist for JIS standardization of the format of the accident investigation report, say by including the form detailed in the study, or for administrative guidance or other means for instructing the parties involved? It appears that something of this nature would increase the usefulness to society of the research described in this study. I believe it would be beneficial to include in this paper a description of the outlook for future social implementation and any related problems.

Answer (Yuji Wada)

One example of APFC utilization in analysis has occurred, in the case of an explosives accident. In a separate example, under instructions by the accident investigation committee, an investigating party from the involved company visited to consult on analysis by PFA of an accident that occurred at a chemical plant last year. In response to your suggestion, and in accord with our belief that persuasive examples of achievements obtained from this type of utilization will be necessary, and as part of our effort for increased awareness among administrative personnel and experts selected as accident investigation committee members, I have added the following paragraph near the beginning of the Conclusion chapter.

"At present the utilization of PFA is centered on post-accident analysis of accident investigation reports. Ideally, however, its utilization for accident investigation immediately following its occurrence is also desirable. Part of it, specifically its APFC has, in fact, been used for immediate analysis of an explosives accident. On one occasion, the PFA has also been directly utilized for analysis of an accident at the request of the company in which it occurred, with demonstrated effectiveness. Tasks that lie ahead include examining the methods of its investigation implementation, which will enable its application to accident investigations, and gaining wider recognition of its effectiveness, and thereby expanding its utilization."

Capacitor devices for rapid charge/discharge storage

— R&D strategies of electrode materials for high performance capacitor devices —

Hiroaki HATORI*, Osamu TANAIKE, Yasushi SONEDA and Masaya KODAMA

[Translation from *Synthesiology*, Vol.6, No.4, p.228-237 (2013)]

Energy storage devices now require rapid charge/discharge performance, not only high storage capacity for convenient and energy efficient devices. Research and development of rapid charge/discharge storage devices are carried out in an interdisciplinary field of nanotechnology and device manufacturing, where the scope of research is very different in size and scale. This R&D is an interesting subject from the viewpoint of synthesiology, because the keys to device manufacturing are selection and combination of element technologies. In this paper, approaches and methods employed in the R&D of high performance capacitors are introduced from the discovery of innovative materials to device manufacturing, by citing examples carried out in research projects under industry-academia-government collaboration.

Keywords **:** Capacitors, energy storage device, electrode materials, quick charge/discharge, carbon materials

1 Background

The electric storage device that can be repeatedly charged and discharged include the secondary battery such as lead storage battery and lithium ion battery, and the electric double layer capacitor (EDLC) used specifically for rapid charge/discharge. We are surrounded by devices referred to as "batteries," and the application range of storage devices is extremely wide. In the recent years, there are active developments for the storage devices to fulfill the social demand for energy saving cars that can run as far as gasoline cars and for electric power leveling that enable the employment of natural energy. The performance requirement of a storage device is, first, the achievement of high energy density to improve the convenience of long hour use. Lithium ion batteries were created to meet such a requirement, and the rapid development and market expansion mainly for portable devices were astounding. On the other hand, even with the excellent performance of the lithium ion battery, it seemed to be difficult to commercialize the electric vehicle with the same running distance as the gasoline vehicle. However, the entry of the hybrid cars kicked off the active development of a storage device that allows high input/output and withstands repeated charge/discharge. Currently, the demand for plug-in hybrid and electric vehicles has increased along with the development for residential power storage in view of the diffusion and promotion of natural energy, and the development of low cost yet high energy density storage devices is in demand. Such changes in the development trend occurred in the past ten years, and the technological demand shifts continuously due to the social background. The demands for the performance requirement of storage devices are diverse.

The EDLC is a power storage device without chemical reaction, and in principle, it has rapid charge/discharge performance and excellent durability.[1][2] The market for small capacitors with electrostatic capacitance of 1 F or less has been established in the latter half of the 1970s. Later, large devices of 1,000 F class were developed for the power regeneration system of automobiles and construction machines. The devices specializing in rapid charge/discharge (power density) are expected to play important roles in attaining the outcome "to allow people to live comfortably" in various scenes. The application to copiers is a case study of practical application of large capacitors to reduce the standby power needed for preheating, and thereby allowing start-up without waiting time. This was made possible by rapid heating using the high output property of the capacitor. It is an excellent example of industrial technology where energy saving was accomplished while maintaining convenience in everyday use. There is a toy train that can run continuously on a circuit rail by instantly charging the capacitor when passing through a charging point. The basic concept of the modern electric vehicle is to charge the high energy density storage device at a time with energy needed for long distance drive. In the future, a new concept electric vehicle may emerge where the car runs along the road and is repeatedly charged without the passenger knowing, allowing long-distance travel by combining a rapid charge/discharge device and a noncontact charger.

The EDLC currently used has an extremely simple structure, where the activated carbon is used as the electrode material for both the anode and cathode, and other main parts are the electrolyte solution and the aluminum collector. As it can be said for storage devices in general, the energy density and

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power density are in a trade-off relationship. Currently, when an attempt is made to improve one, the other is sacrificed, and this cannot be avoided in creating a device. As the social demand for rapid charge/discharge storage device increases, we have conducted R&D of carbon electrode materials that may be used as the electrode active materials for capacitors. As already mentioned, the application range of the storage device is wide, and the performance requirements of the system directly linked to the social demand are diverse. Also, when an innovative potential appears and the performance limit (or projection of such) increases, new demands will appear and the development toward that goal will become activated. With this background, we conducted R&D on how to increase the energy density without losing the excellent rapid charge/discharge property of the capacitor. While this development strategy set the performance required by the current social demand as a goal to be achieved, it was the development of electrode materials that involved a wide range of stances, from the exploration of breakthrough that enabled breaking the existing principles (*Type 1 Basic Research*), the accurate understanding of the existing phenomenon (core research of *Type 2 Basic Research*), and the realization of the performance limit based on the existing principle (*Type 2 Basic Research*) (Fig. 1).

2 Categorization of the technology to achieve advanced performance of capacitors and the selection of technology

2.1 Principle of the EDLC and the electrochemical capacitor

The electric double layer capacitor (EDLC) is a storage device that stores electricity by using the ion adsorbing layer formed at the interface of the electrode surface and the contacting electrolyte solution (Fig. 2). Storage by electric double layer is based on the electrostatic adsorption and desorption. Since it does not involve chemical reaction as in a secondary battery, rapid charge and discharge are possible, and it has small deterioration despite repeated charge/discharge. Since the electric double layer capacitance related

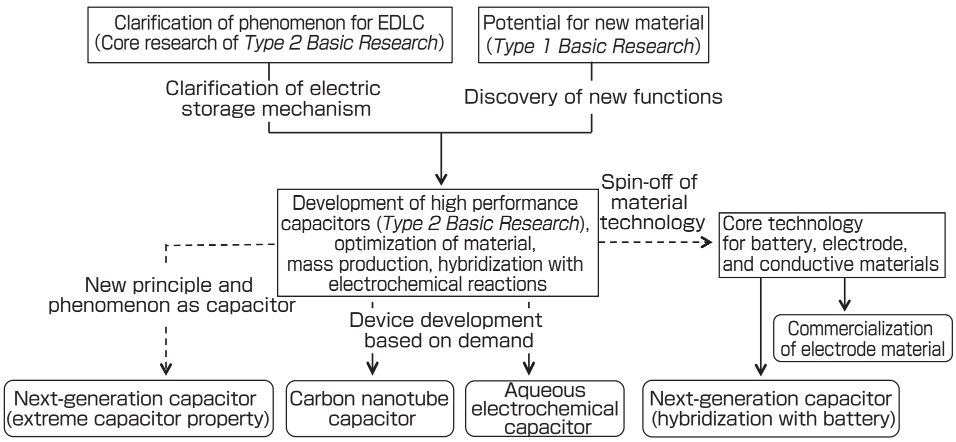

Fig. 1 R&D model of the electrode material for high-performance capacitor

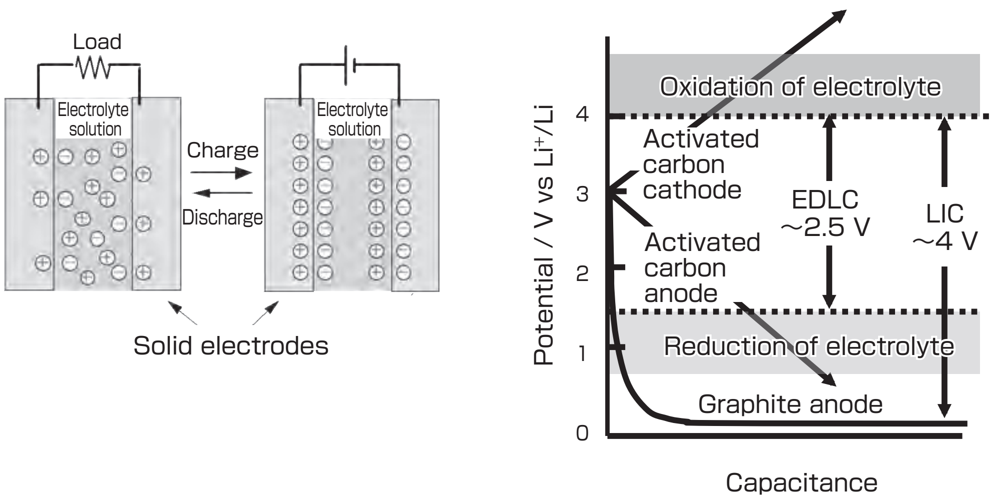

Fig. 2 Electric storage principle of the EDLC (left) and comparison with the LIC

As shown in the figure on the right, the operating voltage of the EDLC is limited by the oxidation-reduction voltage of the electrolyte solution, while the LIC can take large operating voltage since the reduction potential of the graphite anode is low.

Table 1. Categorization by capacitor and secondary battery types

		Cathode	Anode
Electric double layer capacitor		Electric double layer (activated carbon, porous carbon)	Electric double layer (activated carbon, porous carbon)
Electrochemical capacitor	Lithium ion capacitor	Electric double layer (activated carbon, porous carbon)	Redox reaction (graphite, hard carbon)
	Redox capacitor	Redox reaction (RuO_2, MnO_2, conductive polymer, etc.)	Redox reaction (RuO_2, MnO_2, conductive polymer, etc.)
	Third-generation capacitor	Redox reaction (phosphoric acid iron lithium in nanoparticle form, etc.)	Redox reaction (phosphoric acid iron lithium in nanoparticle form, etc.)
Lithium ion battery (secondary battery)		Redox reaction (oxides)	Redox reaction (graphite, hard carbon)

to energy density is proportional to the electrode surface area, activated carbon, a high surface area material, is used in the commercial EDLC.

On the other hand, the disadvantage of the capacitor is that the amount of energy that can be stored is limited compared to batteries. The electrochemical capacitor is a capacitor that employs the electrochemical reaction (oxidation-reduction or redox) to improve the energy density, and is categorized as “capacitor” in a wide sense, assuming it possesses rapid charge/discharge property. The categorization is shown in Table 1. Among the capacitors in the intermediary position where the electrochemical reaction is used in either the cathode or anode, the lithium ion capacitor (LIC), shown in Fig. 2, leads the way in terms of practical application. Recently, the so-called third-generation capacitor that incorporates electrochemical reaction in both the cathode and anode for higher energy density has been proposed.

Figure 3 shows the relationships of the energy density and power density for the representative secondary batteries and capacitors discussed in this paper.

2.2 Reasons for technological selection

As indicated in the above technological categorization, the orthodox development for improving the energy density that is the disadvantage of capacitors is to add the capacitance gained by the electrochemical reaction at the electrode surface (this is called “pseudo-capacitance” in capacitors). However, introducing the chemical reaction means that a battery element must be added to the capacitor, and the disadvantage of the battery must be accepted in return for increased capacitance. This means that the capacitance and lifespan are traded off in many cases, and it is not easy to increase the capacitance without losing the superiority of capacitors against batteries. Amongst the potential nanocarbon manufacturing materials, we found nitrogen-doped carbon and exfoliated carbon fiber (ExCF) through the development of electrode materials to which electrochemical reaction could be introduced, while utilizing the characteristic of the capacitor. We aimed for the development of an aqueous electrochemical capacitor where the structural control of the carbon materials was conducted at nano level to achieve increased capacitance by introducing the electrochemical reaction. On the other hand, it was a challenge of how much performance of the carbon nanotube capacitor could be realized in an actual device, using only the original functional principle of a capacitor without electrochemical reaction. These two developments will be explained.

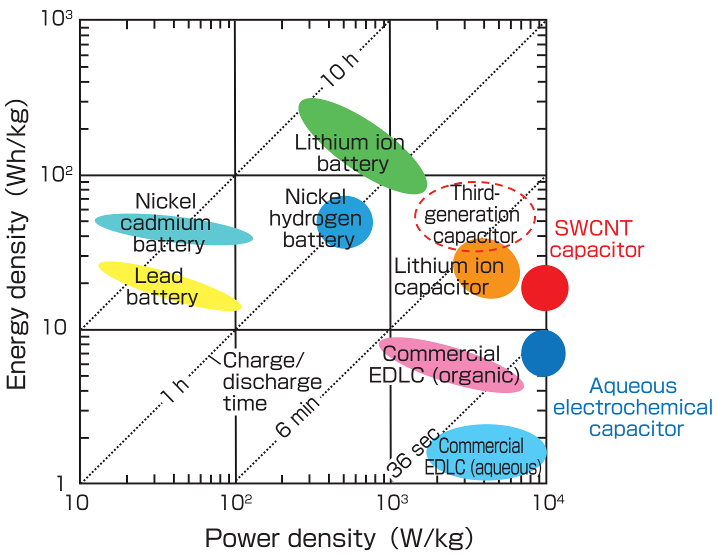

Fig. 3 Energy density and power density of various storage devices

3 Development of the aqueous electrochemical capacitor by hybrid nanocarbon electrode

3.1 R&D for potential technologies: ExCF and nitrogen-doped carbon

Carbon materials such as the activated carbon used for capacitor electrodes are low crystalline carbon materials that have undergone heat treatment at low temperature. The high crystalline carbon material (graphite material) that was high-temperature treated is expected to have superior conductivity and withstand voltage, but it is hard to obtain a wide surface area necessary for capacitor electrodes. Soneda *et al.* found that the exfoliated carbon fiber (ExCF) obtained by rapid pyrolysis after electrolyzing the graphitized carbon fiber possessed high crystallinity and a relatively large surface area, and showed characteristic behavior as a capacitor electrode material.[3][4] The capacitance of ExCF in the sulfuric acid electrolyte solution was twice the capacitance compared to activated carbon in diluted sulfuric acid, but increased rapidly with increased sulfuric acid concentration, and reached dozen times more in concentrated sulfuric acid (Fig. 4). Such large capacitance is considered to be a pseudo-capacitance effect due to the charge transfer interaction between the ExCF and sulfuric acid molecules.

