Research on the Application of Sprout Technologies in other Fields to Micromachine Technology for Fiscal 1999 (Part II)

Since 1992, the Micromachine Center has taken up various seeds of technology as themes for joint research by academic, governmental and industrial sectors, aiming to reinforce basic technologies by searching for technology seeds, especially in the scientific and technological fields, that are necessary to build various micro systems. In fiscal 1999, research has been carried out on nine themes. Continuing from the last issue, the remaining five themes are summarized below.

Investigation of the Trend Related to the Fusion of Biosensor Technology with Micromachine Technology

Masuo Aizawa
Professor, Graduate School of Bioscience and Biotechnology,
Tokyo Institute of Technology

1. Introduction

The research and development of biosensors has rushed into an age of upheaval. The main reason for this drastic change may be found in the rapid diversification of needs for biosensor technology and the progress of related technologies.

In response to these diversified needs, targets of the research and development of biosensor technology have been clarified as described below:

(1) On-site sensing, (2) massive information sensing, (3) complex information sensing, and (4) ultimate sensing technology. This paper will describe what can be realized when biosensor technology is fused with micromachine technology, and it will investigate the current status of the application of micromachine technology to the foregoing items.

2. Massive information sensing and micromachine technology

The importance of molecular information about DNA and chemical substances has come to be recognized, which in turn has led to attaching greater importance to massive information sensing technology with which molecular information contained in a trace amount of sample can be analyzed at one time. Massive information sensing is used for or expected in the detection of DNA, evaluation of substances synthesized by combinatorial chemistry, and detection of environment-related substances. This paper summarizes the trend of massive information sensing related to the analysis of gene information chiefly on DNA chips, and a report is presented on the findings of the investigation of micromachine technology required in that field. Also summarized are the evaluation of molecular functions in combinatorial chemistry where massive information sensing is expected to develop in the future, the trend of research in the micro total analysis system, µTAS, in neural network information sensing, and the application of micromachine technology.

3. Ultimate sensing and micromachine technology

Chapter 2 deals with the trend toward research of massive information sensing and the utilization and technical problems of micromachine technology. In addition to the micromachine technology chiefly related to processing, another micromachine technology for evaluation and observation is also available. This is probe microscope technology (SPM), including AFM. In recent years, SPM has developed rapidly as a technology for sensing minute targets, and it is beginning to be utilized. Particularly for developing research that delves into the constituents of microorganisms and materials a technology is required that will allow a single molecule to be observed.

With this background, “a probe microscope”, which enables topologic information to be obtained by probing for a sample without relying on light or electron rays, is considered essential as a new technology by which observation and function measurement can be made possible on a single molecular level. This chapter deals with the contribution of micromachine technology in the technology of sensing minute molecules and minute areas with emphasis on various probe microscopes to probe for single molecules and single cells as their targets.

4. Bio-system microprobe

For those with health problems, the aged and disabled, it is necessary to routinely monitor their health management information so that they can participate in social activities. For that purpose, it is most effective to use a sensor embedded in a biosystem for measurement. This makes it inevitable not only to micronize a sensor device, but also to realize the application of the device using materials compatible with a living body. This paper summarized the trends in research of microprobes that can be used directly for a living body along with tasks for which micromachine technology is required.

5. Conclusion

Research and development of biosensor technology has entered a new stage aiming at high performance by micronization and integration. In a narrow sense, DNA chips and µTAS are not categorized as sensing devices. With the enlargement of the base of biosensor technology, however, they have had a strong impact. In this investigative research, by assuming the future targets of biosensor research, the present state of related research was generalized after reviewing how micromachine technology can contribute to the achievement of those targets. Since the related research branches out broadly, its investigation was limited. However, many themes of research and development to be promoted in the future have come to the fore.

Microprocessing technology is making rapid progress. However, sizes that can be processed at present are considered to be on the submicron order. It will be necessary to transfer to a processing form unlike the present one if processing to the nanometer order is required. Further miniaturization is needed, particularly to permit a sensing device to be embedded in a living body. In addition, the device should have a structure wrapped in a material compatible with a living body. Developing a technology capable of using various materials compatible with a living body as the raw materials of micromachines or the importance of developing materials compatible with a living body, suitable for micromachine processing, is expected to grow in importance. Again, for micronizing sensing devices, it is necessary to develop a method suitable for modifying molecules (enzymes and antibodies) precisely into minute materials.

