from Tsukuba, Japan to the world

NIMS NOW International

National Institute for Materials Science

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Special Features

# Biomaterials
## — New Interdisciplinary Area and Future Prospect —

Junzo Tanaka
Director-General
Biomaterials Center (BMC)

Interdisciplinary Research and Development I
"New Developments in Nano-Bioscience"

### Development of long-term slow-release ceramic material

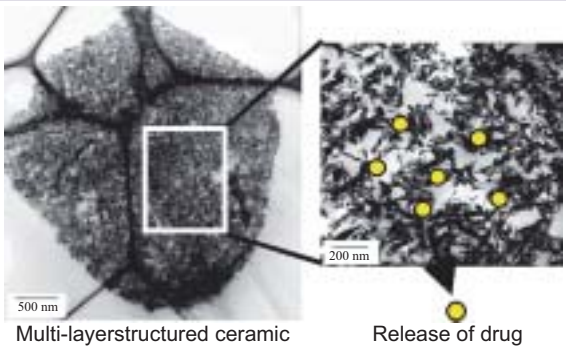


Fig. 1 Long-term slow-release materials for treatment of lifestyle diseases: Successful development of a series of materials which enable slow release of drugs over 2 weeks or more.

### Development of nanoparticle polymer with high targeting performance

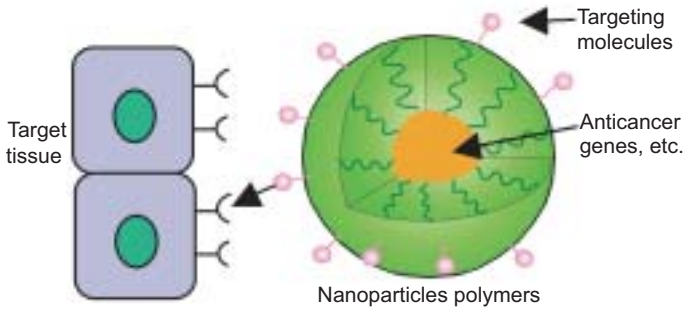


Fig. 2 Targeting carrier for treatment of cancer: Creation of material which targets morbid parts, resulting in 5 times higher concentration than surrounding tissue.

Biomaterials involve research in a typical borderline area where materials science and biology/medicine overlap. Moreover, with recent progress in regenerative medicine, strong cooperation with clinical medicine is also now demanded from the initial stage of research.

In the beginning of 2004, the NIMS Biomaterials Center launched a project called "Development of Carrier Materials for Innovative Nano Drug Delivery Systems (DDS)." Research in this project is being carried out cooperatively by the materials and pharmaceuticals research institutes (NIMS, The University of Tokyo School of Engineering, Kyoto University Graduate School of Pharmaceutical Sciences) and various medical research organizations (Hokkaido University Graduate School of Veterinary Medicine, The University of Tokyo Faculty of Medicine, University of Tsukuba School of Medicine, Tokyo Medical and Dental University).

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NIMS News

## Japan-US Workshop on the Future of Sensors and Sensor Systems

Dr. Atkinson gives an opening address.

(Feb. 28- Mar. 2, Tsukuba) -- The Japan-US Workshop on the Future of Sensors and Sensor Systems was held at the Okura Frontier Hotel Tsukuba. Approximately 50 persons made presentations and the total number of participants exceeded 170. Considering these impressive numbers and the spirited discussions, the event concluded very successfully. < Continued on p.2

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# Nano Drug Delivery Systems

## —Reducing Side Effects and Improving Drug Effectiveness—

Toshiyuki Ikoma
Regeneration Materials Group
Biomaterials Center (BMC)

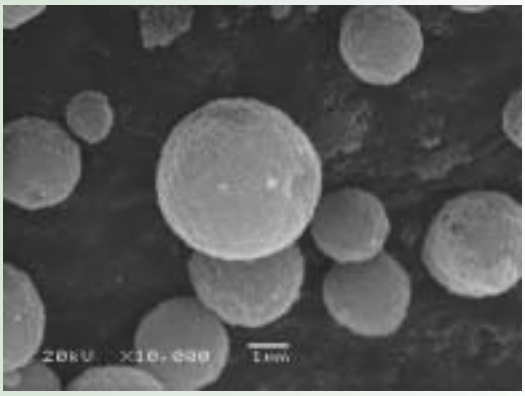

Fig. 1 SEM image of ultrafine apatite particles.