On the other hand, Kodama *et al.* studied the template method to control the pore structure using the template to design porous electrodes for capacitors. In this process, they discovered that template carbon that contained nitrogen in the carbon structure showed high electric capacitance in the sulfuric acid electrolyte solution.[5][6] Particularly, the capacitance per surface area reached 1.2~2.2 F/m^2, and this was over 10 times that of activated carbon (Fig. 5). Such a high figure was not from storage by an ordinary electric double layer, but was considered to be the pseudocapacitance by the action of nitrogen atoms in the carbon skeleton. After this report, many studies were conducted on the capacitor property of the nitrogen-containing carbon prepared from various raw materials, and recently, there were new findings that the nitrogen doping of carbon electrode material increased the voltage withstand property of the capacitor using an organic electrolyte.[7]

3.2 Research strategy for the aqueous electrochemical capacitor development and the results

The capacitors can be categorized according to the type of electrolyte solution used: aqueous (operating voltage: ~1.2 V) and organic (operating voltage: ~2.7 V). For use in large electric storage, the organic capacitor is considered

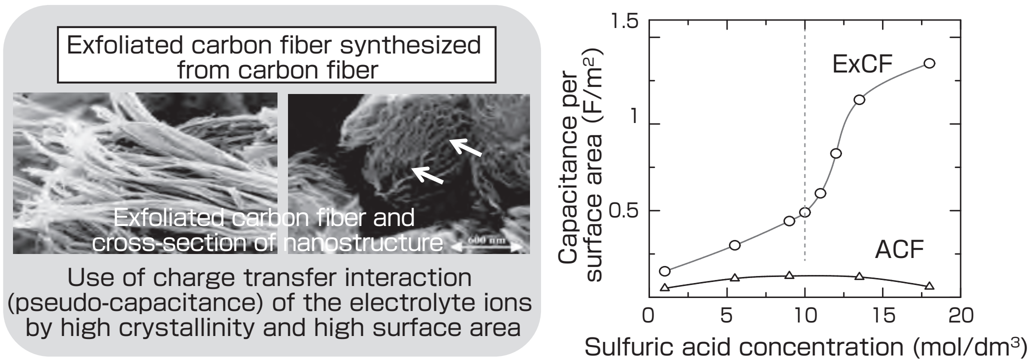

Fig. 4 Clarification of high capacitance occurrence mechanism in the sulfuric acid electrolyte solution by exfoliated carbon fiber

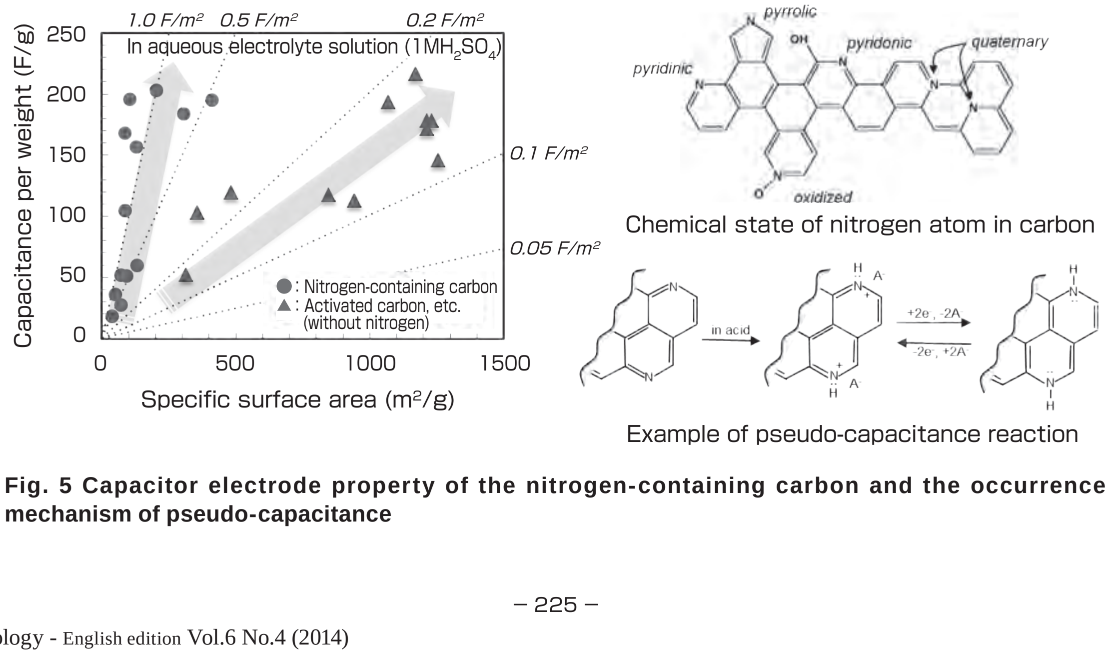

Fig. 5 Capacitor electrode property of the nitrogen-containing carbon and the occurrence mechanism of pseudo-capacitance

advantageous since it has high operating voltage and high capacitance. On the other hand, the aqueous capacitor, although it has low operating voltage, is known to be superior to the organic capacitor in almost all electric properties including internal resistance and frequency property, as well as the physical properties such as the operating temperature range.[8] Moreover, strict dehydration and sealing are required for the organic capacitor, since the electrolyte is highly water prohibitive, and as a result, the cost of the electrolyte solution dominates 40 % of the raw material cost. In contrast, in the aqueous capacitor, diluted sulfuric acid is used as the electrolyte solution, just as in the widely available lead batteries, and this is advantageous in terms of quality control, cost, as well as environmental control when considering the toxicity and flammability seen in many organic solvents. The aqueous capacitors with such excellent properties are expected to be used in small, high-output devices for the control systems of automobiles and energy management of mobile devices.

Although still in the basic research stage, it was found that the aforementioned nitrogen-doped carbon and ExCF did not loose the cycle property despite the pseudo-capacitance.[3][9] The NEDO R&D for the Practical Utilization of Nanotechnology and Advanced Materials "Development of the aqueous electrochemical supercapacitor by hybrid nanocarbon electrode" was started as joint research with carbon manufacturers and capacitor manufacturers.[10] As a result, by selecting the carbon fiber material, the capacitance of 500 F/g, which was unseen in conventional activated carbon (commercially available activated carbon for capacitors shows 100-200 F/g), was observed in the 40 % sulfuric acid electrolyte solution for ExCF. For the pseudo-capacitance by nitrogen doping, polymers that reacted similarly were developed to effectively cause the redox reaction as shown in Fig. 4. By coating the aforementioned ExCF with sufficient thickness, an extremely high energy density could be achieved for the aqueous capacitor. It was necessary to obtain a film at nanometer order considering the capacitance, diffusion resistance, and time constant of charge/discharge when using the polymers as the active material for pseudo-capacitance, and in principle, this was because ExCF had an appropriate structure as a supporting material, and ExCF itself possessed high capacitance that could not be attained earlier. Also, the fact that ExCF had high conductivity and polymer coating had high binding property, and therefore did not need a binder and an auxiliary conducting agent that were components that did not contribute to capacitance and were components of electrodes made of conventional activated carbon powder, helped increase the electrode capacitance. Further advances are expected in the future for hybrid carbon materials with such properties, and for the creation of practical devices and verification of their performance.

3.3 Commercialization of new porous carbon

In this project, the achievement of higher surface area of nitrogen-containing carbon was studied using magnesium oxide (MgO) as the template. The MgO method is a new method for synthesizing porous carbon materials by using low cost organic acid magnesium salts and polymers that are carbon precursors.[11] The aforementioned nitrogen-containing carbon was found to have extremely high capacitance per surface area, but the issue was how to increase the surface area. In this investigation, detailed knowledge and know-how were accumulated for the synthesis condition of porous carbon with abundant mesopores of 2 nm or more using magnesium citrate as the raw material. Toyo Tanso Co., Ltd., one of the companies that participated in the project, commercialized the "CNovel R" that is characterized by abundant fine pores categorized as mesopores (diameter 2~50 nm), as well as a large surface area equivalent to that of activated carbon.[12][13] Ordinary activated carbon has micropores, where the fine pore diameter is 2 nm or less, and mass transfer resistance inhibits the rapid charge/discharge of the capacitor. With CNovel R, it was found that mass transfer resistance was small, and it had an extremely excellent property as a capacitor for rapid charge/discharge. Until now, carbon materials with mesopores were synthesized by grams in a laboratory setting, but with the development of this method, the supply could be obtained by kilograms, and it is now being applied to wider use such as secondary batteries and fuel cell electrodes, other than capacitor electrodes. This is an excellent case where the material that could be used for various purposes was commercialized in an extremely short period as a spin-off from the core technology of *Type 2 Basic Research* for the capacitor electrode material development.

4 Development of the SWCNT

4.1 Development strategy of the carbon nanotube capacitor and the initial goal

Carbon nanotube is a fibrous material made by rolling and closing the hexagonal mesh sheet of carbon called the graphene into a hollow cylindrical shape without seams. As mentioned earlier, the electric quantity that can be stored in the electrode interface is, in principle, proportional to the surface area of the electrode surface. Since the theoretical surface area of one sheet of graphene is 2,630 m^2/g, the theoretical surface area of single-walled carbon nanotubes (SWCNT) that is made by rolling the sheet should be the same as the graphene, combining the exterior and interior walls of the tube. However, in multilayered carbon nanotubes where the cylindrical graphene is rolled concentrically, there will be planes where parts of graphene are in contact with each other, and the surface area will become smaller than the theoretical value because the electrolyte cannot reach such areas. Therefore, to achieve high energy density, it is important to obtain a nanostructure that maximizes the surface of the carbon nanotubes for charge storage.

On the other hand, power density is determined by the transfer resistance of the electron and ion in parts that comprise the cell. Since activated carbon is an aggregation of minute graphene layers and has nano-scale fine pores in its structure, it has a high surface area, but the transfer routes of the electron and ion in the particles are complex and the resistance is great. However, if the transfer route of the electron and ion can be controlled precisely by the nanostructure design where the individual SWCNTs are arranged in line, an electrode with ideally small charge transfer resistance of the electron and ion, or a capacitor with extremely small internal resistance can be achieved (Fig. 6).

Although SWCNT was expected to be good as a capacitor electrode material because it possessed high conductivity and high surface area, there were over 10 % of impurities such as catalyst metals and noncrystalline carbons in the synthesis stage, and it was not easy to make highly pure SWCNT in large volume. Coincidentally, a technology called the super growth method[14] that enabled the manufacture of extremely highly pure SWCNT at impurity concentration of several hundred ppm or less by weight was developed at the Nanocarbon Research Center, AIST. To create a high performance capacitor using the innovative materials and to aim for a synergetic effect of inducing mass production and low cost of SWCNTs, the Carbon Nanotube Capacitor Technology Development Project was started with the cooperation of two companies and AIST, and with Dr. Sumio Iijima of the Nanocarbon Research Center as the project leader. The main topics of this project were the mass production of the commercial level SWCNTs and the establishment of a manufacturing technology for a practical capacitor device that used the mass-produced SWCNTs as electrodes.

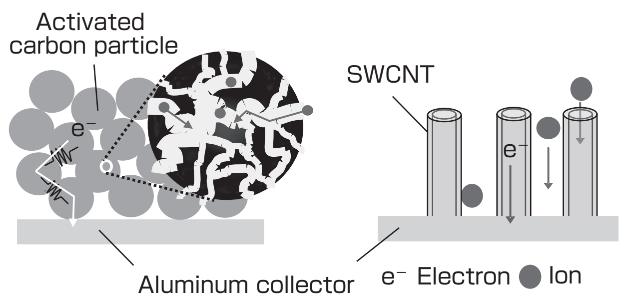

Fig. 6 Model structure of the SWCNT electrode that is vertically aligned with activated carbon electrode and the passageway of electrons and ions

4.2 Results achieved in the development of a practical capacitor device

In this project, the characteristic electrochemical property of SWCNT was clarified (Fig. 7).[15]-[17] Originally the electric capacitance arising from the electric double layer does not depend on voltage and is constant, while the SWCNT electrode increases in capacitance approximately proportional to the voltage. It is known that in SWCNTs, the electron structure becomes metallic or semiconductive depending on the chirality or the way graphene is rolled. The voltage dependency observed in SWCNTs arises from this unique electron structure, and can be explained as a phenomenon similar to the electrochemical doping of conductive polymers. It has been experimentally confirmed that the electroconductivity of the electrode sheet increased to 10 times or more since potential polarization occurs in the electrolyte through the injection of electrons and holes in the SWCNTs.[16] Moreover, with ordinary activated carbon electrodes, the upper limit of single cell voltage is 2.5~2.7 V, while with the electrode consisting only of highly pure SWCNTs, it has been found that sufficient durability is maintained even when operated at high voltage of over 3 V. This is thought to be because there is only an extremely small amount of contaminants such as functional groups or metal elements on the graphene surface that may promote the breakdown of the electrolyte solution. Since the energy density of the capacitor is proportional to the square of the charge voltage, this property is extremely important to increase the energy density.