Currently, various research themes to be promoted in the future have surfaced. At the same time, it has been demonstrated that the fusion of biosensor technology with micromachine technology is an important theme for development of future biosensor technologies.

Investigative Study of Chemical Reactions and Synthesis Using Microreactors

Jun-ichi Yoshida
Professor, Graduate School of Engineering,
Kyoto University

Microreactor technology has recently become a new and very promising field within a very short time in the fields of chemistry, process engineering, and biotechnology. The application of micromachine technology to chemical synthesis is progressing at a particularly rapid rate. On finding that this technology could be realized, the chemical industries in Europe and the U.S. have aggressively set about the trial manufacture and operation of microreaction systems in only a few years.

Downsizing as represented by microreactors is expected to contribute greatly not only to future chemical synthesis but also to industry and society as a whole. This has prompted the investigation of chemical reactions and syntheses using microreactors with the emphasis on the nature of reactions, the manufactures of reactors and application to the development of functional materials and drugs.

Several organic reactions using microreactors have already been reported. Particularly noteworthy is the fact that microreactors, characterized by a large specific surface area per unit volume, could realize reactions hitherto considered impossible to achieve. In addition, heterogeneous catalytic reactions and electrochemical reactions that take place on a solid surface will develop dramatically using microreactors in the future. Microreactors are also expected to enable chemical manufacture using hitherto considered difficult to use due to limitations of process engineering and safety. What is more, microreactors enable the realization of a comparatively small-scale economical plant easily and quickly when set in parallel, making it possible to transfer the findings of research and development more promptly to the manufacture of materials. This will simultaneously enable more rapid compliance with market demands.

The technology of chemical analysis or biochips, so-called micro-TAS or Lab-on-a-chip, can be used for manufacturing microreactors. However, other technologies will also be required for the manufacture of microreactors suitable for chemical synthesis because of the great difference in the requirements for organic synthesis and those for analysis and biotechnology. For example, technologies of materials for reactors, joints and connectors that are resistant to solvents frequently used for organic synthesis will become increasingly important.

The applications of microreactors to chemical synthesis involve the development and manufacture of functional materials and drugs. In the former case, it is particularly worth noting that, by the use of microreactors, the process of manufacturing functional materials, including microcapsules, dispersion of micro-particles and polymers, so far considered impossible to manufacture with conventional reactors, will be revolutionized. In the latter case, the development of new drugs by combinatorial synthesis and their manufacture using microreactors attract our attention. Although not many examples have been reported in either case, great developments can be expected in those fields in the future.

Our investigation, which emphasized the above points, reveals that a potential of microreactors has not yet been fully utilized, leaving much room for dramatic and revolutionary development in the future. It is, therefore, premature to completely forecast and evaluate the direction of the development of microreactors. It is beyond doubt, however, that microreactors will bring about a revolution in research, development and manufacture in the chemical industry, presumably wielding great influence on the future shape of the chemical industry as well as our entire society. Microreactors will bring about a new paradigm of science and technology, leading to the creation of new disciplines and new fields of industry. It is indispensable for the development of microreactors in theory, design, manufacture, reaction, and application to concentrate the intelligence in a variety of fields, including microfluidics, microfabrication, process engineering, reaction engineering, microanalysis, catalyst and organic synthesis. Since these fields spread widely over electric and electronic engineering, mechanical engineering, chemical engineering, analytical chemistry, physical chemistry, and organic chemistry, they should be organized to work together. Although the research into the application of microreactors to chemical synthesis is not mature in Japan. However, energetic research and development should be made in the future in view of the growing expectations in this field.

