February 28 - March 1, 2013
Nogami President Hotel, Iizuka, Fukuoka, JAPAN

The proceedings of the First BMIRC International Symposium on Frontiers in Computational Systems Biology and Bioengineering

Organizer

Host
Biomedical Informatics R&D Center (BMIRC) at Kyushu Institute of Technology (Kyutech)

Co-Host
Kyushu Branch at Japanese Society for Bioinformatics
Division of Biochemical Engineering at The Society of Chemical Engineers, Japan

Sponsor
Iizuka City

Preface

The First BMIRC International Symposium on Frontiers in Computational Systems Biology and Bioengineering (http://www.csbb2013.jp/) is held at Nogami President Hotel, Iizuka, Fukuoka, JAPAN, during February 28 - March 1, 2013.

To activate the Asian research of Computational Systems Biology and Bioengineering and to make friendships among Asian countries, the Biomedical Informatics R&D Center (BMIRC) in Kyushu Institute of Technology (Kyutech) (http://www.kyutech.ac.jp/english/) holds the first international conference with Iizuka City, Kyushu Branch at Japanese Society for Bioinformatics, and Division of Biochemical Engineering at The Society of Chemical Engineers, Japan.

For over 20 years, we have been extensively applying bioinformatics, systems biology, and bioengineering to medical research and development at the School of Computer Science and Systems Engineering in Kyutech. At present, we should consider directly contributing to drug design/development; disease diagnosis, prevention, and treatment; and patient care/welfare, while reducing their economic costs. We are devoted to establishing a center of excellence in Asia that collaborates with medical schools, hospitals, companies, and the government.

In this symposium, we accepted a total of 39 presentations, consisting of 6 invited talks, 9 oral presentations, and 24 poster presentations. We thank all the invited speakers, all the authors of presentations, and the staffs of Kyutech and Iizuka City. we hope that this symposium will be fruitful and enjoyable for all attendees.

Symposium chairman

Hiroyuki Kurata
Director, Biomedical Informatics R&D Center (BMIRC)
Professor, Department of Bioscience and Bioinformatics
Kyushu Institute of Technology, Iizuka, Fukuoka 820-8502, JAPAN

Registration

Registration fee is free. For registration, send an e-mail to the office (bmirc2013@kys.jtb.jp) with the attached registration file (http://www.csbb2013.jp/). On-site registration is available.

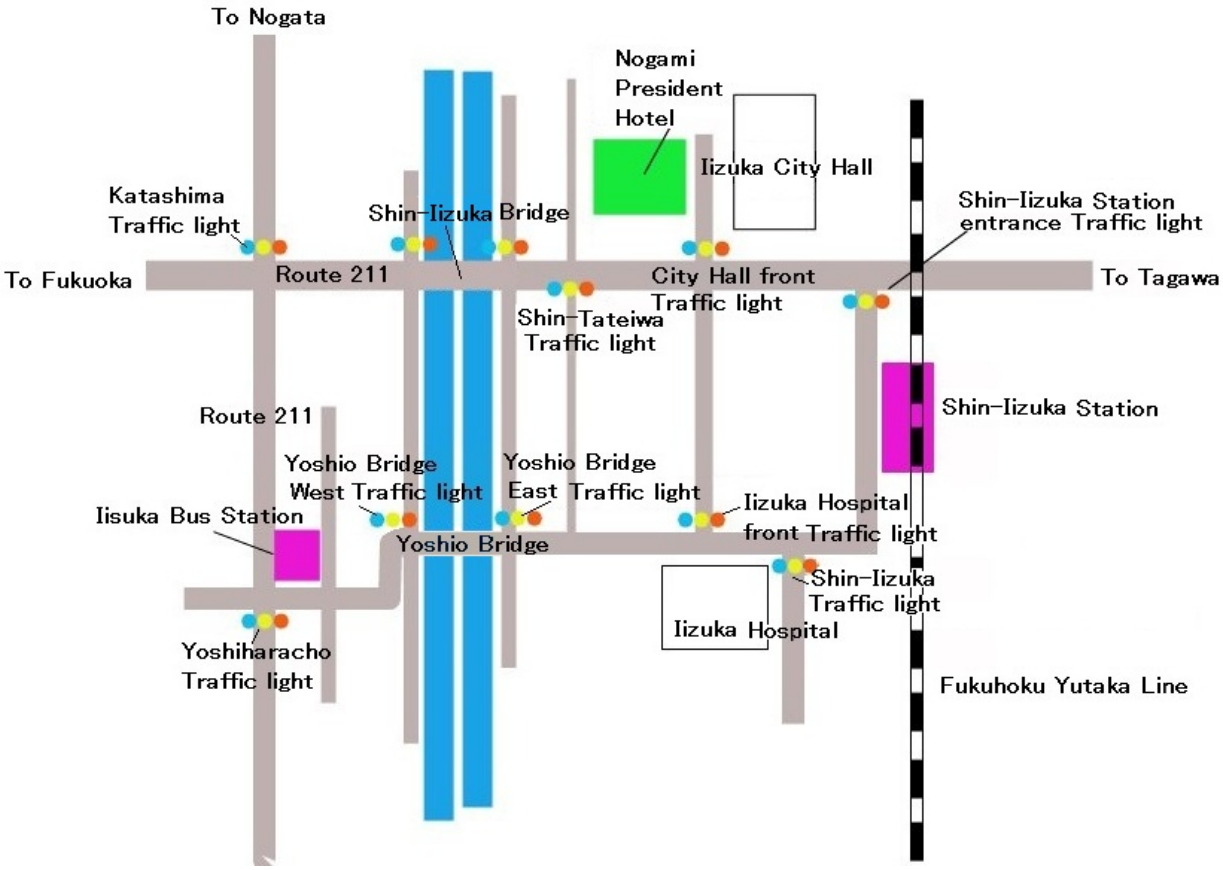
Conference Dinner

To join the conference dinner, please ask H. Kurata (kurata@bio.kyutech.ac.jp) about it. Participants pay the expense necessary for the conference dinner (¥ 3,000-5,000).