The SWCNTs have the potential for high voltage operation when used as capacitor electrodes due to the structure where there are very few graphene terminals that may cause the breakdown of the electrolyte. The currently commercially available activated carbon electrode is made by kneading the powdered activated carbon particles with polymers called the binders and carbon black, an auxiliary conducting agent

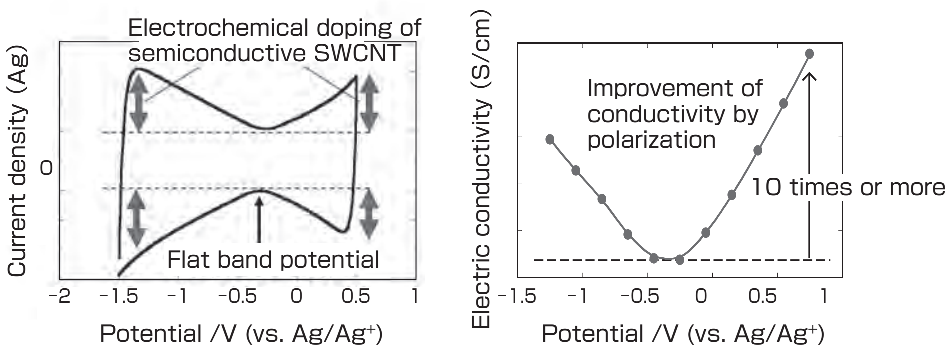

Fig. 7 Characteristic electrochemical property of the SWCNT

to reduce the contact resistance between the particles. These additives induce the breakdown of the electrolytes in high voltage conditions and inhibit increasing the energy density. In contrast, since SWCNT is fibrous, it requires no binder and can be made into a sheet in the manner of papermaking. Also, SWCNT made by the super growth method can be made into a flexible electrode sheet simply by pressing. The SWCNT itself is highly pure, and the SWCNT, itself an electrode active material, can gain 100 % electrode property on its own. Moreover, the project was successful in achieving the adhesive-free bonding of the SWCNT electrode sheet and the aluminum collector (Fig. 8).

In addition to the high voltage withstand property originally possessed by SWCNT and by avoiding the mixing and inclusion of the impurities that induce the breakdown of electrolytes under high voltage conditions, the SWCNT capacitor showed two to three times higher performance compared to the current activated carbon electrode in both energy density and power density. Moreover, the durability was over 15 years, and thereby the goal of the project was achieved.[18]

The SWCNT electrode that showed a vertical alignment as shown in Fig. 6 had an ideal structure to reduce the diffusion resistance of the ion and to maximize the power density, and the potential for the forming technology that can achieve such an electrode structure was found.[19] However, it was also found in this project that sufficient power density could be achieved by selecting the papermaking method or a simple pressing method, and it can be said that the success of device manufacturing was the selection of an electrode manufacturing method with high productivity from the perspective of practicality rather than an ideal structure.

With SWCNTs, generally, the tubes aggregate together to form a bundle structure, but when they are used as capacitor electrodes, the surface where the tubes are in contact with each other cannot be used for charge storage because the electrolyte ions cannot approach the outer surface of the SWCNT inside the bundle structure. We were aware of this point, and studied the method for releasing the bundles electrochemically, and verified this method in the commercially available SWCNTs that formed the bundle structure.[20] The SWCNTs manufactured by the super growth method were idiosyncratic products where most of the surface area could adsorb the materials. Similar to the aforementioned electrode formation technology by the papermaking method, it is important to have versatile manufacturing technology options in preparation of diverse SWCNT products, and this bundle releasing technology is considered to be one such option.

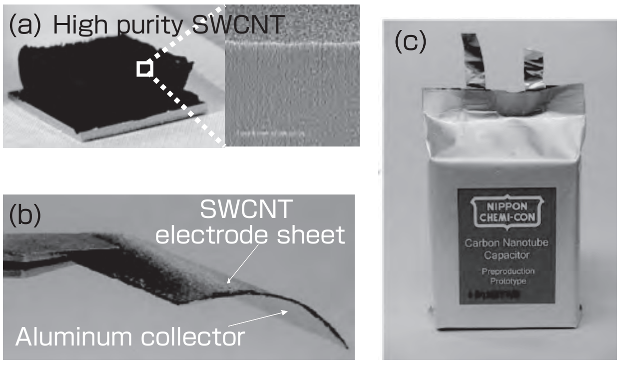

Fig. 8 Carbon nanotube capacitor
a) SWCNT that grows vertically on the substrate, b) SWCNT electrode sheet, and c) 1000 F class SWCNT capacitor.

The Carbon Nanotube Capacitor Technology Development Project ended in FY 2011 and was successful in manufacturing the SWCNT capacitor of 1,000 F level (Fig. 8). Moreover, the excellent conductivity and electrode forming properties were discovered for the SWCNT material, and direction of using the SWCNT for conductive and binding materials, not just as an electrode active material, was indicated. As a result, the development of an electrochemical capacitor in which the energy density was increased to 30 Wh/kg or more by compositing with nano-crystalline lithium titanate was successfully done.[18] At this point, the use of the expensive SWCNT could be decreased to about 15 %, and the device is expected to be adopted earlier for practical use.

4.3 Understanding the electrochemical property of the SWCNT and possibility of further increased capacitance

We propose that it is possible to increase the energy density of the carbon nanotube capacitor by utilizing the semiconductivity of the SWCNTs and by conducting the diameter and chirality control, based on the evaluation of the capacitor property by the metal semiconductor separation of the SWCNTs.[21] Comparing the storage behavior of EDLC where the charge storage at the electrode is proportional to the charge potential, and the storage behavior of the secondary battery where the charge storage occurs at constant voltage, the latter will have twice the energy density of the former in the electrode that can ultimately store the same charge capacitance. This means that the energy density of the device will double if we can optimally control the charge-discharge potential by conducting the electronic property control of the semiconductive SWCNT. However, since the diameter and chirality control of SWCNTs are technologies that add cost hurdles to the mass production technology, we must first see that SWCNTs can be mass produced and commercialized as metal-semiconductor mixtures, and hope that the SWCNT manufacturing technology will advance further in the next step.

5 Summary and future prospect

While new potentials are found for improving product performance through ever-evolving materials technology, recent development of electric storage technology progresses by mutual linkage from *Type 1 Basic Research* to *Product Realization Research*, as the devices and systems are constructed through the selection of fast moving technologies to meet the current social demand for practical application. Since there are diverse usages for storage devices, one way is to conduct development of a system that can handle lower performance or to compromise the usage due to cost concerns, instead of aiming for a high goal. Through the linkage of innovative materials such as carbon nanotubes and the practical outlet of developing an energy device, the researchers of wide ranging fields conducting *Type 1 Basic Research* engaged in the research of electrode materials with renewed desire for development. Also, from the *Type 2 Basic Research* that headed for the outlet of developing a capacitor, a material with wide application and versatility was discovered. As seen in the commercialization of the porous carbon made by the MgO template method, there is expectation for the birth of products other than capacitors from the spin-off of material technology.

With carbon nanotube capacitors, the excellent capability of SWCNTs was verified at the actual device level, and the various technological options needed for its manufacture is being accumulated. However, in the world of practical electrode materials, several thousand yen per kg is even considered expensive, and it cannot be denied that SWCNT is still expensive, and the expansion of the market including other uses and time are necessary. Carbon fiber, which is the same fibrous carbon and for which an industrial manufacturing method was invented by a Japanese, grew into an industry in which the Japanese company dominates about 70 % of the world share.[22] Currently, it is used as structural material of aircrafts and strengthening material for buildings. Now the price of general-purpose products has decreased to the level of several thousand yen per kg, but it was about 100,000 yen/kg at the beginning of its commercialization. Looking at the history of carbon fiber that proved that a truly excellent material could overcome the economic valley of death, we hope that the nanocarbon material with excellent characteristics will be commercialized for a wide range of fields starting with the capacitor electrode material.

Acknowledgements

The development of the aqueous electrochemical capacitor was conducted in the NEDO (New Energy and Industrial Technology Development Organization) R&D for the Practical Utilization of Nanotechnology and Advanced Materials “Development of the aqueous electrochemical supercapacitor by hybrid nanocarbon electrode” (FY 2008~2011). We are grateful to the people who engaged in the joint research at Oita University, Toyo Tanso Co., Ltd., and NEC Tokin Corporation. The development of the carbon nanotube capacitor was conducted in the NEDO Energy Innovation Program “Development of the carbon nanotube capacitor” (FY 2006~2010). We are grateful to all the people of the companies, universities, and AIST that participated in the joint research, particularly to the people of Nippon Chemi-Con Corporation.

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Discussions with Reviewers

1 Carbon nanotube capacitor

Question (Shuji Abe, Evaluation Department, AIST)

When creating a fine nanostructure like carbon nanotubes, it is obvious from the beginning that it will be more expensive compared to activated carbon, and the situation has not changed now even though we have advanced the mass production technology. I think the significance of the carbon nanotube development project is to actually present the potential of the carbon nanotube property, and to lead and induce mass production. How do you view such a research strategy?

Answer (Hiroaki Hatori)

Of the material cost, as you indicated, there was a concern from the beginning of the development. The R&D was conducted by assuming how much competitiveness can be gained against the current material by cost reduction due to the mass production of carbon nanotubes and by material cost reduction due to the improvement of the capacitor performance, and several options were kept at all times to attain realistic specs. As explained in the final paragraph of subchapter 4.2, through the design that is equivalent to the redox capacitor of Table 1, the development of device that required less amount of carbon nanotubes was conducted in the same R&D project, and a high performance was verified for the energy density.

In view of cost reduction of carbon nanotubes, unless the demand rises dramatically and the production technology improves, it is not possible to achieve. Therefore, it is explained at the end of subchapter 4.1 that one of the objectives of the R&D was the induction of mass production and commercialization of the SWCNTs through performance verification of the high-performance capacitor. For material cost and a path to commercialization, the example of carbon fiber is given at the end of “5 Summary and future prospect.” Although carbon fiber is currently gaining attention as a structural material that may replace iron, it took 20 years from patent to use in niche products such as sporting goods, and 20 more years were necessary before it was used as a structural material that has the prospect of heavy demand. When considering SWCNTs as storage parts that demand prices at the level of general-purpose products, the history of the commercialization of carbon fiber is instructive. Since the carbon fiber R&D strategy has been analyzed in *Synthesiology*, I added this article as a reference.

2 R&D model (Fig. 1)

Question (Shuji Abe)

In “Fig. 1 R&D model,” the “potential for new material (*Type 1 Basic Research*)” on the top right seems to indicate the SWCNT research. What specifically do you mean by the “discovery of new functions” on the arrow that leads from there?

Answer (Hiroaki Hatori)

Seen from the perspective of capacitor electrode material, the mass synthesis method of carbon nanotubes by the super growth method can be positioned as *Type 1 Basic Research*. The discovered “new functions” are the electrochemical properties that were found in the initial experiments: 1) high surface area due to the unique aggregate structure obtained in manufacturing, 2) potential dependency (as a result, more electricity can be stored in the limited potential window), and 3) capability of charge/discharge at high voltage. At the point when this R&D was started, 1) was written in the patent as a property expected of SWCNT as capacitor electrode but was not experimentally verified, and there were no scientific evidences for 2) or 3) in the academic papers or patents.

3 Aqueous capacitor

Question (Yasuo Hasegawa, AIST)

Compared with the conventional organic capacitor, what kind of characteristic does the newly developed aqueous capacitor have, and what are the expected fields of application?

Answer (Yasushi Soneda)

Although the electrochemical capacitor is a high-output, low-capacitance storage device compared to the conventional secondary battery, the device is designed according to actual usage such as high-output, high-capacitance, or somewhere-in-between capacitors. When pursuing the extreme limit of performance in the high-output type, the aqueous capacitor with a highly conductive electrolyte is more appropriate than the organic capacitor. Also, for the temperature property that is important in automobiles, the aqueous type is superior in both high and low temperatures than the general organic electrolyte. In terms of environmental load, the diluted sulfuric acid used in aqueous electrolyte solution is widely accepted, as seen in the diffusion of the lead battery, but some of the organic electrolytes may be toxic or dangerous when burnt, and there are different attitudes for their use in Japan and overseas.

There is a strong demand that small, substrate-implemented capacitors used in mobile devices have small environmental load and low cost, because the individual device cannot be recovered. The aqueous capacitor is also advantageous in these points.

Physical separation technology to support the strategic development of urban mining

— Development of unused/hard-to-use resources and a future vision of resources for Japan —

Tatsuya Oki

[Translation from *Synthesiology*, Vol.6, No.4, p.238-245 (2013)]

Most of the natural metal resources supporting manufacturing in Japan are imported from foreign countries. In recent years, the need for a stable supply has become a serious ongoing concern in the face of sudden price increases and unfavorable export regulations. Urban mining offers a promising means of utilizing domestic resources in order to minimize this risk. However, because the degree of integration of metals, including rare metals, in manufactured products is not necessarily high, the use of physical separation technology which can concentrate such metals and minimize costs is indispensable. Especially given the lack of experience in recovering certain types of rare metal elements from waste products, innovative separation technologies are needed. In this report, I introduce techniques for achieving rare metal recycling through innovations in physical separation, and present a plan for 'strategic urban mining,' based on physical separation technology and aimed at domestic circulation of metal resources.

Keywords **:** Urban mine, recycling, rare metal, physical separation, tantalum, strategic urban mining

1 Introduction

Japan is dependent on foreign imports for almost all its metal resources required for manufacturing. Recently, stable supplies have been jeopardized due to sudden increases in rare metal prices and/or changes in export regulations. Since the various metal resource elements have distinctive functions, unlike energy resources, each is difficult to replace with other metals. Therefore, even if the amount used is small, products utilizing such metals cannot be produced in Japan as long as the supply of these metals is interrupted; and over the long-term, this may threaten the foundation of Japan, a nation based on technology. When a manufactured product reaches the end of its lifespan, its contained metal elements remain unchanged; and thus in principle can be recovered as original raw materials. This means that horizontal recycling is possible. There are many waste products in Japan, and these are expected to become useful resources; thus the term 'urban mine,' coined by Dr. Michio Nanjo of Tohoku University in the 1980s, has been revived. However, such waste products are scattered throughout Japan, and the concentration of metal contained in them is often significantly less than in natural mines. To develop such hard-to-process resources, it is necessary to apply physical separation technology that enables the primary concentration of metals at a low cost. However, rare metals, in fact, have yet to be extracted as individual elements from waste products, and thus physical separation technology based on a new way of thinking is necessary. In this report, I shall describe a technique for metal recycling through innovations in physical separation, and initiatives to construct 'strategic urban mines' which form the foundation for domestic metal resource recycling.

