Chapter 3

The East Asian path of economic development
A long-term perspective

Kaoru Sugihara

Introduction

This chapter attempts to explain how and why East Asia’s share in world GDP increased between 1500 and 1820, decreased between 1820 and 1945, and then increased rapidly over the last half century.

Table 3.1 suggests that between 1500 and 1820 there was only a marginal increase in the world’s per capita GDP, while after 1820 there was both an accelerated increase in population and a dramatic rise in per capita GDP. The most plausible interpretation of the first shift is that the industrial revolution in Britain constituted a major watershed in global history, ushering in a deepening of the penetration of the modern world system, emanating from Western Europe and encompassing the rest of the globe from the nineteenth century.

The same table, however, reveals a significant increase in world GDP and a much slower increase in per capita GDP between 1500 and 1820. This is primarily because world population was on the rise, with much of this rise coming from Asia, particularly China and India. According to Maddison’s 1995 data, as much as 52 per cent of world GDP in 1820 came from Asia, of which China contributed 29 per cent and India 16 per cent. Table 3.2 shows that in 1820 six East and Southeast Asian countries accounted for 35 per cent of world GDP, while the share of six advanced Western countries was 18 per cent. Angus Maddison’s figures, drawing on the work of regional specialists, in my view, reflects the general trend of recent scholarship (for a summary of progress in demography, see Saito

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<td>World population (million)</td>
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The East Asian Path of Economic Development

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The argument

In the standard literature on the evolution of the modern world system, industrialisation is understood to have emanated from Western Europe and spread to the rest of the world, and all industrialisation is simply taken as a chain of technological diffusion. In this paper, I argue that in fact there were two paths of economic development, the industrial revolution path, which started in Western Europe, and the industrious revolution path, which developed in East Asia. From this perspective, global development since 1500 consisted of three phases roughly divided by 1820 and 1945. This paper seeks to explain how and why East Asia’s share in world GDP increased in the first phase, decreased in the second, and increased rapidly in the third.

The industrious revolution path

In the first phase, the two paths developed independently of each other, with broadly similar results in terms of the standard of living. However, China’s population increased to nearly 400 million by the end of the eighteenth century. As a result, East Asia’s economy became much larger than Europe’s. This was a world demographic landmark, and its impact on world production far outweighed that of post-industrial revolution Britain, whose share of world GDP in 1820 was less than 6 per cent. There is an important, relatively unexplored question of how China managed to escape Malthusian checks, and maintain such a vast population without serious deterioration in the standard of living. Essentially the same observation can be made with regard to developments in Japan, which, originally under the influence of the China-centred international economy, began to show the slow but steady rise in the standard of living.

The argument of this paper is that it did this because East Asia successfully responded to natural resource constraints, particularly the scarcity of land, by developing a set of technological and institutional devices for full absorption of family labour. This path, named here the industrious revolution path, sought to mobilise human, rather than non-human, power wherever possible, to sustain and increase output. The development of labour-intensive technology, comprising rice cultivation enabled small scale production labour-intensive and efficient, while the identification of the peasant family as a production unit made labour absorption easier and the incentive to work greater. It also encouraged the peasant’s will to develop managerial and inter-personal skills, and anticipate and prevent potential problems. Commercialisation of agriculture and proto-industrialisation reinforced this path.

While this contributed to East Asia’s escape from Malthusian checks in the form of famine, epidemics and war, the region failed to significantly increase labour productivity, which suggests that it fell into a Malthusian “trap”, often resulting in resource depletion. Under such circumstances there was no chance to foster big innovation, a scientific revolution and the industrial revolution.

Labour-intensive industrialisation

The second phase was led by British industrialisation, and during the nineteenth century, it spread principally to Europe and the regions of recent European settlement, leading to the rise of the Atlantic economy. The standard account highlights the growth of the United States economy, which brought Western technology to a new height, exploiting abundant resources and economies of scale.

In fact, there were two routes of global industrialisation, one represented by the American experience which developed capital-intensive and resource-intensive technology, the other represented by the East Asian experience which developed labour-intensive and resource-saving technology.

The West European variety of industrialisation did not spread into the non-European world in its original form, as the malthusian ratio was very different there, and the straightforward introduction of Western technology proved to be problematic. Thus Japan pursued an alternative pattern of industrialisation, with greater labour inputs relative to capital. This I call labour-intensive industrialisation.

Beginning in the 1880s, Japan created a wide range of modern Asian industrial goods, and reactivated traditional Asian local institutions, which later emerged as modern corporations committed to raising the quality of labour. During the first half of the twentieth century other East Asian countries followed suit.

However, during this phase East Asia’s labour productivity lagged behind that of the West, which went through a period of further technological advance (the second industrial revolution), and the gap in per capita income between the West and East Asia increased until about 1930. The region’s share in world GDP decreased significantly.

The fusion of the two paths

After 1945 the trend was reversed, and East Asia’s GDP, as well as per capita GDP, grew faster than that of the West. The growth of Japan’s per capita GDP from 1955 to 1973 was the most conspicuous example of this new trend. And the “Japanese miracle” turned out to be the beginning of an East Asian miracle.

Geopolitical considerations in the early stages of the Cold War were crucial to the changes in the American attitude towards Japan’s economic future. Japan was now expected to use her economic strength to counter communist penetration in Asia, and was able to import all the necessary raw materials and resources, including oil, from the rest of the world. She also began to export manufactured goods to advanced Western countries. This allowed Japan to pursue the systematic introduction of capital-intensive and resource-intensive industries to an economy with relatively cheap and disciplined labour.

Thus, Japan, and later a number of other Asian countries, acquired...
the highest level of Western technology while retaining the East Asian institutional framework, which permitted a more thorough exploitation of human resources than had been possible following the American path. It was the fusion between Western technology and East Asian human resource exploitation that produced the very high rate of economic growth. This fusion turned out to be much more powerful than prewar labour-intensive industrialisation, involving deeper clashes and articulations of technology and institutions. It represents the third phase of global development.

Implications for global history

The emergence of this third phase has had major implications for global history. First, it suggests the possibility of a move to end worsening global income inequality (see Figures 1 and 2). Under colonialism the Western path failed to push up the real wage of non-white population. By contrast, the possibility of labour-intensive industrialisation is now a real one for the majority of developing countries. If the “European miracle” was a miracle of production which initiated the transformation of the world economy, the “East Asian miracle” has been a miracle of distribution which brought the benefits of global industrialisation to the majority of the world’s population.

Second, the resurgence of the East Asian path has contributed to the diffusion of industrialisation by retaining and promoting energy-saving technology. In spite of the rising concern about environmental destruction as a result of the diffusion of industrialisation and the very high level of energy consumption in advanced countries, few would argue for a complete halt of this process. The only way to make global industrialisation possible is a further improvement in energy efficiency on a global scale. If the miracle of distribution to continue, the Western path must converge with the East Asian path, not the other way round.

Discussion which followed

The Great Divergence

In his award-winning book, Pomeranz emphasised the crucial importance of North American resources in accounting for the global dominance of the West since the nineteenth century. The earlier Smithian growth path, which had been shared by all the core regions of the world, suffered inherent resource constraints, especially with regard to land. With the sudden and unexpected availability of vast land and other resources in North America, however, Western Europe escaped such constraints. It was a great divergence from the general trend.

Pomeranz commented that the assumption, made in my paper (in the form of Osaka University working paper at that time), that Western Europe and East Asia were already following different paths obscures this sudden divergence (Pomeranz 2000, 16-17). In the revised version of my paper I replied that while I substantially agree with Pomeranz’s view, I wish to retain my emphasis on the differences in the man-land ratio between the core regions of East Asia and those of Western Europe before 1800. The latter never experienced the type of land scarcity seen in eighteenth-century Japan, and it was in Japan that land productivity rose to the extreme and the perception of work was most systematically moulded around labour-intensive technology. It is as crucial to formulate the concept of the industrious revolution on the basis of the typical East Asian (Japanese) experience as to formulate the concept of the industrial revolution on the basis of the typical European (English) experience. It is surely possible to plot both experiences in the broadly Smithian–Malthusian comparative perspective, without denying the notable differences in factor endowments in Japan and England.”

In his 2001 article, Pomeranz supported my idea that “there is a distinctive East Asian style of development, in large part based...
on more intensive use of human resources (and on less capital and land-intensity), that, because of that basis, the East Asian path could give rise to impressive growth even without equal access to natural resources, and that this East Asia pattern of growth has partially fused with the Western path since 1945". He suggested that this perspective offers an alternative to both the Eurocentric convergence theory and the structuralist position held by those who argued for the persistence of the North-South divide (Pomeranz 2001: 324-26).

If my perspective is taken as a holistic alternative to the standard interpretation of global history in this way, there are a number of issues that should be missed and discussed. For example, my definition of the industrious revolution path was based on the considerations of supply side factors, and it has not been clear what kind of industrious revolution path existed in Western Europe before the industrial revolution. At the first GEHN (see below) workshop held in London in September 2003, I suggested that there were two types of agricultural development behind two paths, and that in Western Europe where cultivation was combined with pasture and the man-land ratio was much lower, animals as capital played such an important role that, while the hard-working spirit of peasants and agricultural workers was certainly present, they did not result in the industrious revolution of East Asian variety where human capital was the sole centre of attention in technological and institutional innovation (see Sugihara 2004a).

Meanwhile, a further connection between the Great Divergence and East Asia’s industrialisation had been identified at the second GEHN workshop held in Irvine in January 2004 (see Sugihara 2004b). The rise of the Atlantic economy pushed up the real wage of all major Western economies. This gave room for a non-Western country, deprived of mass migration to the new continents, to produce and export competitive manufactured goods by combining the low wage with Western technology. But most of the non-Western world were colonised and industrialisation was often discouraged. It was Japan, and later China, that took advantage of the Great Divergence and developed a resource-saving and labour-intensive path of industrialisation.

British imperialism and decolonisation

An important corollary to the argument for the persistence of the East Asian path during the second phase is that the development of the City of London as the international financial centre favoured, rather than hindered, East Asia’s industrialisation. In a comment on British Imperialism (originally published in 1999), one of the most influential works on British imperial history in recent years, I related this argument to the progressive separation of the City’s economic interests from the British empire (Sugihara 2002).

In their preface to the second edition of British Imperialism (2001), Cain and Hopkins took up my argument (published in several places at that time) and commented: although "Sugihara suggests that Japan’s economic development capitalised on long-standing commercial ties within Asia that were independent of Western influences, ...he goes on to emphasise that this process was greatly assisted by the complementarity that existed between Japan and the City of London". "Japan’s ‘national purpose’ was to become an internationally competitive industrial power", and "the City ‘came to depend on the global diffusion of industrialisation.’ As important centres of manufacturing developed outside the empire, the City’s commitment to what might be termed national imperialism steadily weakened."

Cain and Hopkins concluded that how far this interpretation modifies or extends our own is a matter that is open to discussion. Intensive of the outcomes, however, Sugihara’s analysis illuminates the international ramifications of national expansion and suggests how the unraveling of empire helped to produce the globalised world of today. The broadening of the perspective in this way urges us not only to make a connection between labour-intensive industrialisation and the changing role of the City during the second phase, but to extend it to link the postwar process of decolonisation with the beginning of the East Asian miracle.

The formation of GEHN

The original version of this paper was read and discussed in Hong Kong in 1998 and in Baltimore in 1999 for an American research project. Separately from this group, I organised a workshop in Osaka in 2001, which was followed up in Buenos Aires in 2002, in which an extensive discussion on labour-intensive industrialisation took place. Meanwhile, a British group of global historians invited me to speak at several workshops and conferences in Europe.

These contacts were partly responsible for the formation of GEHN (Global Economic History Network) in September 2003. Headed by Professor Patrick O’Brien at the London School of Economics and with Professor Kenneth Pomeranz at University of California, Irvine, Professor Peer Vries at Leiden University and myself at Osaka University as organisers of the other three centres, the network plans to hold ten workshops around the world in three years, involving at its core about 40 economic historians. Under the sponsorship of the Leverhulme Trust research and teaching fellowships, and publication at the website and in the form of working papers are in progress. With additional assistance from the Suntory Foundation, the fifth GEHN workshop will be held in Osaka in December 2004.

References
Evidence for a Narrow \( S = +1 \) Baryon Resonance in Photoproduction from the Neutron

The \( \eta n \to K^+K^-n \) reaction on \(^{12}\)C has been studied by measuring both \( K^+ \) and \( K^- \) at forward angles. A sharp baryon resonance peak was observed at \( 1.54 \pm 0.01 \) GeV/c\(^2\) with a width smaller than 25 MeV/c\(^2\) and a Gaussian significance of 4.6\( \sigma \). The strangeness quantum number \( S \) of the baryon resonance is +1. It can be interpreted as a molecular meson-baryon resonance or alternatively as an exotic five-quark state \( (uudds) \) that decays into a \( K^+ \) and a neutron. The resonance is consistent with the lowest member of an antidecuplet of baryons predicted by the chiral soliton model.

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The search for baryon resonances with the strangeness quantum number \( S = +1 \) that cannot be formed by three quarks has a long and interesting history. In fact, the summary of the \( S = +1 \) baryon resonance searches has been dropped from the Particle Data Group (PDG) listings although the possible exotic resonances were noted in the 1986 baryon listings [1]. Most of the previous searches were made using the partial wave analyses of kaon-nucleon (\( KN \)) scatterings [2]. These searches resulted in two possibilities, the isoscalar \( Z_{DD}(1780) \) and \( Z_{DD}(1865) \), for which the existence of the existence was reviewed to be poor by PDG.

The present work was motivated in part by the recent work by Diakonov, Petrov, and Polynov [3] who studied antidecuplet baryons using the chiral soliton model. The mass splittings of the established octet and decuplet were reproduced within accuracy of 1% in this model, and those of the new antidecuplet were also estimated using the nucleon sigma term [4] and the current quark-mass ratios. The antidecuplet was anchored to the mass of \( P_{11}(1710) \) nucleon resonance, giving the \( Z^* \) (spin 1/2, isospin 0, and \( S = -1 \)) a mass of \( 1530 \) MeV/c\(^2\) and a total width of less than 15 MeV/c\(^2\). The \( S = +1 \) baryon resonances in this mass region have not been searched for in the \( KN \) scattering experiments in the past because momenta of kaons were too high as pointed out in Refs. [5].

The concept of a molecular meson-baryon bound state has been proposed by Refs. [6-8] in conjunction with the well-known \( \Lambda(1405) \) particle. The mass spectrum of the \( \Lambda(1405) \) can be dynamically generated [6,7] suggesting that this “particle” can be described as a molecular meson-baryon bound state with a quark configuration \( uudds \). However, the validity of this assumption is not

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Evidence for a Narrow $S=+1$ Baryon Resonance in Photoproduction from the Neutron

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Introduction

Quarks are ultimate building blocks of subatomic particles although an isolated quark has never been observed. According to the fundamental theory of quarks, quantum chromodynamics (QCD), each quark can have three colors: red, blue, or green. And only the colorless combination (superposition) of quarks can travel freely as a particle. An example of such a combination is a proton, which is made of two ‘u’ quarks and one ‘d’ quark. The relatives of a proton which are made of three quarks are called baryons. A particle consisting of one quark (q) and one anti-quark ($\bar{q}$) is called a meson. Note an anti-quark can have the anti-colors so that a pair can be colorless too. Mesons and hadrons together form a qq particle type called hadrons.

There were no clear experimental evidence for existence of a hadron with a quark configuration rather than three quarks (three anti-quarks) or a qq pair although QCD does not forbid the existence of other combination such as qq or qqqq. The absence of the hadron state with more than three quarks was one of the unsolved mysteries in particle physics for decades.

$S=1$ Baryon

Baryon resonances with the strange quark number $S=+1$ cannot be made of three quarks since they must contain one anti-strange (s) quark. To make the baryon number equal to be 1, the minimal quark configuration is qqqq, where q stands for a ‘u’ quark or a ‘d’ quark. In late ’60s and ’70s, many kaon-nucleon (KN) scattering experiments were carried out. These searches resulted in two possibilities, the isoscalar $Z_0(1780)$ and $Z_0(1865)$, for which the evidence of the existence was reviewed to be poor by Particle Data Group (PDG) [1]. In fact, they dropped the summary of the S=+1 baryon searches from the PDG listing after 1986 saying that “The general prejudice against baryons not made of three quarks and the lack of any experimental activity in this area make it likely that it will be another 15 years before the issue is decided.”

In 1997, Diakonov, Petrov and Polyakov studied anti-decuplet baryons using the chiral soliton model [2]. The mass splittings of the established octet and decuplet were reproduced within accuracy of 1% in this model, and the lightest member of the anti-decuplet with $S=+1$, which we now call $\Theta^-$, was predicted to have a mass of 1830 MeV/$c^2$ and a total width less than 15 MeV/$c^2$. The very narrow predicted width motivated us to search for evidence of the $\Theta^-$ at the LEPS facility (Fig. 1).

LEPS facility

The Spring-8 facility (Fig. 2) is the most powerful third-generation synchrotron radiation facility in the world. The energy of the electrons in the storage ring is 8 GeV and the beam current is 100 mA. The laser-electron photon (LEP) beam at the SPring-8 is generated...
ated by Backward-Compton scattering of laser photons with the 8-GeV electrons [3]. The maximum energy of the beam is currently 2.4 GeV, which is above the threshold for $\bar{s}s$ productions. The LEP energy is determined by measuring the energy of a recoil electron. The energy resolution of the tagged photon is 15 MeV. The Laser-Electron Photon facility at SPring-8 (LEPS) is operated by an international collaboration with about 60 members from Japan, Taiwan, Korea, US, Canada, and Russia. The LEPS collaboration constructed a forward angle spectrometer (the LEPS detector) in March, 2000, and started experiments in May, 2000.

Figure 3 shows a schematic drawing of the LEPS detector. For the determination of the momentum of a charged particle, tracking counters were placed before and after a 0.7 T magnet. A time-of-flight (TOF) scintillator array was positioned 3 m behind the dipole magnet to measure the velocity of a charged particle. A mass of a charged particle was reconstructed from the momentum and velocity information.

A 0.5-cm thick plastic scintillator (SC) located 9.5 cm downstream from the 5-cm thick liquid hydrogen (LH$_2$) target ensured at least one charged particle produced in the LH$_2$ target. For the $\theta^*$ search at LEPS, the events from the SC were used to study events generated from neutrons in carbon nuclei at the SC.

Fig. 3: The LEPS detector. It analyzes a momentum and velocity of charged particles in forward angles.

Fig. 4: Vertex position for $K^+K^-$ events along the photon-beam direction. Cut points to select the SC events or the LH$_2$ events are indicated by the arrows. (Ref. [4])
Evidence for $S=+1$ baryon resonance at LEPS

Baryon resonances with strangeness quantum number $S=+1$ were searched for in the $K^-$ missing mass spectrum in the $\phi n \rightarrow K^+K^-\pi^-$ reaction [4]. Since the LH2 target contained no neutron, we selected $K^+K^-$ pair events produced in the SC, which accounted for about half of the $K^+K^-$ pair events (Fig. 4).

The main physics background events due to the photo-production of the $\phi$ meson. They were eliminated by removing the events with the invariant $K^+K^-$ mass to be consistent with a mass of $\phi$ ($1019\,\text{MeV}/c^2$).

In case of reactions on nucleons in nuclei, the Fermi motion (motion of a proton or neutron inside a nucleus) has to be taken into account for the calculation of a missing mass. The correction was made by using a fact that the undetected particle in the final state is a nucleon, and its validity was checked with the $\phi n \rightarrow K^+\Sigma^- \rightarrow K^+\pi^-\pi^-$ sequential process, where the $K^+$ and $\pi^-$ were detected as shown in Fig. 7.

Figure 8 shows the Fermi motion corrected $K^-$ missing mass distribution for the $N\phi$, $K^+K^-\pi^-$ reaction, where $N$ stands for a proton or a neutron. A prominent peak at $1.54\,\text{GeV}/c^2$ ($1540\,\text{MeV}/c^2$) is found. The broad background centered around $1.6\,\text{GeV}/c^2$ is most likely due to non-resonant $K^+K^-$ production and the background shape in the region above the peak has been fitted by a distribution of events from the LH2. The upper limit for the width was determined to be less than $25\,\text{MeV}/c^2$ with a 90% confidence level. The statistical significance of the peak was 4.6 $\sigma$.

The observed narrow peak strongly indicates the existence of an $S=+1$ resonance which may be attributed to the exotic 5-quark baryon proposed as the $\Theta^+$. The observed narrow peak strongly indicates the existence of an $S=+1$ resonance which may be attributed to the exotic 5-quark baryon proposed as the $\Theta^+$.

Conclusion

We performed a search for an $S=+1$ baryon in the $K^-$ missing mass spectrum of the $\phi n \rightarrow K^+K^-\pi^-$ reaction on $^{12}$C, using a newly built photon-beam facility at the SPring-8. A sharp baryon resonance peak was found at $1540\,\text{MeV}/c^2$. The both measured mass and width are in good agreement with a prediction by Diakoniov et al. Further experimental efforts to confirm the existence of the state are in progress all over the world.