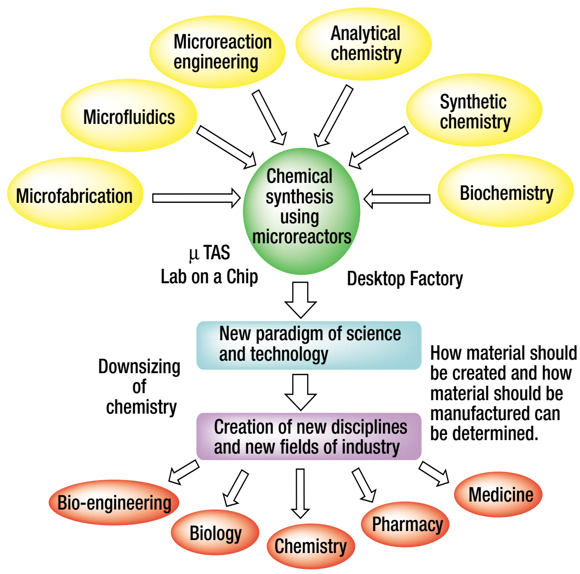

Fig. 1 Chemical Reactions and Synthesis Using Microreactors

Investigative Study of Micro Heat Design Technology

Takayoshi Inoue
Professor, Department of Mechanical Sciences and Engineering,
Tokyo Institute of Technology

It is well known that many problems related to engineering and industry arise from poor heat design and control. This also applies to micromachines, which may break down unexpectedly as seen in malfunctions and failures without a prediction of temperature and heat elimination needs based on appropriate heat design, and heat control based on the above prediction. For instance, deformation due to thermal expansion of component parts, changes in action characteristics at high temperatures, and the progress of corrosion can be cited. This may be attributable to the failure in a temperature prediction for the part that goes out of order and in heat control stemming from poor temperature prediction. It is important, however, to include an appropriate heat design in the design stage.

In the heat design of micromachines as well, it is equally important as in the heat design of conventional size machines to evaluate local heat value and thermal load along with the quantity of heat to be removed when considering how to remove the heat generated. However, the distribution of temperature and heat conduction characteristics in an infinitesimal area have not been entirely clarified because of the very small size of the target machines. This may also explain why no effective cooling system has been satisfactorily established.

This investigative study reports on a technique for measuring temperatures on an immeasurably short scale, the importance of which should particularly be considered in the heat design and control of micro devices, a method for theoretical and experimental handling of contact and interface heat resistance at the component interface, and a technique for calculating heat conduction for heat design.

In micro devices, the area in which temperature information is required is incalculably too small to handle by conventional temperature measurement techniques in many cases. This area may be characterized by requiring a technique of high-degree space resolution measurement. Accompanied by progress in micro processing techniques, measuring techniques have also made progress recently so that it can meet the needs for measuring temperatures at sites in such micro systems. In this investigative study, various techniques for measuring temperatures in the proposed micro areas were investigated for analysis to compile a report on the findings, citing actual examples.

In addition to the foregoing, it is possible to list various problems in thermal engineering as specific to micro devices. Important among these is thermal resistance at the interface of dissimilar materials. Thermal resistance stands for an index by which the difficulty of heat conduction is represented. It may safely be called a physical volume that controls a rise in device temperature because of a large difference caused in an area with a large heat resistance. For example, heat is transferred by conduction in device components such as substrates or thin film devices. However, as is clear from Fourier's law relative to heat conduction, a temperature difference is sure to be caused in the elements unless a material is present with an infinitely large thermal conductivity. This will result in the presence of a thermal resistance, large or small, in those elements. What is more, a temperature difference is caused at the interface of the elements because of the presence of a thermal transfer resistance that differs from the inside. As is clear from Newton's cooling law, no heat can be transferred unless a temperature difference exists between the perimeter of the device and the surrounding environment as we see in the final removal of heat to the surrounding environment outside the device. Particularly in the case of micro devices, because of the small size of each device component, the contribution of thermal resistance arising from the heat of conduction inside those elements becomes relatively smaller and smaller. Generally, thermal resistance at the interface of elements does not depend on the size of the device. It therefore follows that thermal resistance at the interface comes to be regarded as relatively important. In this investigative study, the considerations described above are classified into the following problems for discussion:

1) A surface-related problem at the interface, which becomes important in various film-forming processes.
2) A volume-related problem arising from an incomplete layer near the interface.
3) A problem at the joining interface where respective materials are present as if pasted together.