2 Physical separation technology for developing hard-to-process resources

2.1 Importance of physical separation technology in the development of urban mines

Although there are very few metal mines currently operating in Japan, imported metal materials exist throughout the country, in the form of waste manufactured products. Such waste products are now referred to as 'urban mines.' However, for a mine to be properly functional, it must be economically feasible to extract the respective resources; thus, the mere existence of such products throughout the country does not, in itself, constitute a proper 'mine,' even in an extended sense. Moreover, whereas natural mines mark localized concentrations of terrestrial resources over a long period of time, such concentrations do not occur 'naturally' in the case of waste products with significant metal content. This means that 'urban mines' do not possess such localized existence, but rather must be identified and artificially 'concentrated' through intentional human engagement in urban mining, which, in technological terms, refers to techniques for minimizing the energy required for such artificial concentration.

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Initially (in the -1980s-'90s), Japan's recycling priority was on the 'achievement of quantity' through the construction of a social system involving the collection of waste products. After the legal reform in the 1990s, recycling infrastructure for large home appliances was established, and when rare metals recycling began (2008-09), many thought rare metals could be recovered easily once the waste products were collected. However, in practice, such metals could not be extracted from the waste products at existing recycling facilities. At the same time, in the 1990s, shortage of landfill space became a social issue, and due to environmental restrictions, 'recycling of quantity' was the main concern. Therefore, iron, aluminum, plastics, and other materials found in large quantities were recycled to reduce the landfill volume; and with respect to the recovery of small home appliances, which had been conducted in designated regions from 2008, the target shifted to rare metals. However, because the concentration of certain rare metals is typically several hundred to several thousand ppm, 'recycling of quality,' based on the concept of limited resources, is necessary; attempting to recover rare metals from small appliances using conventional recycling infrastructure is similar to performing surgery with a pickaxe. Thus, by around 2010, awareness of the need for technological conversion from recycling of quantity to recycling of quality had emerged.

Rare metals are typically used in small quantities in manufactured products, and are thus found in lower concentrations than structural materials such as iron or aluminum. Therefore, economically feasible recovery through hydrometallurgical methods employing chemical reagents is difficult. In pyrometallurgy, involving high-temperature reactions, while it is possible to efficiently recover copper and precious metals even at low concentrations, the recovery of rare metals is technologically difficult since many of these metals melt and disperse in the glasslike slag. To recover rare metals from waste products, it is essential to separate them from copper and precious metals, through physical separation, before smelting.

In addition, the precise meaning of 'rare metal' is not universally agreed upon. In Japan, 47 elements, including 17 rare earth elements, were designated as rare metals in the 1980s. Alternatively, rare earth is considered to be one type, and reference is made to 31 mineral types. Many countries, in fact, do not use the term 'rare metal,' and if they do, the definition may vary. Recently, the English-speaking world has adopted the term 'rare metal,' as used in Japan. However, questions have been raised about the utility of lumping everything into one group since, for example, platinum and palladium are rare metals, while gold and silver are not, though all are precious metals. Therefore, this study employs the term 'strategic metals' to describe metal resources that are strategically significant for Japan.

2.2 Technological issues in physical separation

Although individual issues are involved for each type of waste product, we will here consider the common fundamental issues involved in the preliminary physical separation of rare metals and copper/precious metals. Waste products typically consist of composite particles which are broken apart in the process of 'crushing.' The effects of crushing in many industrial processes include improvement in mobility, processability, and reactivity; and the objective of crushing is to obtain 'uniformity' of the resulting powder. On the other hand, the sole objective of crushing in physical separation is to promote liberation. Liberation is the creation or condition of a state in which each particle is composed of only a single substance, allowing us to designate a specific 'ingredient' as the target of the recovery, the element, alloy, or part that one wishes to recover. Therefore, crushing is positioned as a pretreatment in which the 'non-uniformity' of the powder is prepared for liberation. Since physical separation is the process in which the individual particles are sorted, the particles must be liberated before this process, or no advanced separation can be achieved, regardless of the technology employed. Figure 1 shows the relationship between the progress of liberation through crushing and the uniformity of the powder, from the perspective of this study. When the composite particle (initial particle) is broken down by crushing, it becomes an aggregation of liberated particles composed of single ingredients, and the non-uniform condition is achieved as the compositions of the individual domains become distinct. The ideal is to achieve this state in the stage of coarse (large) particles (achieving the 'mixed nuts' state as a result of crushing), since, if further crushing is necessary or the liberation can only be achieved through fine crushing, the uniformity of the composite (state of being well mixed) increases, and it becomes difficult to recover specific particles through separation (similar to attempting to separate the ingredients of mixed spices). The promotion of liberation by crushing sacrifices non-uniformity of the aggregate while achieving non-uniformity of the individual particle. Therefore, it is important to achieve liberation in the coarse-particle stage as much as possible, and excessive fine grinding must be avoided. Also, items whose crushing will result only in fragmentation without liberation (such as instant coffee) will not be useful targets for physical separation.

In the crushing process schematized in Fig. 1, it is possible to achieve good liberation through selective crushing, rather than 'random crushing' where the composite particles are equally crushed. Such a method, whereby liberation is achieved in the coarse-particle stage, is called 'selective crushing,' and this is one of the most important pretreatments for physical separation. However, since it is necessary to deal with diverse properties and structures in the target materials, selective crushing is technologically very difficult, and there is no device that serves as an all-purpose selective crusher.

Currently, we must wait for suitable selective crushing functions for specific targets to be discovered by chance among various crushers; therefore, a systematic and logical organization of relevant technology is required.

Even if liberation occurs, various particles are typically still mixed after crushing, and separation will be necessary. In physical separation, differences in particle properties are exploited. Dry separation, conducted in a gas (usually air), can be done at low cost and with low environmental load, since drying and water treatment are not necessary. In contrast, wet separation, conducted in a liquid (normally water), though typically resulting in high separation precision, requires power for water circulation as well as drying, and is therefore disadvantageous in terms of energy and cost. In wet separation employing a large amount of surfactants to exploit particle surface properties, the load of wastewater treatment increases in comparison with methods exploiting particle bulk properties. For these reasons, dry separation is preferred in recycling, but there are limitations on the applicable particle size for each separation method, and the process cannot be completed through dry separation alone. Although it is difficult to delineate the minimum applicable particle size, it is roughly 1 mm for dry separation and roughly 50 μm for wet separation using bulk properties, while anything below this will require wet separation using surface properties. Thus, energy and cost savings in physical separation primarily depend on the extent to which liberation can be achieved in the coarse-particle stage of the preliminary crushing process.

Figure 2 shows a model of the simplest physical separation process, consisting of one crushing and one separation process. The initial products are either a single type of waste product, an assortment of such products, or extracted printed circuit boards. There are various types of crushers, and the manner of crushing varies widely, depending on the conditions of the specific device and its operation. If liberation is achieved in the coarse-particle stage, through selective crushing by establishing optimal crushing conditions, the subsequent separation process can be performed with great efficiency. However, there are only a few conditions under which such selective crushing can be achieved, among the various combinations, and such selective crushing conditions have not been established for most waste products. In rare metal recycling, it is often the case that subsequent separation methods are sought without recognizing that the liberation of the crushed material is inadequate under the given conditions. The overall effect of the physical separation process is determined by the synergetic effect between the crushing and separation functions. Therefore, it is useless to deploy an excellent separator in the latter process without due consideration of the former process, and the initial key to success is the efficient achievement of liberation through selective crushing.

However, even if optimal liberation is achieved here, the particles remain in a mixed state; thus this process is properly understood only as a preparation for separation. As noted above, there are applicable particle sizes for

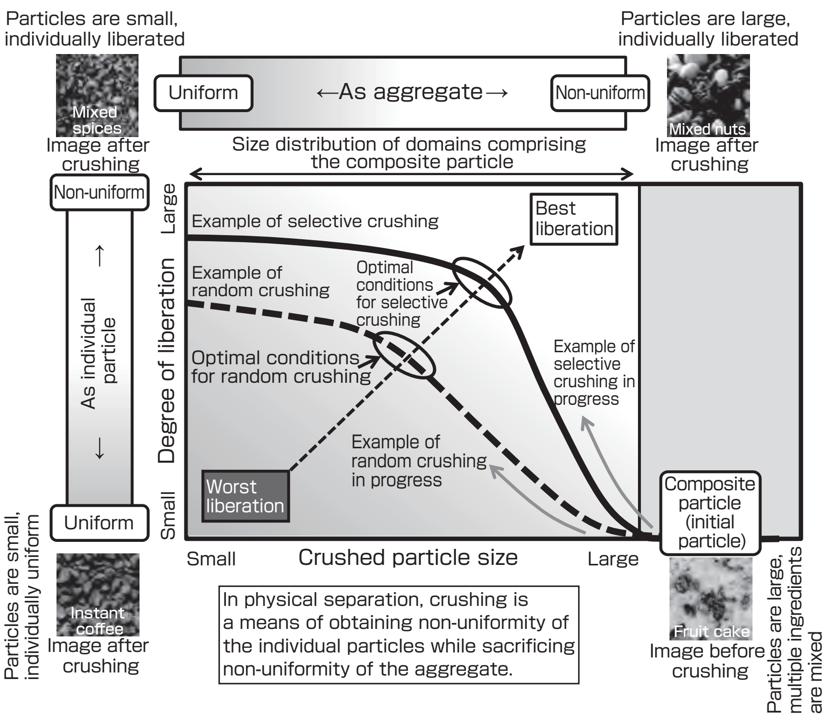


Fig. 1 Relationship between the progress of liberation through crushing and the non-uniformity of the powder

each separation method, and even if dry separation can be applied, there are various types of devices for the various exploitable particle properties (size, shape, specific gravity, magnetism, conductivity, color, x-ray transmittance, etc.), and an even greater variety of separators available for a given property characteristic. Moreover, as in the case of the crushing process, the separation products may vary widely, depending on the conditions of the particles and the specific operation. In the simple, one crushing/one separation model shown in Fig. 2, there are seven parameters, each with tens of selections, and the overall patterns can number in the hundreds of billions. In practice, there will be two or three viable crushing processes and three to ten viable separation processes, and the number of patterns will be astronomical. However, the conditions for achieving optimal physical separation of hard-to-process resources from urban mines are limited to only a few patterns. Furthermore, in contrast to the lifespan of natural mines, from which ores with uniform composition can be mined for decades, the product cycle in urban mines is typically brief. Therefore, the viability period of a given separation pattern for a specific target is typically short, often only a few years, since the type, form, and quantity of rare metals in the respective waste products vary. Since, at the present time, it is difficult to identify the optimal conditions among such a vast number of possibilities in a reasonable time, processing is typically done under extremely unsatisfactory separation conditions.

3 Achievement of recycling through innovations in physical separation

3.1 Alternative technology to manual dismantling and sorting – Easy sensing

While it is difficult to determine the conditions for selective crushing that will achieve liberation, liberation can be accomplished through ‘dismantling’ individually if the size of the recovered object is relatively large. For example, the process of recovering the motor from large appliances is performed by hand, even in Japan, and it is not uncommon to recover target parts by hand sorting. Since waste products have complex structures and the mix of such products in recycling varies from day to day, manual dismantling and sorting are the most reliable methods for liberation and recovery. However, as there are limits on the application of this method in Japan due to considerations of economy, productivity, and international competitiveness, research into automation is underway. While there is, at present, no example of completely automated dismantling technology, various automated sorting technologies have been devised to replace traditional hand sorting. These, however, often involve expensive devices that deploy sophisticated sensing technology used in manufacturing processes; and while they are good at removing unwanted elements from almost uniform products, adequate performance may not be achieved in the case of dismantling waste products with numerous variations.

Therefore, the author has developed a low-cost, ‘easy sensing’ device, which automizes the dismantling and sorting of specific waste products. In this device, instead of expensive sensor technology, several inexpensive sensors, mimicking the five human senses, are combined to achieve

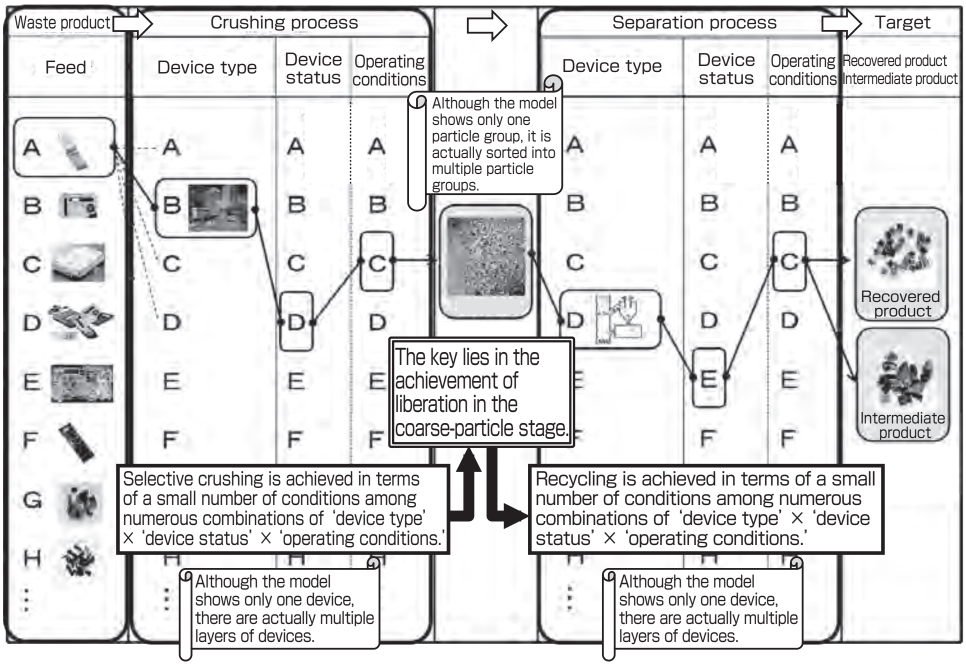
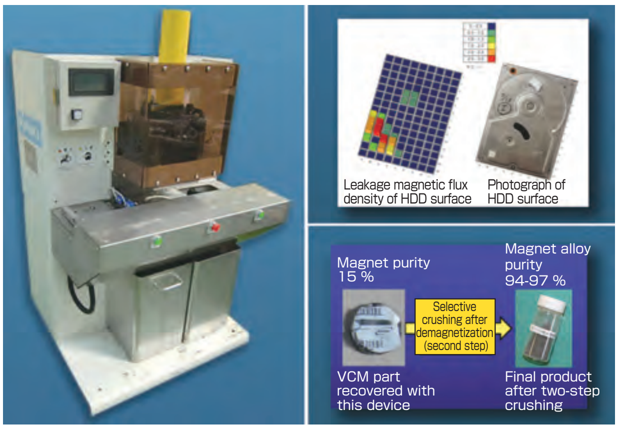