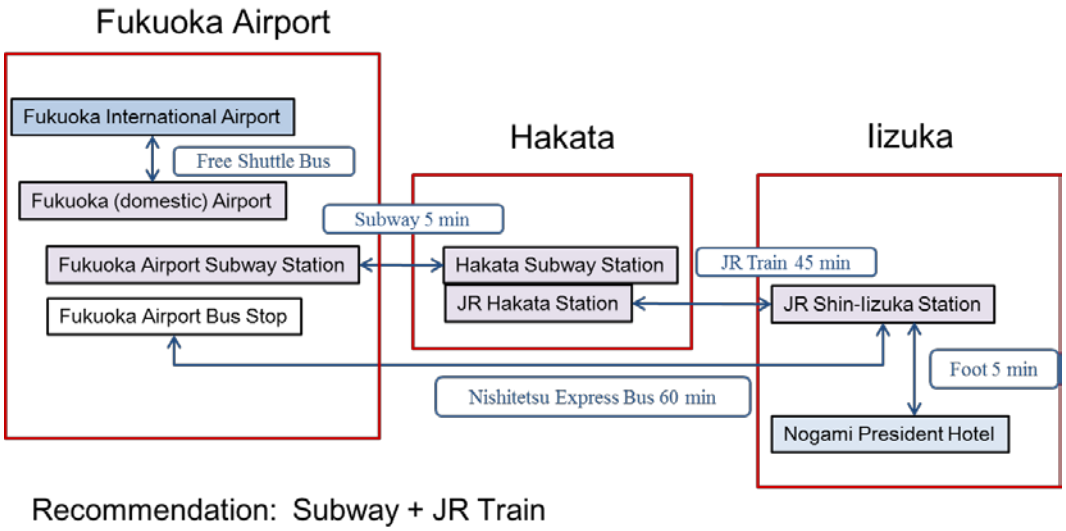
Venue

The Nogami President Hotel: 12-37 Shin-Tateiwa, Iizuka, Fukuoka, 820-0004, Japan.

It is located closed to the Iizuka City Hall, and is 2 km far from the BMIRC at Kyutech.



Travel



Accommodation

The Nogami President Hotel (Conference place) is available. Make reservation at bmirc2013@kys.jtb.jp.

Optional Tour

Inspection in Iizuka and Fukuoka on March 1-2 (at one's own expense).
Please ask H. Kurata about its details.

Schedule

February 28 (Thursday)

Greetings and messages

9:00-9:10 Morichika Saito (Mayor of Iizuka City)

9:10-9:20 Hiroyuki Kurata (Director of BMIRC)

Session 1 Synthetic Biology (Chair: Shunsuke Aoki)

9:20-10:00 Kareenhalli V Venkatesh (Indian Institute of Technology, India) -Invited

10:00-10:30 Masahiro Okamoto (Kyushu University, Japan) -Invited

Coffee Break

10:30-10:40

Session 2 Bioinformatics (Chair: Koichi Hirata)

10:40-11:20 Hsuan-Cheng Huang (National Yang-Ming University, Taiwan) -Invited

11:20-11:40 Hideo Hirose (BMIRC, Japan)

11:40-12:00 Christian Schönbach (BMIRC, Japan)

Lunch

12:00-13:20

Session 3 Systems Biology (Chair: Toshimasa Yamazaki)

13:20-14:00 Kwang-Hyun Cho (Korea Advanced Institute of Science and Technology (KAIST)) -Invited

14:00-14:30 Hiroshi Matsuno (Yamagushi University, Japan) -Invited

14:30-14:50 Katsuya Nagayama (BMIRC, Japan)

Coffee Break

14:50-15:00

Session 4 Bioengineering (Chair: Takeshi Saitoh)

15:00-15:40	Chengkuo Lee	(National University of Singapore) -Invited
15:40-16:00	Takahiro Ito	(BMIRC, Japan)
16:00-16:20	Kakuji Tojo	(BMIRC, Japan)
16:20-16:40	Kiyohisa Natsume	(BMIRC, Japan)

Poster Presentation

16:40-18:30

Conference Dinner

18:30-20:00

March 1 (Second day)

Session 5 Bioinformatics and Systems Biology (Chair: Satoshi Fujii)

9:00-9:20	Hiroto Saigo	(BMIRC, Japan)
9:20-9:40	Akinori Sarai	(BMIRC, Japan)
9:40-10:00	Hiroyuki Kurata	(BMIRC, Japan)

Discussion and Concluding Remarks

10:00-11:30

Inspection in Iizuka and Fukuoka

TABLE OF CONTENTS

Oral presentation

Poster presentation

<Bioinformatics>

<Synthetic and Systems Biology>

<Bioengineering>

Cross linking steady state response of gene regulatory networks to metabolism as applied to anaerobic growth of *Escherichia coli*

Sumana Srinivasan and K. V. Venkatesh

Department of Chemical Engineering, Indian Institute of Technology, Powai, Mumbai, India 400076

Contact: venks@iitb.ac.in, 91-22-25767223, 92-22-25726895 (fax)

Recent advances in techniques that analyze massive amounts of expression data from microarray experiments have led to the understanding of gene-regulatory networks (GRN). GRNs control various metabolic and signaling pathways in living cells. Bayesian inference and Boolean modeling have helped in extracting the topology of GRNs from the microarray data, but, they lack in providing the exact mechanistic details as to how a gene or a combination of genes control a given metabolic reaction. We have developed a modeling methodology based on the steady state performance of GRN -- Steady State Gene Expression System (SSGES), wherein the mechanistic details of the GRN is used to obtain the steady state gene expression profiles. The gene expression data is used to simulate the microarray data which can be compared with experimental data. By generating log fold change in mRNA abundance and protein expression data, we simulate microarray experiments and the model can therefore be used to perform gene knock out studies *in silico*. We show that modeling structural aspects of a GRN such as dimerization, multiple site binding, auto regulation etc., using our steady state gene expression simulator makes the predictions less erroneous when compared to experimental microarray data and helps gain understanding as to how these network artifacts actually regulate protein expression and thereby control the phenotype.

Further, we connect the mRNA and protein expression levels to the metabolic network to predict the fluxes in reactions in the central metabolic pathway in *E. coli*. The methodology links the steady states of the GRN and metabolic network to characterize the phenotype. Phenotypic states of mutants emerging from deletion of transcriptional regulators can be predicted. Their growth rates were predicted from the combined model under anaerobic conditions and compared with experimental data. The effect of transcriptional activator on metabolism and the phenotype is quantified. We have predicted the evolutionary path from a quadruple transcriptional regulator mutant to the wild type using our model and validated the same by building a phylogenetic tree thus obtaining evolutionary insights regarding the role of transcriptional activators in controlling the central metabolic pathway in *E. coli*.