Drug Delivery Systems (DDS) are systems which deliver drugs only to the necessary focus of diseased parts, and only when necessary. DDS are classified as the controlled-released type, which slowly releases a constant supply of a drug in the body in small increments, and the targeting type, which delivers the drug to the focus of the diseased part. If excess amount of drugs with strong beneficial effects (for example, anticancer drugs) is given in the human body, the side effect is immediately appeared. This can cause the patient intense suffering. It is, thus, necessary to minimize these side effects on the body while maximizing the efficacy/effects of the drug. With advances in proteome technology (analysis technology for all proteins produced by designated cells and tissue) and genetic analysis technology, a large number of effective protein products have been developed. Proteins are generally unstable in aqueous solutions and in our body; protein stabilization, slow release, and sustainability have become important issues for research and development. Hydroxyapatite (calcium phosphate) is the principal inorganic component of bone, and is a biologically safe material already used in clinical applications as a bone repairing material. It also applied to a column filling material in liquid chromatography for the separation/refining of proteins as industrial processes.

We prepared porous ultrafine spherical particles with sizes of 1-10 μm, as illustrated in the scanning electron microscope (SEM) image in **Fig. 1**. The specific area of these materials shows large values, from 90-180 $m^2$/g, or approximately 2 times that of commercially-available hydroxyapatite powders. **Fig. 2** shows a transmission electron microscope (TEM) image of the cross section with a thickness of less than 100 nm. It shows that the constituent hydroxyapatite is a nanocrystal, and furthermore, it contains pores with sizes of 10-100 nm. By controlling the crystal size/specific area, protein adsorption can be increased to more than 1.5 times than with conventional powders. We are also carrying out technical development aimed at crystallizing proteins in the "nano-spaces" provided by these pores. Combining this ultrafine particle development, protein crystallization technology, and other technologies will achieve stable slow release of proteins in the body for a period of 1-2 weeks. In the future, we intend to develop safer carriers with stability and slow release of proteins by further improving the characteristics of these materials and formulations methods.

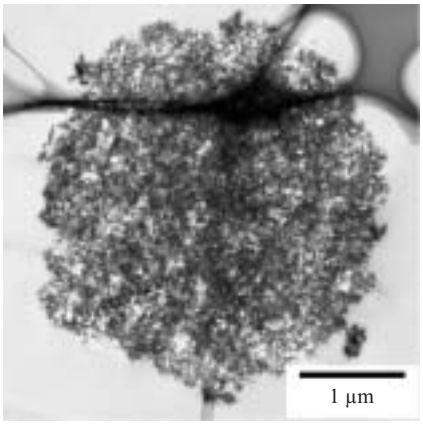


Fig. 2 TEM image of cross section of ultrafine apatite particles.

For more details: http://www.nims.go.jp/bmc/index_e.html



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# Japan-US Workshop on the Future of Sensors and Sensor Systems

The purpose of the Workshop was cooperation on basic research and long-term prospects, as part of science and technology cooperation for a secure and safe society between the US and Japanese governments. The event was sponsored by the Science Council of Japan, the National Academies (US), and NIMS, with co-sponsorship by the Japan Science and Technology Agency and support from Japan's Ministry of Education, Culture, Sports, Science and Technology (MEXT), the US Department of State, and Japan's National Institute of Advanced Industrial Science and Technology (AIST). Mr. Murata, Deputy Director-General, Science and Technology Policy Bureau, MEXT, and Dr. Atkinson, Science and Technology Adviser to the Secretary of State, USA, gave opening addresses, and discussions were held, mainly in panel format. These discussions reaffirmed the importance of sensors and sensing systems in creating a safe and secure society, and concluded that deeper basic research is indispensable for the development and expansion of the related science and technology.

It should be noted that this Workshop was part of the new US government program called Global Dialogues on Emerging Science and Technology (GDEST). In the future, the US will serve as a model for expanding this kind of dialogue in various international/interregional contexts.

Opening Ceremony

# Faster Bone Regeneration

## —High Biocompatible Material Accelerates Tissue Invasion—

Masanori Kikuchi
Regeneration Materials Group
Biomaterials Center (BMC)

The bones in vertebrates are composed mainly of an inorganic substance called hydroxyapatite and an organic substance called collagen. Bones not only support the body, but also have the function of protecting important organs such as the brain and heart. At the same time, they have the function of regulating the concentrations of calcium and phosphorous in the body. Moreover, contrary to the idea that bone is "hard and nearly indestructible," bone is gradually replaced every day, much like other kinds of tissue. Thus, even if a bone broken, it can be healed by the appropriate fracture treatment.

However, if a large amount of bone is lost due to illness or injury, bone filler to assist the bone regeneration is necessary for healing the bone to its original form. At present, the most commonly-used material for this purpose is autologous bone taken from the patient's own hip (ilium). However, as problems with this procedure, patients are frequently left with chronic pain, and it may be impossible to take an adequate amount of bone to fill the deficit part, because this procedure involves surgically taking bone from a healthy part.