Fig. 2 Highlights of the process of optimization based on the physical separation (one crushing/one separation process) model

high-precision separation, through manipulation based on respective product information. For example, the author has proposed a two-step crushing/separation method in which high-purity neodymium magnets containing rare earth are recovered from hard disk drives (HDDs). The 'HDD cutting separator (HDD-CS)' is one example used in this method. When a HDD is crushed, the powerful neodymium magnet typically adheres to the inside of the crusher, causing difficulties such as screen clogging. Even if it should fortunately be expelled from the crusher, a magnetic aggregate may immediately form on the nearby crushed steel plates, and liberation cannot be achieved. Therefore, the typical practice is to incorporate a demagnetizing process as part of the physical separation. Since the neodymium magnet has a low Curie temperature, its magnetism can be removed by heating to around 350 °C. However, since it is not efficient to heat 50-times more metal in order to demagnetize the neodymium magnet comprising only about 2 % of the total HDD weight, the search for an efficient demagnetization method continues. The author focused on the fact that HDDs, unlike other small appliances, have roughly the same shape and structure regardless of the manufacturer, year, or model. The HDD-CS (Fig. 3), developed jointly with Kinki Industrial Co. Ltd., senses the stray magnetic field of the HDD surface, using four magnetic sensors and two position sensors, and detects the position of the neodymium magnet using a nondestructive method. The HDD is then transported directly beneath the non-magnetic cutter, and the magnet part is punched out before demagnetization. A database for leakage magnetic flux density for each HDD is created, in order to increase the detection precision based on device optimization data. Although the device is small and inexpensive, it can automatically process 400,000 to a million HDDs per year. The magnetic parts, concentrated roughly tenfold by the device, undergo demagnetization, impact crushing, and screening, and magnet powder of 94-97 % purity has been recovered.



Jointly developed by author and Kinki Industrial CO. Ltd., license agreement with Kinki Industrial CO. Ltd.

Fig. 3 Recycling of neodymium magnets using an HDD cutting separator (jointly developed with Kinki Industrial Co. Ltd.)

3.2 Automated control of separation – Smart operation

In the case of HDDs, we were able to recover the magnet merely through impact crushing and screening, but normally separation optimization is difficult even if liberation is achieved. As noted earlier, there are typically three to ten steps in a separation process, and the combinations of separation conditions are astronomical. In the face of such a massive number of possibilities, the typical response is to abandon the thought of device separation, before ever having sought to optimize the performance of the device. The author investigated a method for quickly obtaining such optimal conditions, through numerical computation using a database; and the resulting 'smart operation' system automatically operates the device under optimal conditions, without need of skilled worker involvement. By applying this technology to the recycling of printed circuit boards, we were able to develop the world's first separation process that enables successful recycling of tantalum capacitors; and in the spring of 2012 the system was installed in a recycling plant promoting the urban mining business model.

Tantalum is an expensive metal among rare metals. As it is rarely recycled at present, it has been designated by the Japanese government as one of the five mineral types (tungsten, tantalum, cobalt, neodymium, and dysprosium) to which recycling should be given priority. Most of the tantalum in use is employed in the tantalum capacitors on printed circuit boards. In the early stages of system development, the author followed the conventional separation theory (Fig. 1) and attempted liberation by finely grinding the printed circuit boards, focusing solely on the liberation of tantalum elements (which exist mainly as oxides). However, recovery was not possible after fine grinding and separating, because of tantalum's oxide properties. Although the tantalum could be concentrated several times, it could not be recovered since the weight ratio of tantalum in the printed circuit board was about 1,000 ppm, and it could only be recovered as a heavy product along with precious metals and other heavy metals. As noted above, rare metals such as tantalum must be separated from copper/precious metals before pyrometallurgical treatment, and thus tantalum could not be extracted as a resource using the above method. However, at a joint-research partner company, an electronic device was exfoliated from the printed circuit board in its original form using a particular crusher. Nonetheless, it seemed impossible to recover only certain electronic devices among the wide variety of such devices. However, the author reasoned that each electronic device, among this seemingly disorderly amalgam, would possess unique separation properties because all were artificial; and thus attempted to determine the optimal separation pattern in which the tantalum capacitor was targeted as the liberation item. It seemed impossible, however, to determine such optimal conditions based on conventional separation experiment data. Therefore, we categorized over 400,000 electronic devices, recovered from PCs, into 1,680 categories, and created a database containing their characteristics and separation properties. Then, roughly two quadrillion separation patterns, including repeated use, were generated through numerical computation, for three separation methods, including size, specific gravity, and magnetic separation, to narrow down the optimal conditions for concentration of the tantalum capacitors. By this means, separation conditions were discovered in which the recovery rate (weight percentage of recovered tantalum capacitors among the tantalum capacitors in the exfoliated electronic devices) was 80 % or more, and the quality (weight percentage of tantalum capacitors in the recovered product) was 80 % or more, in six steps, beginning with the separated electronic devices (Fig. 4).

Although the optimal separation pattern became apparent, there was no existing device that satisfied these separation conditions; and therefore dedicated devices were developed. The inclined and low-intensity magnetic-shape separator (Fig. 5a) is a small device that plays a supplementary role. It is a hybrid device that recovers aluminum electrolytic capacitors in the inclined conveyor separating area, and quartz resonators in the weak magnetic separating area. In the shape-separating area, the cylindrical aluminum electrolytic capacitors are recovered by rolling, and a constant load swing pin-gate mechanism was newly developed to enhance the rolling process. In conventional magnetic separators, some of the tantalum capacitors adhered to the magnet. Therefore, a mechanism for accurately maintaining an extremely weak and uniform magnetic flux density on the conveyor surface was developed, and this was successful in recovering only the quartz resonators that contained high amounts of iron. Using this device, iron and aluminum are recovered separately, and the supply volume is restrained by sending the remnant, including tantalum capacitors, into a pneumatic separator. This double-tube pneumatic separator (Fig. 5b) is the main device in the separation process. The air velocity inside the two tubes can be accurately controlled using one blower. In the first tube, electronic devices heavier than the tantalum capacitors are collected by gravity, while the tantalum capacitors and lighter devices are sent to the second tube, where only the tantalum capacitors are recovered, again by gravity (Fig. 5c). Based on numerical computation, the air velocity in the first tube is set slightly higher than that in the second tube. Normally, when updraft is generated in a tube, the velocity will be greater in the center than on the periphery. Given this, in the present system, even among similar electronic devices some will rise and others will fall, and precise separation cannot be expected. Therefore, the author developed a mechanism

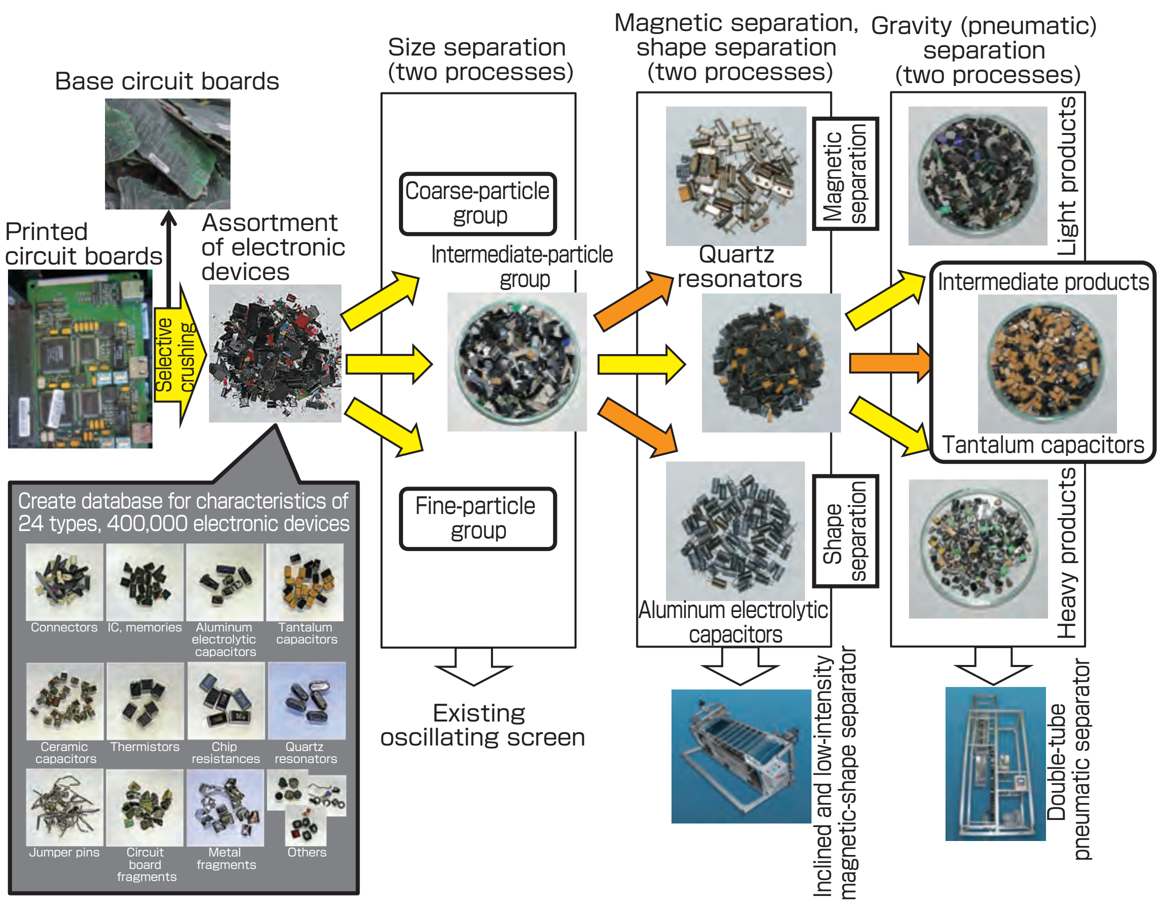


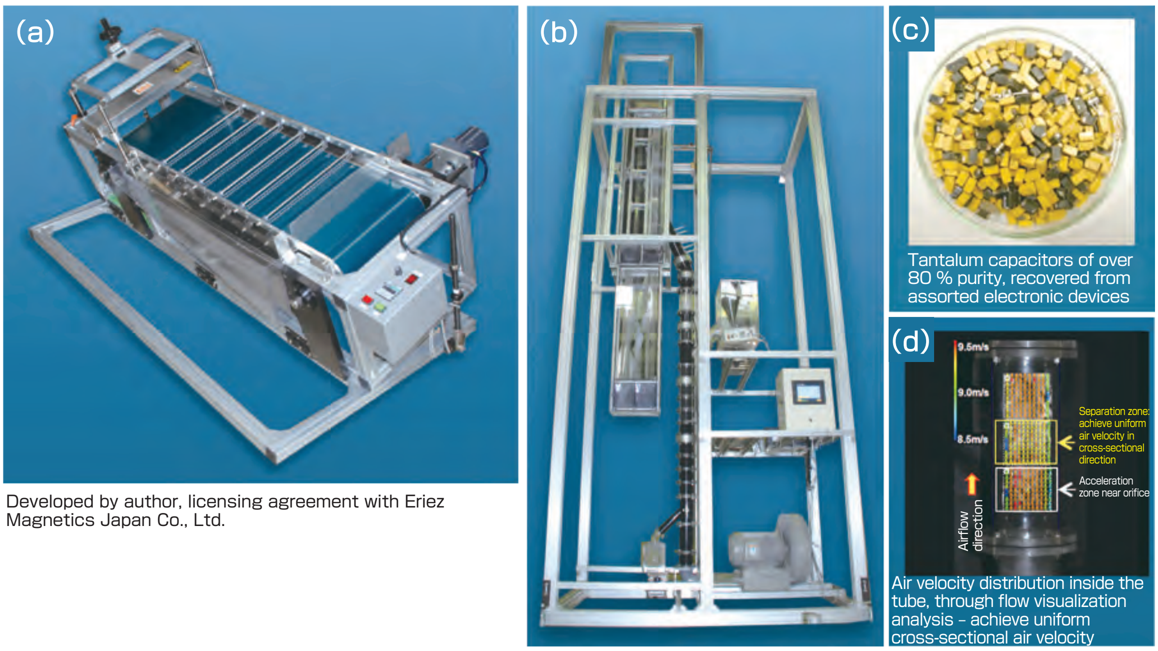
Fig. 4 Recovery process for tantalum capacitors extracted through calculation based on the database

for creating uniform cross-sectional air velocity in the tube (Fig. 5d), which enables clear-cut separation. Also, devices with falling velocity near to that of the updraft inside the tube tend to fall into an irregular up-down motion, based on the posture of the devices in the tube, thereby impeding rapid separation. To avoid this, an orifice structure was installed to increase separation speed. Also incorporated, for the first time ever in such a device, were several mechanisms acting as pneumatic separators, including a joint mechanism whereby the devices travel quickly while the air velocity is held constant in the two tubes. Through operational control based on the electronic device database, the entire operation, from calibration to the recovery of devices, can be automated merely by selecting the target devices (such as the tantalum capacitor) on the display.

By means of these developments, the previous grade of recycled tantalum capacitors (limited to roughly 10-30 %), was dramatically improved, to a maximum of 97 % quality, in the test run at a commercial plant in which the two separators were installed. Moreover, even if the target product specifications are partially changed, there is no need to start from scratch: recalculation of the optimal separation conditions can be easily performed simply by updating the respective product information in the database. Although installation of easy sensing and smart operation technology is only recently underway, it is expected that several hard-to-process resources will be efficiently recovered through these innovations in physical separation technology.