The surface-related problem is important, particularly at low temperatures. Explanation of this viewpoint is therefore given. In addition, a technique for measuring thermal resistance is proposed in various ways for verifying the value of thermal resistance, obtained theoretically. This is also under study.

Further, it becomes necessary to study the technique of calculating heat transfer with all of these factors combined. It is possible to select a technique for the respective purposes, ranging from a technique of simple analysis for a basic order estimate to a more exact one that solves a three-dimensional energy equation numerically. Those techniques and related problems are introduced along with the concept of the thermal resistance.

Investigative Study of the Possibility of Greatly Upgrading Micromachine Technology by Utilizing Physical Phenomena that Characterize the Mesoscopic Area

Tokio Kitahara
Professor, Mechanical Engineering,
The Faculty of Engineering, Shonan Institute of Technology

1. Introduction

Micromachine component parts are as small, ranging from 1 mm to 1 μm, which is larger than an atom or a molecule by 3 to 4 orders of magnitude and smaller than conventional machine parts by 1 to 3 orders of magnitude. This area lies between the area to which a macro physical phenomenon model can be applied, hitherto used by conventional technology, and the area to which a micro phenomenon model is applicable, with atoms or molecules used as units, an area that has been making marked progress in recent years.

The modeling and practical application of physical phenomena in this mesoscopic region is seldom seen except for the technology related to hard disk drives. It is indispensable to grasp physical phenomena in this area so as to establish methods for utilizing them so that micromachine technology can grow into a basic industrial technology.

2. Physical phenomena and related research trends

In this investigative study, physical phenomena related to greatly upgrading macro mechanisms were itemized (Refer to Table 1). The items considered particularly important were investigated relative to their research trends.

One of them is tribology. The coefficient of friction in the mesoscopic region often grows into a large value, and interfacial force or the surface tension of a liquid film are closely related to this value.

Water repellency has much to do with minute surface structure and chemical factors. The contact angle between a liquid and a solid is related with the surface tension of the two.

Water repellency is exhibited when a liquid with a high surface energy is combined with a solid having a low surface energy. Again, it has been clarified that water repellency is enhanced when the minute structure on the surface of a solid or an air layer is formed.

The effect of viscosity on macro mechanism components can be measured by the law of similarity if it is within the range where Newton's viscosity law holds good. From the Reynolds numbers of microorganisms, the Reynolds numbers of the micromachine mechanism parts are assumed to be below 1.

Many thin-film parts are used for micromachines. To measure their mechanical properties, it is necessary to make a model in which the effect of the surface layer is considered. At present, however, methods for measuring various mechanical properties are still in the proposal stage.

3. Application map and the status of research and development

There are physical phenomena that stand out in the mesoscopic region work as a positive factor in some cases, and as a negative factor in other cases. Those phenomena were itemized into interfacial force, surface tension, viscous force, adsorption layer, and mechanical strength, and their relationship to the basic technology and manufacturing technology of micromachines and device system technology was arranged in order as their application map.

Various surface forces lead to an increase in friction force in tribology. It is reported that minute unevenness formed on the sliding surface reduces friction. On the other hand, an attempt is being made to handle micro parts by taking advantage of the surface force. A traction drive is also considered by utilizing high friction force.

An example is reported in which the minutely uneven functional surface having super water repellency was used for sealing an axis. Viscous force can be considered applicable to simple-structure devices, including torque converters, brakes, and vibration dampers.

Various methods of joining are used for micro application. Adhesives can be used as a substitute method for separable thread fastening. An adhesion and tensile strength tester was manufactured on a trial basis for butt adhesive joint of slender axes with a diameter of less than 2 mm. A strength of 18 MPs was attained with an epoxy adhesive. This enabled confirmation of the possibility of adhering micro parts.

Many prototypes of micro fluid devices were manufactured by taking advantage of the laminar flow, high heat transfer, and other characteristics of a micro fluid. In the μ-TAS, now attracting our attention, the above characteristics are integrated.

4. Conclusion

In upgrading micromachine technology to a higher degree, it is important to utilize and overcome physical phenomena in the mesoscopic region. There are many cases in which useful functions are exhibited, accompanied by multiple phenomena. It will be necessary to grasp quantitatively their synergistic and counterbalancing effects in the future.