Synthetic systems biology for the comprehension of biomolecular networks

Masahiro Okamoto[1,2]

[1] *Department of Bioinformatics, Graduate School of Systems Life Sciences, Kyushu University,*
8-812 WestWing, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

[2] *Synthetic Systems Biology Research Center (SSBRC), Kyushu University*

Contact: okahon@brs.kyushu-u.ac.jp Tel 81-92-642-2291 Fax 81-92-642-6744

In order to make the paradigm shift to the concept of “synthetic and analyzed or utilized biology”, the innovative research, synthetic biology was started from 2000 in US, such as designing synthetic genetic circuit by combining known interrelated biomaterials, realizing a certain bio-functional behaviors such as switch, oscillation *in vivo*, designing synthetic metabolic pathways by incorporating enzyme coded genes from other origins into the cells. These attempts have been done on a small scale and with a trial-and-error method, however, the objectives of this project is to establish the coordination between the fundamental technologies for synthetic biology in order to comprehend biomolecular networks by integrating the following three missions: 1) design synthetic genetic circuit or metabolic pathway with using the methods of computational science, 2) construct the circuit in vitro with using the method of engineering, 3) construct the circuit in vivo or in the cell with using the methods of molecular biology. In order to construct and control a large scale of dynamic and complex synthetic genetic circuit or metabolic pathways, the following fundamental technologies for synthetic biology are essential: Biochemical Engineering, Embryological Engineering, Molecular Biology, Evolutional Molecular Engineering, Micro Fluid Engineering, Biomolecular Chemistry, Simulation Engineering, and Knowledge-based Engineering. Our mission is to construct dynamic and multi-elements synthetic genetic circuit, followed by the construction of differentiation-induced system against stem cell and by the realization of cell factory, in which cells can produce the target metabolites by themselves according to the cell environment. By integrating systems biology and synthetic biology, we can build in synthetic genetic circuit and synthetic metabolic system followed by system analysis of system built in synthetic circuits. This integration is so-called “synthetic systems biology”, which can sure to lead us to the comprehension of biomolecular networks.

MicroRNA Regulation in Human Protein Interaction Network

Hsuan-Cheng Huang[1]
1 Institute of of Biomedical Informatics, National Yang-Ming University
Taipei, Taiwan,11221, Taiwan

Contact: hsuancheng@ym.edu.tw Tel 886-2-2826-7357 Fax 886-2-2820-2508

MicroRNAs are small non-coding RNAs, which regulate the protein encoding genes at post-transcriptional level. Topological and dynamic features of protein-protein interaction network provide insights of biological processes. We have performed topological analysis to elucidate the global correlation between microRNA regulation and protein interaction network in human. The results showed that microRNA targets tend to be hubs and bottlenecks in the network. While proteins directly regulated by microRNA might not form a network module themselves, the microRNA targets and their interacting proteins jointly show significantly higher network density and modularity. We also found that microRNAs may engage in a wider diversity of biological processes by coordinating with transcription factors, and this kind of cross-layer co-regulation may have higher specificity than intra-layer co-regulation. We further investigated the combinatorial regulatory effects of transcription factor and microRNA pairs on the protein interaction network and observed significant crosstalk between non-overlapping targets of co-regulators through protein-protein interactions. With gene expression profiles in different biological states, we have examined the dynamic structure of microRNA-regulated networks, and developed a network-based method to identify active microRNAs and reveal their functional roles in specific biological condition. Applying the analysis to gastric cancer, we found a key microRNA that plays an important role in tumor suppression and elaborated its regulatory mechanism in cancer cells.

A Seasonal Infectious Disease Spread Prediction Method by Using the Singular-Value Decomposition

Hideo Hirose[1]

1 Department of Systems Design and Informatics, Kyushu Institute of Technology
680-4 Kawazu, Iizuka, Fukuoka,820-8502, Japan

Contact: hirose@ces.kyutech.ac.jp Tel 81-948-29-7711 Fax 81-948-29-7709

Prediction methods for infectious disease spread have been dealt with from a variety of mathematical approaches. Among them are 1) the SIR/SEIR model (ordinary/stochastic differential equations), 2) statistical model (likelihood approach with conditional probability), 3) agent-based model, and 4) the internet-used model. Here, we propose a new method for the seasonal infectious disease spread prediction method by using the singular-value decomposition (SVD).

The SVD is one of the most powerful methods in recommendation systems. In the recommendation system, we can assume an incomplete matrix consisted of observed evaluation values by users and items, then we predict the vacant elements of the matrix using the observed values. This method is applied to a variety of the fields, e.g., for movie recommendations, music recommendations, book recommendations, etc. In this presentation, we apply the SVD to predict the seasonal infectious disease spread. Applying the method to the case of infectious gastroenteritis caused by Norovirus in Japan, we have found that the early detection and prediction for the prevalence of the disease spread can be expected accurately. Comparing the root mean squared error between the predicted and observed data, we have found that the proposed method shows the superiority over the conventional methods using the method of artificial neural networks. To demonstrate the advantageous point and effectiveness of the SVD method, we applied the method to the influenza spread prediction in Japan, where missing observations are admitted for computation unlike other prediction methods.

HLA-binding peptide affinity prediction and T cell-mediated response

Christian Schönbach
Department of Bioscience and Bioinformatics, Kyushu Institute of Technology, Fukuoka 820-8502, Japan

Email: schoen[-at-]bio.kyutech.ac.jp

Human leukocyte antigen (HLA) allele and supertype peptide binding motif scanning of viruses are routinely used to predict conserved peptides that may trigger cross-reactive HLA class I and/or class II restricted T cell responses. Yet, “good” HLA-binding peptide affinity does not necessarily translate into a “good” T cell-mediated response that can control infections for example with pandemic and seasonal influenza strains. Aside HLA micropolymorphisms, other important factor that affects the T cell-mediated response is the quality of T-cell receptor interaction with the HLA/peptide complex. The design and use of a combined affinity- and structure-based prediction approach, allows to take steric and topological effects of TCR contact residues on TCR binding affinity into consideration when evaluating peptides for further candidate vaccine testing. While it is possible to successfully infer potential differences in recognition and cross-reactivity for a few alleles, extension to population level is limited. The bottom line in *in silico* inference of epitope candidates that may induce a broad T cell response is data.