To solve these problems, we developed a completely new porous artificial bone material, which is as soft as sponge, as a material which allows easy invasion by cells and tissue, thereby facilitating regenerating of the bone.

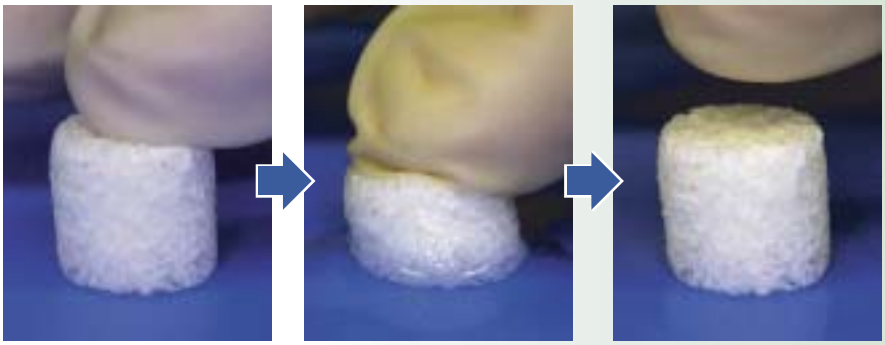


Fig. Artificial bone with soft, elastic properties like sponge.

The main component of this material is a "self-organizing nanocomposite fiber" which consists of hydroxyapatite and collagen and indicates a regular arrangement from the nanometer order, like that in natural bone. When a gel is prepared by mixing this material with a collagen solution, a jelly-like substance in which the composite fibers uniformly distributed is formed. Porous material is obtained by freezing followed by a freeze-drying this jelly. In this process, the pore size can be controlled by the freezing temperature. It is also possible to control the decomposition speed in the body with increasing in crosslink amount of the porous material.

Although this porous material is hard when in a dried condition, it becomes elastic like sponge when wet, as shown in the **figure**. Therefore, when implanted in the body, it normally shows behavior like that of sponge, and blood and cells can readily invade into its pores. This material is currently being developed to the practical level by PENTAX Co.

For more details: http://www.nims.go.jp/bmc/index_e.html



# Appointment of New Vice Presidents

(Apr. 1) -- Dr. Koinuma, former Director of Materials and Structures Laboratory, Tokyo Institute of Technology, and Dr. Noda, former Director-General of Materials Engineering Laboratory (MEL), NIMS, were newly appointed as Vice Presidents of NIMS, replacing Dr. Watanabe, who became an Auditor, and an outgoing Vice President, Dr. Yoshihara.

## Dr. Hideomi Koinuma

Doctor of Engineering. Completed doctoral course in School of Engineering, The University of Tokyo (1970). Served as Postdoctoral Research Associate at the Department of Chemistry, The University of Kansas, USA (1970-1972). Joined the Faculty of Engineering, The University of Tokyo as Assistant (1972), and became the Assistant Professor (1979) and the Associate Professor of the Graduate School of Chemical Energy Engineering (1981). Joined the Research Laboratory of Engineering Materials, Tokyo Institute of Technology as Professor (1987) and became Director of the Ceramics Research Center (1994-1996). Became the Guest Professor of the Helsinki University of Technology, Finland (1996). Served as Guest Researcher at the National Institute for Research in Inorganic Materials (NIRIM; 1999). Became the Professor of the Frontier Collaborative Research Center of the Tokyo Institute of Technology (2000) and the Director of the Materials and Structures Laboratory (2002). Appointed as Vice President of NIMS (2005).

## Dr. Tetsuji Noda

Doctor of Engineering. Completed doctoral course in School of Engineering, Hokkaido University (1973). Joined the Nuclear Reactor Materials Division of the National Research Institute for Metals (NRIM), Science and Technology Agency (STA) as Researcher (1973) and became the Senior Researcher (1979), Senior Researcher of the 2nd Group of the Tsukuba Laboratories (1988), and the Supervising Researcher of the High Resolution Beam Research Station, Center for Materials Science under Extreme Environments (1996). Appointed as Chief of the Planning Office of NRIM (1998). Became the Senior Researcher of the Nanomaterials Laboratory (NML; 2001) and the Director-General of the Materials Engineering Laboratory (MEL) of NIMS (2003). Appointed as Vice President of NIMS (2005).