3.3 Strategic Metal Resource Circulation Technology (Urban Mining) Project

In urban mining, recycling cannot be achieved merely through the introduction of new technology in the resource recycling loop; the peripheral environment must also be restructured. To achieve sustainable cycling of strategic metals, it is important to construct not only appropriate resource processing technology such as physical separation devices, but a series of complementary systems, from product design to supply of recycled materials. Thus, the author initiated the Strategic Metal Resource Circulation Technology (Urban Mining) Project, whose aims extend from the technological development of strategic metal recovery from current urban mines to the creation of future strategic urban mines, supported by the strategic budget of AIST (the project was renamed the ‘Strategic Metal Domestic Resource Circulation Project’ in 2013). The project aims to promote AIST’s resource circulation vision, and to organize and coordinate the research bases for strategic metal recycling in Japan, over a three year period beginning in FY 2012. This project consists of 5 topics that will be studied by over 30 AIST researchers across 7 research units (Fig. 6). Topic 1 is the selection of next-generation strategic metals and the evaluation of their true recycling potential. Topic 2 is the construction of a property and separation database for waste products that are targets for strategic metal recovery, and the development of automated separation technology for products containing significant quantities of strategic metals. Topic 3 is the establishment of pretreatment technology for smelting, to ensure that recovered waste products become



Developed by author, licensing agreement with Eriez Magnetics Japan Co., Ltd.

Developed by author, licensing agreement with Eriez Magnetics Japan Co., Ltd.

Fig. 5 Recycling of tantalum capacitors using inclined and low-intensity magnetic-shape separator and double-tube pneumatic separator

appropriate smelting materials. Topics 1-3 advance the ‘recycling vision’ in which strategic metals are recovered from the current ‘disorderly’ urban mines. Topic 4 involves study of the necessary minimum recycling design guidelines to enable recycling of products that remain difficult to recycle even after the investigation in Topics 2 and 3, particularly from the perspective of physical separation technology. The proposal of a recycling ‘production vision’ in Topic 4 aims at the construction of ‘strategic urban mines’ whose future waste products will be suited to the Japanese recycling infrastructure from the production stage. Topic 5 advances AIST’s ‘production-recycling integrated vision,’ which is a fusion of Topics 1-4. Highly efficient and internationally competitive resource circulation cannot be achieved as long as individual recycling technologies developed in Japan are scattered and disorganized. Therefore, the ‘Strategic Urban Mining Research Base (SURE)’ has been organized as a base for the industrialization of Japanese recycling technology, and it aims at full operation after the project’s completion.

4 Summary – Prospects for R&D

Japan has very few natural metal resources, and urban mines are one of its most promising domestic resources. Fortunately, it has utilized an abundance of rare metals in manufacturing and has focused on recycling in a timely fashion as a means of maintaining supplies. Therefore, as of 2013, the level of rare metal recycling technology in Japan is unparalleled in the world, exceeding that of Europe and the United States. If this advantage can be maintained in future, it can be exploited as a resource development tool comparable in value to the natural endowments of resource-rich countries. However, many challenges must be overcome. First, since it is difficult to forecast the future product market, it is difficult to design the recycling technologies that will be needed in, for example, 30 years; and even if such technology is designed, the period during which it can be employed will typically not be long because the product cycle is short. Furthermore, as the products are updated, resource savings and switchovers to less expensive metals will increase in the mid- to long-term. The concentration of important metals in products will gradually decrease, and further advanced recycling technologies will become necessary. On the other hand, though a stable supply of rare metals is of decisive importance to manufacturing, the distribution volume of the rare metals themselves is low and the market is not large. Therefore, they do not require large-scale recycling infrastructure, and new technologies developed by Japan are likely to be implemented relatively quickly in other countries. Thus, for Japanese technology to remain preeminent, it is necessary to maintain a technological advantage of three to five years at all times, and be able to swiftly and continuously introduce new recycling technologies.

In the development of urban mines, many issues center on physical separation. However, in the current situation, the comprehensive effort to tackle large issues and the development of new technologies are progressing sluggishly because the number of researchers in the field is small. Therefore, the development of urban mines may lag behind the social demand, even before encountering international competition. Thus, the Strategic Metal Resource Circulation Technology (Urban Mine) Project, in which strategic efforts, from production to the development of recycling technologies, are made in concert with corporate collaboration and human resource training; along with the resulting Strategic Urban Mining Research Base (SURE); are expected to provide visionary leadership with regard to resources in Japan, in order for the country to survive in the face of resource nationalism on the part of other countries.

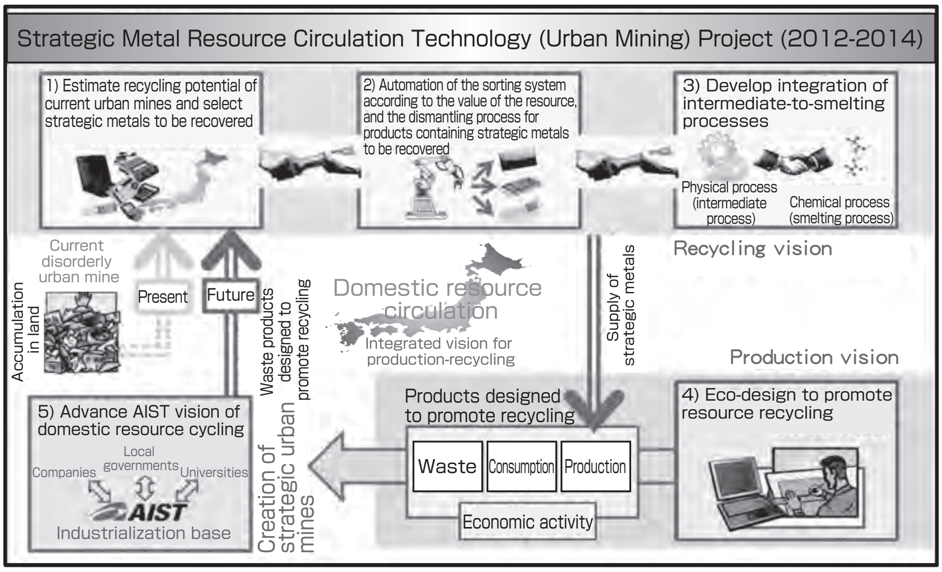


Fig. 6 Outline of Strategic Metal Resource Circulation Technology (Urban Mining) Projec

Author

Tatsuya OKI

Completed the doctoral program at the Graduate School of Science and Engineering, Waseda University, in 1994. Ph.D. (Engineering). Worked as a research associate at Waseda University, and then joined the National Institute of Resources and Environment, part of the Agency of Industrial Science and Technology, of the Ministry of International Trade and Industry, in 1995. Leader of the Advanced Recycling Technology Research Group, of the Research Institute for Environmental Management Technology at AIST, in 2009. Engages in the development of recycling technology for rare metals, including tantalum capacitors, mineral processing technology for submarine hydrothermal polymetallic sulfide, and others. Participated in several NEDO and JOGMEC projects involving resource processing technology. Established the Strategic Urban Mining Research Base (SURE) at AIST in 2013.

Discussions with Reviewers

1 Overall comment

Comment (Yasuo Hasegawa, AIST; Mamoru Nakamura, Materials Research Institute for Sustainable Development, AIST)

This paper describes R&D in which rare metals are successfully recovered from waste home appliances through optimal physical separation; whereas, before, this technology was not viable due to cost. I think this research paper is appropriate for *Synthesiology*, both in composition and content. The proposal for the design of processing technology that allows “waste products” to be used as “urban mines” by efficiently extracting valuable rare metals from various discarded products, as well as the related testing process, are useful and will also be of value to researchers in other fields.

Question & comment (Yasuo Hasegawa and Mamoru Nakamura)

Please explain in detail why rare metal recovery from waste home appliances was not successful until now, and the precise nature of the breakthrough for the author?

Answer (Tatsuya Oki)

Rare metals account for only a very small fraction of the composition of most manufactured products, far below the concentration of structural materials such as iron and aluminum. Therefore, economically feasible recovery through pyrometallurgical methods involving high-temperature reactions, or hydrometallurgical methods involving chemical reagents, has not been possible. It is important to achieve primary concentration by means of physical separation. To this end, it is necessary to develop technology capable of liberating large particles as much as possible, or separating intact electronic devices from printed circuit boards, and to selectively recover the elements containing rare metals.

In the case of the study’s tantalum capacitors, the characteristics and separation properties of 400,000 electronic devices recovered from PCs were entered into a database, and projections were made, through numerical computation, for the results of roughly two quadrillion separation patterns, including repeated use, for the size, specific gravity, and magnetic separation methods. We discovered separation conditions that enabled the recovery of tantalum capacitors at a rate of over 80 % both in purity and recovery, in six steps, from the separated electronic devices. I think the greatest breakthrough consisted in determining the optimal separation conditions, and this process is described in subchapter 3.2.

The development of technology for recovering neodymium magnets containing rare earth from HDDs, described in subchapter 3.1, involved the unique process of punching out the neodymium magnets that had been detected nondestructively by leakage magnetism using magnetic and position sensors. By concentrating the magnetic material roughly tenfold, significant energy savings and increases in economic efficiency were achieved in the subsequent demagnetization, impact crushing, and screening processes. In this technological development, the leakage magnetic flux densities of various HDDs were entered into the database; and, through optimization based on this data, automated processing of 400,000 to a million HDDs per year could be achieved by a small, low-cost device.

System design management and *Synthesiology*

— Methodology to tackle the issues of modern society and to utilize the research results in society —

[Translation from *Synthesiology*, Vol.6, No.4, p.246-254 (2013)]

The Graduate School of System Design and Management, Keio University was established in 2008. This school aims to create a comprehensive and integrated discipline that offers creative solutions to various issues in our society. Since their way of thinking is instructive for *Synthesiology*, a journal that seeks synthetic methodology for disseminating the research results into society, we discussed some common interests and ways of collaboration in the future.

***Synthesiology* Editorial Board**

Participants of the round-table talk

Takashi MAENO	Professor, Graduate School of System Design and Management, Keio University
Hidekazu NISHIMURA	Professor, Graduate School of System Design and Management, Keio University
Ken'ichi TAKANO	Professor, Graduate School of System Design and Management, Keio University
Naohiko KOHTAKE	Associate Professor, Graduate School of System Design and Management, Keio University
Hideyuki NAKASHIMA	President, Future University Hakodate

< Editors in charge of dissemination of *Synthesiology*>

Motoyuki AKAMATSU	AIST
Naoto KOBAYASHI	Waseda University

Kobayashi

Because the Graduate School of System Design and Management (SDM), Keio University was established in 2008, and *Synthesiology* was launched in the same year, we feel a special connection. I have heard that SDM aims to understand the social issues systematically, to analyze them, and to creatively design the solutions. I think this way of thinking has something in common with the objectives of *Synthesiology*. Now, Prof. Maeno, can you start by explaining the characteristics of the SDM education and research activities?

Tackle the issues of modern society by practice of overarching integrated discipline

Maeno

The conventional disciplines focused on specific fields and analyses, and were separated into individual compartments. However, in modern society, everything has become large-scale and complex, and this is causing numerous problems. Even if one has a core specialty, that alone cannot solve problems. A rocket cannot be created by mechanical engineering alone, nor can a policy be formulated with the discipline of economics or law alone. Therefore, SDM was established to create a new interdisciplinary study that can integrate the disciplines based on the demands of society.

Although there are graduates fresh out of college at SDM, the majority of our students have work experience, and people who already have their specialties can learn here. First, we thought there would be many engineers, but it became a gathering place of people with diverse backgrounds including marketing consultants, artists, business managers, university professors, and others. This is one characteristic. The second characteristic is the creation of the discipline of SDM that integrates diverse research domains, and people of diverse backgrounds speaking a common language. That's our new attempt.

One of the cores of SDM is "systems engineering." In Japan, system engineering tends to be seen in its narrow sense of IT engineering, but actually it has recently been defined as a discipline for interdisciplinary problem solving. In our education, system engineering is expanded into research of social systems.

Another core is "design thinking." This originated from Stanford University and IDEO, and it is a discipline for creating something new from scratch by innovative co-creation. It is a discipline for “thinking as you make” and “go ahead and fail rather than receiving proper evaluation,” and therefore, it has been thought incompatible with engineering. I think our characteristic is to do both. This means we somehow integrate the development of large-scale systems through systems engineering and the activities for innovative and free creations.

I think our goal is similar to *Synthesiology*. However, we use the word “system.” The difference between “system” and “synthesis” is, “system” includes the meanings of “to synthesize” and “to break down systematically,” and it takes the stance of doing both synthesiology as well as conventional studies. By doing both, the “parts” and the “whole” can be designed. Through the unique method of SDM studies, we fill in the conventional, so-called “valley of death” research areas just as in synthesiology.

Nakashima
The word “synthesiology” emphasizes synthesis, but I think we need both analysis and synthesis. To synthesize, it is necessary to analyze after something is made as well as analyze before making.

How to seek out the social issues

Kobayashi
One of the methods of synthesiology is: to set a clear social goal, to create a scenario by backtracking from the goal, to synthesize the elemental technologies according to the scenario, to provide feedback after social test run and evaluation, and then to further elaborate the scenario. In case of SDM, do the students themselves decide, “I want to set this subject as the social goal”?

Maeno
In systems engineering, the initial requirement analysis of the V model, and in design thinking, the activities of design thinking itself correspond to the setting of issues and goals. It is the phase of going out into the field and capturing the demand of society, and it is indeed the entrance of both disciplines. We are putting plenty of emphasis here in our education and research.

Kobayashi
We use the phrase “problem-solving type,” but it seems extremely difficult for the students or researchers to go out and find the problems.

Maeno
It is difficult, but it is the point on which we must spend our maximum effort. Speaking in the context of design thinking, I think it is important to do fieldwork such as participant observation (ethnography) to jump in and to contemplate the world, to understand the world by appreciating other people’s ideas as diverse people gather in lively brainstorming, and to understand the world by making various prototypes and having the people of the world see it.

It is “co-creation” rather than staying in the framework of academia. By working together with people of various fields and society, time is spent to clarify what competence one has and what should be set as the goal. In the prerequisite course called “design project,” this part is structuralized in the first half of the course where the student spends effort to fine-tune the goal. The “why” is visualized through various methods such as a thorough modeling of society.