Exploring the core information processing unit in a cell

Kwang-Hyun Cho

Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology (KAIST), 291 Daehak-ro, Yuseong-gu, Daejeon 305-701, Republic of Korea

Contact: ckh@kaist.ac.kr http://sbie.kaist.ac.kr Tel&Fax +82-42-350-4325/4310

Cells encounter numerous environmental changes during their life and, therefore, to survive, they must make right decisions and cope with such changes. To this end, they might have evolved a sort of information processing machinery that senses external inputs and actuates right responses. What is this machinery and how does it work? In this talk, I argue with a range of examples that cell signaling networks might have such information processing capability and show that there exists a core processing unit embedded in the large complex signaling network. This new concept would open the possibility of controlling 'cellular thinking' in an efficient and plausible way.

I will first show a proof-of-concept example with the core regulation module, a commonly involved regulation structure in the regulatory networks of yeast and demonstrate that the core regulation module constitute a hierarchical backbone of the yeast regulatory network. I will then further extend this concept and show that there is, in general, a condensed framework or kernel within a large complex biomolecular interaction network that preserves the essential network dynamics. Intriguingly, we found that such a kernel contains many important molecules and has interesting network structures.

I will close my talk by discussing that this new concept would provide us with a new insight into the large and complex biomolecular interaction networks and open a new way to control network dynamics such that we can change cell fate determination.

Estimation of signaling flow timings from the structural information of a Petri net model of signaling pathway

Hiroshi Matsuno[1] and Qi-Wei Ge[2]

1 Graduate School of Science and Engineering, Yamaguchi University

1677-1 Yoshida,Yamaguchi,753-8512, Japan

2 Faculty of Education, Yamaguchi University

1677-1 Yoshida,Yamaguchi,753-8513, Japan

Contact: matsuno@sci.yamaguchi-u.ac.jp Tel&Fax 81-83-933-5697

Basic architecture of a signaling pathway can be considered as a combination of paths constituted by static elements (molecules) and dynamic elements (reactions) which alternately appear along each path. This alternation architecture of signaling pathway inspires us to employ Petri net technique to the modeling of signaling pathway because of the natural correspondence of Petri net elements place and transition, to the static and dynamic elements of signaling pathway, respectively.

Although structural information of Petri net is important for the qualitative evaluation of signaling pathway, the action of a signal, which is propagated from the cell surface to the nucleus, should be expressed with a quantitative manner. Furthermore, this quantitative representation need to be as simple as possible for determining signaling dynamics with low-computational cost.

In this report, we demonstrate how the dynamics information of signaling pathway is realized by means of the concept of time using timed Petri net. Incorporation of delay times into a Petri net model makes it possible to conduct quantitative evaluation on a target signaling pathway. However, experimental data describing detailed reactions are not available in most cases. We developed algorithms that determine delay times of a timed Petri net only from the structural information of it.

Formal descriptions on the construction of the modeling method are presented with focusing on the smooth signaling flows and the conflict resolutions in a signaling pathway. The proposed method permits quick determination of delay times only from the structural information of a signaling pathway whose detailed reaction data are not provided by biological experiments.

Numerical simulation of biological phenomena using particle model

Katsuya Nagayama
Division of Mechanical Information Science and Tech., Kyushu Institute of Technology

Contact: nagayama@mse.kyutech.ac.jp Tel&Fax 81-948-29-7778

Biological phenomena in the body are often difficult to understand for a long time change, and also difficult to observe. Numerical simulation is useful to visualize and predict these phenomena. But commercially available software for fluid and heat flow is difficult to express the changes such as cell division and deformation. We propose a particle model to simulate complex biological phenomena. In our particle model, the computational domain is divided into particles, and biological phenomena is simulated by pursuing the particles motions, deformations and transitions directly .

Our particle model has features such as

1. The model can handle changes such as cell division and growth.
2. Inter-particle force is represented by two forces. One is the force to keep the particle volume constant and another is spring force to express elastic body.
3. Non-spherical cell deformation can also be analyzed.
4. Multiple types of particles (such as pieces of tissue, blood vessels) can be used, and can represent complex changes.

Applications of particle model will be exhibited in the poster cession as follows.

1. Particle simulation of cancer growth and angiogenesis - based on the image of rabbit ear - Yuki Oshiumi et al.
2. Numerical simulation of hair formation using particle model, Shogo Matsuoka et al.
3. Numerical simulation of epidermal skin formation using particle model Takahiro Uehara et al.
4. Particle simulation of alveolar bone regeneration and angiogenesis - Study on basic mode l - Kenta Kisu et al.
5. Numerical simulation of liver cell proliferation - basic model - Yusuke Tsuji et al.

The simulated results could visualize and predict the phenomena in the body.

In future, the modes will be expected as tools for health diagnosis and prediction of therapeutic effect.

Progress of MEMS/NEMS technology for biomedical applications

Chengkuo Lee
Department of Electrical and Computer Engineering, National University of Singapore
4 Engineering Drive 3, Singapore 117583, Singapore
Contact: elelc@nus.edu.sg; Tel: 65-6516-5865

Since the invention of silicon microfabrication technology in early 1960s, the integrated circuit (IC) has changed our world. During last 40 years, the semiconductor industry has come up as the fastest growing industry in our history. This silicon microfabrication technology was later extended to machining mechanical microdevices—that was later called microelectromechanical systems (MEMS). The ever-advancing semiconductor process technology renders making single-crystal silicon nanowires (SiNWs) via top-down fabrication approach. This technology further enables the potential of downsizing the piezoresistive MEMS sensors to a new category of sensors in nanometer scale, i.e., nanoelectromechanical systems (NEMS) sensors. These piezoresistive NEMS sensors using SiNWs as sensing elements demonstrate higher sensitivity and lower power consumption with great potential of being implantable sensors because of small footprint.

On the other hand, self-sustained autonomous sensor nodes have attracted great interests in the home healthcare and point-of-care applications. To facilitate these sensor nodes, sensors of low power consumption and self-sustained power source are required to be developed. Thus MEMS based energy harvesting technology has been considered as an enabling technology for self-sustained power source. While thermoelectric MEMS power generators aim at scavenging body heat, piezoelectric and electromagnetic MEMS energy harvesters can collect kinetic energy associated with human walking and gesture. The progress in development of MEMS based energy harvesters opens the opportunity of self-sustained MEMS sensor nodes in wireless sensor networks.