References

High-Performance Computing Service Over the Internet for Intraoperative Image Processing


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Abstract—This paper presents a framework for a cluster system that is suited for high-resolution image processing over the Internet during surgery. The system realizes high-performance computing (HPC) assisted surgery, which allows surgeons to utilize HPC resources remote from the operating room. One application available in the system is an intraoperative estimator for the range of motion (ROM) adjustment in total hip replacement (THR) surgery. In order to perform this computation-intensive estimation during surgery, we parallelize the ROM estimator on a cluster of 64 PCs, each having two CPUs. Acceleration techniques such as dynamic load balancing and data compression methods are incorporated into the system. The system also provides a remote-access service over the Internet with a secure execution environment. We applied the system to the actual THR surgery performed at Osaka University Hospital and confirmed that it realizes intraoperative ROM estimation without degrading the resolution of images and limiting the area for estimations.

Index Terms—Cluster computing, computer-assisted surgery, high-performance computing, medical image processing, message-passing programs, range of motion (ROM) estimation.

I. INTRODUCTION

With rapid advances in information technology, three-dimensional (3-D) image processing plays an increasingly important role in surgery. 3-D image processing is a key technique for preoperative surgical planning and intraoperative guidance systems [1]–[3] that assist surgeons in developing surgical plans and performing surgery according to preoperative plans. For example, range of motion (ROM) estimators [4]–[6] support surgeons in selecting and aligning the optimal components of changeable artificial joint in total hip replacement (THR) surgery. However, such image processing requires a large amount of computation because recent X-ray computed tomography (CT) scans produce high-resolution 3-D images. Therefore, high-performance computing (HPC) approaches are necessary for intraoperative image processing, which requires real-time processing.

One emerging platform in HPC is the cluster system [7], [8], or a collection of interconnected computers. Although, as compared to shared-memory systems, cluster systems are loosely coupled systems, rapid advances in hardware technology have made such systems attractive because processors become much faster and interconnections offer higher bandwidth with lower latency. Some cluster systems consist of off-the-shelf hardware, which allows the utilization of HPC resources at a lower cost as compared to vendors’ supercomputer systems. In addition, because cluster systems enable high-speed and large-scale data processing by multiprocessor and distributed memory architecture, developing medical image processing systems on clusters realizes the HPC-assisted surgery with both real-time and high-resolution image processing at a low cost. Moreover, cluster systems have the flexibility to extend their performance for the increasing computational cost of medical image processing.

In order to realize this novel type of surgery, cluster-enabled medical systems need to possess several extra facilities in addition to those on single systems. These facilities can be classified into two groups based on whether they are intended for preoperative or intraoperative assistances. For preoperative supports, cluster-enabled medical systems require 1) a secure execution environment to keep patients’ confidential information and 2) necessary data distribution for data-intensive applications. For intraoperative assistances, in addition to the above facilities 1) and 2), also 3) parallel processing is needed for real-time processing of compute-intensive applications.

To realize the HPC-assisted surgery and share this novel procedure with several hospitals, we developed a testbed, named Medical Image Processing Cluster (MIP-Cluster), composed of 64 off-the-shelf symmetric multiprocessor (SMP) PCs with two CPUs per node. MIP-Cluster allows surgeons to utilize remote HPC resources via the Internet and resolves facility issues 1)–3) outlined above in the following medical applications: an accurate estimation for the ROM adjustment in THR surgery, a rigid/nonrigid registration [9], [10] for surgical planning, and real-time volume rendering [11] for the 3-D visualization of invisible parts inside patients.

In the present paper, we report our work as follows. Section II reviews the related work concerning the use of HPC during surgery. Section III describes the design and implementation of...
High-Performance Computing Service Over the Internet for Intraoperative Image Processing

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Introduction

With the rapid advances in information technology, three-dimensional (3-D) image processing plays an increasingly important role in surgery. 3-D image processing is a key technique for preoperative surgical planning and intrasurgical guidance systems [1, 2] that assist surgeons in developing surgical plans and performing surgery according to preoperative plans. However, such techniques require a large amount of computation because recent X-ray computed tomography (CT) scans produce high-resolution 3-D images. Therefore, high-performance computing (HPC) approaches are necessary for intrasurgical image processing, which requires real-time processing.

Many HPC approaches [3, 4] have realized medical image processing on various parallel computers, including the cluster system [5], or a collection of interconnected computers. However, to the best of our knowledge, work on developing a framework to utilize HPC resources remote from the operating room is lacking.

The paper presents the design and implementation of a framework that is suited for high-resolution image processing over the Internet during surgery. Our testbed, named Medical Image Processing Cluster (MIP-Cluster), aims at realizing the HPC-assisted surgery and sharing this novel procedure with several hospitals. In order to achieve this, the testbed tackles the following issues: a) physical proximity, b) security environment, c) network bandwidth, and d) network latency between the operating room and the remote HPC system, and e) scheduling of high-priority jobs on the shared system. These issues are resolved in key medical applications, including a range of motion (ROM) estimator for total hip replacement (THR) surgery.

MIP-Cluster: A Medical Image Processing System for Remote Parallel Processing

Fig. 1 illustrates hardware overview of the MIP-Cluster system, including a client PC in the operating room at Osaka University Hospital, located approximately 5 km from the MIP-Cluster. The Internet connection from the client to the MIP-Cluster solves a physical proximity issue because it provides HPC resources for any hospital at any time, such as with ubiquitous computing. Ubiquitous computing is a key factor for preparing emergency surgeries. However, because the Internet is a public network, this cor
connection misses b) the security issue. To address this issue in terms of hardware architecture, the system is divided into two components: a cluster of node PCs that executes parallel medical applications and a gateway PC that connects the cluster with the Internet. The gateway also serves as a network firewall that protects the cluster from malicious accesses and provides the cluster’s HPC resources for remote client PCs in operating rooms.

Each node in MIP-Cluster runs on free software: the Linux operating system and the SCore cluster system software [6]. SCore provides a multiuser environment with fault tolerance based on checkpointing. This environment addresses issue e), because it uses a gang scheduling mechanism with priority queues, which enables time-shared scheduling and provides an interactive parallel programming environment. In an emergency case, surgeons can submit parallel jobs with the highest priority, and these jobs are always executed immediately.

On the top of the above software, we have developed a client-server system, providing an automation framework for remote parallel processing. This framework has the following facilities in order to address issues b)-d) in terms of software architecture.
- **Secure execution environment**: The framework has to realize an environment that 1) protects patients’ data transmitted over the Internet and 2) prevents any unauthorized/unauthenticated/uncertified access to the cluster system. Requirement 1) is ethically obligatory and requirement 2) is required to prevent operating hijacking based on spoofing. Our framework addresses these requirements by public key cryptography.
- **High-speed data transmission**: The framework has to provide a mechanism that efficiently transmits data over the Internet. This efficient mechanism is necessary for real-time remote processing, especially when a high-bandwidth network with a low latency is unavailable. Our framework satisfies this requirement by compressing data as well as avoiding retransmission of the previously transmitted data.
- **Automatic parallel execution**: The framework should enable users to submit their jobs in the same way as they do in sequential systems. This is necessary to prevent human error originated from the procedure for remote parallel execution. Thus, the procedure must be simplified in a mission-critical system, so that our framework hides it from the users by automation.

### Parallelizing Range of Motion (ROM) Estimator

ROM estimation aims at assisting surgeons in selecting and aligning the optimal components of changeable artificial joint: the cup, head, neck, and stem components, as illustrated in Fig. 2(a). This assistance is important for both the surgeon and patient, because either inappropriate or improperly positioned components increase the risk of clinical problems such as dislocation, wear, and loosening.

Existing ROM estimators [1, 2] are useful in developing preoperative surgical plans, which determine the optimal components of an artificial joint, its implant position, and orientation. However, the preoperative plans may need to be altered in view of unpredicted conditions revealed during surgery. For example, if the bone
tissue around the preoperatively planned position is proven to be fragile, the surgeon has to realign the cup components in a stable position and to reselect the optimal combination of head and neck components for the new position. Therefore, in order to address this problem, a fast estimator based on the actual positions and orientations of the implanted components is required.

To describe the details of ROM estimation, we first show a brief representation of hip joint motion. Let $M_{hf}$ denote the transformation from the pelvis coordinate system (pelvis-CS) to the femur coordinate system (femur-CS). As illustrated in Fig. 2(b), the hip joint motion $M_{hf}$ is given by:

$$M_{hf} = T_{pc} T_{cs} R_{cs} T_{sf},$$

where $T_{pc}$ is a 4x4 transformation matrix representing the orientation of the cup in the pelvis-CS, $T_{cs}$ is a fixed transformation matrix constrained to the rotational motion, and $T_{sf}$ is a transformation matrix representing the reverse orientation of the stem in the femur-CS. Both $T_{pc}$ and $T_{sf}$ are determined by one of the following two methodologies. For preoperative assistances, the surgeon determines them by visualization and experience. For intraoperative assistances, optical position sensors give them by measuring implanted components during surgery.

Given $T_{pc}$, $T_{cs}$, and $T_{sf}$, the safe ROM is defined as a set of rotation transformation matrices, $S$, such that for all $R_{cs} \in S$, $R_{cs}$ avoids any implant-implant, bone-implant, and bone-bone impingements.

Our parallel implementation employs a master-worker paradigm, where master nodes manage the safe ROM and assign computational tasks to the idle workers, as illustrated in Fig. 3. Here, a task corresponds to collision detections for a set of rotation transformation matrices. This paradigm provides a dynamic load-balancing mechanism, enabling us to achieve high performance on heterogeneous systems.

**Experimental Results**

We applied our ROM estimator to a THR surgery performed at Osaka University Hospital. The estimator is implemented using the C++ language and message passing interface (MPI) routines [7]. Fig. 4 shows the turnaround times of ROM estimations when processing in sequential and remote parallel. Although our system required additional times for remote parallel processing, it reduced the turnaround time from 22 minutes on a single system to 23.4 seconds. This turnaround time of less than one half of a minute is speedy enough for intraoperative processing. It was also evident that the data-compression algorithm successfully reduced the turnaround time by approximately 33%.

**Conclusions**

We have presented a remote parallel-processing system for medical image processing, the MIP-Cluster system, developed for the HPC-assisted surgery. Our new system provides an intraoperative ROM estimation by parallel processing based on the master-worker or dynamic load balancing. It also provides an automation framework for remote parallel processing, which includes a secure execution environment by public key cryptography and high-speed data transmission by data compression.

As a result, as compared to a sequential system which takes one half of an hour for the estimation, MIP-Cluster accelerates the process to less than one half of a minute, and thereby realizes intraoperative surgical planning without degrading the resolution of images and limiting the area for estimations. We believe sharing the HPC-assisted surgery will improve the quality and safety of surgery at a low cost.

**References**

Face MOUSE: A Novel Human-Machine Interface for Controlling the Position of a Laparoscope


The following is a comment on the published paper shown on the preceding page.

FAce MOUsE: A Novel Human-Machine Interface for Controlling the Position of a Laparoscope

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Introduction

In current laparoscopic surgery, the vision of the operating surgeon usually depends on the camera assistant responsible for guiding the laparoscope. The assistant holds the laparoscope for the surgeon and positions the scope according to the surgeon's instructions. This method of operation is frustrating and inefficient for the surgeon, because commands are often interpreted and executed erroneously by the assistant. Also, the views may be suboptimal and unstable because the scope is sometimes aimed incorrectly and vibrates due to the assistant's hand tremors (see Fig. 1). The introduction of robotic technologies, specifically, the development of robotic laparoscope positioning systems to replace the human assistant, is a major step toward the solution of this problem. In such robotic systems, the human-machine (surgeon-robot) interface is of paramount importance because it is the means by which the surgeon communicates with and controls the robotic camera assistant.

Several robotic laparoscope positioning systems have been devised in the last ten years. The human-machine interface of most laparoscope positioners proposed in the early years included a joystick or foot pedal, and each required the use of the surgeon's hand and/or foot [1-3]. These types of interfaces, however, seem generally difficult to use because surgeons already use their hands and/or feet to control a variety of surgical tools. To solve this problem, several researchers have introduced a voice-activated system based on the verbal aspect of human speech [4-6]. However, this system does have some inherent limitations, such as reduced accuracy in positioning, long reaction times, and erratic movements in a noisy environment. We believe that a motion-based laparoscope controller, using the movement of the surgeon's head, is the best solution because nonverbal instructions such as face gestures are more intuitive and faster than verbal instructions. Also, because these gestures have the potential ability to represent not only the direction of scope motion but also the degree of motion, such as velocity, laparoscope positioning accuracy may be improved. Several laparoscope manipulators with a head navigation interface have previously been developed [7-9]. Such systems, however, failed to fully utilize the nonverbal features of facial motion. These systems were limited to detecting dominant head gestures, which only served as discrete (verbal) commands, and required not only head movements but also simultaneous control of an additional footswitch. Furthermore, the surgeon had to wear head-mounted sensing devices, such as a headband and gyro sensor, which were stressful for the surgeon.

To make the most of the advantages of nonverbal and noncontact instructions, we have designed a novel human-machine interface, called “FAce MOUsE,” for controlling the laparoscope positioner. This proposed human interface is an image-based system which tracks the surgeon's facial motion robustly in real time and does not require the use of body-contact sensing devices. Using the FAce MOUsE interface, we have developed a new robotic laparoscope positioning system for solo surgery. Our system provides the surgeon with a means of total hands-off and feet-off laparoscope operations, while also achieving rapid reaction and high positioning accuracy.
Step 3) Make a Trigger Action to Change the SHIFT/ZOOM State to the STILL State: All the surgeon has to do is roll the face. As soon as the rolling motion is detected, the laparoscope motion stops and the state returns to STILL. Note that this action is very easy to do.

This control scheme is analogous to that of a computer mouse device (with two buttons). Accordingly, this is why we called our scheme FAcE MOUSE. Guiding Action, in which the 2-D translation in the face plane is dominant, corresponds to the mouse body movement on the mouse pad plane. Trigger Action, in which the 1-D rotation in the face plane is dominant, corresponds to mouse button operations such as click (i.e., press and release the button).

To maintain high levels of “safety” during surgery, we must note the following two points. (1) Without exception, unintentional movements, which could be misunderstood as Trigger Action (to SHIFT) or Trigger Action (to ZOOM) in the STILL state, should be avoided, and (2) Trigger Action (to STILL) should be definitely and immediately recognized in the SHIFT/ZOOM state. We performed a successful FAcE MOUSE implementation by paying great attention to these points.

Implementation and Results

We designed a novel human-machine interface for controlling the laparoscope with the above method. The system overview is shown in Fig. 3. Our laparoscope positioning system, the FAcE MOUSE system, consists primarily of a CCD camera placed just over the TV monitor, an all-purpose PC with a video-capturing device, a robot manipulator that holds the laparoscope, and a scan converter for superimposing graphics on the scope image. Once the camera is set in the appropriate position and pose, the core system in the PC can detect and track the surgeon’s facial features in the zoomout and zoomin movements, respectively, of the laparoscope.

Concept of FAcE MOUSE

Fig. 2 illustrates the FAcE MOUSE control scheme. As shown in this figure, the state of the robotic laparoscope positioning system can be broken down into the following three states: (1) SHIFT state: guiding the laparoscope for maintaining the surgical point of interest in the center of the video frame, (2) ZOOM state: guiding the laparoscope for providing the required target magnification, and (3) STILL state: keeping the laparoscope still. All surgery work time can be classified into any of these states from the viewpoint of laparoscope operation.

Let us consider how to control not only the laparoscope motion itself but also the transition between these states by making face gestures only. We refer to the face motion for the transition state as the Trigger Action, and that for guiding the laparoscope as the Guiding Action (see Fig. 2). The method for positioning the laparoscope through face motions is summarized as follows.

Step 1) Make a Trigger Action to Change the STILL State to the SHIFT/ZOOM State: To complete the transition, the following three consecutive face motions are required: (1) put the position and pose of the face in the standard position and pose; (2) roll the face counterclockwise (for SHIFT) or clockwise (for ZOOM); and (3) return the face precisely to the standard position and pose. Note that the surgeon cannot make this action unconsciously.

Step 2) Make a Guiding Action in the SHIFT/ZOOM State: Once the system comes into the SHIFT or ZOOM state, the face translation is represented as a vector from the standard position, and the direction and magnitude of the vector are, respectively, transformed into the direction and velocity of the laparoscope motion. As shown in Fig. 2, the face intuitively shifts parallel to the scope image plane, corresponding to the identical pan and tilt movements of the laparoscope when the state is SHIFT. On the other hand, when the state is ZOOM, the up and down movements of the face correspond to the zoomout and zoomin movements, respectively, of the laparoscope.

To evaluate the performance of the proposed system and its applicability in clinical use, we set up an in vivo experiment, in which the surgeon used the system to perform a laparoscopic cholecystectomy on a pig.
real time (30 Hz) from a sequence of video images captured through the CCD camera. Assuming that the surgeon’s face is moving on a virtual plane parallel to the TV monitor screen, the system estimates the position and pose of the surgeon’s face in real time from the image-processing result and then recognizes the surgeon’s face gestures (i.e., the Trigger and Guiding Actions). According to the state of the system and the gestural action recognition result, the control command is sent to the laparoscope manipulator. The system state and image-processing results are also superimposed graphically on the laparoscope image using the scan converter (as feedback information for the surgeon), and the resulting image is displayed on the TV monitor.

To evaluate the performance of our system, an in vivo experiment was carried out, in which a surgeon used our system in a conventional laparoscopic operating room environment and a regular set of instruments to perform a laparoscopic cholecystectomy (gall-bladder removal) on a pig. As a result, the entire operative procedure was successfully and safely completed with our system. In this experiment, the robot never obstructed the surgeon’s work, and worrisome incidents and technical problems did not occur. Fig. 4 shows scenes of the surgeon’s facial motions in the experiment. The upper part of Fig. 4 consists of the scope images which the surgeon looked at; the lower part consists of the images of the surgeon’s face from the surveillance camera. Each pair of images was taken at the same time.

The system never mistook any other motion of the operating surgeon or any other surgeon who was present during the experiment (e.g., see the second, third, and fourth images of Fig. 4, which show a surgeon walking behind the operating surgeon.) Also, the face gestures to stop the laparoscope motion were all correctly recognized. These results demonstrate that our face-gesture recognition system worked well. We received many positive comments, such as fast reaction time, high positioning accuracy, and easy and intuitive camera guidance, from the surgeons who performed or looked in during the experiment. The operating surgeon, however, did make the negative comment that after the experiment he felt a little fatigue in his neck from a lot of rolling face motions. In fact, he made rolling gestures 4.2 times/min during the operation.

Conclusion
We have developed a new robotic laparoscope positioning system for solo surgery based on a real-time, face-tracking technique. Our system succeeded in freeing the surgeon’s hands and feet from the laparoscope guiding task while achieving safety, rapid reaction, and high positioning accuracy. Now we are studying an improved method for guiding the laparoscope based on the visual tracking of both the surgeon’s face and the surgical instruments, with the goal of reducing not only mental stress but also physical stress, such as neck fatigue. An exhaustive comparative study between our system and other human-machine interfaces is also important and ongoing [10].

References
A Synthesis of Sumanene, a Fullerene Fragment

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Bowl-shaped \( n \)-conjugated compounds are important not only as model compounds of fullerenes but also as possible synthetic intermediates for artificially designed fullerene derivatives, such as hetero-fullerenes (1). Most of the attention has been focused on the compounds derived from \( C_60 \) symmetric coronene (2), which was first synthesized in 1966 (2) and for which a practical synthetic route has been established (3). Sumanene (1) (4), which is a key partial \( C_60 \) symmetric structure of fullerenes, has some advantages over coronene derivatives, including the presence of three benzylic positions that should permit further functionalization to create new bowl-shaped species via the corresponding radicals, cations, anions, carbenes, etc. Although several approaches to sumanene have been attempted (4–6), there is no report of its successful synthesis (7). We have synthesized sumanene in short steps from commercially available norbornadiene under mild conditions.

Previous attempts at the synthesis of sumanene were based on approaches from planar aromatic compounds. For example, tris(bromomethyl)phenylene has been reported to undergo flash vacuum pyrolysis to create monocylic and dcyclized products with one or two broken outer-ring bonds, without formation of the desired sumanene (4). This finding suggests that a route from the planar compounds is unlikely to gain the strain energy, resulting effectively in the termination of single or double cyclization.