For more details: http://www.nims.go.jp/eng/topics/050401/index.html

# Regenerative Medicine for Multicellular Organs

## —Construction of Organoid Array—

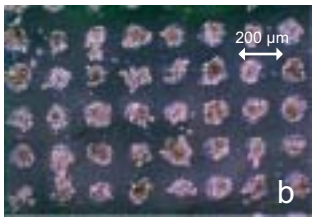
Hidenori Otsuka
Artificial Organ Materials Group
Biomaterials Center (BMC)

Stable cultivation of stem cells and primary cells outside the body, use as sensors, and development to regenerative medicine by creating 3-dimensional structures (spheroids) are now becoming increasingly important issues. In the present research, our objectives are to create spheroids with biofunctions closer to those of living tissue than is possible with independent cells, and to develop regenerative organs in which nutritive blood vessels are induced by forming composites with nanostructured materials. Normally, a complicated method is necessary in spheroid culture, and there is no simple, mass production technology for cultivating homogeneous spheroids which also enables free control of the size and shape of cell populations.

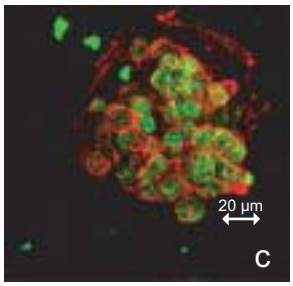
The authors developed the world's first technology for efficiently constructing cellular spheroid arrays, as illustrated in **Fig. 1**. In this technology, various patterned surfaces are prepared by fabricating a high-density hydrophilic macromolecular brush on a substrate surface, followed by micropatterning by semiconductor technology. Endothelial cells, which serve as a feeder layer, are then cultured on the patterned surface. After formation of a set cell pattern, primary cells are introduced, resulting in formation of a cellular spheroid array (**Fig. 2**). As primary cells, hepatic, pancreatic, cartilaginous cells, etc. are used. It was found that the hepatic spheroids prepared in this manner continued to maintain liver-specific functions (albumin production and P450 enzyme activity) over a period of more than 1 month (**Fig. 3**). The key and essential problems for maintaining the tissue functions/long-term viability of the spheroids are to replenish nutrients to the cells from their surroundings and to supply oxygen.

Future objectives include the development of novel technologies for cell therapy and regenerative organs (liver/pancreas) capable of inducing nutritive blood vessels in close cooperation with 3-dimensional scaffold material technologies for cells with high material permeability and vascular induction technology, as well as application to the preclinical test method, such as screening of various drugs and hormone disrupters using human cells.


a) 10,000 hepatocyte spheroids arranged in 2$cm^2$.




b) Enlargement photo of a.




c) Hepatocyte spheroid and confocal laser-scanning microscope (CLSM) image (cytoskeleton: red, albumin production: green).

Fig. 1 Two-dimensional multiarray formation of hepatocyte heterospheroids, underlaid with endothelial cells, on a microfabricated PEG-brush surface.

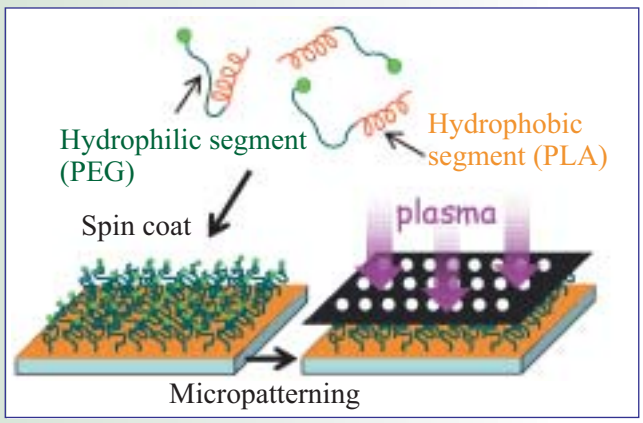



Fig. 2 Substrate for cellular array culture prepared by micropatterning of nano-thickness macromolecular brush surface.

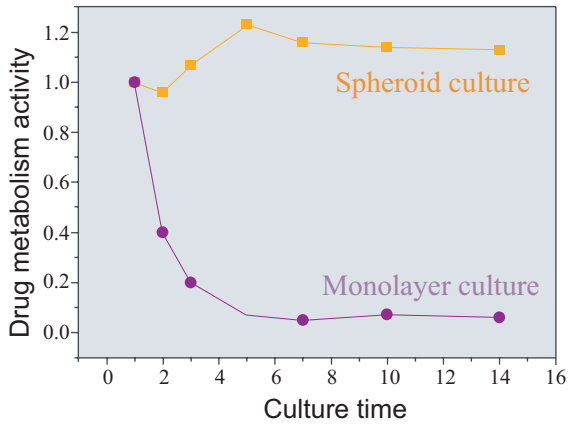



Fig. 3 Drug metabolism-(P450) enzyme activity and differences due to its assembly mode.