Polymer based microfluidics have shown great impact in various applications. Integration of microfluidics with MEMS and NEMS functional elements enable novel devices for drug delivery and screening, cell manipulation and cancer cell detection etc. A few novel devices are demonstrated accordingly. Portable microfluidic devices with sophisticated function may bring fundamental changes in healthcare and pharmaceutical industries.

Impulse-driven capsule for medical treatment

Takahiro Ito
Faculty of Computer Science and Systems Engineering, Kyushu Institute of Technology
680-4 Kawazu, Iizuka, Fukuoka,820-8502, Japan

Contact: ito@mse.kyutech.ac.jp Tel&Fax 81-948-29-77765

We have developed a traveling small capsule, which has smooth outer surface and is driven by the inertia force and friction force. It is small enough, 11 mm in diameter and 25 mm long, it can be put in the human gullet or intestines. The capsule contains a small magnet and a coil, and electric pulse drives the magnet to move the capsule. To investigate the feasibility of our traveling capsule, we did the theoretical analysis and computer simulation using a simple model. We did the experimental investigation that our capsule can travel on a plastic plate and it can also travel on pig intestine surface. Our capsule is supposed to be useful for medical treatment such as inspection, drug delivery or operation.

In Silico Prediction of Skin Penetration of Drugs

[1]K. Tojo, [1]Hikima T. [2]Mori D.

[1]Kyushu Institute of Technology, [2]Biocom Systems Co Ltd.

Introduction

In skin penetration of drugs, various events take place simultaneously in the stratum corneum, viable skin and on the sc/viable skin boundary. These events are diffusion, partitioning, metabolic reaction, tissue binding and uptake into the microcirculation. The tissue and blood concentration can be evaluated by solving the partial differential equation based on the unsteady state mass balance equation.

Method

It is well established that major factors that determine the skin absorption rate are the diffusion coefficient and partition coefficient in the stratum corneum, outermost layer of the skin. We have found both D and Cs for the hairless mouse, determined from the in vitro penetration experiment well agree with these under clinical conditions[1] Once D and Cs were determined, the plasma concentration is evaluated theoretically by solving the governing partial differential equation[2]. If D or Cs is not available, we can determine experimentally on the basis of the bi-layer skin model.[3] D and Cs are influenced by the metabolic reaction as well as the binding in the skin. These values are therefore calculated carefully by taking account of the effect of binding and bioconversion.

SKIN-CAD consists of skin diffusion/partitioning, body PK(multi-compartment model) model and drug diffusion in the polymer matrix. The PK parameters for the body compartment such as the number of the compartment, the elimination rate constant, are usually available in the literature.

Results

The clinical performances of transdermal drug delivery were compared with the profiles predicted from SKIN-CAD simulator, including the following two cases: Rivastigmine patch and pulsed fentanyl delivery by iontophoresis. The clinical profiles were excellently predicted by SKIN-CAD.

Conclusion

The present virtual mouse (or virtual patients) is extremely useful to make new TTS development faster, cheaper and even more efficient with minimum animal and clinical studies.

References

1. Nakamura A., Mori D. ,Tojo K.,Chem. Pharm.Bull. 60(3)300-305(2012)

2. Tojo K., Mathematical models for transdermal and topical drug delivery, Biocom Systems, Fukuoka, Japan, 2nd Ed. 2005

3. Martin A., Physical Pharmacy, 4th ed. Chapter 19, 1993

Tojo K. Yakuzaigaku, 70(3),162-166(2010)

Brain computer interface using human brain waves

Kiyohisa Natsume[1]

1 Department of Brain Science and Engineering, Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology

2-4 Hibikino, Wakamatsu-ku, Kitakyushu, 808-0196, Japan

Contact: natume@brain.kyutech.ac.jp, Tel&Fax 81-93-695-6094

Human has the several brain waves, for example, θ, β, γ waves. They are related to the memory process. Spoken English have the different rhythms from Japanese. Hence it is hard for Japanese students to learn English. After the students learned the English rhythm using rhythmic instruction materials, which was developed by Graham (1979) and modified by Nakano (1997), they could have better performance of the rhythm. During the learning period we recorded the brain wave from the learners. In results, the power of theta rhythm at the frontal region of a brain increased, and the power was correlated with the performance of the students.

The neurophysiological results from rodents suggest that theta (θ, 4–8 Hz) wave is related to memory encoding. In a brain, long-term potentiation (LTP) at neuronal synapse is a basic phenomenon of the memory learning process. Theta wave can be reproduced in a hippocampal slice. We found that during the generation of the theta wave, LTP is facilitated. Hence, theta wave facilitates the synaptic plasticity, and in results memory encoding process can be occurred.

Theta wave can facilitate learning process, and the facilitation can be caused by the modulation of synaptic LTP. In the case of humans, detecting the theta wave, whether he/she is learning English rhythm or not intensely may be detected. Thus, we are developing e-learning system for English rhythm monitoring students' brain waves. Brain waves can be used for brain-computer interface for an e-learning educational system.

Learning from treatment history to predict response to anti-HIV therapy

Hiroto Saigo
Department of Bioscience and Bioinformatics, Kyushu Institute of Technology
680-4 Kawazu, Iizuka, Fukuoka,820-8502, Japan

Contact: saigo@bio.kyutech.ac.jp Tel: +81-948-29-7802

Infections with the human immunodeficiency virus type 1 (HIV-1) are treated with combinations of drugs. HIV responds to the treatment by developing resistance mutations. For ensuring an effective treatment the genome of the viral target proteins is sequenced and inspected for resistance mutations. For predicting response to a combination therapy, currently available computer-based methods rely on the genotype of the virus and the composition of the regimen as input. However, they do not take full advantage of the knowledge about the order of and the response to previously prescribed regimens. The proposed machine learning system is trained for exploiting such knowledge utilizing the recent advance in frequent sequence mining and support vector machines. When applied to predicting the latest treatment outcome of 3,759 treatment-experienced patients from the EuResist data, prediction accuracy was boosted from 77% to 81%, which constitutes a statistically significant improvement. The major discovery obtained by analyzing the discriminative treatment records is that the information on the composition of a regimen coupled with their short time treatment outcome is as valuable as the composition of a regimen coupled with genotype of the virus. We show that the decision made by our machine learning system is based on clinically relevant rules; such as predicting negative for patients who have already experienced a treatment failure by using standard regimen, or predicting negative for patients who have received regimens which are nowadays known to be ineffective or rather toxic.