Our strategy for synthesis lies in constructing the three-dimensional framework using tetrahydrofulvalene \( \text{THF} \) carbons, which leads to the required \( n \)-conjugated structure by oxidative aromatization. The most closely related strategy is that which Barth and Lawton used in 1966 to synthesize coronene (3). In our synthetic route (Fig. 1), the key intermediate is hexacyclohexamannene 3, which may be prepared from the isomer 2 by transferring the alkene bridges. This isomeric transformation from \( n+3 \) to \( n+2 \) is expected to be exothermic by 51.4 kcal mol\(^{-1}\) estimated by density functional theory calculation (B3LYP:yP=6-31G*). In contrast, the reaction from unit isomer of 2 is

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First and Practical Synthesis of Sumanene, a C_{3v} Symmetric Partial Structure of Fullerene

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Fullerene (1) and carbon nano tube, which are key compounds in carbon chemistry, are recognized as potential materials. Attention has been also drawn to bowl-shaped \( \pi \)-conjugated compounds including a partial carbon skeleton of fullerene, due to their unique physical and chemical properties\[1\]. One of such bowl-shaped \( \pi \)-conjugated compounds with \( C_{5v} \) symmetry is corannulene (3), which was first synthesized in 1966\[2\]. Furthermore, some practical synthetic routes have been developed for corannulene synthesis\[3\]. Another key fullerene fragment is sumanene (2)\[4\], which possesses a \( C_{3v} \)-symmetric structure. An important advantage feature of sumanene over corannulene depends on the presence of three benzylic positions that should permit further functionalization to create new artificially-designed bowl-shaped species via the corresponding radicals, cations, anions, carbenes, etc. Generally, functionalization of corannulene requires the electrophilic substitution on the aromatic ring. The structure and depth of the bowls can characterize the \( \pi \)-conjugated compounds. The bowl of sumanene (1.15 Å) is anticipated to be deeper than that of corannulene (0.89 Å).
Although several approaches to sumanene have been attempted [4-6], there is no report of a successful route to synthesize it [7]. Previous strategies for the synthesis of sumanene were based on approaches from planar aromatic compounds as reported in the synthesis of corannulene and heterofullerene. For example, tribromomethyltriphenylene has been reported to undergo flash vacuum pyrolysis to afford mono-cyclized and dicyclicized products with one or two broken outer-ring bonds, without formation of the desired sumanene as shown above [4]. This finding suggests that a route from the planar compounds is unlikely to gain the strain energy effectively, resulting in the termination of single or double cyclization. Another synthetic strategy should be developed to overcome this problem.

Our synthetic route lies in constructing the three-dimensional framework using tetrahedral sp³ carbons, which is converted to the required π-conjugated structure by oxidative aromatization. As illustrated below, the key intermediate is hexahydrosumanene 6, which may be prepared from the isomer 4 by transferring the alkene bridges. For this purpose, metathesis reaction provides a useful method for the carbon skeleton transformation.

Trimerization of norbornadiene affords syn- and antiserotactically (norbornadiene), which was achieved by a modified procedure based on the organocopper-mediated cyclization [8]. Alternatively, stepwise transmetallation via an organotin compound increased the total yield of syn-4 from 2% to 11% [9]. The alkene-bridge exchange was examined by the Ru-catalyzed tandem ring-opening metathesis (ROM) and ring-closing metathesis (RCM) reaction. syn-4 was treated with 10 mol% of Cl₂(PCy₃)₂Ru=CHPh in toluene at 0 °C, then at room temperature under an atmospheric pressure of ethylene, giving 6 via 5 in 24% yield. On the other hand, tandem ROM-RCM reaction did not proceed from anti-4, probably due to the steric demanding. This isomeric transformation from syn-4 to 6 is achieved through the following synthetic route:

**Synthetic Route to Sumanene**

1. **Condition a**: BuLi, potassium tert-butoxide, B(CH₃)₃Br, tetrahydrofuran, -78 °C to -45 °C then CuCl, room temperature. 7% yield (syn: anti = 1:3).
2. **Condition b**: BuLi, potassium tert-butoxide, B(CH₃)₃Br, tetrahydrofuran, -78 °C to -45 °C then tributyltin chloride, room temperature.
3. **Condition c**: Cu(2,3-C₄H₃SO₂), 20 °C to room temperature. 47% yield (2 steps; syn: anti = 1:3). 10 mol% Cl₂(PCy₃)₂Ru=CHPh in toluene at 0 °C, then at room temperature under an atmospheric pressure of ethylene, giving 6 via 5 in 24% yield.
4. **Condition d**: DDQ, toluene, 110 °C, 3 h. 70% yield.

Illustration:

![Synthetic Route to Sumanene](image-url)
considered to be exothermic by 51.4 kcal/mol estimated by DFT calculation (B3LYP/6-31G*). On the other hand, the reaction from anti isomer of 4 is calculated to be endothermic by 37.4 kcal/mol, indicating that the transformation from syn-4 to 6 is preferable. Finally, 6 underwent dehydrogenative aromatization with organic oxidant, DDQ (2,3-dichloro 5,6-dicyano-1,4-benzoquinone) to give sumanene (2) in 70% yield. All of these steps were performed under mild conditions, so no severe conditions such as flash vacuum pyrolysis are necessary[7,10,11].

1H-Nuclear magnetic resonance spectra elucidate the symmetrical structure of sumanene. In the NMR spectrum of 2 in CDCl3, only three signals were observed. One singlet corresponds to the aromatic protons and a pair of doublets is assignable to the benzylic protons. 13C-NMR showed four kinds of carbon signals. These results indicate that sumanene is present as a C3 symmetric structure in solution.

Further dynamic behavior of the bowl-shaped compounds lies in bowl-to-bowl inversion. Conannulene exhibits rapid bowl-to-bowl inversion at room temperature with an energy barrier of 10.2 kcal/mol at 64 °C[10,11]. In contrast, three five-membered rings of sumanene are believed to make it more rigid. The first estimation by MNDO predicts the inversion energy barrier as 24.2 kcal/mol[12], while by recent ab initio calculations the barrier ranges from 16.8 to 19.3 kcal/mol[13]. These estimations indicate that sumanene should not undergo bowl-to-bowl inversion on the short time like NMR time scale. Variable temperature NMR of sumanene in p-xylene-d10 solution revealed that a pair of doublets assignable to the benzylic protons gradually broadened at above 60 °C in the 300-MHz NMR spectra, indicating that the bowl-to-bowl inversion process occurs. Both doublets disappeared at 140 °C, but a new singlet peak was not observed under 150 °C. The findings suggest that sumanene appears to be rigid. The inside and outside moieties of the bowl can be differentiated. In this sense, the dynamic behavior may permit the design of functional carbon materials.

In conclusion, we succeeded in the efficient synthesis of sumanene for the first time. Sumanene is of potential for the design of a variety of bowl-shaped π-conjugated compounds, which are considered to be useful as materials.

References
Polymerization within a Molecular-Scale Stereoregular Template

Enzymes efficiently synthesize biopolymers by organizing monomer units within regularly structured molecular-scale spaces and exploiting weak non-covalent interactions, such as hydrogen bonds, to control the polymerization process. This ‘template’ approach is both attractive and challenging for synthetic polymer synthesis, where structurally regulated molecular-scale spaces could in principle provide solid-phase reaction sites for precision polymerization. Previously, free-radical polymerization of methyl methacrylate in solutions containing stereoregular isotactic (i) or syndiotactic (s) polystyrene (iPMMA) has been shown to result in template synthesis of the opposite PMMA based on stereocomplex formation with van der Waals interactions. However, using the structure of a solid to determine the stereochemical structure of a polymer has not been satisfactorily achieved. Here we show that macromolecularly porous ultrathin films, fabricated by a single assembly step, can be used for the highly efficient stereoregular template polymerization of methacrylates through stereocomplex formation. This reaction would accurately transfer its structural properties of regularity, molecular weight and organization within the template to the new polymer.

Structurally regulated molecular-scale spaces (nanospaces) in ultrathin polymer films are potentially valuable as solid-phase reaction sites for precision polymerization. As the macromolecular mobility is restricted in the solid state, the template effect of a constituent polymer is potentially accelerated. It is, however, difficult...
Bioinspired Template Polymerization: Polymerization within a molecular-scale stereoregular template

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In the field of synthetic polymer chemistry, template polymerization is one of the final goals in structure and molecular weight regulating polymerization. In 1955, Natta used Ziegler organometallic catalysts to initiate the stereoregular polymerization of vinyl monomers such as propylene to create polymers superior in some physical properties to conventional polymers (Nobel Prize in 1963). Nowadays, these commercially available polymers have become very important and indispensable materials. After Natta’s epoch-making research, many basic studies on stereoregular polymerization were initiated. Concurrently, Watson and Crick clarified the structure and functionalities of double stranded DNA by X-ray analysis in 1953 (Nobel Prize in 1962). Even at that time, I think that chemists noticed the possibility of molecular duplication. As these bioinspired concepts influenced synthetic chemists, trials on template polymerization originated and evolved with enthusiasm. Thus far, several strategies have been developed for the realization of template polymerization. Our research group considers that enzymes efficiently synthesize biopolymers by organizing monomer units within regularly structured molecular-scale spaces and exploiting weak non-covalent interactions, such as hydrogen bonds, to control the polymerization[1] process. This ‘template’ approach is both attractive and challenging for synthetic polymer synthesis, where structurally regulated molecular-scale spaces could in principle provide solid-phase reaction sites for precision polymerization. As shown in Fig. 1, stereoregular poly(methyl methacrylate)(PMMA) is known to form a DNA-like double-helical structure.

Figure 1. DNA and stereocomplex of PMMA

Previously, free radical polymerization of methyl methacrylate in solutions containing stereoregular isotactic (i) or syndiotactic (st) poly(methyl methacrylate) (PMMA) has been shown to result in template synthesis[2,3] of the opposite PMMA based on stereocomplex formation[4,5] with van der Waals interactions. However, using the structure of a solid to determine the stereoregular template polymerization of methacrylates through stereocomplex formation. This reaction would accurately transfer its structural properties of stereoregularity, molecular weight and organization within the template to the new polymer.

Structurally regulated molecular-scale spaces (nanospaces) in ultrathin polymer films are potentially valuable as solid-phase reaction sites for precision polymerization. As the macromolecular mobility is restricted in the solid state, the template effect of a constituent polymer is potentially accelerated. It is, however, difficult to prepare such films using conventional methods. We selected a methodology involving the solvent extraction of certain polymer components from ultrathin polymer films for the construction of porous host films for template polymerization. The precursor films were fabricated using layer-by-layer assembly[7], which can be demonstrated by the simple alternate immersion of solid substrates into interactive polymer solutions. Although layer-by-layer assembly conventionally produces polyelectrolyte multilayers based on polyelectrolytes, stereocomplexes between it-PMMA and st-polymers of methacrylates were also assembled on solid substrates[8-10], thus forming ultrathin stereocomplex films with a double-stranded helical structure, in which it-PMMA was surrounded by twice the unit-molar amount of st-polymers (1:2 stoichiometry)[5]. In the case of the stereocomplex film composed of it-PMMA and st-PMAA, st-PMAA was selectively extracted from the film in an aqueous alkaline solution, resulting in a macromolecularly porous it-PMMA film[11]. This porous film subsequently incorporated st-PMAA previously extracted, dependent on the st-PMAA concentration, thus demonstrating an unusual macromolecular recognition. However, it-PMAA was not extracted from the film in organic solvents, indicating that a vesicle host composed of it- or st-polymers for template polymerization cannot be prepared by this method.

In this study, we focused on the formation of a stereocomplex between it-PMMA and st-PMMA with a 1:1 unit-molar stoichiometry[12,13]. Layer-by-layer assembly of these polymers under suitable conditions produced a stereocomplex film with a 1:1 stoichiometry, and the subsequent selective extraction of a single component successfully produced porous st-PMAA or it-PMMA films, of which the macromolecular nanospaces could be used in stereoregular template polymerization of it-PMMA and st-PMMA, respectively. Although it is more difficult to obtain it-polymers of methacrylates by free radical polymerization owing to the steric hindrance of lateral groups, the stereoregularity of polymers synthesized by this method was absolutely dependent on that of the template polymers. Accordingly, the present study demonstrated the novel template synthesis of valuable polymers using...
both weaker van der Waals interactions and artificially constructed nanospaces in films. The present template polymerization method is schematically represented in Fig. 2.

Figure 2. A schematic representation of template polymerization using ultrathin porous films. Layer-by-layer assembly prepares the ultrathin film of a stereocomplex comprising it-PMMA and st-PMMA. Two polymer chains are shown as rigid helical rods, but should be partially distorted and entangled in the film. There must be a disordered region of the stereocomplex. A single component is selectively extracted from the film, resulting in the preparation of the porous film with regular nanospaces. Then, the porous film is used as a reaction mold for free radical template polymerization of MMA or st-PMMA, followed by the regeneration of the stereocomplex film.

A 9-MHz quartz crystal microbalance (QCM) substrate, which could determine the amount of assembled polymer from its frequency decrease, was used to quantify the assembly of it-PMMA and st-PMMA. To obtain an assembly with 1:1 stoichiometry, dimethylformamide (DMF) and DMF/water (2/3, v/v) were selected as solvents for it-PMMA and st-PMMA, respectively. This solvent combination was determined by a detailed assembly analysis, following methods used in a previous study. Alternate immersion in both solutions produced a film with the objective stoichiometry of 1.0±0.2 (st/it-unit ratio). The thickness and the mean roughness (Ra) for six cycles (it-PMMA/st-PMMA) were estimated to be 20.1±0.3 nm and 3.2 nm, respectively. Considering the assembly amount analysed by the QCM (4.1±0.1 µg cm⁻²), the mean density was estimated to be 1.0 g cm⁻³. The immersion of the film in both chloroform and a 10 mM sodium hydroxide aqueous solution resulted in desorption of approximately half the amounts of polymers in the film. As the desorption amounts were consistent with the amounts of each polymer totally assembled, this suggests that it-PMMA and st-PMMA were selectively extracted from the film. Attenuated total reflection (ATR) spectra in the carbonyl vibration region also demonstrated the selective disappearance of peaks at 1,731 cm⁻¹ and 1,717 cm⁻¹, corresponding to respective it-PMMA and st-PMMA. The thickness after the extraction of it-PMMA and st-PMMA was 18.3±2.8 nm and 19.4±2.8 nm, respectively, and these values were significantly consistent with the initial thickness of the stereocomplex film within experimental error. In addition, the Ra was 2.1 nm and 2.8 nm, respectively, and was slightly smoother than before. These observations indicated that a porous film composed of st-PMMA or it-PMMA suitable for template polymerization was successfully prepared by the solvent extraction. It is difficult to explain reasonably why the films were not compressed by the extraction. The terminals of the polymers as well as some segments that did not join in the complex might support the film structure. This observation was similar to the previously reported case of selective extraction from a double stranded stereocomplex film.

For the first step of the analysis of template polymerization, the QCM substrate coated with the porous st-PMMA film was immersed in a 10 mM solution of methyl methacrylate (MMA; 1.7 mg ml⁻¹) for 3 h at 70°C in the presence of a free radical initiator, 2,2'-azobisobutyronitrile (5 mg ml⁻¹) under a nitrogen atmosphere. After gentle rinsing with DMF, approximately 90% of the it-PMMA previously extracted was recovered (the percentage was almost the same for all template st-PMMAAs used). The ATR spectrum of the obtained film demonstrated the same peaks as those observed for the stereocomplex film, suggesting that it-PMMA was prepared, and that it formed a stereocomplex with the st-PMMA in the film. In order to analyse the stereoregularity and the molecular weight of the st-PMMA as the second step, the porous film was similarly prepared on silica particles (10 g, mean diameter 1.6 µm), following methods described in a previous study. MMA was then polymerized, and the PMMA was characterized by extraction using chloroform. Approximately 0.4 g PMMA was obtained from the feeding of 1.5 g MMA per 500 ml DMF, thus resulting in a yield of approximately 25% using these polymerization conditions. A typical 1H-NMR spectrum of the PMMA clearly demonstrated the it-specific polymerization of MMA in the porous st-PMMA film (Fig. 3a), thus indicating that the it-specific template polymerization was achieved on the basis of stereocomplex formation with the st-PMMA. Furthermore, size exclusion chromatography (SEC) curves potentially demonstrated the control of molecular weights with a narrow distribution (Fig. 3b).

The experimental data from the template polymerization of MMA are summarized in Table 1. The isoelectricities were greater than 92% in all cases. The number-average molecular weight (Mn) of the host st-PMMA significantly controlled the Mn of the it-PMMA, and was almost the same. These observations are surprising because the polymerization conditions, such as concentrations of monomers and initiators, were the same in all cases except for the molecular weight of the template st-PMMA. Although the same it-PMMA (Mn=20,000) was used for the preparation of host films, the molecular weight of the it-PMMA prepared is absolutely dependent on that of the host st-PMMA.

The porous film of it-PMMA was used to prepare st-PMMA. Silica particles coated with the porous it-PMMA film were similarly used for free radical polymerization of MMA in water in the presence of a water-soluble free radical initiator for 2 h at 40°C under a nitrogen atmosphere. The PMMA prepared in the film was extracted in an alkaline solution, methylated to prepare PMMA, and then characterized, as also shown in Table 1. St-PMMA was successfully prepared by using the porous it-PMMA film, and the molecular weight of the host it-PMMA similarly regulated that of the st-PMMA. These observations indicate alternative utilization of the porous films for stereoregular template polymerization of methacrylates. We note that conventionally prepared spin-casting films did not realize the above template polymerization, even under the same polymerization conditions. Furthermore, template polymerization of the combination between it-PMMA and st-PMMA in the solution system only demonstra-
ed the acceleration of polymerization rates, because the association is relatively weaker than that of stereoregular PMMAs[15]. These observations also confirmed the potential of the present porous films. Preliminary experiments of template polymerization of MAA in a porous it-PMAA film[11] prepared from the 1:2 (it:st) complex assembly revealed that the molecular weight of the st-PMMA polymerized was approximately twice that of the template it-PMMA, indicating the potential transferring of the assembly structure as well as further applications of porous thin films.

We now consider the polymerization mechanism in the films. Two contradictory polymerization processes would be expected: (1) polymerization after sufficient coordination of monomers with templates, and (2) stepwise polymerization with gradual incorporation (or slow diffusion) of monomers into the films. The quantitative QCM analysis did not show the sorption of monomers into the films, and did not support the former mechanism. In order to understand these mechanisms in detail, time-dependent SEC curves of the it-PMMA prepared by the st-PMAA host were obtained (data are not shown). The curve with a single and narrow peak width shifted to a higher molecular weight, thereby supporting the latter mechanism, which is similar to living radical polymerization rather than conventional free radical polymerization. As we stopped the polymerization of MMA after 3 h by opening the reaction vessel to the air, the radical terminals, which had been present in the films for at least 3 h, seemed to react with oxygen. The molecular weight of the st-PMMA prepared was similarly shifted, and a similar mechanism was supported. This is, to our knowledge, the first report of an artificially constructed polymerization template and subsequent polymerization with the efficient transfer of structural information, similar to that seen in biosynthetic processes. Porous polymer matrices provided a reaction mould for stereoregular polymerization of methacrylates. It- and st-polymers with high stereoregularity and with a narrow molecular weight distribution were successfully prepared.

Table 1. Analytical data on stereoregular template polymerization of methacrylate.

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Because particles coated with functional ultrathin films are readily handled and reusable (the porous films were reused at least 3 times), we expect large-scale synthesis of the stereoregular polymers to be achieved in the near future. Easier synthesis of stereoregular polymers of methacrylates potentiates their applications in technological and biomedical fields. Regulated nanospaces prepared in synthetic polymer assemblies should open the way to a new field of macromolecular recognition and synthesis.

Figure 3. Characterization of it-PMAAs polymerized in porous st-PMAA films for 3 h at 70°C. a: A typical 1H-NMR spectrum of it-PMMA polymerized in a porous it-PMAA film. b: SEC curves of it-PMAAs polymerized in porous films of st-PMAAs with various molecular weights.

References
Localization of Electromagnetic Waves in Three-Dimensional Fractal Cavities

Paper in journals: this is the first page of a paper published in Physical Review Letters.

The following is a comment on the published paper shown on the preceding page.

**Localization of Electromagnetic Waves in Photonic Fractals**

KIRIHARA Soshu and MIYAMOTO Yoshinari

(Joining and Welding Research Institute)

**Introduction**

Propagation properties of electromagnetic waves in periodic and quasiperiodic structures have been of theoretical and practical interest for the past two decades. Photonic (electromagnetic) crystals consist of a periodic dielectric array with different dielectric constants that can totally reflect light or electromagnetic waves with a wavelength similar to the periodicity due to Bragg diffraction. Formation of photonic band gaps, localization of light, control of spontaneous emission, and other properties associated with photonic crystals have been studied intensively [1-3]. A photonic band gap is understood as an analogy to the electronic band gap in semiconductors.

On the other hand, interaction of optical, electromagnetic, and acoustical waves with fractal structures has been of interest in recent years as well. A fractal is defined as a rough and irregular structure with self-similarity [4]. In other words, the local configuration or substructure is similar to the whole configuration or the entire structure. The fractal structure is essentially different from the periodic structure because it has no periodicity and no translational symmetry.