Nakashima
Thinking in terms of information systems, I feel that the “technology” and “goal” of system design are two sides of the same coin. A dream is useless unless it is realizable. Things cannot be realized without the supporting technology. In that sense, the goal and technology must form a loop in which we go from one end to the other, and then come back. It’s also related to Prof. Kobayashi’s previous question. Although information researchers can think of all sorts of goals because they’ve got plenty of technology, what is a truly good goal? When you ask this question, it must be considered together with sociology to be successful. However, there are many people who do social analysis, but there are few who do social design. In that sense, I am very interested in SDM.

Maeno
It is exactly as you say. We present the solution to a problem using the V model. We require the humanities students to learn research in the form of design and verification of systems. Inversely, the science students must thoroughly learn to clarify the social goal.

Nishimura
I think the expression “in systems engineering” narrows things slightly. Therefore, speaking of the social goal for SDM, it is difficult to set the goal. When we do workshops copying the Future Center, for example, and say, “let us discuss the energy problem” or “how should regional mobility be,” we’ll never be able to reach a conclusion even

Dr. Takashi Maeno

after two or three hours of discussion. It doesn't necessarily mean that the goal can be set if we spend more time. If we have to set a goal, it is necessary to academically study how to set the goal. Yet, we can't start anything unless we decide on something. Therefore, in educating our students, we show, in some kind of form, how things may progress once the goal is set and actions are taken toward achieving it, and get feedback. If we say, "Failure is not allowed," nothing will move, so we say any action can be taken during a certain period, and then we move on.

Kobayashi
An abductive inference, being the third-type inference that is different from either deduction or induction is, important. Here, the hypothesis must be formed, and the ability to formulate a hypothesis is important.

Takano
I am working mainly in the field of social science, and I think the primary key point of research is "how to form the hypothesis," as you mentioned. The problem definition starts with "it really should be so." However, there is a gap with the real situation. Because the problems are complexly correlated with many issues in the modern society, one may fix an overview in a certain domain by following a certain process if one can analyze and identify the overall structure of the problem, such as this problem is affected by this issue and therefore the result is leading to this way. After gaining the overview, although it is impossible to solve all the problems that are complexly intertwined, the student can concentrate on the domain in which he/she can pragmatically and empirically research during two years. The student then forms a hypothesis and sees whether the hypothesis is correct using the social science methods such as questionnaires, ethnography, or interviews.

I mainly use the questionnaire surveys and apply the covariance structure analysis to see whether there is a cause-effect relationship as stated in the hypothesis. By doing this analysis, new cause-effects and new perspectives arise, and I think this generates possibilities that may lead to new problem solution. If one finds the cause-effect of a problem, one must make some proposals. In shaping the proposal into specific projects, the collaboration with companies become necessary, and I feel that verification cannot be achieved unless a long-term view is taken.

Dr. Hidekazu Nishimura

Verification and validation of research

Kobayashi
Yes, I think a lot of time is needed when we try to take research all the way to verification. How about the methodology, Dr. Akamatsu?

Akamatsu
From the discussions so far, because the activities of SDM lies on the side of real society, verification might be difficult. I think it is impossible to evaluate without bias to see whether a problem had been solved. If it is mere technology, the verification is somewhat easier. But if it is about whether the technology is truly being used in society, we must evaluate how the technology is positioned in society. In natural science, we have no method for verification in a non-stationary society.

Takano
There is irreversibility in the social phenomenon. For example, we cannot compare under completely same conditions the situation in which action A was taken or not taken. It cannot be verified that there was no other factor involved, and that makes sufficient verification impossible.

Akamatsu
That is true. I'd like to ask a question. Although natural science type verification is impossible, a student works on a project at SDM and says, "This worked!" or "This didn't go well." To do so, there must be some kind of evaluation or decision involved. From what perspective do you evaluate?

Maeno
Our research theme is to "think of things as systems," and so, it's diverse. The case of a technological system such as, for example, the verification of whether a human-machine interface works properly can be done with clarity. On the other hand, we had a student research the "design of negotiation for world peace," but complete verification is not possible for such a topic. However, we instruct the students to do research from the perspective of creating some sort of system design, doing some kind of verification, and executing both verification (do the right thing) and validation (do the thing right) as much as possible.

I think good research is to design a clear, novel system regardless of the theme or scale, and to conduct verification and validation. In case of a system that has been narrowed down, the verification can be done clearly, and the student who engages in such research is questioned about the novelty of the system to check whether it is not merely nitpicking.

On the other hand, the student who takes on a large and ambiguous system like the research of peace or happiness must conduct the research as systematically as possible, by clearly stating the basic concept and then engaging in questionnaires, interviews and multivariable analysis. I think good research is when one knows what can be verified and what cannot be verified.

Takano

Since two years is a limited time, it may be difficult to verify the proposal. Therefore, I think it is necessary to carry on the research to the following generation of the laboratory. The hypothesis is formed, verified, and a proposal is made. It is verified over the next two years before the final evaluation is made. If such continuity at the lab is guaranteed to some degree, I think verification can be done in a large, continuous flow.

Maeno

You mean the students engage in small verifications, while actually being part of a greater verification?

Takano

Yes. Like accumulating and stacking the V. That’s the idea.

Kohtake

In the social system, a behavior does not necessarily reoccur, and it is more difficult to clarify what is the boundary of the system compared to a technological system, and I think it is important to be aware of this limitation. When the students conduct verification, I tell them to work with hands and heads after firmly understanding what the range of verification is, which methods are used, and why these methods are applied. The assumption is that not everything can be included as subjects, but the verification may be possible if the definitions are set solidly. To have them understand that there are various verifications other than actually running the system, I think that is the value of being at the graduate school for two years.

Methodology of synthetic research

Kobayashi

On synthesiology, Prof. Nakashima wrote an article “Discipline of constructive research fields: toward formalization of ‘synthesiology’” in Volume 1. May I ask you to introduce it?

Nakashima

My research theme is artificial intelligence (AI), and I am very interested in situatedness or dependence on the environment of human behavior. When we represent a piece of knowledge as a rule, there are many cases that do not match the expression. This is the frame problem often addressed in AI. Simply taking out a piece of knowledge formally does not work. A computer cannot run unless there is a program to express the rule completely but somehow human beings can manage without it. There were researchers who studied situational theory at Stanford University, and I thought they were studying something similar but it was different. What I learned from reading Dr. Atsunobu Ichikawa’s *Boso Suru Kagaku Gijutsu Bunmei* (Runaway Science and Technology Civilization) was that Stanford researchers look down at situations from above. This means that they assume there is a being like god or the constitution that transcends the system in question, while Japan allows different rules for different groups. We want a situated representation, or a view from inside the system. I think that is the difference.

The experiment introduced by linguist Dr. Yoshihiko Ikegami is illuminating. The first sentence of Yasunari Kawabata’s *Snow Country* translates into English as “The train came out of the long tunnel into the snow country.” When a reader of the English version draws a picture, it is drawn as the train exiting a tunnel from the bird’s eye perspective, while a reader of the original Japanese version draws a picture from the passenger’s point of view, from inside the train. Anyway, the position of synthesis includes the analysis as its part. I am thinking recently that synthesis is not the counterpart of science, but contains science within. Something larger is constructed only after proper science. In fact, when we excersize science, we run the loop of hypothesis and verification. The hypothesis is made, experiment is done, and if the hypothesis is rejected, we revise it.

Another point is about dealing with multilayered

Dr. Ken’ichi Takano

Dr. Hideyuki Nakashima

systems. There is the loop of noesis and noema, which are terminologies first used by Husserl and then used by phenomenologist Bin Kimura. Taking music as an example, the "future noema" is a score of the music that one wishes to play, "noesis" is the sound actually played, and "current noema" is the music conceived by hearing the sounds played. Assume that there is an idea or a requirement, and say that it is externalized and an object is created, but when the object is analyzed, there is a slight gap between the object and the initial idea. Therefore, it goes back to the requirement again. There are cases where the design is adjusted, but there are also cases where the initial requirement is found to be wrong and reconsidered. However, I think the interaction with the environment that is not present in the initial assumption plays a large role. When we talk about service science, I would say that this interaction with the environment corresponds to the actual execution of service. Hence, design is what is done at the level of conceptual layer, or noema, and service is what is actually done at the physical layer, or noesis, and I think we must run back and forth from one to the other.

Maeno

Although the manner of expression is different, I agree. I think we are doing the same thing.

Nishimura

I think musical performance is an extremely good example. It means that what was imagined in the mind, or what one only thought about is actually put into action. The actual action may go in a completely different direction than imagined, or it's called controllability in control engineering, but one may realize that the input in full force is meaningless. Then one must approach from a different direction. There is relatively a large number of people who end up with an armchair theory only, but one will understand if some of the theory is put into action. I think it is like turning the loop in a short time.

Maeno

Exactly as you say. The old system engineering said, "It is entirely possible if it is planned. There is supposed to be no noesis." However, current systems engineering is about repeating or taking in the design thinking. We include in the education the way of problem solving by subjectivity or immersion of oneself rather than taking the god's point of view.

Takano

In relation, I think the perspective of QCD (quality, cost, and delivery) is extremely important. To complete the project successfully, the upstream process in the project implementation is important. One must think about the concept of operations, consider the use cases of the product at the beginning, ponder what kind of usages there are and which demands will arise, and then think through on behalf of the stakeholders. If this is done, there is the merit of being able to develop, at the initial stage, only the functions that are frequently used. We engage in such verification research.

Nishimura

I think it is important to think as much as possible of the environment around the system as well as the interaction with the external systems.

Analysis of synthesis method for linking the research result to society

Kobayashi

The requirements of *Synthesiology* are "to describe the research goal" "to describe the social value of the research goal," "to present the scenario and to select the elements," and "to correlate the elements and to integrate and synthesize them." To study what types of synthesis methods were used, in 2012, we analyzed 70 papers published in *Synthesiology*. Through this study, I considered three basic forms of synthesis method: 1) aufheben type that is a method of creating new technology by integrating very different elemental technologies A and B, 2) breakthrough type that is a method of combining the realized important elemental technology with peripheral technology to nurture them into an integrated technology, and 3) strategic selection type in which the synthesis is done by strategically selecting the elemental technologies. We conducted the analysis based on these three types, but realized that feedback was also important. The feedback loop must be turned several times, particularly in biotechnology, life science, and human technology that require verification through test runs in the real society. Also, the method for introducing the technology into society did not readily emerge from these papers. Dr. Akamatsu, would you explain the situation?

Akamatsu

Our target is mostly natural science and technology, but if we create a product, it is meaningless unless it is used in society. Considering how the products are introduced to society, I categorized the ways in which the authors of the papers accomplished this.

Roughly categorizing the cases where "the demand is clear

Dr. Motoyuki Akamatsu

in industry,” “the demand is not clear in industry,” and “it is established and diffused as an industry,” the ones with “clear demands” include, for example, the construction of a traceability system for the metrology standard. In the world of standards for precision verification, the goal is clear, and although there may be more than one answer, it is a world that allows a logical scenario of what is necessary, what systems are necessary in order to supply the standard, and where it is supplied. However in the case where “the demand is not clear in industry,” there is no logic that fills the holes because you do not know where the holes are. By exhibiting the elemental technology and providing samples, we get the potential target users to actually use the prototypes, and have them extract the issues. This is fairly simple, but there is a great hurdle in getting the people of the companies to use the research results in reality. In general, people are all conservative, and although they know the merits of introducing a new technology, they cannot take the step. What do we do? In this case, we build a strong relationship with the corporate people to promote the understanding of the product value, and wait until they feel, “We got to do this.” In the case of “establishment and expansion as industry,” we see examples among papers of a product being introduced to the perceptual lead user who is one step ahead of the trend and everyone else follows. Another example is a product spreading through collaboration and joint development with competitors on a common issue of standardization as seen in the diffusion of car navigation. The researchers choose the method that they feel is the best, and I think it will be good if we can see beforehand what method should be taken for certain types of products.

Issues of system design and management science and synthesiology toward innovation

Kobayashi

My expectation is by deepening the study of such patterns, we might be able to find out what elements are needed or how things can be combined to achieve innovation. Is it possible in SDM studies to say, “Innovation happens if we do this and that”?

Nakashima

If we know that, it’s not innovation!

Dr. Naoto Kobayashi

Nishimura

I really think so. Recently, there’s the system of systems, and even if a product or service is introduced thinking that one understands the requirement, it turns out that rather than following the requirement, it is used completely differently due to the interaction with other systems. The person who devised the current email system probably thought it would be a great idea to be able to send a simple message like, “Hey, let’s go have lunch together,” but now it’s become a system where we’re not sure whether it’s useful or not useful for work. Whether it was made according to requirement, perhaps it was not, we don’t know, but it’s somehow generating innovation. We try to intentionally design an innovation, but it’s quite difficult.

Maeno

There are methods that are widely diffused in society, and although we can’t make Steve Jobs just by using them, I think an ordinary person can become slightly more creative and innovative. I think our education is one such method where design thinking and systems engineering are combined.

Nishimura

Explaining from the systems engineering aspect, if, for example, there is a product and we define its category by saying, “This can be used only for a certain requirement,” it ends there. We must take one step back, and derive some function from the requirement. Considering what should be done in achieving the function, perhaps something different may work better than a certain physical object. In that case, a different thing leads to innovation for this particular function, and this can be considered as relatively simple systems engineering.

Nakashima

When we teach software to students, I say exactly that. Creating a system procicely following the requirement is not enough. In IT, there is a term called “demand development” where we must think what it is that is really wanted.

Maeno

We are thinking in the same way. Continuing what I was saying, the system is broken down into physical, function, and purpose in systems engineering. Structuralization of the problem is the first thing to do in systems engineering, and it is done by backtracking to the function. In design thinking, the objective itself is structuralized by methods such as building a value ladder. When you track back to “what is the origin?” you may arrive ultimately to peace and happiness. You write them out, and when you change the structure in the highly abstract level, it becomes very innovative. When innovation is seen from systems engineering, it is exactly the design change at the highly abstract level. Innovation that seems way off the wall for an ordinary person may merely be a design improvement when we analyze the objective. I think we can understand it in this manner.