Biophysics of molecular interaction network

Akinori Sarai
Department of Bioscience and Bioinformatics, Kyushu Institute of Technology
680-4 Kawazu, Iizuka, Fukuoka,820-8502, Japan

Contact: sarai@bio.kyutech.ac.jp Tel: 81-948-29-7811

The network of molecular interactions plays a key role in many cellular functions such as signal transduction, gene expression and metabolic process. The molecular interaction network is usually represented by a collection of independent binary connections between a pair of molecules, since many experimental data have been collected by the biochemical detection of binary interactions. However, molecular interactions are often highly cooperative, that is, the interaction between a pair of molecules depends on the presence of other interactions. Such cooperativity of molecular interactions plays a critical role in the biological function of network. Therefore, it is important to analyze the semantics or context of the molecular interaction network.

Structural data of molecular interactions, in particular complex structures consisting of multiple molecules, provide insight into the semantics of molecular interactions. The structural information of molecules and their interactions are also essential for understanding the molecular mechanism of biological networks and to develop drugs. Therefore, we have been developing a database/tool of biomolecular network, PDBnet, based on the structural information of Protein Data Bank (PDB), and integrated it with the biochemical interaction data.

In the case of protein-protein interactions (PPI), the domain as a structural and functional component of proteins has been recognized as a key player of molecular interactions, and widely used for predicting PPI. The domain information is usually identified based on sequence similarity. On the other hand, non-domain regions, which are usually variable in sequence and length, are often involved in the interactions by themselves or in combination with other domains, and serve function as well. Thus, we have implemented the information of non-domains as well as domains into PDBnet, and analyzed the cooperativity in the PPI network.

We also show the role of cooperativity in the transcription regulatory network, based on the structural context of protein-DNA interactions.

Bioalgorithms for rational design of biological systems

Hiroyuki Kurata[1,2], Kazuhiro Maeda[1], Toshikazu Onaka[1], Takenori Takata[1]
1 Department of Bioscience and Bioinformatics at Kyushu Institute of Technology
2 Biomedical Informatics R&D Center (BMIRC) at Kyushu Institute of Technology

Contact: kurata@bio.kyutech.ac.jp Tel&Fax 81-948-29-7828

In synthetic biology and systems biology, a bottom-up approach is a powerful strategy to understand complex, modular, hierarchical systems of biochemical networks.

To analyze or design biochemical networks where the biological parts or molecular modules interact with each other, it is critically important to understand a variety of the network-function relationships (NFR), the mechanism of how the biological parts are assembled to form building blocks or subnetwork modules with particular functions. To make clear NFRs, a new term "bioalgorithm" is defined as the step-by-step molecular process of how molecular modules and subnetwork modules are combined to generate their particular functions. The bioalgorithms would provide the mechanism of how we analyze the structures of large-scale biochemical networks and the instruction of how we create robust biological circuits that carry out a target function.

We develop a database of bioalgorithms that potentially can cover the whole cells at the molecular interaction level. This database provides the sound bases for an understanding of how elementary networks are assembled to create biological functions and for rational design of biochemical networks for engineering purpose. Extensive study of bioalgorithms would lead to an exploration of biological design principles underlying molecular architectures. The proposed database takes an advantage in simulation function of mathematical models, facilitating an understanding of each bioalgorithm.

A fast homology search algorithm using dynamic seeding

Hiroyuki Ishii[1], Haijiang Tang[2], Sei-ichiro Kamata[2] and Toshimasa Yamazaki[1]

1 Department of Bioscience and Bioinformatics, Kyushu Institute of Technology 680-4 Kawazu, Iizuka, Fukuoka 820-8502, Japan

2 Graduate School of Information, Production and Systems, Waseda University, 2-7 Hibikino, Wakamatsu, Kitakyushu, Fukuoka 808-0135, Japan

Contact: t-ymzk@bio.kyutech.ac.jp Tel 81-948-29-7818 Fax 81-948-29-7801

Homology is a structural correspondence among different organisms that infers their revolutionary relationship. Classical homology search approaches such as BLAST and FASTA work through a heuristic scheme to expand seed matches (hit) and locate homologous region between sequences. Typical seed models possess an arbitrarily designed concatenated pattern. In recent years, some approaches using spaced seed pattern to improve the homology search performance were proposed. However, these seed patterns are still arbitrarily defined. There is a dilemma on traditional seeding strategy that bigger seeds lead to faster speed but less sensitivity while smaller seeds perform the opposite.

We propose a novel seeding strategy that determines the seed dynamically along the heuristic search process. It performs a rapid heuristic expansion from short exact match to local alignment. The expansion of each step is done by searching for the sequence segments in a search window instead of exhausted character by character search in traditional methods. Both the segments and window sizes are determined by previous expansion. The experimental results on DNA sequence homology search show that our algorithm significantly outperformed BLAST algorithm in both speed and sensitivity. Our algorithm dynamically optimizes the hit-and-expand process and reduces the search space. We believe this strategy provides a new direction on reducing the computational complexity without losing sensitivity due to approximation or arbitraries. It helps to solve the dilemma lies in traditional homology search algorithms and improve the search efficiency.

Clustering of Positions in Nucleotide Sequences by Trim Distance

Takaharu Shimada[1], Shunsuke Makino[1], Kouichi Hirata[1],
Kouki Yonezawa[2] and Kimihito Ito[3]

1 Kyushu Institute of Technology, Kawazu 80-4, Iizuka 820-8502, Japan

2 Nagahama Institute of Bio-Science and Technology, Tamura 1266, Nagahama 526-0829, Japan

3 Hokkaido University, North 20 West 10, Kita-ku, Sapporo 001-0020, Japan

Contact: hirata@ai.kyutech.ac.jp. Tel 81-948-29-7622, Fax 81-948-29-7601

A trim distance [1,2] is a distance between positions in nucleotide sequences through a trimmed phylogenetic tree for every position. In this report, we present experiments for clustering of positions by the trim distance as applying a group average method in agglomerative hierarchical clustering techniques to the nucleotide sequences of influenza A viruses provided from NCBI (http://www.ncbi.nlm.gov/genomes/FLU/).