Though there are many reports concerning the localization of light or electromagnetic waves in various fractal structures, they are restricted to one-dimensional or planar fractals [5,6]. A 3D fractal structure is necessary to completely localize the light or electromagnetic waves in 3D space. However, 3D fractal structures have not been investigated due to their difficult construction. We have succeeded in fabricating 3D fractal structures called Menger sponge, which are made of dielectric media such as epoxy and ceramics. These structures exhibit an electromagnetic wave that is strongly localized in the central air cavity region of the 3D fractal without reflection and transmission. Such a material has not been previously reported, thus we defined this localization as "photonic fracton" in the "photonic fractal".

**Design and Fabrication of 3D Fractal Structures**

We designed the Menger sponges of size comparable with microwave range by using a CAD (Computer Aided Design) program and then automatically fabricated them from epoxy resin using a rapid prototyping method called stereolithography [8]. This method enables us to form three-dimensional complex objects via a layer-by-layer process using CAD/CAM (Computer Aided Manufacturing) system. Each layer of about 100 μm in thickness is solidified by scanning the surface of the photosensitive liquid resin with an ultraviolet laser beam. When ceramic particles are dispersed in the liquid resin, we can form the Menger sponges of ceramic-epoxy composite with high dielectric constant. It is very difficult to fabricate such a complex fractal structure by other methods except CAD/CAM systems.

We constructed the Menger sponge structure from a dielectric cube with a side length a, which is composed of epoxy or TiO₂-SiO₂ ceramics dispersed epoxy composite. The cube is divided into 27 identical cube pieces, and the seven pieces at the body- and face centers are extracted. By repeating the same extraction process for the remaining 20 pieces we create the Menger sponge. Menger sponge structures with different stages of the repeating process (0, 1, 2) are illustrated in Fig.1. The side length a of the initiator is 27mm. The lengths of the longest, middle, and shortest sides of the square air rods in the stage 3 Menger sponge are 9mm, 3mm, and 1mm, respectively.
Strong Localization of Electromagnetic Waves

Normally incident reflection and transmission spectra of the Menger sponge of stage 1, 2, and 3, and those of simple cubic photonic crystals with square air rods of 3mm and 1mm formed by the same CAD/CAM stereolithography were measured by using a network analyzer and two mono-pole antennae. The measurement system is schematically illustrated in Fig. 2.

The results for the stage 3 Menger sponges made of epoxy and TiO2-SiO2 ceramics dispersed epoxy are shown in Fig. 3. In the transmission spectrum of the Menger sponge made of epoxy as seen at the upper figures, a sharp transmission attenuation as large as -31dB was observed at 12.8 GHz and a relatively broad attenuation of reflection as large as -7dB was observed at around 13.0 GHz. The dielectric loss of the material was 0.2. In addition, for the stage 2 Menger sponge, a sharp attenuation and a corresponding broad attenuation of reflection were both observed at around 12.8GHz as well. In the case of the stage 3 Menger sponge made of TiO2-SiO2 dispersed epoxy, both highly sharp attenuations for reflection and transmission to -40dB were observed at about 8 GHz as seen in the lower figures. The dielectric loss of the fractal material was 0.1.

In contrast, such an anomalous attenuation was observed neither in the transmission and reflection spectra of simple cubic photonic crystals and Menger sponge of stages 0 and 1. Therefore, the origin of the anomalous attenuations observed both in the reflection and transmission spectra of the Menger sponge of stage 2 and 3 should be intrinsic to the fractal structure because they have the self-similar structure.

Figure 4 shows the spatial distribution of the electric field at 12.8 GHz in the stage 3 Menger sponge of epoxy, which was measured at positions along the central air-rod by a probe method using two mono-pole antennae. A mono-pole antenna for emission was placed at the same position in the case of the transmission measurement and another antenna was inserted into the largest air rod at the center. The electrical field intensity shows a typical double maximum curve symmetric for the center point. Apparently this mode is strongly localized almost within the central largest cubic air-cage region and the electric field decreases abruptly outside the central cube. The localized mode has a cubic-shell shape whose edges and corners are rounded. A similar localization mode was

Figure 2. Schematic illustration of experimental setup for the measurement of microwave transmission and reflection properties of a photonic fractal.

Figure 3. Localization of electromagnetic waves in Menger sponge fractals. The wavelength $\lambda_{loc}$ of the localized mode in the dielectric Menger sponge fractal is calculated using the empirical equation $\lambda_{loc} = \frac{2\pi}{f} \tau_{eff}$ where $g$ and $\tau_{eff}$ are the edge length and the spatially averaged dielectric constant of the fractal cube, respectively. The calculated and measured frequencies of the localized modes in the stage 3 Menger sponges of epoxy (upper figures) and 10vol% TiO2-SiO2/epoxy (lower figures) showed good agreements.
observed in stage 3 Menger sponge of TiO$_2$-SiO$_2$ dispersed epoxy as well.

Discussion

Let us compare these propagation characteristics of the Menger sponges to those of photonic crystals. In the case of the localized mode due to a structural defect in a photonic crystal, we must observe a sharp transmission peak in a nontransparent region due to the photonic band gap and a sharp dip of reflectance in the total reflection region. The characteristics observed in Fig.3 do not meet any of these features.

The optical length of the stage 3 Menger sponge, which is calculated as a product of its actual thickness and spatially averaged refractive index, is 35.6 mm. This value is larger than the relevant wavelength by only 50%: that is, the Menger sponge confines the electromagnetic wave with a wavelength corresponding to 2/3 of its optical length. It is reported that the optical or electromagnetic wave excitations in one dimensional or planar fractals localize in small subwavelength areas [5,6]. On the other hand, in the case of photonic crystals, the localization length is several times of the lattice constant of the crystal. So, the optical length necessary to confine a localized mode is several times the relevant wavelength in free space. We can, thus, conclude that the confinement of the electromagnetic energy by the Menger sponge is quite strong.

These strong localizations of electromagnetic waves in the 3D fractal structure cannot be explained by simple Bragg diffraction and band gap formation. It is inferred that such a localization may occur due to the interference of multiple reflections in the fractal structure. The theory necessary to account for the localization of electromagnetic waves in 3D fractal structures is a very interesting challenge.

Conclusions

We observed localization of microwaves in the Menger sponges that is intrinsic to their fractal structure, and this is the first report on the light localization in 3D fractal cavities. This localization is not caused by the presence of a photonic band gap as in photonic crystals but should be attributed to a singular photon density of states realized in the fractal structure. Confinement of electromagnetic radiation energy in the fractals may be useful for various devices in communication, information, energy, medical and other fields.

References

Involvement of Histone H1.2 in Apoptosis Induced by DNA Double-Strand Breaks

The following is a comment on the published paper shown on the preceding page.

Involvement of Histone H1.2 in Apoptosis Induced by DNA Double-strand Breaks
SHIMIZU Shigeomi and TSUJIMOTO Yoshihide
(Graduate School of Medicine)

Introduction
Programmed cell death or apoptosis plays an important role in various biological events in metazoans, including development, maintenance of tissue homeostasis, and elimination of harmful cells. The process of apoptosis is driven by a family of proteases called caspases, which cleave various cellular proteins to cause apoptotic death. It has been shown that the mitochondria play a crucial role in apoptosis by releasing several apoptogenic molecules such as cytochrome c, which activate downstream destruction programs including the caspase cascade [1]. The best-characterized regulators of apoptosis are the Bcl-2 family of proteins, which directly modulate outer mitochondrial membrane permeability during apoptosis. This family of proteins comprises anti-apoptotic members, such as Bcl-2, as well as pro-apoptotic members [2]. Although several molecules have been reported to be involved in transmission of DNA damage-induced apoptotic signals to the mitochondria, the mechanisms of signal transmission are not fully understood.

In the present study, we took a biochemical approach to the identification of a signaling molecule involved in DNA damage诱导ed apoptosis by searching for a cytochrome c-releasing factor that appeared in the cytoplasm after X-ray irradiation.

Purification of an X-ray-induced cytochrome c-releasing factor as histone H1.2
To identify DNA damage-activated signaling molecule(s) with cytochrome c releasing activity, we set up an in vitro assay system using isolated rat liver mitochondria and rat thymus cytosol. The cytosol collected from the thymus of rats subjected to whole-body X-ray irradiation, was capable of inducing cytochrome c release from the mitochondria. Following the purification protocol described in Fig. 1A, we identified a 34 kD protein with cytochrome c-releasing activity (Fig. 1B). Sequence analysis indicated that the 34 kD protein was rat histone H1.2. We also showed that mouse H1.2 has cytochrome c-releasing activity. Among several mouse histone H1 isoforms, only histone H1.2, but not other isoforms, possesses cytochrome c-releasing activity (Fig. 2).

Figure 1. Purification of a cytochrome c-releasing factor as histone H1.2
(A) Diagram of the purification method. (B) Purification of cytochrome c-releasing factor from rat thymus. Aliquots of the Mini S column fractions were subjected to SDS-PAGE, followed by silver staining (upper panels), and also assessed for cytochrome c-releasing activity with the mitochondria (lower panels).

Figure 2. Histone H1.2 induces cytochrome c release from isolated mitochondria
(A) Histone H1 from mouse thymus was separated by RP-HPLC. (B) Each histone H1 subtype as well as a low molecular weight protein in peak 1 were assessed for cytochrome c-releasing activity. Peak 6 corresponds to H1.2.

ANNUAL REPORT OF OSAKA UNIVERSITY - Academic Achievement - 2003-2004
p53-dependent release of nuclear histone H1.2 after X-ray irradiation

Histone H1 is not detected in the cytosol of healthy mouse thymocytes and mouse embryonic fibroblast cells (MEFs), whereas X-ray irradiation induced a cytoplasmic increase of histone H1s (Fig. 3), which was suppressed by an inhibitor of nuclear export, leptomycin B, and depended on p53. Cytoplasmic H1 did not show any X-ray irradiation-specific modifications.

Inhibition of X-ray-induced apoptosis by reducing H1.2 expression

The level of histone H1.2 was reduced in MCF7 cells by the expression of H1.2 antisense RNA. Two clones (AS#1 and AS#2) with almost complete absence of histone H1.2, but not the other H1 subtypes were more resistant to X-ray-induced cytochrome c release and cell death than control cells (Fig. 4). AS cells were also more resistant to etoposide, but not to UV, paclitaxel and TNF-α than control cells (Fig. 5). These results indicated that histone H1.2 is specifically required for apoptosis induced by etoposide and X-rays, both of which cause DNA double-strand breaks.

Figure 3. Cytoplasmic accumulation of histone H1.2 after X-ray irradiation

E1A/Ras-transformed MEF were exposed to X-ray irradiation (20 Gy). After 24 hr, the cells were immunostained with an anti-histone H1 monoclonal antibody.

Figure 4. Inhibition of X-ray-induced apoptosis by reducing histone H1.2 expression

MCF7 variants transfected with caspase-3-cDNA and GFP DNA were exposed to irradiation (20 Gy) (IR) or were not treated (NT). After 24 hr, the cells were stained with Hoechst 33342, and apoptotic cells were detected by examining the nuclear morphology.
Concluding remarks

By adopting a biochemical approach to investigate the transmission of X-ray-induced apoptotic signals to the mitochondria, we identified histone H1.2. Histone H1.2 is specifically involved in apoptosis induced by DNA double-strand breaks by translocating from the nucleus to the mitochondria, and subsequently inducing mitochondrial membrane permeabilization. It was particularly interesting that histone H1.2 did not play an important role in apoptosis induced by UV irradiation, which also causes DNA damages. DNA double-strand breaks, but probably not UV damages, trigger a megabase range of chromatin remodeling, which likely leads to release of H1 from the chromatin. Histone H1.2 probably cooperates with other pro-apoptotic proteins in DNA damage-induced apoptosis.

Histone H1.2-deficient mice show cellular resistance to X-ray-induced apoptosis

Finally, we examined mice lacking histone H1.2. H1.2-KO thymocytes showed superior viability to WT thymocytes over a wide range of X-ray radiation doses. We also examined X-ray-induced apoptosis of small bowel cells. When WT mice were exposed to X-ray irradiation (10 Gy) and sacrificed after 2 days, the small intestine was severely damaged, with denudation of the crypt and villus system (Fig. 6), as well as positive TUNEL-staining of a large number of epithelial cells and enterocytes (Fig. 6). In contrast, the small bowel looked normal after X-ray irradiation of H1.2 KO mice, and only a few TUNEL-positive cells were observed (Fig. 6).

References

Nuclear Cataract Caused by a Lack of DNA Degradation in the Mouse Eye Lens

Paper in journals: this is the first page of a paper published in Nature.

Nuclear Cataract Caused by a Lack of DNA Degradation in the Mouse Eye Lens

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(Graduate School of Frontier Biosciences and Graduate School of Medicine)

Introduction

The eye lens is composed of fiber cells which develop from the epithelial cells on the anterior surface of the lens [1]. Differentiation into a lens fiber cell is accompanied by changes in cell shape, the expression of crystallins, and the degradation of cellular organelles [2]. The loss of organelles is believed to ensure the transparency of the lens, but the molecular mechanism behind this process is completely unknown. Here, we show that DLAD (DNase II-Like Acid DNase) [3], also called DNase IIβ [4] is expressed in lens cells. Mice deficient in the DLAD gene were incapable of degrading DNA during lens cell differentiation, and undigested DNA accumulated in the fiber cells. The DLAD+ mice developed cataracts of the nucleus lentis, and their response to light on electroretinograms was severely reduced. These results indicate that DLAD is responsible for the degradation of nuclear DNA during lens cell differentiation, and that if DNA is left undigested in the lens, it causes cataracts of the nucleus lentis, blocking the light path.

Specific Expression of DLAD in the lens

To identify the DNase responsible for the degradation of nuclear DNA during lens cell differentiation, we first examined by real-time PCR the expression of three DNases (DNase II, DLAD, and CAD) in various mouse tissues. DNase II is an acid DNase found in lysosomes that has an essential role in the degradation of nuclear DNA expelled from erythroid precursor cells [5], and in the degradation of the DNA of apoptotic cells after macrophages engulf them [6]. DLAD is also an acid DNase that has homology to DNase II [3, 4]. DLAD was reported to be expressed in the mouse liver and human salivary glands and lungs, but the physiological role of DLAD remained unidentified. CAD, caspase activated DNase, is a neutral DNase, and is responsible for the cell-autonomous DNA degradation in apoptotic cells [6]. An analysis by real-time PCR indicated that the CAD mRNA was expressed in various mouse tissues, but not in the lens (data not shown). The DNase II mRNA was also ubiquitously expressed, but its expression level in the lens was low. On the other hand, the DLAD mRNA was highly expressed in the mouse lens (Fig. 1a). All the lens fiber cells are nucleated at the beginning of mouse embryogenesis, and begin to lose their nuclei after embryonal day (E)16. Accordingly, the DLAD mRNA level in the lens was low at E14.5, but highly increased at the late stage of mouse embryogenesis (Fig. 1b). The DLAD mRNA was detected in human lens cells from patients with senile cataracts. An epithelial cell line established from human lens also expressed a significant level of DLAD mRNA. But, little expression of DLAD mRNA was found in the other types of cell lines.

Fig. 1. Expression of DLAD mRNA in the lens. a and b. The DLAD mRNA level in the indicated mouse tissues (a), and in the mouse lens at the indicated developmental stages (b) was quantified by real-time PCR, and is expressed as a relative value to β-actin mRNA.
Establishment of DLAD-deficient mice

To assess the physiological role of DLAD, we generated DLAD−/− mice by gene targeting. The murine DLAD gene is encoded by 6 exons within 15.0 kb of genomic DNA. A targeting vector was constructed by replacing exons 3 and 4 with the neo gene, and introduced into mouse embryonal stem (ES) cells. ES clones carrying the mutation were identified by PCR, and mice were generated from one representative ES clone. The heterozygous animals were then intercrossed, and the mice carrying the wild-type, heterozygous, and homozygous mutations in the DLAD gene were obtained. To examine the existence of acid DNases other than DLAD in the mouse lens, and to confirm the null-mutation of the DLAD allele in DLAD−/− mice, cell extracts were prepared from the lenses, and the DNase activity was assayed. As shown in Fig. 2, the lens extracts from wild-type and heterozygous mice showed a DNase activity at pH 5.9. On the other hand, little DNase activity was detected under these acidic conditions in the lens extracts from DLAD−/− mice. These results indicated that DLAD is the major acid DNase in the mouse lens, and the DLAD−/− allele is a null-allele for DLAD. The three genotypes (DLAD+/+, DLAD+/− and DLAD−/−) were represented according to Mendelian inheritance. Except for the cataract described below, DLAD−/− mice showed no gross developmental abnormalities, and were fertile with normal fecundity.

Development of cataract in DLAD-deficient mice

The eyeballs of DLAD−/− mice had normal morphology and were similar in size to the eyes of DLAD+/+ mice. The lens fiber cells were well differentiated into mature cells, and normal levels of crystallins were found in the lens of DLAD−/− mice (data not shown). Histochemical analyses of midsagittal sections of the lens showed a monolayer of cuboidal epithelial cells covering the anterior surface of the lens. Elongating fiber cells at the equator and outer cortex of the lens contained nuclei that stained with Feulgen and DAPI (Fig. 3a). They also contained mitochondria because the cells in this area could be stained by an antibody against mitochondrial ATP synthase. In the inner cortex of the DLAD+/+ and DLAD−/− lens, there was an abrupt loss of nuclei, and mitochondria, which formed an "organelle-free zone". In contrast, Feulgen and DAPI-positive materials were found even in the mature fiber cells located in the nucleus of DLAD−/− lens, although these cells seemed to be well differentiated morphologically.

Analyses of the mature lens cells by transmission electron microscopy confirmed that the mature DLAD−/− fiber cells did not contain ER or mitochondria (Fig. 3b). But they contained materials that could be condensed DNA. A higher magnification showed that the condensed materials were surrounded by loosely-packed substances, and some lens fiber cells had amorphous materials that could be unpacked DNA. These materials were not surrounded by membrane-like structures, suggesting that the lens membranes were destroyed.

The eyes of DLAD−/− mice showed a weak but recognizable cataract (Fig. 4a). That is, there was visible opacity in the nucleus of the DLAD−/− lens, and this was enhanced in aged mice. To examine the effect of the DNA that was left in the fiber cells on the transmission of light, electroretinograms (ERGs) were compared between...
Discussion

In mammals, erythrocytes and lens fiber cells have no nuclei; they are removed during the differentiation into mature cells. We previously reported that the DNA of the nuclei expelled from erythroid precursor cells was cleaved by DNase II in macrophages after the nuclei were engulfed by the macrophages [5]. Here, we showed that DLAD, a DNase II-like molecule, is responsible for the degradation of DNA in the lens fiber cells. As found for DNase II, DLAD is active under acid conditions and seems to be present in lysosomes [3]. However, unlike the DNase II-null mice in which undigested DNA from erythroid precursor cells accumulates in the lysosomes of macrophages [5, 6], the undigested DNA was found in the fiber cells of the DLAD-/- lens, indicating that DLAD works cell-autonomously to degrade the DNA of fiber cells. This agrees with the fact that the lens is composed only of fiber cells, and no macrophages are present in the lens. Lens fiber nuclei often become TUNEL-positive as they degenerate, suggesting that apoptotic process is involved in this process [7, 8]. This apparently contradicts with the biochemical property of DLAD that generates DNA fragments carrying 3'-phosphate [3]. It is possible that under some circumstances, phosphatase(s) may remove 3'-phosphate from the DLAD-generated DNA fragments. Degradation of organelles is often mediated by its own lysosomes through a process called autophagy [9]. The essential role of DLAD, a lysosomal DNase, in the degradation of DNA in the lens fiber cells suggest the involvement of autophagic process in the lens cell differentiation. Finally, the development of cataract in the DLAD-/- mice indicates that DNA must be degraded to ensure the light path in the lens. DLAD is expressed in human lens cells as well. It is possible that some human cataract patients carry a deficiency in the DLAD gene, and the DLAD-/- mice established here will provide a good model system for human cataract.

References


Fig. 4. Development of cataract in DLAD-/- mice. a. Nuclear cataract in DLAD+/mice. The eyes of DLAD+/ and DLAD-/- mice at the ages of 6 and 26 weeks were photographed. b. Electrophoretograms in response to diffuse stimuli of increasing illumination intensities were recorded with 11-week-old DLAD+/ and DLAD-/- mice. The numbers on the left indicate the values of the neutral density (ND) filter in log units.
Zinc transporter LIVI controls epithelial-mesenchymal transition in zebrafish gastrula organizer

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Vertebrate gastrulation is a critical step in the establishment of body plan. During gastrulation, epithelial-mesenchymal transition (EMT) occurs. EMT is one of the central events of embryonic development, organ and tissue regeneration, and cancer metastasis. Signal transducers and activators of transcription (STATs) mediate biological actions such as cell proliferation, differentiation, and survival in response to cytokines and growth factors, in a variety of biological processes. STATs are also important in EMT during gastrulation, organogenesis, wound healing and cancer progression. It was previously shown that STAT3 is activated in the organizer during zebrafish gastrulation and its activity is essential for gastrulation movements. The requirement for STAT3 is cell-autonomous for the anterior midline of gastrula organizer cells, and non-cell-autonomous for the convergence of neighbouring cells. The molecular mechanisms of STAT's action in EMT, however, are unknown. Here we identify LIVI, a breast-cancer-associated zinc transporter protein, as a downstream target of STAT3 that is essential and sufficient for STAT3's cell-autonomous role in the EMT of zebrafish gastrula organizer cells. Furthermore, we demonstrate that LIVI is essential for the nuclear localization of zinc-finger protein Snail, a master regulator of EMT. These results establish a molecular link between STAT3, LIVI, and Snail in EMT.