For more details: http://www.nims.go.jp/bmc/index_e.html



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## Biomaterials

The purpose of this work is to develop new DDS materials for treatment of hard-to-treat diseases such as cancer, hepatitis, genetic disorders, and lifestyle-related diseases. In theory, drugs should be adequate if they are delivered in the necessary amounts at the necessary time to diseased organs such as the liver or pancreas. In reality, however, injected drugs circulate through the entire body, and the drug concentration in the blood becomes extremely high immediately after injection. Depending on the case, this may cause side effects. We are therefore developing DDS materials to heighten the desired effects of drugs while reducing their side effects. For example, we have developed a protein carrier (**Fig. 1**) which enables long-term slow release of interferon to treat type C hepatitis, a targeting nano carrier (**Fig. 2**) which stabilizes unstable nucleic acids in the blood for treatment of genetic disorders, and a ceramic-type carrier of anticancer drugs for treatment of metastatic osteogenic sarcoma, among others.

For more details: http://www.nims.go.jp/bmc/index_e.html

# Genetic Field Effect Transistor for Clinical Diagnostics

Toshiya Sakata[1,2], Yuji Miyahara[2]
[1] International Center for Young Scientists (ICYS)
[2] Bioelectronics Group, Biomaterials Center (BMC)

Sequencing of the human genome was completed in April 2003, and genetic analyses based on this achievement are now in progress. If the relationship between a contributing factor to disease and a functional role of individual genes is clarified, "tailored medicine" adapted to each person's genetic makeup can be realized. DNA chips and DNA microarrays are currently used in various research fields, mainly in molecular biology, medicine, and development of pharmacological agents. The important challenges for using these devices for clinical diagnostics include improved accuracy, improved reliability, and reduced cost. Therefore, we propose the novel concept of genetic analysis based on potentiometric measurement of intrinsic DNA molecular charges, which is different from the conventional method such as fluorescent detection.

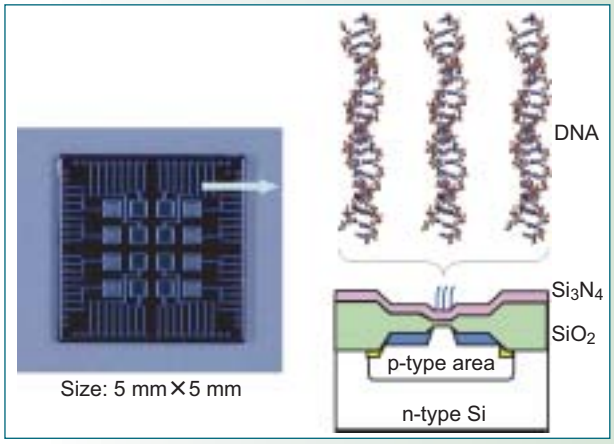


Fig. 1 Structure of genetic field effect transistor.

**Fig. 1** shows the device structure for genetic analysis using a field effect transistor (FET). This is a structure in which a DNA fragment called a DNA probe is immobilized on the surface of the FET gate insulator, and a double-stranded DNA is formed on the gate surface when a sample solution including target DNA is introduced. Since DNA molecules have negative charges in aqueous solutions, the charge density changes due to the formation of the double-stranded DNA from the single-stranded DNA (DNA probe). As the charge density change on the surface can be directly converted to electrical signal by the field effect and can be detected, this device has been named the "genetic field effect transistor." Using the genetic FET combined with various molecular recognition events on the gate surface, it is possible to analyze one-base variation, base sequences, and other features of genes.

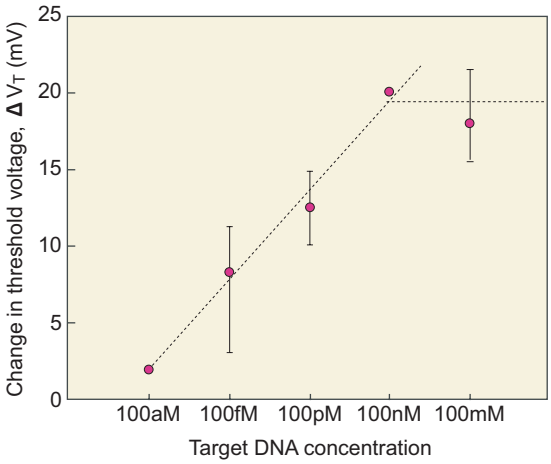


Fig. 2 Detection sensitivity of genetic field effect transistor.

The relationship between the threshold voltage change of the genetic FET and the target DNA concentration is shown in **Fig. 2**. We could successfully detect the formation of double-stranded DNA from DNA probe on the gate at a lower concentration of approximately 100 fM (femtomol: $10^{-13}$ M). We are now going to achieve a further improvement in sensitivity by optimizing the structural parameters and measurement conditions of the FET device.

The genetic FET makes it possible to analyze gene polymorphism and base sequences without using fluorescent molecules. Based on the genetic FET platform, we intend to investigate drug susceptibility and drug side effects and develop a simple, compact genetic detection system for "tailored medicine" capable of providing treatment matched to each patient's makeup.