For influenza A (H1N1) viruses, we consider 895 positions in the NA segment [1]. Focusing on the positions where the number of leaves in the trimmed phylogenetic trees is less than 100, we compare 513 positions for non-pandemic viruses with 543 positions for pandemic viruses. Then, we found 5, 10, 15 and 20 clusters by the threshold of the trim distance in the intervals of (34.464,35.187), (28.78,29.199), (24.562,25.275) and (22.16,22.501) for non-pandemic viruses and in the intervals of (32.666,33.676), (25.487,27.392), (23.003,23.549) and (21.881,22.153) for pandemic viruses.

For influenza A (H3N2) viruses, we consider 6125 positions in 8 RNA segments of PB2, PB1, PA, HA, NP, NA, MP and NS, and give the following two experiments.

In the first experiment, we focus on 32 positions including 3 positions as packaging signals, that is, NA1253, NS48 and NS49, where the number of leaves in the trimmed phylogenetic trees is less than 20 [2]. Then, we found the threshold 1.00 of the trim distance such that each of the 3 positions is contained by just one cluster and the total number of clusters is smallest, which is 14.

In the second experiment, we focus on all the 600 positions as packaging signals [2]. Then, we found 5, 10, 15 and 20 clusters by the threshold of the trim distance in the intervals of (42.5,49.83), (37.305,37.321), (34.583,35.95) and (29.906,30.871).

[1] S. Makino, T. Shimada, K. Hirata, K. Yonezawa, K. Ito: *A trim distance between positions in nucleotide sequences*, Proc. DS'12, LNAI 7569, 81-94, 2012.

[2] S. Makino, T. Shimada, K. Hirata, K. Yonezawa, K. Ito: *A trim distance between positions as packaging signals in H3N2 influenza viruses*, Proc. SCIS-ISIS'12, 1702-1707, 2012.

Mapping the Groups of DNA Sequences using Hidden Markov Model Self Organizing Maps

Hiroshi Dozono , Gen Niina and Yutaro Kaneko
Department of Advanced Fusion, Saga University
1 Honjyo Saga 840-8502 JAPAN

Contact: hiro@dna.ec.saga-u.ac.jp Tel&Fax 81-952-28-8652

Recently, Next Generation Sequencers(NGS) produces large amounts of sequences. The produced sequences are applied to many areas of genome science. Meta-genome analysis and Comparative genome analysis are examples of such applications. Meta genome analysis For both applications, the global comparison of DNA sequences among the species will be effective.

For the global comparison of DNA sequences, Self Organizing Map(SOM)[2]s are often used. The frequencies of N-tuples, which denote the occurrence of each N-tuple for fixed N, were shown as effective, and analysis of DNA sequences by SOM using the vectors of frequencies of N-tuples as input vector was proposed, and achieved good resolution among the genome sequences of some species [T. Abe, T. Ikekura,et.al, Informatics for unreveiling hidden genome signatures, Genome Res., vol.13, p.693-702 (2002)].

In this research, we propose a method for mapping DNA sequences using Hidden Markov Model SOM (HMM-SOM). HMM is widely used for series of data, and it is also applied to sequence analysis in bioinformatics. Our approach organizes the small scale HMM on the map as to classify the sets of input sequences. However, the conventional learning algorithm for HMM requires large computational costs. In this research, we propose a learning algorithm based on the reinforcement learning to decrease the computational costs. Furthermore, using the SOM, which selects effective N-tuples, as preprocessing, the computational cost is much more decreased.

The experiments of mapping DNA sequences of genes categorized by species and metabolic pathways are conducted using HMM-SOM, and the availability for clustering DNA sequences is examined.

Two distinct histidine-containing metal-binding motifs in prion-derived peptides predicted by fluorescence spectroscopic assays

Reina Inokuchi,[1] Ken Yokawa,[2] Tadashi Okobira,[3] Kazuya Uezu[1] and Tomonori Kawano[1]

1 Faculty and Graduate School of Environmental Engineering, The University of Kitakyushu, Kitakyushu, 808-0135, Japan

2 IZMB, University of Bonn, Kirschellee 1, 53115 Bonn, Germany

3 Ariake National College of Technology, Omuta, Fukuoka 836-8585 Japan

Contact: kawanotom@kitakyu-u.ac.jp Tel 81-93-695-3207 Fax 81-93-695-3304

Prion proteins are infectious agents causing transmissible spongiform encephalopathies in a misfolded protease-resistant form of protein. Human PrP possesses seven potential copper-binding sites. Notably, four of putative copper-binding sites are located in the octarepeat region (PrP 60-91). Recent studies have shown that peptides derived from human PrP effectively bind Cu^{2+} to form the Cu-centered catalytic complex required for generation of superoxide by coupling the oxidation of neurotransmitters and their analogues. In this study, we have studied the minimal motifs required for binding of metals within human PrP, by assessing **(a)** the peptide-dependent quenching of Tb^{3+} fluorescence and **(b)** the Cu^{2+}-dependent quenching of intrinsic fluorescence in human PrP octarepeat-derived peptides. Assays with peptide-dependent quenching of Tb fluorescence supported the positive role for the His-ended X-X-H motif (in this case P-Q-H tripeptide sequence) rather than His-started H-G-G-G-W motif, as metal chelating motifs in short peptides. Controversially, the role of His-started motif was supported by the Cu-dependent peptide fluorescence quenching assay. Above data suggested that there are two distinct modes of metal binding to His residues in the octarepeat regions in PrP, possibly by co-ordinations of His-started and His-ended motifs around the target metals depending on the conditions given.

EdaFold: A Probabilistic Fragment-based Method for Protein Structure Prediction

David Simoncini [1] and Kam Y. J. Zhang [1]
1 Zhang Initiative Research Unit, Advanced Science Institute, RIKEN,
2-1 Hirosawa, Wako, Saitama 351-0198, Japan

Contact: kamzhang@riken.jp Tel&Fax 81-48-467-8792

Fragment assembly is a powerful method of protein structure prediction that builds protein models from a pool of candidate fragments taken from known structures. Stochastic sampling is subsequently used to refine the models. The structures are first represented as coarse-grained models and then as all-atom models for computational efficiency. Many models have to be generated independently due to the stochastic nature of the sampling methods used to search for the global minimum in a complex energy landscape. We have developed a new method for fragment-based protein structure prediction based on an Estimation of Distribution Algorithm called EdaFold. This algorithm learns from previously generated decoys and steers the search toward native-like regions. A distribution over fragments is estimated from a pool of low energy all-atom models. This iteratively-refined distribution is used to guide the selection of fragments during the building of models for subsequent rounds of structure prediction. A comparison with Rosetta AbInitio protocol shows that EdaFold is able to generate models with lower energies and to enhance the percentage of near-native decoys on a benchmark of 20 proteins.