We isolated a complementary DNA encoding zebrafish LIVI (ZLT-Drh) by a subtraction screening. LIVI belongs to a subfamily of ZIP zinc transporters (Zrt-, Ire-like proteins), termed ZLT (LIVI-1 subfamily of ZIP zinc transporters). Its sequence contains eight transmembrane domains (TM) with a long extracellular amino terminus, a short extracellular carboxy terminus, a long variable region in the cytoplasmic loop between TM III and IV, an HNF motif in TM IV, a HEXXHHE motif in TM V, and numerous histidine-rich repeats. All these motifs indicate LIVI's relation to the LZT subfamily of ZIP zinc transporters. The phylogenetic tree and alignment across the two domains IV and V of the LZT subfamily of ZIP zinc transporters revealed that the cDNA was the zebrafish counterpart of LIVI (LZT-Hr8; Supplementary Fig. 1b). The zebrafish LIVI mRNA was expressed maternally and zygotically throughout the shield stage and accumulated in the prechordal mesendoderm cells, in which STAT3 is activated (Fig. 1a-f). The expression of LIVI mRNA in the gastrula organizer was abolished in stat3-depleted embryos, indicating that LIVI is a downstream target of STAT3 (Fig. 1g, h). Consistent with this, gp130-stimulation by G-CSF induced LIVI expression in the mouse proβ cell line, Bal31/B03 cells expressing a chimeric receptor G-CSFR-gp130 (Fig. 1i, G133), but not the Bal31/B03 cells expressing the mutated chimeric receptor defective in STAT3 activation (Fig. 1j, G133-F1). Furthermore, the dominant negative form of STAT3 inhibited gp130-mediated LIVI expression in Bal31/B03 cells (Fig. 1l, G133-STAT3F). Moreover, transfection of siRNA for human STAT3 in the human prostate cell line, DU145 cells downregulated the expression of human LIVI (Fig. 1j). Together, these results showed that the LIVI gene is regulated by STAT3 not only in zebrafish organizer cells but also in mammalian cells.

To address the early embryonic roles of LIVI during zebrafish gastrulation, we analysed embryos lacking LIVI activity using an antisense morpholino (LIVI-MO). Embryos receiving injections of LIVI-MO displayed a mispositioned head and shortened anterior–posterior axis at the end of gastrulation and later stages, whereas the injection of control LIVI14-MO did not lead to any obvious phenotype (Fig. 2a–d). The axial hypochord layer (notochord and somite) was formed in LIVI-MO-injected zebrafish embryos, but was shortened and thickened, suggesting that anterior movement of the axial mesendoderm was severely impaired, whereas the internalized, epiboly, and dorsal convergence move-
Zinc Transporter LIV1 Controls Epithelial-Mesenchymal Transition in Zebrafish Gastrula Organizer

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(Graduate School of Frontier Biosciences and Graduate School of Medicine)

Introduction

During embryonic development, organ and tissue regeneration, and cancer progression, epithelial cell subpopulations actively downregulate cell-cell adhesion systems, and leave their local neighborhood to move into new microenvironments. This regulated phenotypic modulation including cell-cell dissociation and cytoskeleton remodeling, is called epithelial-mesenchymal transition (EMT). The Snail/Slug family zinc-finger transcription factors, master regulators of EMT, are responsible for the transcriptional repression of epithelial genes, and for the transcriptional activation of mesenchymal genes [1]. The transcriptional activity of Snail is regulated by its intracellular location [3], suggesting that the regulatory mechanisms for Snail location are present. The signal transducer and activator of transcription (STAT) molecules mediate biological actions in response to cytokines and growth factors and play critical roles in EMT during gastrulation, organogenesis, wound healing, and cancer progression, however, the molecular mechanisms of STATs action in EMT are unknown [3,4]. In this report, we identified LIV1, a breast cancer associated zinc transporter protein, as a downstream target of STAT3 that is essential and sufficient for STAT3's cell-autonomous role in the EMT of zebrafish gastrula organizer cells. Furthermore, we demonstrated that LIV1 is essential for the nuclear localization of Snail. These results establish a molecular link among STAT3, LIV1, and Snail in EMT.

STATs in EMT

STATs mediate biological actions, such as cell proliferation, differentiation, and survival, in various biological processes. In addition, STATs play a crucial role in cell migration during morphogenetic processes. Mouse Stat3 is essential for the gastrulation, and for the keratinocyte migration in skin-wound healing. The Drosophila JAK/STAT pathway functions in border cell migration during oogenesis, and the establishment of planar polarity during eye development. Dictyostelium STAT is required for normal chemotaxis during early development, and for the correct movement of prestalk cells during terminal differentiation. These observations raised the possibility that the role of STAT signaling in morphogenetic movements is conserved throughout evolution [4].

In the zebrafish embryo, the activation of STAT3 is observed in the dorsal organizer and is regulated by the maternal Wnt/β-catenin pathway, which induces the dorsal organizer. A gp130-related molecule and JAKs are involved in this activation, suggesting that the targets of the maternal Wnt/β-catenin pathway that activates STAT3 may be an IL-6 family cytokine. The downregulation of STAT3 function with antisense morpholino oligonucleotides impairs the anterior movement of the organizer cells and the dorsalward convergence of neighboring cells, so that at the end of gastrulation the head is mispositioned and the embryonic axis is dramatically shortened. The activation of STAT3 is restricted to the organizer region during gastrulation; thus, STAT3 is required for the anterior movement of the organizer cells in a cell-autonomous manner and the non-cell-autonomous attraction of the neighboring cells, but does not have a significant effect on cell-fate specification (Fig. 1) [5].
STAT3 controls EMT through Zn transporter LIV1

To understand the molecular mechanism of STAT3 function in EMT, we performed a subtraction screening using normal and STAT3-depleted zebrafish embryos. The cDNA we isolated was zebrafish LIV1 (LZT-Dr3), which belongs to a subfamily of ZIP zinc transporters (Zrt-, Irt-like Proteins), termed LZT (LIV-1 sub-family of ZIP zinc Transporters), and had been implicated in metastatic progression of breast cancer [6]. The zebrafish LIV1 mRNA was expressed in the gastrula organizer cells, in which STAT3 is activated. In STAT3-depleted embryos, the expression of LIV1 mRNA in the gastrula organizer was completely abolished, indicating that LIV1 is a downstream target of STAT3. Loss of function analysis of LIV1 using antisense morpholino highlighted the phenotypical similarity to STAT3-depleted embryos, which showed severe defect in cell movements during gastrulation. LIV1-depleted embryos displayed a mispositioned head and shortened anterior-posterior axis at the end of gastrulation, and all marker genes were expressed, but the expression domain of these genes was vegetally mispositioned. These results indicated that LIV1 plays essential roles during gastrulation by affecting cell movements, without significantly altering the early cell fate specification (Fig. 1). To further clarify how LIV1 affects cell movements during gastrulation, we performed cell-tracing experiments. In the LIV1-depleted embryos, the anterior movement of the marked organizer cells was perturbed, however, marked cells in the lateral blastoderm margin moved normally, clearly showing that LIV1 is essential for the active migration of organizer cells, but not for the dorsal convergence of non-axial mesodermal cells. These observations suggested that LIV1 is an essential target gene of STAT3 that is required for STAT3’s cell-autonomous, but not non-cell-autonomous, roles. Actually, LIV1 mRNA rescued the cell-autonomous defect in the anterior migration of the STAT3-depleted organizer cells. This specific role of LIV1 was further indicated by the fact that LIV1 mRNA could not rescue the failed non-cell-autonomous role of STAT3 in the gastrula organizer. All these data established that LIV1 is essential and sufficient to carry out STAT3’s cell-autonomous role, but not its non-cell-autonomous role, and suggested that LIV1 is a key molecule to regulate the mobility of organizer cells (Fig. 2).

LIV1 is essential for the nuclear translocation of Snail, a master regulator of EMT

To clarify how LIV1 regulate the mobility of organizer cells, we next analyzed the migratory behavior of organizer cells in LIV1-depleted embryos. During gastrulation, the organizer cells in normal embryos actively downregulate cell-cell adhesion systems, and leave their local neighborhood to migrate individually, resulting in the body axis being fully extended anteriorly at the end of gastrulation. However, in LIV1-depleted embryos, the organizer cells could not downregulate their association, resulting in severe perturbation of the active migration of organizer cells. Similar defect in the migratory behavior of organizer cells was also seen in Snail-depleted embryos. Although the expression of LIV1 and Snail1 are independently regulated in gastrula organizer cells, both Snail and LIV1 repressed transcription from the reporter construct under the control of the human E-cadherin promoter, and LIV1 enhanced the repressor activity of Snail in a dose-dependent manner. Importantly, the effect of LIV1 was completely abolished in Snail-depleted zebrafish embryos, clearly showing that LIV1 activity is dependent on Snail. Since activity of the Snail transcriptional factor is regulated by its intracellular location, we examined if LIV1 regulates the mobility of organizer cells in Snail-depleted embryos. Although the expression of LIV1 and Snail1 are independently regulated in gastrula organizer cells, both Snail and LIV1 repressed transcription from the reporter construct under the control of the human E-cadherin promoter, and LIV1 enhanced the repressor activity of Snail in a dose-dependent manner. Importantly, the effect of LIV1 was completely abolished in Snail-depleted zebrafish embryos, clearly showing that LIV1 activity is dependent on Snail. Since activity of the Snail transcriptional factor is regulated by its intracellular location, we examined if LIV1 regulates the mobility of organizer cells in Snail-depleted embryos. Although the expression of LIV1 and Snail1 are independently regulated in gastrula organizer cells, both Snail and LIV1 repressed transcription from the reporter construct under the control of the human E-cadherin promoter, and LIV1 enhanced the repressor activity of Snail in a dose-dependent manner. Importantly, the effect of LIV1 was completely abolished in Snail-depleted zebrafish embryos, clearly showing that LIV1 activity is dependent on Snail. Since activity of the Snail transcriptional factor is regulated by its intracellular location, we examined if LIV1 regulates the mobility of organizer cells in Snail-depleted embryos. Although the expression of LIV1 and Snail1 are independently regulated in gastrula organizer cells, both Snail and LIV1 repressed transcription from the reporter construct under the control of the human E-cadherin promoter, and LIV1 enhanced the repressor activity of Snail in a dose-dependent manner. Importantly, the effect of LIV1 was completely abolished in Snail-depleted zebrafish embryos, clearly showing that LIV1 activity is dependent on Snail. Since activity of the Snail transcriptional factor is regulated by its intracellular location, we examined if LIV1 regulates the mobility of organizer cells in Snail-depleted embryos. Although the expression of LIV1 and Snail1 are independently regulated in gastrula organizer cells, both Snail and LIV1 repressed transcription from the reporter construct under the control of the human E-cadherin promoter, and LIV1 enhanced the repressor activity of Snail in a dose-dependent manner. Importantly, the effect of LIV1 was completely abolished in Snail-depleted zebrafish embryos, clearly showing that LIV1 activity is dependent on Snail. Since activity of the Snail transcriptional factor is regulated by its intracellular location, we examined if LIV1 regulates the mobility of organizer cells in Snail-depleted embryos. Although the expression of LIV1 and Snail1 are independently regulated in gastrula organizer cells, both Snail and LIV1 repressed transcription from the reporter construct under the control of the human E-cadherin promoter, and LIV1 enhanced the repressor activity of Snail in a dose-dependent manner. Importantly, the effect of LIV1 was completely abolished in Snail-depleted zebrafish embryos, clearly showing that LIV1 activity is dependent on Snail.
Conclusion

Our results establish that LIV1, a downstream target of STAT3, plays a critical role in EMT of gastrula organizer cells by affecting Snail activity (Fig. 4). Previous work has indicated roles for the Snail/Slug family of transcription factor in EMT during cancer progression and gastrulation [1]. Although zebrafish Snails are expressed in both axial and non-axial mesendoderm, active anterior migration is observed only in the anterior axial mesendoderm, indicating the involvement of additional unknown mechanisms in active migration. The STAT3-dependent expression of LIV1 specifically in the anterior axial mesendoderm and the requirement for LIV1 for normal EMT are consistent with the co-operative roles of Snail and LIV1 in the invasive behavior of organizer cells during gastrulation. A similar mechanism might contribute to cancer progression, since LIV1 and Snail are reported to be involved in the metastatic spread of breast cancer cells [7,8] and STAT3 is constitutively activated in many tumors, including breast cancer [9], although this possibility remains to be clarified.

References

This article discusses portraiture in Renaissance art, in which accurate depiction of the sitter's appearance was not considered to be of primary importance. The portraits had to depict the sitter's personality or better, his social and political standing. With this in mind, we may re-examine the Feast of Herod (1435 c.) in the Masolino fresco cycle in Castiglione Olona (the birthplace of Cardinal Branda Castiglioni). Here we can recognize Sigismund, king of Hungary, in the elderly person with a typical hat known as a shapka, holding a knife in his left hand like Saint Peter in the Last Supper and a chalice in his right; the painter commemorates the significant role played by Sigismund (who was a personal friend of Branda Castiglioni and in 1433 wore the crown of Emperor of the Holy Roman Empire in Rome), as a Christian king in the Council of Constance (1414-18).

A further example is that of Gentile da Fabriano's Adoration of the Magi (1423). Once more we assume the elderly king with shapka in this altarpiece to be Sigismund, and we undertake this hypothesis for the same reason mentioned above.

Other Renaissance portraits are analyzed in order to clarify this most important aspect of the Italian Renaissance portraiture.

This paper was first presented in the International Congress “Lombardy and Hungary in the period of Humanism and of Renaissance” held in Milan and in Castiglione Olona, Italy, 2-4 December 2002.

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**Kinetic and Thermodynamic Control by Chemical Bond Rearrangement on a Si(001) Surface**

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No.8 in "100 Papers Selection" (p.67)

The (2x1)-reconstructed Si(001) surface, where the surface lattice structure undergoes a reconstruction in which adjacent silicon dimers pair together and form dimers through a π bond and a π bond, is intriguing in that the chemistry at the surface is frequently analogous to that in organic chemistry owing to its covalent nature. Alkenes, for example, are known to bind to silicon dimers on the Si(001) surface to produce four-member ring analogs in a similar way to [2+2] cycloaddition reactions in organic synthesis. The mechanisms of cycloadditions on the surface have also been argued in terms of orbital symmetry in a similar fashion to organic chemistry. However, it seems likely that adsorbate formation and organic synthesis are different in that it is usually difficult to control the product distributions of surface species on the Si(001) surface, that is, the relative efficiencies of specific reactions to side reactions, by changing reaction temperature. The conversion from kinetically controlled reactions to thermodynamically controlled ones for the same organic compound by means of heating has not been observed on the Si(001) surface to date. This may be because the binding of organic molecules to the silicon surface is usually weak, which makes reactions irreversible.

We have found evidence that the driving force that determines the product distribution for acetone adsorbed on the Si(001) surface can be changed from kinetic (producing a four-member ring species; see scheme) to thermodynamic (producing the dissociation species) upon raising the surface temperature. This means that it is possible to control the product distribution on the Si(001) surface by changing the determinant factor from kinetic to thermodynamic control, which is a result of reversible binding of the surface species. These results suggest approaches for future applications to increase the degree of selectivity in the attachment of organic molecules to the Si(001) surface.
An X-Ray Measurement of Titan’s Atmospheric Extent from its Transit of the Crab Nebula

TSUNEMI Hiroshi
(Graduate School of Science)
No.11 in ‘100 Papers Selection’ (p.67)

Saturn’s largest satellite, Titan, transited the Crab Nebula on 2003 January 5. This is the first event occurred since the birth of the Crab Nebula in 1054. The Crab nebula is one of the strongest X-ray source in the sky while Titan emits no X-rays. We observed this astronomical event with the Chandra X-Ray Observatory in order to obtain the X-ray shadow image. The shadow has clearly been detected and is found to be larger than the diameter of Titan’s solid surface. The difference gives a thickness for Titan’s atmosphere of 880±60 km. The value measured is slightly larger than those estimated from Voyager observations at other wavelengths in 1980. The Cassini spacecraft arrived at Saturn on 2004 July. It is planned to execute many flybys of Titan, coming as close as 550km above the surface, which may be reconsidered due to our results.

The X-ray image of the Crab nebula is shown where the trajectory of Titan is indicated. The upper right box shows the Titan’s shadow in 10° square region.

Collapse and Search Dynamics of Apomyoglobin Folding Revealed by Submillisecond Observations of α-Helical Content and Compactness

TAKAHASHI Satoshi
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No.16 in ‘100 Papers Selection’ (p.67)

To characterize structural transitions associated with protein folding dynamics, we used a rapid-mixing device combined with circular dichroism and small-angle x-ray scattering and observed the submillisecond folding dynamics of apomyoglobin in terms of helical content and radius of gyration, respectively. The folding of apomyoglobin from the acid-unfolded state at pH2.2 was initiated by a pH jump to 6.0. A significant collapse, corresponding to ~50% of the overall change in radius of gyration from the unfolded to native conformation, was observed within 100µs after the pH jump. The collapsed intermediate has a helical content of 33% and a globular shape. Subsequently, a stepwise helix formation was detected, which was interpreted to be associated with a conformational search for the correct tertiary contacts. The folding dynamics of apomyoglobin is similar to our previous observation on cytochrome c and indicates the importance of the initial collapse, which is suggested to facilitate the subsequent conformational search to the native structure.
Polymer Thin Films Containing Eu(III) Complex as Lanthanide (III) Lasing Medium
HASEGAWA Yasuchika and WADA Yuji
(Graduate School of Engineering)
No.18 in ‘100 Papers Selection’ (p.68)

Fabrication of Lotus-type Porous Iron and its Mechanical Properties
HYUN Soong-Keun, IKEDA Teruyuki and NAKAJIMA Hideo
(Institute of Scientific and Industrial Research)
No.21 in ‘100 Papers Selection’ (p.68)

Lotus-type porous iron whose long cylindrical pores are aligned in one direction was fabricated by unidirectional solidification of the melt in a mixture gas of hydrogen (or nitrogen) and argon. Both hydrogen and nitrogen saturated in the molten iron are rejected at the solid-liquid interface during the solidification due to the difference of solubility between the liquid and the solid. Such insoluble hydrogen and nitrogen evolve the pores in the solidified iron.

The nitrogen concentration in the lotus iron fabricated under nitrogen atmosphere increases linearly with partial pressure of nitrogen, leading to improvement of the mechanical properties of the lotus iron. The ultimate tensile strength and the yield strength of the lotus iron with the pore orientation parallel and perpendicular to the tensile direction are about twice as high as those under hydrogen atmosphere. Such superior strength is attributed to the solid solution hardening due to nitrogen atoms in iron.

The threshold level for laser transmission <0.05 mJ

Amplified Spontaneous Emission
Excitation by laser pulse

Eu(III) complex thin-film on the glass substrate

Lotus-type porous iron

1 mm

Solidification direction

Stress / MPa

Strain

Solidification direction

1 mm

Lotus-type porous iron

Nitrogen 2.5 MPa (Fe- 0.69 wt.%N)

Hydrogen 2.5 MPa

Fe-N (Pore // Tension)

Fe-N (Pore \ Tension)

Fe-H (Pore // Tension)

Fe-H (Pore \ Tension)

Fe- 0.08 wt.%N

Ultimate tensile strength / MPa

Porous (%)

54
Synthesis of c-axis Oriented NaCo$_2$O$_4$ Thermoelectric Oxide by the Citric Acid Complex Method
ITO Mikio
(Graduate School of Engineering)
No.27 in 100 Papers Selection (p.68)

The citric acid complex (CAC) process and subsequent pressureless sintering were explored towards the synthesis of a c-axis oriented NaCo$_2$O$_4$ thermoelectric polycrystal. The NaCo$_2$O$_4$ thermoelectric material is a layered oxide composed of an electric conductive CoO$_2$ layer and an insulating Na layer, which are perpendicular to the c-axis. Therefore, synthesis of the NaCo$_2$O$_4$ polycrystalline sintered body with high crystallographic orientation has been desired. The c-axis of each grain in the sintered body is required to be aligned along the pressing direction. The CAC process provided a plate-like powder precursor composed of the NaCo$_2$O$_4$ phase, reflecting its layered crystal structure. During compacting and sintering of this powder, the plate-like grains were well aligned along the pressed plane because of their specific shape, resulting in the sintered body with large crystallographic anisotropy. The CAC method was also effective for synthesizing the sample with compositional homogeneity and fine microstructure. The electrical resistivity of the CAC sample was almost the same as that of the sample prepared by the conventional solid state reaction (SSR) method in spite of its high degree of c-axis orientation. The Seebeck coefficient was significantly improved by adopting the CAC method, resulting in the large enhancement of the power factor, $P$.