For more details: http://www.nims.go.jp/bmc/index_e.html



# Results of Nanotech Business Forum

NIMS Booth

(Feb 23, Tokyo) -- As part of Nanoweek, a Nanotech Business Forum was held at the Tokyo Big Sight International Exhibition Center. The lecture session featured 3 presentations by NIMS and 2 by the Japan Synchrotron Radiation Research Institute (JASRI). Participants were extremely interested, as evident in "standing room only" conditions for a time. With a total of 127 participants, this event was a great success.

NIMS Workshop; "Nanomaterials Frontline"

# Sensor Cells Indicate Poison/Drug with Green Light

Akiyoshi Taniguchi, Ken-ichi Wada
Bionic Materials Technology Group
Biomaterials Center (BMC)

Cells have the ability to respond sensitively to slight changes in various environments. By applying the sensor capability possessed by cells to safety assays of pharmaceuticals and biomaterials, the authors have created a functional cell capable of obtaining high-sensitivity biological information from multiple angles, which had been impossible with conventional technology.

A method of measuring cytotoxicity with high sensitivity was developed using this cell. By combining the gene promoter (gene switch) which controls the expression of the stress protein (HSP70B') and the genes of light-emitting/fluorescent proteins found in fireflies and jellyfish, we created cells which emit fluorescent light in response to stress. When a stimulus such as stress is applied to the cells, the gene switch of the firefly or jellyfish light-emitting/fluorescent protein is switched on, causing light emission. The sensitivity of this method was studied using cadmium chloride as a cytotoxic substance. The results showed that the new method has high sensitivity, more than 5 times greater than that of the conventional technique of judging cytotoxicity by cell death. Moreover, because measurements can be made before cells death with the new method, quicker judgment was possible than with the method of judging cells death.

In addition to the above, two other types of sensor cells are currently under development. Because each of the three sensors is based on inducing a different gene expression, classification of the mechanism of cytotoxicity is possible. That is, because types of cytotoxicity which could not be distinguished in conventional assays of toxicity by cell death can be clarified, it is expected to be possible to obtain more detailed information on the effects of toxic substances. For example, if antitumor agents with strong cytotoxicity are classified by this method, more detailed classification by the cause of cytotoxicity will be possible. High expectations are placed on this technology as an assay method which offers an alternative to animal experiments.

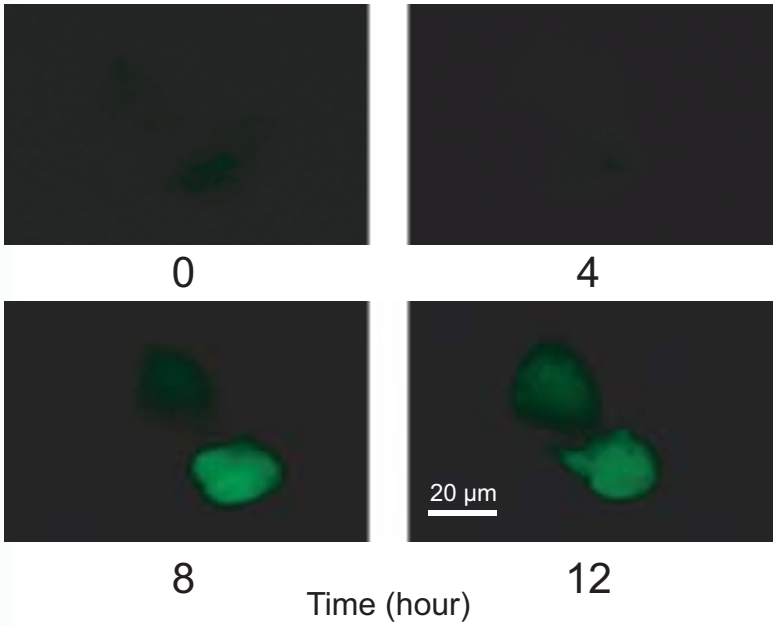


Fig. Cells emit light when toxicity is detected. If toxicity is detected in the sample, the sensor cells light approximately 8 hours after adding the sample to be investigated.

For more details: http://www.nims.go.jp/bmc/index_e.html



# Prediction of Material Properties by MD Simulation

Masato Shimono, Hidehiro Onodera, Tetsuro Suzuki
Particle Simulation & Thermodynamics Group
Computational Materials Science Center (CMSC)

With improvement in computer performance, computer simulation is now applied in a variety of fields as a third basic methodology, following the experimental and theoretical approaches. In particular, the method called Molecular Dynamics (MD) simulation makes it possible to obtain, from "virtual experiments," information which is difficult to investigate in conventional experiments. Here, we will discuss attempts to predict the properties of new types of materials using MD simulation.