Table 1 Main physical phenomena that stand out when micronizing

Items	Related matter
Interfacial force	Van der Waals forces Electrostatic force
Surface tension	Capillary phenomenon
Adsorption (layer)	LB film, surfactants, Stiction
Viscous force	Electric viscosity effect, Magnetic fluid, Low Reynolds number
Super water repellency	Surface tension, minute form on solid surface
Mechanical strength	Crystal size, crystal anisotropy

Summary of Investigative Study of the Possibility of Innovative Gene Therapy by the Use of Micro-machine Technology

Kazunori Kataoka
Professor, Graduate School of Engineering,
The University of Tokyo

Interest is growing rapidly in gene targeting to deliver genes into the living body for the purpose of cancer therapy, and the study of the delivery system is being actively pursued utilizing liposomes, viruses, and cationic polymers as the carriers of genes. Those carriers are required to have various functions, such as stability in blood flow, accumulation inside the targeted cells, transfer to cellular nuclei, and release of effective genes inside the nuclei. An additional important point is the need for those functions to be realized on the micro scale, say, in order of micrometers or nanometers so that they can be used for a living body. In this sense, the carriers (gene vectors) for gene targeting, applicable to clinical uses, that surpass the properties of viruses would be worthy of the term “biomicromachines”. Recently, an accidental death was reported in gene therapy using adenoviruses in the U.S. This poses a serious problem for spreading gene therapy in the future. It is urgently required to develop non-viral vectors with excellent safety and transfer characteristics without relying on conventional virus vectors if gene therapy is to break the category of a hitherto-used special method of medical treatment and grow into a universal method of medical treatment, applicable to a wide range of diseases.

In this case, an active approach is increasingly desired from the fields of medicine and biology as well as from the field of engineering. This approach includes the establishment of a chemical engineering methodology to grasp the trends in the bio-environment beginning with a vector design based on molecular assembly engineering (artificial viruses), and the development of new analytical techniques to measure quantitatively and over time the behavior inside the cells.

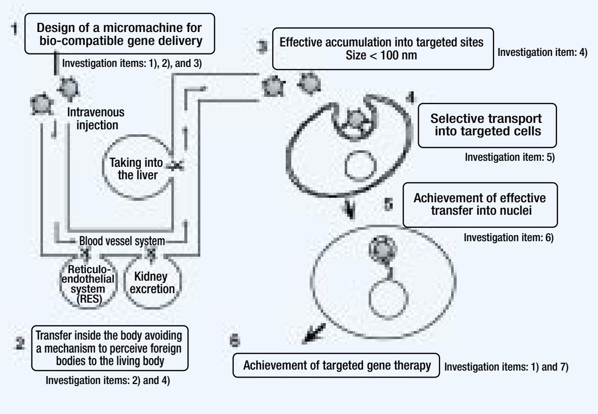

Figure Image of a micromachine used for intravenous in-vivo gene therapy and study items

In this investigative study, therefore, specialists in polymer synthesis and researchers from the companies that have succeeded in developing the materials for targeting carcinostatic agents. In addition, researchers who have been carrying out the study of gene targeting carriers also individually participated in systematic investigation of the merits and demerits of the many trials carried out thus far with the intention of establishing a guideline for the design of micromachines for gene targeting.

The major study items are summarized below together with a diagram of the positioning of each item in intravenous in-vivo gene therapy:

① method for introducing various genes and its commercialization
② A technique for device surface treatment using biocompatible elements
③ A gene including association based on molecular assembly
④ Polymeric nanocapsules oriented toward gene vectors
⑤ Structuring of an environment-responsive material system
⑥ Clarification of a DNA delivery system in the cell
⑦ Various technical problems and their solutions in in-vivo gene therapy

The author believes that a series of important points as described below can be clarified thus to contribute to the development of next-generation micromachines for gene delivery by carrying out the investigative study of the above items.

A series of important points are: 1) structuring of micromachines for gene delivery, 2) mounting of genes onto micromachines, 3) grasping of movements inside the body and accumulation in targeted sites, 4) establishing of routes into targeted genes, 5) clarification of traffic inside the cells and the routes for transferring to nuclei, and 6) release of mounted genes and gene expression.