In-Situ Observation of Alloy Phase Formation in Nanometer-sized Particles in the Sn-Bi System
LEE Jung-Goo and MORI Hirotaro
(Research Center for Ultra-High Voltage Electron Microscopy)
No.30 in 100 Papers Selection (p.69)

Alloy phase formation in nanometer-sized particles has been studied by in-situ transmission electron microscopy using particles in the Sn-Bi system. Observations have been carried out at a temperature (i.e. 80°C) above the eutectic temperature. In the tin-rich side, with increasing concentration of bismuth, an approximately 8-nm-sized particle of the terminal tin solid solution directly changed into a particle of the liquid phase, without taking a stage of solid/liquid coexistence. On the other hand, in the bismuth-rich side, an approximately 8-nm-sized particle of the terminal bismuth solid solution (Fig.(a)) changed first to a particle with a crystalline two-phase microstructure (Fig.(b) and (c)) and eventually to a particle of the liquid phase (Fig.(d)), with increasing concentration of tin. Thermodynamic model calculations indicate that the contribution of the solid/liquid interfacial energy to the total Gibbs free energy of an alloy particle with a solid/liquid two phase microstructure becomes large enough to change the phase equilibrium when the size of particle is reduced down to a nanometer range, and that the difference in the alloy phase formation between the tin-rich and bismuth-rich sides observed here can be consistently explained in terms of the difference in the relative contribution of the solid/liquid interfacial energy between the two sides.
**Synthesis of Aligned Carbon Nanofibers at 200°C**

LEE Kuei-Yi*1, KATAYAMA Mitsuhiro*1, HONDA Shin-ichi*1, KUZUOKA Takashi*1, MIYAKE Takashi*1, TERAO Yasuhiro*1, LEE Jung-Goo*2, MORI Hirotaro*2, HIRAO Takashi*1 and OURA Kenjiro*1,2

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> No. 31 *100 Papers Selection* (p.69)

**A Similarity Measure for Nonrigid Volume Registration Using Known Joint Distribution of Targeted Tissue: Application to Dynamic CT Data of the Liver**

MASUMOTO Jun, SATO Yoshinobu, HORI Masatoshi, MURAKAMI Takamichi, JOHKOH Takeshi, NAKAMURA Hironobu and TAMURA Shinichi

(Graduate School of Medicine)

*Medical Image Analysis, 7, 553-564 (2003)*

> No. 34 in *100 Papers Selection* (p.69)

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**Electron Micrographs of Vertically Aligned Carbon Nanofibers Grown at 200°C**

**Estimated deformation field**

A similarity measure for nonrigid volume registration with known joint distribution of a targeted tissue is developed to process tissue slide at the boundaries between the targeted and peripheral (non-targeted) tissues. Pre-segmentation of the targeted tissue is unnecessary. This measure is applied to registering volumes acquired at different time-phases in dynamic CT scans of the liver using contrast materials and can be derived for the case where only the joint distribution of the targeted tissue is known. The similarity measure is formulated as a likelihood by introducing a concept termed ‘exclusivity condition’ and embedded into a cost function for nonrigid registration to be combined with the smoothness term. In addition, a practical method for estimating the joint distribution of the liver from unregistered clinical CT data is described. We demonstrate experimentally that tissue slide is effectively processed by this proposed measure using simulated dynamic CT data generated from a software phantom and clinical CT data of eight patients.
Direct High-resolution Electron Microscopy of BN Nanotubes with Hexagonal Zigzag Network

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(Institute of Scientific and Industrial Research)
No.41 in *100 Papers Selection* (p.70)

Hexagonal zigzag network of boron nitride (BN) nanotubes was investigated by high-resolution electron microscopy (HREM) and image processing. From the HREM image, lattice planes of [002] and hexagonal rings of BN nanotubes were confirmed by comparing image simulation and nanostructure models. We have assigned the chiralities of quadruple-walled BN nanotubes prepared by arc-melting method to (35, 0), (44, 0), (53, 0) and (62, 0) and proposed an atomic model of BN nanotubes. Direct imaging of hexagonal network of BN nanotubes would be helpful for understanding physical-chemical properties of BN nanotubes and for their future applications.

All-Optical Quantization Scheme Based on Fiber Nonlinearity

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(Graduate School of Engineering)
No.45 in *100 Papers Selection* (p.70)

Recent tremendous advances in digital signal processing have encouraged the research on all-optical analog-to-digital (A/D) conversion which is not limited by electron mobility. We propose a novel scheme for optical sampling and quantizing based on fiber nonlinearity.

Figure 1 shows a schematic diagram of the proposed method. Sampling pulse sequence with which central frequency is $\omega_1$ and an analog signal with $\omega_2$, and a continuous wave (CW) with $\omega_3$ are coupled and launched into a zero-dispersion fiber (Fiber 1). Sampled pulses with which amplitudes are in proportion to the analog signal and CW are generated by four-wave mixing (FWM) at $2\omega_1-\omega_2$ and $2\omega_1-\omega_3$, respectively. These sampled pulses are filtered out by optical band pass filter (OBPF) and launched into a constant anomalous dispersion fiber (Fiber 2). A pulse at $2\omega_1-\omega_2$ behaves as a higher-order soliton depending on the amplitude of the sampled pulse. In order to count the number of solitons, the higher-order soliton is split into the number of separated solitons due to cross-phase modulation induced by a pulse sampled from CW. It shows that the quantization scheme based on pulse number modulation is feasible.

The solid lines in Fig. 2 show the experimentally observed autocorrelation traces of higher-order solitons at the output of Fiber 2 without CW and the dotted lines are numerically calculated traces. Since the agreement between them is quite well, the observed traces in (a)-(d) show the 1st, 2nd, 3rd, and 4th order solitons which correspond to 1, 2, 3, and 4 solitons respectively. The sampled analog signal is converted to the order of higher-order soliton, i.e., discrete number of solitons, so the all-optical quantizing has been successfully demonstrated.
Production of an Ultra-Long-Lived Charge-Separated State in a Zinc Chlorin–C₆₀ Dyad by One-Step Photoinduced Electron Transfer

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(Graduate School of Engineering)

No.49 in “100 Papers Selection”

Photocexcitation of a zinc chlorin-fullerene dyad with a short linkage (ZnCh–C₆₀) results in formation of the charge separated (CS) state by one-step photoinduced electron transfer. The charge separated (CS) state was detected as the transient absorption spectrum obtained upon nanosecond laser pulse excitation (355 nm) of a deoxy-benzilic acid solution of ZnCh–C₆₀. The absorption band at 1000 nm is a clear attribute of the mono-fullerene radical anion. The absorption band at 790 nm agrees with that of the zinc chlorin radical cation. Thus, the transient absorption spectrum indicates formation of the CS state (ZnCh–C₆₀). The CS state was also detected by ESR. The ESR spectra were measured under photolysis of ZnCh–C₆₀ in frozen PhCN. The ESR spectrum consists of two characteristic signals, one of which is attributable to an organofullerene radical anion with the g value (2.0007) smaller than the free spin value (2.0023) and the other to the zinc chlorin radical cation with a higher g value (2.0033). The lifetime of charge separated (CS) state was determined as 120 s in frozen PhCN at -150°C, which is the longest CS lifetime ever reported for donor-acceptor linked systems. We have successfully shown that intramolecular electron transfer from the singlet excited state of zinc chlorin to fullerene occurs efficiently in the dyad with a short linkage to attain an ultra-long lived CS state without loss of energy which is inevitable in multi-step electron transfer processes.

Formation of 10 nm-sized Oxo(phthalocyaninato)vanadium (IV) Particles by Femtosecond Laser Ablation in Water

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Chemistry Letters, 33, 6, 724-725 (2004)
No.61 in “100 Papers Selection”

Preparation of organic nanoparticles has attracted increasing interest as they are expected to be very useful as pigments, cosmetics, drugs and so on. Compared with metals and semiconductors, the difficulty of preparing organic nanoparticles with the size less than 100 nm has been well known. Recently, we have developed a novel method for preparing organic nanoparticles by applying femtosecond laser ablation technique. In this method micrometer-sized crystalline powders were suspended in a poor solvent are exposed to intense laser pulse, which induces fragmentation of the initial crystals. Consequently, the opaque suspension is converted into a transparent colloidal solution. In this paper, oxo(phthalocyaninato)vanadium (IV) (VOCl₄) crystals dispersed in water by stirring vigorously were exposed to regenerative amplified femtosecond Ti:Sapphire laser pulses (800 nm, 200 fs full width at half maximum size). The size of nanoparticles was confirmed to be 17±7 nm using a scanning electron microscope. The size is much smaller than that prepared by other methods such as mechanical grinding and precipitation. It is worth noting that the size and morphology of nanoparticles can be controlled by many parameters of laser excitation such as pulse width, wavelength, repetition rate, and fluence. This finding has opened the door to prepare 10 nm-sized organic nanoparticles.
The First Total Synthesis of Discorhabdin A

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Journal of the American Chemical Society, 125, 11235-11240 (2003)
\( \text{No.65 in '100 Papers Selection'} \) (p.72)

The first stereoselective total synthesis of a potent antitumor alkaloid, discorhabdin A (1), which is a unique sulfur-containing pyrrolidinequinoline alkaloid, is described. The key step in the stereocontrolled total synthesis of 1 involves both a diastereoselective oxidative spirocyclization using a hypervalent iodine (III) reagent and an efficient construction of the labile and highly strained \( \text{N,S-acetal} \) skeleton. Construction of the three stereogenic centers has been achieved successfully by the use of commercially available (L)-tyrosine as the only chiral source and reagent. These methodologies provide a breakthrough in the total synthesis of these promising new antitumor agents, discorhabdins and their analogues, which should serve as valuable probes for structure-activity studies. In addition, the present results should give important clues on the biosynthetic pathway to sulfur-containing discorhabdins and have possibility connecting with new antitumor drugs.

Wavelength Division with Three-Dimensional Couplers Fabricated by Filamentation of Femtosecond Laser Pulses

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\( \text{No.68 in '100 Papers Selection'} \) (p.72)

Micromachining by femtosecond lasers in transparent materials has received much attention. When femtosecond laser pulses are focused inside bulk transparent materials, the intensity in the focal volume can become high enough to cause nonlinear absorption. Nonlinear absorption leads to localized modification in the focal volume, while leaving the surface unaffected. The salient feature of femtosecond micromachining is its ability to fabricate and integrate photonic devices inside transparent materials. The induction of permanent refractive-index change at the laser focal point has been reported in bulk glasses to the order of \( 10^{-3} \). By translation of the sample with respect to the focal point, waveguides and couplers can be embedded in bulk glass. We demonstrate the realization of three-dimensional (3-D) directional couplers inside silica glass using femtosecond laser pulses. Directional couplers constitute an essential component of lightwave technology, however, in conventional techniques, they have been made using fiber optics or planar waveguides. Our three-dimensional, directional coupler consists of three waveguides: a 2 mm-long straight waveguide (waveguide1) and two curved waveguides that are connected to straight sections (waveguide2 and 3). The curved waveguides have arc radii of 17 mm. The straight sections of waveguide2 and 3 were parallel to the straight waveguide at 4 \( \text{mm} \) center-to-center separation. Lengtes of the straight sections in waveguide2 and waveguide3 were 0.5 mm and 1.0 mm. After the fabrication of the 3-D coupler in silica glass by three-dimensional translation of the focal point of femtosecond laser pulses, white light was coupled to the straight waveguide and near-field output pattern was monitored. The cores of couplers are close enough that the fundamental modes propagating in each core overlap partially in the cladding region between cores. Such evanescent wave coupling can lead to the transfer of optical power from one core to another, acting as splitting of the optical power. Spectra are different at the output because the coupling properties are dependent on wave-length. This technique could be useful in three-dimensional spectroscopic devices in a wide variety of glasses.
A chloroplastic signal recognition particle (cPSRP) mechanism has been shown to be involved in targeting abundant light harvesting chlorophyll a/b binding proteins (LHCPs) to the thylakoid membrane. The cPSRP machinery includes a stromal protein complex containing cPSRP54 and cPSRP43, the thylakoid extrinsic protein cpFtsY, and ALB3, an integral membrane protein that functions as a protein insertion channel. Arabidopsis mutants with mutations in genes encoding cPSRP54, cPSRP43, and ALB3 have been isolated and characterized. Interestingly, these mutants vary in their phenotypes and have provided evidence that these proteins actually play an important role in efficient LHCP targeting to the thylakoid membranes in vivo. However, a genetic analysis of cpFtsY function has not been reported.

To investigate its vivo roles of cpFtsY, we characterized maize cpFtsY and maize mutants having a transposon insertion in the corresponding gene. A null cpFtsY mutant, car1-1, showed a substantial loss of leaf chlorophyll and a reduction in the amounts of LHCPs, with some members of the family more severely affected than others. Chloroplasts in car1-1 mutants had a large reduction in their thylakoid membrane content, and the residual membranes were poorly organized. Unlike the cpSRP43 or cpSRP54 mutants, the cpFtsY mutants lacked many other thylakoid-bound components of the photosynthetic apparatus and exhibited severe defects in the architecture of the thylakoid membranes. These findings indicate that cpFtsY plays broad roles in thylakoid biogenesis that extend beyond the integration of the LHCPs.

Maize Mutants Lacking Chloroplast FtsY Exhibit Pleiotropic Defects in the Biogenesis of Thylakoid Membranes

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No. 73 in '100 Papers Selection’ (p.73)

The sterol regulatory element binding protein 2 (SREBP-2), a nuclear transcription factor that is essential for cholesterol metabolism, is synthesized as precursor molecules and bound to the endoplasmic reticulum membrane. When cells are deprived of cholesterol, SREBP cleavage-activating protein (SCAP) escorts SREBP-2 to the Golgi apparatus, where SREBP-2 is proteolytically processed to be a transcriptionally active N-terminal fragment. Released homodimerized SREBP-2 forms a complex with a nuclear transport factor, importin β, and translocates into the nucleus to activate transcription of cholesterol synthesis-related genes. We revealed the crystal structure of importin β complexed with the active form of SREBP-2. Importin β directly interacts with helix-loop-helix leucine zipper domain of SREBP-2 dimer like a pair of chopsticks. Importin β changes its conformation to reveal a pseudo-twofold symmetry on its surface structure so that it can accommodate a symmetric dimer molecule. This structure indicates the possibility that importin β recognizes other dimeric molecules, especially transcription factors known to form a homodimer. These findings suggest implications for the importance of importin β in many transcriptional processes.

The Structure of Importin-β Bound to SREBP-2: Nuclear Import of a Transcription Factor

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No. 82 in '100 Papers Selection’ (p.73)
Prevention of Polyglutamine Oligomerization and Neurodegeneration by the Peptide Inhibitor QBP1 in Drosophila

NAGAI Yoshitaka and TODA Tatsushi
(Graduate School of Frontier Biociences)
Human Molecular Genetics, 12, 1253-1260 (2003)
No.87 in 100 Papers Selection (p.74)

Recently, increasing evidence implicates abnormal protein accumulation as a common pathogenesis of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and the polyglutamine (polyQ) diseases. The polyQ diseases are a group of at least nine inherited neurodegenerative diseases including Huntington's disease and the spinocerebellar ataxias, which are caused by abnormal expansions of the polyQ stretch within the disease proteins. Aggregation of the polyQ stretch is thought to confer toxic properties on the disease proteins through a conformational transition to β-sheet, leading to amyloid fibril-like oligomerization/aggregation and accumulation in affected neurons. Aiming to interfere with this conformational alteration and aggregation, we previously identified QBP1 (Polyglutamine Binding Peptide 1) which preferentially binds the expanded polyQ stretch, by phage display screening. In this paper, we show that co-expression of QBP1 significantly suppresses polyQ aggregation and polyQ-induced neurodegeneration in the compound eye of Drosophila polyQ disease models (Fig. A). Most importantly, QBP1 dramatically rescues premature death of a Drosophila polyQ disease model from a median lifespan of 5.5 days to 52 days (Fig. B), indicating that QBP1 can prevent polyQ-induced neurodegeneration in vivo. Our study indicates that the toxic conformational transition and aggregation of the disease proteins are promising targets for developing potential therapies for the currently untreatable polyQ diseases, and possibly also for other neurodegenerative diseases.
The Atomic Structure of *Rice dwarf* Virus Reveals the Self-Assembly Mechanism of Component Proteins

NAKAGAWA Atsushi and TSUKIHARA Tomitake

*(Institute for Protein Research)*

Structure, 11, 1227-1238 (2003)

> No.89 in “100 Papers Selection” (p.74)

*Rice dwarf* virus (RDV), the causal agent of *rice dwarf* disease, is a member of the genus *Pytorovirus* in the family *Reoviridae*. RDV is a double-shelled virus with a molecular mass of approximately 70 million Daltons.

The atomic structure of RDV was determined at 3.5 Å resolution by X-ray crystallography. The double-shelled structure consists of two different proteins, the core protein P3 and the outer-shell protein P8. The atomic structure shows structural and electrostatic complementarities between both homologous (P3-P3 and P8-P8) and heterologous (P3-P8) interactions, as well as overall conformational changes found in P3-P8 dimer caused by the insertion of amino-terminal loop regions of one of the P3 protein into the other. These interactions suggest a higher-ordered assembly mechanism of a virus core structure using total of 900 protein components.

Intrathecal Injection of HVJ-E Containing HGF Gene to Cerebrospinal Fluid can Prevent and Ameliorate Hearing Impairment in Rats

OSHIMA Kazuo and KANEDA Yasufumi

*(Graduate School of Medicine)*


> No.93 in “100 Papers Selection” (p.75)

Hearing impairment, which is the most prevalent sensory deficit of human beings, needs a breakthrough in therapeutic technologies. One technology is the usage of a vector system to reach the inner ear, and another is by a therapeutic molecule. Here we developed a novel gene therapy strategy by combining hepatocyte growth factor (HGF) with hemagglutinating virus of Japan envelope (HVJ-E) vector. When HVJ-E containing human HGF gene was injected intrathecally into the cerebrospinal fluid via cisterna magna of rats, the vector reached the inner ear region, and human HGF gene expression was detected in the spiral ganglion cells (SGCs) of the inner ear.

Expression of endogenous rat HGF and its receptor, c-Met, was also induced in SGCs by human HGF. Kanamycin treatment results in hearing impairment by inducing degeneration of hair cells (HCs) and apoptosis of SGCs in rats. By HGF gene transfer prior to kanamycin treatment, both loss of HCs and apoptosis of SGCs were prevented. Furthermore, hearing function, evaluated by auditory brainstem response, was maintained at normal level. When HGF gene transfer was performed two weeks after kanamycin treatment, hearing impairment was significantly recovered. These results indicate a novel and effective therapeutic strategy against sensorineural hearing impairment.
Identification of a Cytokine-induced Antiapoptotic Molecule Anamorsin Essential for Definitive Hematopoiesis

SHIBAYAMA Hirohiko, TAKAI Emi and KANAKURA Yuzuru
(Graduate School of Medicine)
No.96 in "100 Papers Selection" (p.75)

We have identified an antiapoptotic molecule named Anamorsin (AM) that has no homology to known antiapoptotic members. The expression of AM was induced by cytokines, and its enforced expression in hematopoietic cells conferred resistance to apoptosis caused by cytokine withdrawal. The in vivo significance of this molecule was confirmed by the observation that AM-deficient mice die in late gestation due to defective hematopoiesis. Fig. A shows the cover page of the Journal. Erythroid cells isolated from fetal liver at embryonic day 16.5 (left panel) and spleen with stomach (right panel) of wildtype control mice (top panel) and mice deficient in AM (bottom panel). The erythroid cells were larger in AM⁺⁺ embrios than in AM⁻⁻ embryos, and mature erythroid cells were markedly decreased in AM⁻⁻ embryos. The spleen of AM⁻⁻ embryos was remarkably smaller than that of AM⁺⁺ embryos and appeared scarce. Furthermore, AM⁺⁺ embryos were small in body size, and were markedly anemic (Fig. B), and their erythroid cells in fetal liver displayed acceleration of apoptosis (Fig. C). Thus, AM is a novel molecule that acts as a survival signal elicited by cytokines and regulates hematopoiesis.


Role of Adaptor TRIF in the MyD88-independent Toll-like Receptor Signaling Pathway

YAMAMOTO Masahiro and AKIRA Shizuo
(Research Institute for Microbial Diseases)
No.99 in "100 Papers Selection" (p.75)

Stimulation of Toll-like receptors (TLRs) triggers activation of a common MyD88-dependent signaling pathway as well as a MyD88-independent pathway that is unique to TLR3 and TLR4 signaling pathways leading to interferon (IFN-β) production. Here we disrupted the gene encoding a Toll/IL-1 receptor (TIR) domain-containing adaptor, TRIF. TRIF-deficient mice were defective in both TLR3- and TLR4-mediated expression of IFN-β and activation of RANKL. Furthermore, inflammatory cytokine production in response to TLR4 ligand, but not to other TLR ligands, was severely impaired in TRIF-deficient macrophages. Mice deficient in both MyD88 and TRIF showed complete loss of NF-kB activation in response to TLR4 stimulation. These findings demonstrate that TRIF is essential for TLR3 and TLR4-mediated signaling pathways facilitating mammalian antiviral host defense.