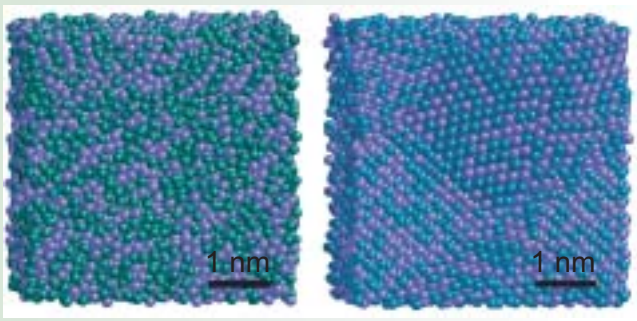


Fig. 1 Snapshots of rapidly solidified phases. An amorphous phase (left, atomic size ratio 0.9) and a nano-crystalline phase (right, atomic size ratio 0.95).

## MD Simulation

MD simulation is a methodology which makes it possible to calculate and track the motion of individual atoms. In this "virtual laboratory," it is possible to realize conditions which are difficult when actually performing experiments, but conversely, there are also limitations on the number of atoms and the time scales which can be handled, depending on the capacity of the computer. It is therefore necessary to apply some ingenuity, for example, by handling phenomena which occur within a short time and objects with a limited size. Two examples will be presented in the following.

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## Amorphous Alloys and Nanocrystals

Amorphous alloys and nanocrystalline alloys with an extremely fine grain size formed by heat treatment of such alloys display properties which differ greatly from those of ordinary crystalline materials. High expectations are placed on these types of alloys as new materials. However, there are many points where researchers must rely on experience in the search for alloys systems which easily form amorphous alloys and techniques for controlling their crystallization. Thus, it would be useful if new guidelines could be obtained by utilizing simulation techniques.

Amorphous alloys are normally formed by rapid cooling from a liquid state. Using MD simulation, virtual experiments can be performed while controlling variables such as the combination of alloys and the cooling rate. In addition, high cooling rates at speeds which would be impossible in actual experiments are also easily simulated. For example, as an empirical rule for increasing the formation capacity of amorphous alloys, alloy combinations with a large difference in atomic size and negative heats of mixing between alloying elements are considered desirable. In MD simulations, the atomic size and the heat of mixing can be varied freely, making it possible to verify the empirical rule and improve quantification. When the composition region for forming amorphous alloys was investigated with various cooling rates while changing only one of the respective variables of the atomic size ratio of the alloying elements and their heat of mixing, it was found that effect of the atomic size makes a larger contribution to formation capacity.

Hints for controlling the structure can also be obtained by choosing the combination of alloys and the cooling rate properly. **Fig. 1** shows the results of cooling under the same conditions while varying the atomic size of the alloying elements. It can be understood that an amorphous alloy is formed when the atomic size difference is large, and nanocrystals are formed when this difference is small.

**Fig. 2** shows the atomic arrangement of a Ti-Al amorphous alloy where crystallization proceeds. As illustrated here, simulations provide the atomic-level information which would be impossible to obtain even with electron microscopes.

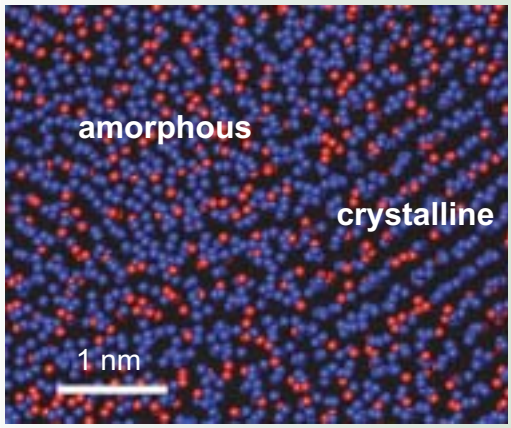


Fig. 2 Snapshot of a crystallization process of a Ti-Al amorphous alloy. The red spheres and the blue spheres denote the Al atoms and the Ti atoms, respectively.

## Metal Nanoclusters

It is known that, when the size of ultrafine metal particles reaches the level of nanometers, their properties, including chemical and electromagnetic properties and others, differ greatly from those at macroscopic size (referred to as "bulk"). Using these properties, application as nanodevices such as catalysts, high density recording media, and optical switches is expected. However, while new properties appear when the size reaches the nano level, there are also cases where the properties expected from the bulk are lost. Thus, it is important to understand how material properties change depending on the size of the ultrafine particle.