Nishimura

When I think of innovation, I actually think it is a matter of the mind such as breaking the framework or transcending the boundary. Of objectives, people don't really question about whether an objective is truly the objective. When a professor says, "This is the objective," the students may write a paper without questioning the statement.

Takano

There is a major problem of psychological confinement, and I think the biggest problem is how to breakthrough this, and also that students can only think of a society that he/she can imagine. I think the engine to overcome this confinement may be to engage in meta-thinking for creative development, and to think about the "why this" and "why that."

Akamatsu

Aside from whether using the word "innovation" is appropriate, in the case of technology, it's whether people will use the product. If the product does not diffuse in society, at least, it won't be called an innovation. Is there an example of a system that was actually tried on site and was autonomously accepted and used, even after the student completed the thesis research and left SDM?

Maeno

Since the majority of our students are working people, there are several cases where the student is a company president, writes the thesis, and actually uses the system at the company. There are many students who are becoming entrepreneurs rather than seeking employment at large companies. There are cases where the themes of the thesis are realized in a corporate setting. So, there are many cases where the results of the thesis lead to actual business. Time is required for the verification of a large-scale system, and in some cases about 10 years are required. In contrast, when a small system is started by one student, there are more than a few cases where business has actually taken off.

Akamatsu

Were they successful because they grasped the social demands accurately?

Maeno

Yes. Moreover, our discipline includes management, and I think one of the major reasons is because appropriate management was done. In the future, we would like to strengthen the management part, and to change into an organization that can achieve innovative development at the same time.

Kobayashi

I think it is great that SDM incorporated management. Are you trying to make a discipline that includes the method of implementation?

Kohtake

The whole lifecycle, from implementation, operation, to disposal, all the way to the end is the subject of the discipline.

Maeno

We have a course called project management in systems engineering, and there, we provide education for managing a large-scale project. Also, there is a course on organization management led by Prof. Takano.

Takano

Currently, we are working on the diagnosis of the organization, and the goals are "productivity" and "safety." Productivity and safety are considered performance, and currently we are doing a large-scale survey where we may be able to explain the level of performance in terms of the culture and climate of an organization. We are getting results that if the corporate culture is changed for the better, the safety performance increases and the business performance rises. We are gaining understanding of the top management of companies, and we are actually conducting diagnosis of the safety culture in many companies. In such cases, we can mutually agree, "This is the problem in your organization," but when we enter into the domain of how to specifically change the organization, it's not easy because it involves people, money, and resource. However, we are getting examples of a couple of companies that succeeded in making improvements autonomously. For productivity, or improvement of business performance, we are like physicians that point out only the bad part, but I hope it leads to autonomous change of the organization in the future.

Akamatsu

Is such system design management for people who already have their own specialty or discipline, or can the people who do not have any specialty, like the students fresh out of college, learn anything if they are taught?

Nishimura

I think the fresh graduates may be at a disadvantage because they have no experience working and may not understand immediately what we are talking about. Those with work experience have a solid framework, so when they are asked something, they can reply, "Are you talking about this?" However, at the same time, a fresh graduate may say something totally off the wall, and that may be quite interesting.

Maeno

Another thing is, it is not just the experienced person teaching the fresh graduates, but there's "learning in teaching." Because there are many people with diverse specialties, there is an atmosphere where everyone teaches everyone else. We learn a lot, too. We must instruct the fresh graduates carefully. In engaging in teamwork, the elders may actually grow by being with inexperienced youths.

Kohtake

The students with work experience are likely to gain insight during the two years they stay with us. On the other hand, the fresh graduates may start up a virtual company in one of the courses, and actually design a service that is actually operable using small robots. They think they know it all, but they don't. But when they join a company, they realize in the real world, "This is what the professor was saying in the class a year ago." They come back to us and say, "Now I understand how I received the education of seeing the forest for the trees." When they have such experience, it becomes clear to them what they must pursue deeply to continue learning, and I'm glad to hear that.

Kobayashi

We want to make *Synthesiology* a much more open journal. I would like to hear if you have any expectations for *Synthesiology* in the future.

Maeno

When I first found *Synthesiology*, I was surprised. I thought we were blazing a trail, but found that *Synthesiology* was heading for the same destination. Although our stances were different, I was very happy to find that the seekers of same goal were present in a Japanese national research institute and a private university. We are confident that the SDM studies has spread in the past five years and is gaining awareness, and we wish to collaborate with you further in the future.

Kobayashi

Thank you very much for joining us today.

This roundtable talk was held at the Graduate School of System Design Management, Keio University at Yokohama on July 25, 2013.

Dr. Naohiko Kohtake

Profile

Naohiko KOHTAKE
After completing the courses at the Keio University Graduate School, joined the National Space Development Agency (NASDA) of Japan. Worked on the R&D and launching of rockets. Researcher at the European Space Agency (ESA), and senior developer at the Japan Aerospace Exploration Agency (JAXA). Lead the independent verification and confirmation of efficacy of the software used in the International Space Station and satellites. Also engaged in international collaboration with NASA and ESA. Associate Professor, Keio University from FY 2009. Member of Sentinel Asia Project, member of the steering committee for Multi-GNSS Asia, and representative of IMES Consortium. Doctor (Policy & Media).

Ken'ichi TAKANO
Completed the master's course at the Graduate School of Engineering, Nagoya University in 1980. Joined the Central Research Institute of Electric Power Industry (CRIEPI) in 1980. Visiting Fellow, University of Manchester in 1995; part-time lecturer, Waseda University; Senior Researcher, CRIEPI; and current position in 2007. Doctor (Engineering). Worked on risk management and human factor in large-scale technology systems. Books include: *Soshiki Jiko* (Organizational Accident) (JUSE Press), *Hoshu Jiko* (Maintenance Accidents) (JUSE Press), and others. Specialties are development of organizational diagnosis and root cause analysis methods as well as practice for emergence of the safety culture. Experience in practice and consultation of safety management.

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Hidekazu NISHIMURA
Completed the doctor's course in Mechanical Engineering, Graduate School of Science and Technology, Keio University in March 1990 (Ph.D.). Assistant Professor, Faculty of Engineering, Chiba University in April 1990; and Associate Professor in 1995. Currently, Professor, Keio University from April 2007. Professor, Graduate School of System Design and Management, Keio University from April 2008. Engages in education and research for model-based systems engineering. Books include: *The System Modeling Language SysML* (translation supervisor for *A Practical Guide to SysML*), *Basics of Control Theory by MATLAB: Control System Design by MATLAB* (joint author), and others. Fellow of The Japan Society of Mechanical Engineers; Vice Chairman and Director of General Affairs for FY 2013, The Society of Instrument and Control Engineers; as well as members of

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Takashi MAENO

Graduated from the Tokyo Institute of Technology in 1984, and completed the master's course at the Tokyo Institute of Technology in 1986. Worked at Canon Inc., visiting researcher at University of California at Berkley, and visiting professor at Harvard University. Currently, Professor and Chairman of the Graduate School of System Design and Management, Keio University. Doctor (Engineering). Books include: *No Ha Naze "Kokoro" Wo Tsukuttanoka* (Why Did the Brain Create Heart?) (Chikuma Shobo, 2004), *Shiko Noryoku No Tsukuri-kata* (How to Make Thinking Brain Power) (Kadokawa Shoten, 2010), and others. Specialties are human-machine interface design, system design management, regional vitalization, innovation education, etc.

Editorial Policy

Synthesiology Editorial Board

Objective of the journal

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

Content of paper

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

Subject of research and development

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

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

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

Peer review

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

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

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

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

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

References

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

Types of articles published

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

Required items and peer review criteria (January 2008)

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

Instructions for Authors

"Synthesiology" Editorial Board
Established December 26, 2007
Revised June 18, 2008
Revised October 24, 2008
Revised March 23, 2009
Revised August 5, 2010
Revised February 16, 2012
Revised April 17, 2013

1 Types of contributions

Research papers or editorials and manuscripts to the "Readers' Forum" should be submitted to the Editorial Board. After receiving the manuscript, if the editorial board judges it necessary, the reviewers may give an interview to the author(s) in person or by phone to clarify points in addition to the exchange of the reviewers'reports.

2 Qualification of contributors

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

3 Manuscripts

3.1 General

3.1.1 Articles may be submitted in Japanese or English.
Accepted articles will be published in *Synthesiology* (ISSN 1882-6229) in the language they were submitted. All articles will also be published in *Synthesiology - English edition* (ISSN 1883-0978). The English edition will be distributed throughout the world approximately four months after the original *Synthesiology* issue is published. Articles written in English will be published in English in both the original *Synthesiology* as well as the English edition. Authors who write articles for *Synthesiology* in Japanese will be asked to provide English translations for the English edition of the journal within 2 months after the original edition is published.
3.1.2 Research papers should comply with the structure and format stated below, and editorials should also comply with the same structure and format except subtitles and abstracts are unnecessary. Manuscripts for "Readers' Forum" shall be comments on or impressions of articles in *Synthesiology*, or beneficial information for the readers, and should be written in a free style of no more than 1,200 words. Editorials and manuscripts for "Readers' Forum" will be reviewed by the Editorial Board prior to being approved for publication.
3.1.3 Research papers should only be original papers (new literary work).
3.1.4 Research papers should comply with various guidelines of research ethics.

3.2 Structure

3.2.1 The manuscript should include a title (including subtitle), abstract, the name(s) of author(s), institution/contact, main text, and keywords (about 5 words).
3.2.2 Title, abstract, name of author(s), keywords, and institution/contact shall be provided in Japanese and English.
3.2.3 The manuscript shall be prepared using word processors or similar devices, and printed on A4-size portrait (vertical) sheets of paper. The length of the manuscript shall be, about 6 printed pages including figures, tables, and photographs.
3.2.4 Research papers and editorials shall have front covers and the category of the articles (research paper or editorial) shall be stated clearly on the cover sheets.
3.2.5 The title should be about 10-20 Japanese characters (5-10 English words), and readily understandable for a diverse readership background. Research papers shall have subtitles of about 15-25 Japanese characters (7-15 English words) to help recognition by specialists.
3.2.6 The abstract should include the thoughts behind the integration of technological elements and the reason for their selection as well as the scenario for utilizing the research results in society.
3.2.7 The abstract should be 300 Japanese characters or less (125 English words). The Japanese abstract may be omitted in the English edition.
3.2.8 The main text should be about 9,000 Japanese characters (3,400 English words).
3.2.9 The article submitted should be accompanied by profiles of all authors, of about 200 Japanese characters (75 English words) for each author. The essential contribution of each author to the paper should also be included. Confirm that all persons who have made essential contributions to the paper are included.

3.2.10 Discussion with reviewers regarding the research paper content shall be done openly with names of reviewers disclosed, and the Editorial Board will edit the highlights of the review process to about 3,000 Japanese characters (1,200 English words) or a maximum of 2 pages. The edited discussion will be attached to the main body of the paper as part of the article.
3.2.11 If there are reprinted figures, graphs or citations from other papers, prior permission for citation must be obtained and should be clearly stated in the paper, and the sources should be listed in the reference list. A copy of the permission should be sent to the Publishing Secretariat. All verbatim quotations should be placed in quotation marks or marked clearly within the paper.

3.3 Format

3.3.1 The headings for chapters should be 1, 2, 3…, for subchapters, 1.1, 1.2, 1.3…, for sections, 1.1.1, 1.1.2, 1.1.3, for subsections, 1.1.1.1, 1.1.1.2, 1.1.1.3.
3.3.2 The chapters, subchapters, and sections should be enumerated. There should be one line space before each paragraph.
3.3.3 Figures, tables, and photographs should be enumerated. They should each have a title and an explanation (about 20-40 Japanese characters or 10-20 English words), and their positions in the text should be clearly indicated.
3.3.4 For figures, image files (resolution 350 dpi or higher) should be submitted. In principle, the final print will be in black and white.
3.3.5 For photographs, image files (resolution 350 dpi or higher) should be submitted. In principle, the final print will be in black and white.
3.3.6 References should be listed in order of citation in the main text.

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

Book – [No.] Author(s): *Title of book* (italic), Starting page-Ending page, Publisher, Place of Publication (Year of publication).

4 Submission

One printed copy or electronic file of manuscript with a checklist attached should be submitted to the following address:

Synthesiology Editorial Board
c/o Website and 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-ml@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).

Inquiries:

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Letter from the editor

From its initial stage, *Synthesiology* took the stance, "Because synthesiological thinking is universal, the submission of papers shall not be limited to AIST and shall be open to external researchers." However, due to the process up to its launch and the limited recognition of the journal, there have not been as many external submissions as we expected. With the sense of crisis that there will be no future for the journal unless this situation is surmounted, we embarked on the effort to get people outside of AIST to join the Editorial Board. As a result, we were able to obtain the cooperation of the people of Sumitomo Chemical Co., Ltd., New Energy and Industrial Technology Development Organization (NEDO), and Keio University. I express my gratitude to the new members who have agreed to give their valuable time to *Synthesiology*.

In recruiting the external Board members, of course, I had to explain what *Synthesiology* is to the people who were new to the concept, and I was reminded how hard it was to correctly communicate the characteristics of this journal, as well as I wondered how well I understood this concept. I explained, "In an ordinary academic journal, the value of what was invented or discovered is stated, but in *Synthesiology*, the process of how something was invented or discovered is stated, along with the social value that was created (or is being created) through such invention or discovery." Some people may wonder whether this is a standard explanation. The formal answer can be found in the purpose of the launch and in Dr. Yoshikawa's paper in the first edition. However, it is rather difficult to explain clearly using brief and concise expressions, and my tendency is to use extra adjectives.

From this perspective, the content of the roundtable talk is extremely interesting. Why did the SDM of Keio University, an organization with which AIST had hardly any research interchange, resonate with the thinking of *Synthesiology* and actively submit articles? I think the answer is concentrated in the words of the roundtable talk participants. Looking at the profiles of the participants, there is no one who was purely bred within the Keio University, and many people have joined SDM after spending time at companies, research institutes, and other universities. I caught a glimpse of the background where synthesiological viewpoints are nurtured. In reflection, there are very few AIST researchers who have experienced other organizations, although their alma maters may vary, and I feel we must actively introduce external human resources and participate in exchanges.

Executive Editor
Hiroshi TATEISHI

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