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100 Papers Selection

*Researchers in bold italic letters are faculty members of Osaka University, and their institutions are indicated in parentheses.
* Green shaded papers are the “100 Papers Selection” with short abstracts written by the authors.
* Blue shaded papers are included in the “10 Papers Selection.”
* Red shaded papers are included in the “24 Graphics Selection.”

- Humanities & Social Sciences .............. 6
- Science ........................................ 10
- Engineering .................................... 56
- Biology .......................................... 28

Total 100

Humanities & Social Sciences

1. Abe, K., Kashiwagi, T., Tsuneto, S. (Graduate School of Human Sciences) Coping Strategies and Its Effects on Depression among Caregivers of Impaired Elders in Japan
   Aging & Mental Health, 7(3), 207-211 (2003)
   ▶ The purpose of this study was to explore the coping strategies of Japanese family caregivers and to investigate relationships between coping strategies, stressors, and caregivers' mental health. Results of factor analysis indicated three factors, categorized “Resignation,” “Consulting and complaining” and “Distancing.” In addition, results of structure equation modeling suggested a significant effect of “Resignation” on the mental health of caregivers. Although the factor structure of coping strategies was similar to other studies conducted in Western countries, the effects of coping strategies were quite different.

2. Ikeda, T. (Graduate School of Law) Now and Future of ADR System in Asian and Pacific Countries
   ▶ This paper describes a summary of a small part of the results obtained by the ADR Taskforce. Increased interest in ADR in the region is derived from various reasons such as a market mechanism rooted in complaints about litigation, strong leadership from governments, and overall reform of the judicial system. The Asian scheme concerning judicial reform and ADR is diversified and profound.

3. Miyamoto, Y. (Faculty of Language and Culture)
   On Three-sentences
   ▶ This paper argues that in principle, the structures given in (1) and (2) are both available for three-sentences: (SC stands for a small clause.)
   (1) There be [NP Predicate] (Mitsukeru 1974; 1999; 1997; 1998)
   (2) There be [NP Modifier] (Jenkins 1972; Williams 1984).
   Specifically, I propose that Mitsukeru’s (1974) ontological existential should be available in some of the three-sentences which appear to have the small clause structure.

4. Sugihara, K. (Graduate School of Economics)
   The East Asian Path of Economic Development: A long-term perspective
   The Resurgence of East Asia : 500, 150 and 50 year Perspectives, 78:123 (2003)
   ▶ pp.10-13

5. Tsutsumi, Y. (Graduate School of Economics)
   Stock Prices in Japan Rise at Night
   ▶ Examining the Nikkei Average, I find that although the mean of the change during the trading hours (RT) is negative, the mean during non-trading hours (RNT) is significantly positive. I also find that RT has a strong relationship with economic fundamentals while RNT does not, and that if the previous trading hours reflected bearish trading, then the bearish sentiment is not taken over to opening time. A possible cause of the positive RNT is optimism of investors.

6. Wakayama, E. (Graduate School of Letters)
   La corte di re Sigismondo e l’arte italiana del Quattrocento (The Court of King Sigismund and Fifteenth Century Italian Art)
   Arte Lombarda, 139 (2003)
   ▶ p.52

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Science


8. Hamai, C.*1; Takagi, A.*2; Taniguchi, M.*2; Masumoto, T.*1; Kawai, D.*1, *2
*1(Graduate School of Science) *2(Institute of Scientific and Industrial Research)
Kinetic and Thermodynamic Control by Chemical Bond Rearrangement on a Si(001) Surface

Signatures of Valence Fluctuations in CuCuSi$_2$ under High Pressure

Total Synthesis of an Antitumor Antibiotic Fossttreicin (CI-920)
Journal of the American Chemical Society, 125, 8269-8275 (2003)

(Graduate School of Science)
An X-Ray Measurement of Titan's Atmospheric Extent from Its Transit of the Crab Nebula

12. Nakano, T.*1; Abe, D.S.; Abe, J.K.; Akimune, H.; Asano, Y.; Chang, W.C.;
Date, S.; Eiji, H.*1; Fujinuma, H.; Fujimura, M.*1; Hixes, K.;
Kino, K.*1; Kohri, H.*1; Kurauchi, N.; Makino, S.; Matsumura, T.*1;
Matsuo, N.*1, Mibe, T.*1; Mii, K.; Miyake, M.; Miyuchi, M.;
Motoo, M.*1; Mori, M.; Niijima, M.; Noguchi, M.*2; Ohashi, Y.;
Ooma, T.; Ohkuma, H.; Ohkita, D.S.; Onnemori, Y.; Sakauchi, A.*2;
Sasada, T.; Shinozaki, M.*1; Shinno, Y.; Shimizu, H.; Sugaya, Y.*2;
Suzumura, M.*2; Toyooka, H.; Wakai, A.; Wang, C.W.; Wang, S.C.;
Yamada, K.; Yamauchi, T.; Yoshimura, M.*3; Yonem, M.; Zegers, R.G.T.*1;
*1(Research Center for Nuclear Physics) *2(Department of Physics) *3(Institute for Protein Research)
Evidence for a Narrow $^{1+}$ Baryon Resonance in Photoproduction from the Neutron

13. Sato, H.; Muro, H.; Hasenawa, A.; Zhao, D. (Graduate School of Science)
Mathematica as a Powerful and Practical Tool for Displaying Animated Three-Dimensional Structures of the Earth's Interior
Geochemistry Geophysics Geosystems, 1, 10343-1 (2003)

Stimuli-Responsive Diblock Copolymers by Living Cationic Polymerization: Precision Synthesis and Highly Sensitive Physical Gelation

15. Tataru, G.*1, Kohno, H.*2
*1(Graduate School of Science) *2(Graduate School of Engineering Science)
Theory of Current-Driven Domain Wall Motion: Spin Transfer versus Momentum Transfer

Collapse and Search Dynamics of Amyloid Cylindricity by Submillisecond Observations of $\alpha$-Helical Content and Compactness

pp.14-17

- Many of current definitions in IPv6 anycast in the protocol standard are unclear. We raise several problems and provide possible solutions to these. Based on this background, we present the Anycast Address Resolving Protocol (AARP) to establish 1:1 connections with a specific anycast address, and then propose a routing protocol for inter-segment anycast. Our proposed architecture makes anycast addresses more useful without (or at most minimum) the need for modifications, extensions to existing applications and/or upper-layer protocols.


p.28


- Novel organic solar cells prepared using quaternary self-organization of porphyrin (donor) and fullerene (acceptor) dye units by clusterization with gold nanoparticles on SnO2 electrodes exhibit the remarkable enhancement of the photovoltaic properties relative to the reference systems.


- RuS2 nanoparticles, smaller than 3 nm in diameter, were prepared by H2S gas injection into the AOT/isoctane reverse micellar system containing RuCl3 aqueous solution. The nanoparticle size was found to be independent of the [Ru]/[water] weight ratio of the reverse micellar system, as shown by TEM observations. The recovery and immobilization of the RuS2 nanoparticles from reverse micelles onto thiol-modified polystyrene particles (PS-SH) were successfully carried out, by the addition of PS-SH into the reverse micellar solution under conditions of mild stirring. The resulting composites, PS-RuS2, showed photocatalytic activity for H2 generation from aqueous solutions containing 2-propanol and Na2SO3 as sacrificial electron donors.


P.54


- The surface characterization of an Sc-O-W(100) system as a Schottky emitter was performed at high temperature. A self-decoration function against surface damage induced by residual gas ion sputtering, which is one of the most important properties required for the stable electron emission from emitters, was confirmed at ~1500 K, the operating temperature of the emitter. The self-decoration function is caused by the surface segregation of Se and O atoms from the bulk at high temperature.


- We present a method for synthesizing insulator-coated carbon nanotubes by pulsed laser deposition. Insulator-multi-walled carbon nanotubes (MWNTs) were coated with an SiOx thin layer in a multishell form. The product showed that a stoichiometric SiOx thin layer was uniformly wrapped around a MWNT, and reflected the shape of the MWNT. The thickness of the SiOx thin layer was precisely controlled in the range from 2 to 8 nm. The insulating property of the product was verified using a template of vertically-oriented carbon nanotubes.


- Novel micro, secondary reaction with an organic catalyst. The oxidations of organic substrates such as nitrates, secondary amines, N-hydroxyamines, and tertiary amines with molecular oxygen (1 atm) was performed in air in the presence of 3-ethyl-5-methylfurilinium perchlorate catalyst and hydrogen tetrachloroiodidate in 2,2,2-trifluoroethanol. It efficiently gives the corresponding oxidized products in excellent yields along with water and molecular nitrogen, which are environmentally benign. The TON of the oxygenation of nitrates amounts to 19,000.


- A novel Li+ ion conducting solid electrolyte with a high Li+ ion conductivity and a high durability in air, which could not be realized for conventional materials, has been successfully developed by artifically designing a new type of solid solution of rare earth oxide and lithium nitrate. The features of the present solid electrolyte are preferable to several electronic devices, and especially, this material is greatly expected to be a component of all-solid-state lithium rechargeable battery.


- A smart carbon dioxide gas sensor has been successfully realized by the combination of two type of conducting solids with an auxiliary detecting electrode. The present sensor shows a rapid, continuous and theoretical response without any interference with the coexisting gas species. This sensor is greatly expected to contribute to the real time monitoring and the present successful operation of carbon dioxide gas emission, which is highly requested in this 21st century as declared in Kyoto COP3.


p.55

68 ANNUAL REPORT OF OSAKA UNIVERSITY—Institute of Industrial Science
*†(Graduate School of Information Science and Technology) †(Graduate School of Medicine)
High-Performance Computing Service Over the Internet for Intraoperative Image Processing
pp.1.8-2.1

(Graduate School of Engineering Science)
Evaluation of Organizational Structure in Emergency Situations from the Viewpoint of Communication
This paper focuses on evaluation of organizational structure in emergency from the communication viewpoints. The communication process in emergency is analyzed first, and a communication model is proposed that considers human related factors such as “competence”, “duty”, “responsibility” and “knowledge” in organization. On the basis of the model, a system to evaluate organizational structure in emergency from the viewpoint of communication is designed. Finally, a prototype system with GUI is developed and its evaluation results are represented.

30. Lee, J.-G.; Mori, H.
(Research Center for Ultra-High Voltage Electron Microscopy)
is-Situ Observation of Alloy Phase Formation in Nanometer-sized Particles in the Sn-Bi System
pp.55

†(Graduate School of Engineering) †(Research Center for Ultra-High Voltage Electron Microscopy)
Synthesis of Aligned Carbon Nanotubes at 200°C
pp.56

32. Maeda, M.; Igarashi, O.; Shibayabangi, T.; Naka, M.
(Joining and Welding Research Institute)
Solid State Diffusion Bonding of Silicon Nitride Using Vanadium Foils
The interfacial microstructure and its evolution of silicon nitride and vanadium formed by solid state diffusion bonding has been analyzed. The strength of the joints is affected sensitively by the interfacial microstructure. The highest strength is obtained with a metastable interface at which the thickness of the V2Si layer is 2.0 μm. The criterion to maintain the metastable interface has been extended.

33. Masaki, T.†,*; Goto, K.†,*; Iinoe, Y.†,*; Kawata, S.†,*
†(Graduate School of Frontier Science) †(Graduate School of Frontier Biologies)
Near-Field Infrared Imaging of Molecular Changes in Cholesterol Oleato by Pico Laser Ultrasonic Absorption
Detailed molecular changes in cholesterol oleate, a primary cause of atherosclerosis, was investigated using infrared absorption spectroscopy. Since IR photons were detected via near field scheme which provides us super-resolving capability, 2 μm resolution was achieved at 5.75 μm wavelength by employing a hand-made apertured caustic line as a near field probe and an optical parametric amplifier as an IR light source. We also succeeded in quantitative evaluation of in-depth molecular structure changes.

†(Graduate School of Engineering Science) †(Graduate School of Medicine)
A Similarity Measure for Nonrigid Volume Registration Using Known Joint Distribution of Targeted Tissue: Application to Dynamic CT Data of the Liver
Medical Image Analysis, 7, 535-544 (2003)
pp.56

35. Matsumoto, T.; Fuji, H.; Ueda, T.; Kamii, M.; Noshi, K.
(Jointing and Welding Research Institute)
Oscillating Drop Method Using a Falling Droplet
An improved oscillating drop method was developed to measure the surface tension and viscosity of liquids without any external forces using a falling droplet. Simple surface oscillations are observed for a falling droplet and the simple basic principles are applicable without any correction. The surface oscillations of a falling droplet were precisely measured using the combination of a laser, optical, and line sensor. Measured surface tension and viscosity of water shows good agreement with previously reported values.

(Graduate School of Engineering)
Magnetic Properties in the High-Temperature Cuprate Superconductors with Nonmagnetic Impurities
We study the effects of nonmagnetic impurities on the magnetic properties of the CuO2 planes in high-temperature cuprate superconductors, on the basis of the d-wave model, within the fluctuation exchange approximation and the quasiparticle potential approximation. The spin correlations between electrons in the neighborhood of the impurity are decreased, due to electron repulsion by the impurity. The antiferromagnetic contribution to the dynamical spin susceptibility decreases due to the nonmagnetic impurities, and the calculated superconducting temperature correspondingly decreases.

(Graduate School of Engineering)
Silica-Water Reaction Media: Its Application to the Formation and Ring Opening of Aziridines
This work demonstrates a new reaction medium (silica-water system) for organic synthesis, which is illustrated by realizing formation of aziridines. This novel concept is based on the adsorptive nature of silica, which would be effective as an organic reaction medium in water because the organic molecule would be adsorbed to silica by hydrophobic interactions between surface of silica and organic molecules. The new process is successfully applied to ring opening of aziridines, indicating that the system is a potential process for organic reactions.

(Graduate School of Engineering)
Chirally-Organized Ferroelectric Receptor Bearing Podand Dipeptide Chains (L-Ala-L-Pro-NH2/PMe) for the Selective Recognition of Dicarboxylic Acids
The ferroelectric receptor bearing the podand dipeptide chains with the C-terminal pyrrolidinifunctional moiety (L-Ala-L-Pro-NH2/PMe) was found to provide a chirality-organized binding site tough two imino-dicarboxylic acid hydrogen bonds between CO (Ala) and NH (another Ala) of each podand dipeptide chain. The size-selective and chiral recognition of dicarboxylic acids was achieved by multivalent hydrogen bonds of the binding site.
39. Nagase, T.; Vinakaishi, Y. (Graduate School of Engineering Science)
Thermal Stability and Electron Irradiation Effect on Zr-based Amorphous Alloys
*Journal of Applied Physics, 93, 912-918 (2003)*
- Specimens of Zr$_5$Ge$_2$, Zr$_3$Al$_5$, Zr$_5$Al$_5$N$_2$, and Zr$_5$Ni$_5$Ge$_2$ were irradiated by high energy electrons. Crystalization of three metallic glasses was accelerated by this irradiation and nucleation structures were obtained. The critical dose required for crystallization of the amorphous phase by electron irradiation depends strongly on the irradiation temperature and stability of this amorphous phase. The phase stability and crystallization behavior of the amorphous phase are discussed based on the electron irradiation effect.

40. Nakamura, N.; Ogi, H.; Hirao, M. (Graduate School of Engineering Science)
Elastic Constants of Chemical-Vapor-Deposition Diamond Thin Films: Resonance Ultrasonic Spectroscopy with Laser-Doppler Interferometry
- We developed an advanced method of resonance ultrasonic spectroscopy to measure anisotropic elastic constants of CVD diamond thin films. Mechanical resonance frequencies of a film/substrate layer allow elastic constant determination through inverse calculation. Mode identification with laser-Doppler interferometry is the key to this measurement. Obtained elastic constants are smaller than those of bulk diamond and show anisotropy. A micromechanical model explains these anomalies as the results of incohesive bond at grain boundaries.

41. Narita, I.; Oku, T. (Institute of Science and Industrial Research)
Direct High-resolution Electron Microscopy of BN Nanotubes with Hexagonal Zigzag Network
- p.25

*(1)Graduate School of Engineering Science, (2)Graduate School of Medicine
*Face MOUSE: A Novel Human-Machine Interface for Controlling the Position of a Single Nanoparticle*
*IEEE Transactions on Robotics and Automation, 19, 825-841 (2003)*
- pp.22 25

43. Nishiyama, N.; Momose, W.; Egashira, Y.; Ueyama, K. (Graduate School of Engineering Science)
Partially Carbonized Polyimide Membranes with High Permeability for Air Separation
*Journal of Chemical Engineering of Japan, 36, 603-608 (2003)*
- Gas separations using microporous inorganic membranes are becoming of great interest. High flux is often required as membrane performance rather than high selectivity to obtain a compact membrane module. In this study, partially carbonized polyimide (CPI) membranes were formed on a porous alumina support. The permeability of the CPI membranes was much higher than that of the reported polymer membranes and the carbon blacks.

Zirconium-Containing Mesoporous Silica Zr-MCM-48 for Alkaline Resistant Filtration Membranes
*Journal of Membrane Science, 218, 165-171 (2003)*
- Hydrophilic membrane elements MCM-48 membranes are attractive for nanofiltration and ultrafiltration. In the present study, Zr-containing MCM-48 (Zr-MCM-48) membranes were synthesized on a alumina support in order to improve alkali stability. The alkaline resistance of the Zr-MCM-48 membranes was much higher than the membranes without Zr. From permeametry the average pore size of the Zr-MCM-48 membrane is estimated to be 2.5 nm. These results show that Zr-MCM-48 membranes have great potential for nanofiltration and ultrafiltration with high performance.

45. Oda, S.; Murata, A.; Kitayama, K. (Graduate School of Engineering Science)
All-Optical Quantization Scheme Based on Fiber Nonlinearity
- p.57

46. Ogata, S.; Shibutani, Y. (Graduate School of Engineering Science)
Ideal tensile strength and bending property of single-walled carbon nanotubes
*Physical Review B, 68, 165401/1-4 (2003)*
- The ideal tensile strength, Young’s modulus, and bond-gap changes of (8,0), (9,0) (10,0), and (8,8) single-walled carbon nanotubes (SWNTs) under uniaxial tensile deformation are analyzed using a tight binding and density functional theory. The bond-gap changes except for (8,8) SWNT are in qualitative agreement with Yang’s theory in which uniform tensile deformation is assumed. However, even though the theory predicts zero gap for the armchair SWNTs, we see a finite gap for the (8,8) armchair SWNT at 20% tensile strain level.

47. Ogi, H.; Tian, J.; Tada, T.; Hirao, M. (Graduate School of Engineering Science)
Elastic-Stiffness Mapping by Resonance-Ultrasonic Microscopy with Isolated Piezoelectric Oscillator
- A resonance-ultrasonic microscopy has been developed for mapping a material’s elastic constant in a localized surface region. It detects the effective elastic modulus through a resonance frequency of free vibrations of a solid probe touching the specimen via a small tungsten-carbide bearing. Langasite (La$_5$Ga$_2$Si$_2$O$_10$) crystal is used as a probe because of the low sensitivity of its elastic constants to temperature and its high piezoelectric coefficients. The vibration of the probe is excited and detected with a surrounding solenoid coil. This noncontacting acoustic coupling isolates the probe vibration and measures the resonance frequency with an accuracy better than one part in 10$^5$. This microscopic method is applied to a composite material consisting of silicon-carbide (SiC) fibers in titanium-alloy matrix. The stiffness distribution inside a single fiber was determined.

48. Ogo, S.; Uehara, K.; Abara, T.; Fukuzumi, S. (Graduate School of Engineering Science)
pH-Dependent Chemoselective Synthesis of α-Amino Acids. Reduction Amination of α-Keto Acids with Ammonia Catalyzed by Acid-Stable Iridium Hydride Complexes in Water
*Journal of the American Chemical Society, 126, 3202-2031 (2004)*
- An acid-stable iridium hydride complex serves as the active catalyst for the highly chemoselective synthesis of α-amino acids by reductive amination of α-keto acids with aqueous NH$_3$ and HCOO$^-$ in water at pH 5-8. pH-dependent catalytic $\alpha$-amino-$\alpha$-amino-annealing has been accomplished by using $\text{Ir}_3$H$_5$ and COO$^-$, which are ideal amine and hydride ions sources, respectively.