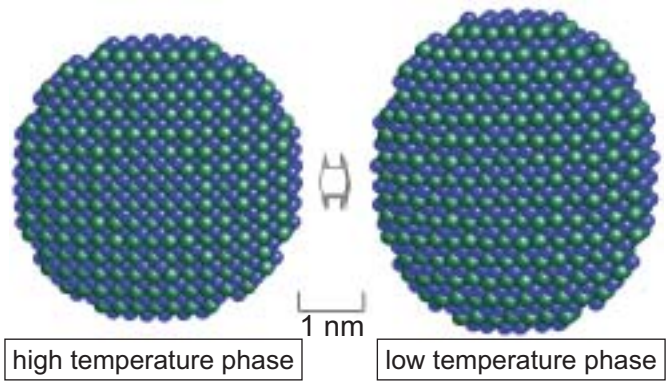


Fig. 3 Snapshots of two different phases of a Ti-Ni alloy nanocluster. The blue spheres and the green spheres denote the Ni atoms and the Ti atoms, respectively.

The martensitic transformation involved in deformation of shape memory alloys normally proceeds completely within a short period of time, and thus is expected to be suitable for MD simulation. Therefore, we attempted to investigate how the transformation properties of ordered alloys, represented by TiNi alloys, would change in clusters. Ultrafine particles of a TiNi ordered alloy were prepared in a virtual laboratory, and structural changes were observed with the holding temperature as the variable. As shown in **Fig. 3**, it was found that reversible change between a high temperature phase with the B2 structure and a low temperature phase with lower symmetry occurred due to the martensitic transformation when the temperature was increased and decreased.

**Fig. 4** shows the simulation results of changes in the temperature of this martensitic transformation and the melting point, using the cluster size as a variable. It was found that both temperatures decreased when the cluster size was reduced, thus providing important information for controlling the operating temperature in use as a material.

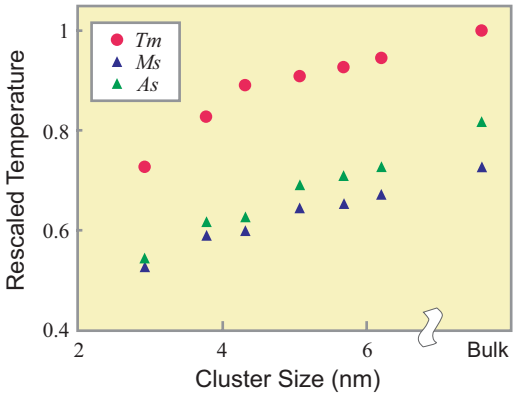


Fig. 4 The size dependence of the melting temperature *Tm*, the martensitic transformation temperature *Ms*, and the reverse transformation temperature *As* of the Ti-Ni alloy nanoclusters, together with those for the bulk phase on the right edge of the viewgraph.

## Summary

MD simulation is a powerful tool which makes it possible to analyze various physical processes at the atomic level. By making active use of simulations, we believe that it will be possible to predict the properties of new materials and obtain guidelines for the development of new devices.

For more details: http://www.nims.go.jp/cmsc/pst/index.html

## Hello from NIMS

My name is Professor John Drennan and I am the Director of the Centre for Microscopy and Microanalysis at The University of Queensland. The university is situated in the city of Brisbane which is the gateway to the Gold and Sunshine coast - a place where most Japanese travelers will know well. Our university has a strong emphasis on research excellence and our centralized microscopy facilities host some of the latest instrumentation for microscopy analysis in the region and are available to all researchers, from a range of disciplines, across the campus.

I have been coming to NIMS and the former NIRIM for more than 20 years. From when I was a young researcher excited about the facilities in the institution to now when I have a more advisory role, I still find the warmth and hospitality of the researchers at NIMS a pleasure to deal with. The facilities have expanded and the sites across NIMS can easily lay claim to being the best equipped materials institution anywhere in the world. The quality of researchers is also of the highest calibre and over the years I have had very successful collaborations in a number of areas.

John Drennan (CMM, The University of Queensland, Australia)
ICYS Adjunct Advisor/EMC Research Advisor/NIMS Overseas Fellow

[ At Namiki Site ]

In addition to what I learn about the latest developments in materials science, I have taken home many lessons in scientific management from NIMS that I can apply to my own circumstances. The management at NIMS is always looking for new ways of managing complex scientific interactions. There is always a sense of change in the air at NIMS, projects come and go and new alliances are made and broken. This approach makes the dynamics of NIMS fascinating and if time is taken to discuss and understand the procedures and structures that are being introduced, very valuable lessons can be learned.

My visits to Tsukuba are always pleasurable and the kindness of the Japanese people and the researchers at NIMS will always draw me back.

## Sakura Season Again in All Over Japan !

Five Stored Pagoda of
Hase Temple, Nara

Matsumoto Castle, Nagano

*Photos by M. Sato*

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