Production of an Ultra-Long-Lived Charge-Separated State in a Zinc Chlorin-C$_6$ Dyad by One-Step Photoinduced Electron Transfer
- p.58

50. Ohno, H.; Miyazawa, K.; Takeoka, Y.; Tanaka, T. (Graduate School of Pharmaceutical Sciences)
Palladium(0)-Catalyzed Tandem Cyclization of Allenenes
- Allenes have become more versatile intermediates in organic syntheses as a result of recent developments in transition metal-catalyzed reactions. However, the tandem carbon-carbon bond formation including C$\equiv$H bond activation of aromatic rings using alkenic substrates is unknown. We found that tri- or tetra cyclic heterocycles can be formed through the tandem cyclization of allenenes upon treatment with aryl iodide, potassium carbonate, and catalytic palladium(0). The reactivity of the palladium(II) intermediates could be controlled by substrates at the olefin termini.
51. Otaka, T.
(Graduate School of Engineering)
A Continuation-GMRES Method for Fast Computation of Nonlinear Receding Horizon Control
Automatica, 40, 563-574 (2004)
- A fast numerical algorithm for nonlinear receding horizon control is proposed. The control input is updated by a differential equation to trace the solution of an associated state-dependent two-point boundary-value problem. The error in the algorithm is analyzed and is shown to be bounded under some conditions. The proposed algorithm is applied to a two-link arm whose dynamics is highly nonlinear. Simulation results show that the proposed algorithm is faster than the conventional algorithms.

52. Otani, M.; Ono, T.; Hirose, K.
(Graduate School of Engineering)
First-principles study of electron transport through C60 cages
- Electron transport properties of C60 molecules suspended between gold electrodes are investigated using first-principles calculations. Our study reveals that the conductances are quite sensitive to the number of C60 molecules between electrodes: the conductances of C60 monomers are near 1 GΩ, whereas those of dimers are markedly smaller, since incident electrons easily pass the C60 molecules and are predominantly scattered at the C60/C60 junctions.

53. Sutclai, K.; Kasamotu, S., Ita, K.
(Graduate School of Information Science and Technology)
Assessing Defect Detection Performance of Interacting Teams in Object-oriented Design Inspection
- Software inspection is one of the methods to ensure the quality of software by finding and repairing defects early in software development process. In this paper we report on a controlled experiment with fifty-four undergraduate students who inspected Object-Oriented design documents. We compare the performance of inspection teams using two reading techniques: Checklist-Based reading and Perspective-based reading. Then, we compare the performance of interacting and nominal teams.

54. Sakamoto, T.*1; Fukuda, T.*1; Kakesita, T.*1; Takeuchi, T.*2; Kishio, K.
*1(Graduate School of Engineering) *2(Graduate School of Science and Engineering)
Magnetic Field-induced Strain in Iron-based Ferromagnetic Shape Memory Alloys
- We found a giant magnetic-field-induced strain in Fe-Pd and Fe-Pt ferromagnetic shape memory alloys. The former alloy expands more than 3% along the field direction, and the latter alloy contracts more than 2% along the field direction. The field-induced strain of these alloys is larger than that of new magnetostrictive materials. So, these alloys are promising candidates for new actuators. We revealed that the large magnetic-field-induced strain is caused by rearrangement of nanosize variants. We also discussed the mechanism of rearrangement of variants under a magnetic field.

55. Sakai, T.*; Yasuda, H. Y.*; Umakoshi, Y.*
*1(Graduate School of Engineering) *2(Research Center for Ultra-High Voltage Electron Microscopy)
Interphase Boundary Fracture and Grain Boundary Precipitation of NiAl(1) Phase in NiAl Diborylate
- NiAl is expected to be a superior high temperature structural alloy for aircraft engine because of high strength and good oxidation resistance at high temperatures but its low ductility at ambient temperature due to grain boundary embrittlement should be improved for an industrial application. In contrast, NiAl shows good ductility at low temperatures but the high temperature strength is lower than that of NiAl. This paper presents effect of the crystalllography of film-like NiAl precipitates along grain boundaries on the fracture stress of beta NiAl bicrystals with controlled orientations and the coincident plane boundary between the precipitates and matrix was found to be effective in ductility improvement of NiAl.

56. Takagi, K.
(Graduate School of Engineering)
Quarter-Plane Problem of a Floating Elastic Plate
- An investigation is made into the hydro-elastic behavior of a floating elastic plate, which occupies a quarter plane to infinity. We showed that the solution is composed of the corner effect and the half plane problem. The corner effect is divided into two parts. The first part is the end effect of the forcing term, which is analytically estimated and its asymptotic form is derived. The second part is the local contribution whose asymptotic form is also obtained.

57. Shimbou, H.; Doiko, T.; Hirose, T.
(Graduate School of Engineering)
A Synthesis of Sumanone, a Fullerene Fragment
Science, 301, 1878 (2003)
- pp.26-29

(Graduate School of Engineering)
Catalytic Generation of Indium Hydrate and Highly Diastereoselective Reductive Aldol Reaction
- The reductive aldol reaction of enolates and acenitones has been established by triethylamine-indium tribromide system to provide one-pot synthesis of gamma-synoxy Me ketones (aldol). In particular, the catalytic use of indium tribromide was permitted. The reaction was highly diastereoselective and no reduction of starting aldehydes occurred. This method is superior to conventional reductive aldol reactions in terms of wide applicability to enones and aldehydes.

*1(Research Center for Solar Energy Chemistry) *2(Graduate School of Engineering)
Photochemical Production of Diphenyl from Oxidized Cumarin Compounds Obtained by Oxidative Deasulfurization of Light Oils
- We previously developed a desulfurization process for light oils based on chemical oxidation of sulfur compounds by H2O2 and acetic acid, whose process decreases successfully the sulfur concentration of the oils to <50 ppm. The present work develops novel photochemical synthetic process of industrially valuable biphenyl from the sulfones obtained by the above desulfurization process. The process can be carried out by photoirradiation of sulfones dissolved in 2-propanol at λ > 280 nm at room temperature.

60. Suhara, K.; Yamamoto, M.; Endo, Y.; Li, D.; Barad, S.D.
(Graduate School of Engineering)
Superparamagnetic Behavior of Ultrathin Fe Films Grown on Al2O3 (0001) Substrates
- We have studied superparamagnetic behavior of ultrathin Fe films grown on the Al2O3 (0001) substrates at various growth temperatures as a fundamental research of high-density magnetic storage media. It is demonstrated that 1.0-nm-thick Fe films are in the superparamagnetic state, and the blocking temperature is strongly dependent on the growth temperature. The observed behavior can be explained by the changes of the magnetic interactions between the Fe particles caused by the growth mechanism with growth temperature.

61. Sugiyama, T.; Asah, T.; Masuda, H.
(Graduate School of Engineering)
Formation of 10 nm-sized Oxido(hypoxyanoyl)vanadate(iv) Particles by Femtosecond Laser Ablation in Water
- p.58

62. Takagi, K.
(Graduate School of Engineering)
Quarter-Plane Problem of a Floating Elastic Plate
- An investigation is made into the hydro-elastic behavior of a floating elastic plate, which occupies a quarter plane to infinity. We showed that the solution is composed of the corner effect and the half plane problem. The corner effect is divided into two parts. The first part is the end effect of the forcing term, which is analytically estimated and its asymptotic form is derived. The second part is the local contribution whose asymptotic form is also obtained.
Realization of Electromagnetic Waves in Three-Dimensional Fractal Cavities 
*pp. 34-37

64. Takesue, N.; Furusho, J.; Innaka, A. (Graduate School of Engineering) 
Influence of Electrode Configuration and Liquid Crystalline Polymer Type on Electrochemical Effect 
*ER fluids are fluids whose apparent viscosity varies with external field strength. The four basic electrode configurations are investigated in this study. The finite element analysis of the electric fields is performed for each of the four basic electrode configurations. Liquid crystalline polymer ER fluids are generally classified into two types (types A and B). It is confirmed that the ER effect is also experimentally observed with types A, B, and D in the uniaxial electrode configuration.

The First Total Synthesis of Discorhabdin A 
*Journal of the American Chemical Society, 125, 11235-11240 (2003) 
*p. 59

66. Tsujii, N.; Saito, Y.; Lee, S.H.; Minamino, Y. (Graduate School of Engineering) 
ARB (Accumulative Roll-Bonding) and other new Techniques to Produce Bulk Ultrathin Grained Materials 
*Accumulative roll-bonding (ARB) is a severe plastic deformation process invented by the authors in Osaka University. The ARB can realize the ultrathin grained metallic materials whose mean grain sizes are smaller than 1 micrometer. This paper showed the principle of the ARB process, formation mechanism of the ultrathin grains during the ARB, and characteristic mechanical properties of the ultrathin grained materials fabricated by the ARB.

67. Watanabe, H.*1; Ikeda, Y.*1; Hayafusa, N.*1; Inagoe, Y.*2; Kawata, S.*1;*3 
*1(Graduate School of Engineering) *2(Graduate School of Frontier Biosciences) 
*3(Harui FPC) 
Tip-Enhanced Near-Field Raman Analysis of Tip-Pressured Adenine Molecule 
*A novel spectroscopic phenomenon which enables us to identify molecular species and their orientation in nanoscale has been found when we measured near field Raman scattering of adenosine nanocrystal while pressurizing it with an atomic force microscope (AFM) cantilever tip. The density functional theory for vibrational calculations of adenine complexes involving a silver atom suggested that unexpected Raman band shifts occur due to the deformation of adenine molecules with the silver atoms coated on AFM cantilever.

68. Watanabe, W.; Asano, T.; Yamada, K.; Inok, K.; Nakajima, J. (Graduate School of Engineering) 
Wavelength Division with Three-Dimensional Couplers Fabricated by Filamentation of Femtosecond Laser Pulses 
*p. 59

Three-Dimensional Viscoelastic Flows through a Rectangular Channel with a Cavity 
*Three-dimensional viscoelastic flows in a rectangular channel with a cavity were studied both numerically and experimentally. The numerical simulation predicted a swirling flow moving towards the center plane in the cavity. In the experiments, the flow of polymer solutions was visualized to observe three-dimensional flow behavior near the cavity part. The experimental results confirmed that the swirling flow emerged in the cavity. The numerical and experimental results confirmed that the swirling flow relates to elastic properties of fluids.

70. Yasuda, H.Y.*1; Nakao, K.*2; Nakahama, T.*2; Ueda, M.*2; Umakoshi, Y.*2 
*1(Research Center for Ultra-High Voltage Electron Microscopy) *2(Graduate School of Engineering) 
Effect of Ordering Process on Giant Pseudoelasticity in Fe$_3$Al Single Crystals 
*We first found giant pseudoelasticity in Fe$_3$Al single crystals regardless of martensitic transformation. The recoverable strain was as much as 5%, comparable with that in TiNi based alloys. We also found that the two-stages of accommodation, transfer, clamping, and transcending antiphase boundaries is responsible for the giant pseudoelasticity in Fe$_3$Al single crystals. The pseudoelasticity depended strongly on the ordering process; refinement of ordered domains developed in Fe$_3$Al was effective in enhancing the pseudoelasticity.

71. Yoshihito, M.; Wang, S.Q.; Fukunaga, K.; Walde, P.; Kuboi, R.; Nakao, K. (Graduate School of Engineering Science) 
Preparation and Characterization of Reactive and Stable Glucose Oxidase-Containing Liposomes Modulated with Detergent 
*Biotechnology and Bioengineering, 81, 695-704 (2003) 
*This project was achieved as an international research exchange between ETH (Switzerland), Yamaguchi Univ. (Japan) and Osaka Univ. (Japan). It was possible to use the glucose oxidase-containing liposomes (GOL) as a functional nanobiosensor, investigating for not only on the reactivity of the liposomes upon external addition of glucose but also on the leakage of the entrapped glucose oxidase (GOD) from the liposomes with the aim of developing a reactive and stable liposomal GOx system. It was clearly shown that the membrane permeability of GOL can be simply modulated by mixing it with a certain amount of cholera to form highly reactive and stable GOx with minimal enzyme leakage.

72. Yoshimou, N.; Hashimoto, T.; Maunudi, M.F.; Umakoshi, H.; Kuboi, R. (Graduate School of Engineering Science) 
Artificial Chaperone-Assisted Refolding of Bovine Carbonic Anhydrase Using Molecular Assemblies of Stimuli-Responsive Polymers 
*Artificial chaperone to assist the refolding of the conformationally abnormal protein was successfully designed by using the smart polymer self-assemblies with the size of 8-10nm. By using the artificial chaperone, the refolding yield of the target protein, bovine carbonic anhydrase, was reduced to 100%, whereas its function was found to be greater than that of other artificial chaperonin molecules and equivalent to that of natural chaperonin system (i.e. GroEL and GroES). The artificial chaperone could also be applied to the control of the conformation of the protein causing "conformational disease" such as Alzheimer's disease (amyloid beta) and Mad Cow disease (Prion).
73. Asakura, Y.*1; Hirohashi, T.*1; Kikuchi, S.*1; Inaba, S.; Oshino, F.; Yamao, S.*2; Terashima, I.*2; Barman, A.; Nakai, M.*1
*1(Institute for Protein Research) *2(Graduate School of Science)
Maize Mutants Lacking Chloroplast PSI Exhibit Pleiotropic Defects in the Biogenesis of Thylakoid Membranes

74. Asakawa, H.*1; Konno, H.*1; Sato, S.*1; Hara, W.K.; Takahashi, I.*1; Gao, X.H.; Sumitaka, Y.*1; Okabe, M.*2; Yoshikawa, K.*1; Itami, S.*1
*1(Graduate School of Medicine) *2(Genome Information Research Center)
Expression of T-cell-mediated Skin Disease-Specific Antigen Transiently Expressed in Keratinocytes

(Institute for Protein Research)
Amyloid Fibril Formation in the Context of Full-length Protein

76. Hashimoto, K.*1; Shimizu, K.*2; Nakashima, N.; Sugino, A.*1
*1(Graduate School of Frontier Biosciences) *2(Radiosurgery Research Center)
Fidelity of DNA Polymerase δ Holozymy from Saccharomyces cerevisiae: The Sliding Clamp Profligating Cell Nuclear Antigen Decreases Its Fidelity

77. Hidaka, O.*1; Yanagi, M.*2; Takada, K.*2
*1(Dental Hospital) *2(Graduate School of Dentistry)
Changes in Massseler Hemodynamics Time-related to Mental Stress

78. Hori, K.*1; Yano, K.*2; Yae, K.*2; Oda, J.*2; Fischer, S.E.J.; Keng, V.W.*2; Hayakawa, T.*2; Mizuno, S.*2; Kondo, G.*2; Iman, T.; Matsuda, Y.; Plasterk, R.H.A.; Takeda, J.*1
*1(Center for Advanced Science and Innovation) *2(Graduate School of Medicine)
Characterization of Sleeping Beauty Transposition and Its Application to Genetic Screening in Mice

79. Kamada, Y.
(Graduate School of Medicine)
Enhanced Carbon Tetrachloride-Induced Liver Fibrosis in Mice Lackng Adiponectin

80. Kang, Y.; Notomi, T.; Saito, M.; Zhang, W.; Shimamoto, R.
(Graduate School of Dentistry)
Bidirectional Interactions between H-Channels and Na--K--Pumps in Mesencephalic Trigeminal Neurons

81. Konishi, A.*1; Shimizu, S.*1; Hirota, J.*2; Takao, T.*2; Fun, Y.; Matsuoka, Y.*3; Zhang, L.*1; Tonedu, Y.*3; Fujii, Y.; Shoukuchi, A.I.; Tsubamoto, Y.*1
*1(Graduate School of Medicine) *2(Institute for Protein Research) *3(Graduate School of Frontier Biosciences)
Interaction of Histo HIF-2 in Apoptosis Induced by DNA Double-Strand Breaks

82. Lee, S.J.*1; Sekimoto, T.*2; Yamashita, E.*1; Nagoshi, E.*2; Nakagawa, A.*1; Imamoto, N.; Yoshimura, M.*1; Sakai, H.*1; Chong, K.T.*1; Tsukihara, T.*1; Tonedu, Y.*1
*1(Institute for Protein Research) *2(Graduate School of Medicine) *3(Graduate School of Frontier Biosciences)
The Structure of Importin-b and Related in Srfrp-2: Nuclear Import of a Transcription Factor

*ANNUAL REPORT OF OSAKA UNIVERSITY—Academic Achievement—2003-2004* 73

The influence of postoperative estrogen replacement therapy on the sensitivity of ovarian cancer to paclitaxel, written in waqaa used for cytotoxic chemotherapy, remains elusive. We examined whether estrogen affects paclitaxel-induced apoptosis in the Caov-3 human ovarian cancer cell line, which expresses estrogen receptor. Estrogen is known to stimulate the activity of Akt, which plays a central role in promoting the survival of a wide range of cell types. It was reported that estrogens stimulate Akt (ASK1) is a substrate of Akt. We showed here for the first time that estrogen inhibits paclitaxel-induced cell damage by inhibiting JNK activity via phosphorylation of Akt-ASK1.


Growth of Streptococcus oralis with Porphyromonas gingivalis was identified and purified. We cloned the gene and found that it was a high homology with GAPDHs of various bacteria. A recombinant protein of GAPDH bound to P. gingivalis fimbriae and inhibited the reaggregation. These results suggest that S. oralis GAPDH functions as a coadhesin for P. gingivalis. Considering the high homology of GAPDHs, these of other plaque forming bacteria may also contribute to the colonization of P. gingivalis.


We used microarrays carrying most of the genes that are developmentally regulated in Dicyostelium to discover those that are preferentially expressed in prestalk cells. Prestalk cells are localized at the front of a slug and play crucial roles in morphogenesis and slug migration. Using whole mount in situ hybridization we were able to verify 104 prestalk genes. These analyses demonstrate the extremely dynamic nature of cell type specific expression in Dicyostelium and further define the changing physiology of the cell types.


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GPI transamidase of Trypanosoma brucei, a causative agent of African sleeping sickness, shares only three components (TbGPA1, TbGPA2, and TbGPA6) with humans and S. cerevisiae, but has specific two other components, TTA1 and TTA2. Homologues of TTA1 and TTA2 are present in Leishmania and Trypanosoma cruzi but not in mammals, yeasts, flies, nematodes, plants and malaria parasites, suggesting that these components may play unique roles in attachment of GPI-anchors in trypanosomatid parasites and provide good targets for anti-trypanosome drugs.


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90. Nakahara, H. *1; Song, J.-W.; Sugimoto, M. *2; Hagihara, K. *2; Yoshizaki, K. *2; Ishikawa, T. *2; Nakamura, N. *3

(1)Graduate School of Medicine) (2)School of Health & Sports Sciences)


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P. gingivalis, an oral bacterium, plays an important role in the biofilm formation in the human periodontal pocket or progression of adult periodontitis. A putative glycosyltransferase gene was isolated from P. gingivalis and designated as gftA. GftA-deficient P. gingivalis lacked mature fimbriae morphologically and showed quite a low ability for autoggregation, and its ability for attachment to epithelial cells was severely impaired. These results suggested that gftA might regulate attachment ability in subgingival biofilms and act as a potent virulence factor.

02. Nishimoto, S. *1; Kanno, K. *2; Watanebe-Fukunaga, R. *1; Fukuyama, H. *2; Ohkawa, Y. *1; Uchiyama, Y. *1; Hashida, N. *1; Ohnuki, N. *1; Tan, Y. *1; Morimoto, T. *1; Fukuda, Y. *1; Nagata, S. *1,2


p.45-46
(Graduate School of Medicine)
Intrathecal Injection of HVJ-E Containing HGF Gene to Cerebrospinal Fluid can Prevent and Ameliorate Hearing Impairment in Rats

(School of Health & Sport Sciences)
Relationship between Excitation and Inhibition Underlying Size Tuning and Contextual Response Modulation in the Cat Primary Visual Cortex

95. Patacchini, R.; Meloni, M.; Tognetti, F.; Toni, M.; Kita, K.
(Hiroshima University)
Developmental-Stage-Specific Triacylglycerol Biosynthesis, Degradation and Trafficking as Lipid Bodies in Plasmodium falciparum-Infected Erythrocyte

(Graduate School of Medicine)
Identification of a Cytokine-induced Antipapoptotic Molecule Anamorsin Essential for Definitive Hematopoiesis

(Gene Research Institute for Frontier Biosciences)
Alteration of the 4-Sphinganine Scaffolds of Ceramides in Keratinocyte-specific ATRT-deficient Mice Affects Skin Barrier Function

98. Umesita, K.; Fujikane, K.; Koyama, K.; Makinouchi, M.; Satomi, S.
(Graduate School of Medicine)
Operative Morbidity of Living Liver Donors in Japan

(Research Institute for Microbial Diseases) (Graduate School of Medicine)
Role of Adaptor TRIF in the MyD88-Independent Toll-like Receptor Signaling Pathway

100. Yamashita, S.*; Miyagi, C.*; Fukuda, T.*; Kagura, N.*; Cho, Y.*; Hirano, T.*
(Graduate School of Medicine)
Zinc Transporter LIVI Controls Epithelial-Mesenchymal Transition in Zebrafish Gastrula Organizer

*1Graduate School of Medicine, *2Center for Advanced Science and Innovation