We have used this EdaFold method to participate in the recent “10th Community Wide Experiment on the Critical Assessment of Techniques for Protein Structure Prediction (CASP10)”. Our method was ranked No. 1 out of 143 groups from world-wide participants in the template-free modeling category as judged by the average Z-score in GDT_TS. This prospective exercise has further validated the utility of method.

Identifying Differentially Expressed Genes by Robust Hierarchical Clustering in Microarray Gene Expression Data Analysis

Md. Bahadur Badsha*[1], Nusrat Jahan[1]and Hiroyuki Kurata[1]

[1] *Department of Bioscience and Bioinformatics, Kyushu Institute of Technology*

680-4 Kawazu, Iizuka, Fukuoka, 820-8502, Japan

*Contact: m791703b@bio.kyutech.ac.jp and mbahadur_stat_ru@yahoo.com

Abstract

Bioinformatics has successfully explored the information of the function of the genes in the computational system biology and influence on the others fields like biotechnology, medicine, agriculture and human health. One of the most important areas in bioinformatics is to identify the differentially expressed (DE) genes for the understanding of physiological and pathological processes of any organism. Hierarchical clustering (HC) algorithms are one of the most widely used unsupervised statistical techniques to identify DE genes for analyzing microarray data. However, it suffers from the robustness problems, which is important issue in gene expression data analysis. So, HC often produces misleading clustering results if there exist some contaminations in the gene expression data. To solve this problem, we present a development of HC.

To investigate the performance of the proposed method in a comparison of the HC, we investigate the artificially generated gene expression data in both cases absence and presence of outliers. A gene-set is said to be biologically relevant to the phenotypic variations under study if it classify the individuals with the highest sensitivity (TPR) and specificity (TNR) which is equivalent to the minimum misclassification of the individuals. We compare our proposed method with HC and other existing robust algorithms such as Minimum Covariance Determinant (MCD), Minimum Volume Ellipsoid (MVE) and Orthogonalized Gnanadesikan-Kettering (OGK) using true positive rate (TPR), true negative rate (TNR), false positive rate (FPR), false discovery rate (FDR), misclassification error rate (MCR). Simulation data results show that the proposed method significantly improves the performance over the HC and other existing robust algorithms in presence of gene contaminations; otherwise, it keeps equal performance.

Pandemic Analysis using SIR Stochastic Differential Equation

Yoshihiro Maki, Hideo Hirose[1]
1 Department of Systems Design and Informatics, Kyushu Institute of Technology
680-4 Kawazu, Iizuka, Fukuoka,820-8502, Japan

Contact: maki@ume98.ces.kyutech.ac.jp, hirose@ces.kyutech.ac.jp

Pandemic simulation is considered to be crucial as a scenario simulation and it is performed by many kinds of methods; the classical ordinary differential models (SIR model), agent-based models, internet-based models, and etc are among them. The SIR model is one of the fundamental methods to see the behavior of the pandemic with easy computation, where *S, I,* and *R* denote susceptible, infected and removed populations respectively, and it computes the number of people infected with a contagious disease in a closed population over time. The model can quickly deal with simulations of infectious disease spread among homogeneous populations using simple simultaneous ordinary differential equations and a few parameters. However, there are no stochastic variation terms in the equations. The objective of our study is to obtain the confidence intervals for stochastic variations for the predicted values using real world cases.

The stochastic differential equations (SDE) can provide such kind of variations. Although the SDE are applied to many fields such as economics, less attention has been paid to the SIR simulations. In this paper, we propose a SDE version of the SIR simulation model by using Euler-Maruyama method as a simple numerical method. The diffusion is added to the $dI(t)$ term, which corresponds to infected population derivative. The SIR mean parameters were obtained by using the difference equations, and the parameters of the SDE was obtained by using a well-known property of the quadratic variation associated with the stochastic process for $I(t)$.

The proposed method was applied to SARS (Severe Acute Respiratory Syndrome) case in 2003 in Hong Kong. In that case, we pursued the appropriate number of runs to to obtain the confidence intervals for the estimates, resulting in 10000 runs in the simulations. We have found that the SIR model gives us the final value around 2300 at the time of day 40. This estimated value and the observed value of 1755 are close to each other. However, the confidence interval show a possibility that the number of infected people would be twice as many as the actually observed number. As time goes on, the highest value in 95% confidence intervals, which we can interpret the possible worst case, is becoming lower.

CADLIVE Toolbox for MATLAB: Comprehensive Analysis Tool for Dynamic Models in Systems Biology

Kentaro Inoue[1], Kazuhiro Maeda[1], Takaaki Miyabe[1] and Hiroyuki Kurata[1,2]
1 Department of Bioscience and Bioinformatics, Kyushu Institute of Technology
680-4 Kawazu, Iizuka, Fukuoka, 820-8502, Japan
2Biomedical Informatics R&D Center (BMIRC), Kyushu Institute of Technology,
680-4 Kawazu, Iizuka, Fukuoka, 820-8502, Japan

Contact: kurata@bio.kyutech.ac.jp Tel&Fax 81-948-29-7828

Systems biology aims to understand how all the cellular molecules work in concert as a living system. An attempt to clarify the dynamics within cells not only predicts the consequences for genetic or environmental changes, but also analyze some design principles underlying their molecular architectures, e.g., a mechanism of how cells acquire complex systems showing robust properties to strict environmental variations. We have been developing the CADLIVE system that implements various application modules to perform both the topological and dynamic analyses for biological systems (http://www.cadlive.jp). For CADLIVE, regulator-reaction equations written in the 'sanac' format, which is an extension of SBML, connect these application modules directly.

In this study, as an extension of CADLIVE, we develop a new application, CADLIVE Toolbox, for mathematical modeling, simulation, parameter estimation and robustness analysis. This application works on MATLAB. A network model of a biological system created in CADLIVE is automatically converted into a mathematical model and subsequently the dynamic behaviors of the system are simulated. This application has two-phase search (TPS) and quasi-multiparameter sensitivity (QMPS) to estimate the values of unknown kinetic parameters that determine the dynamic behavior of the systems and to measure a robust property of the model to the uncertainty of all kinetic parameters, respectively. These algorithms greatly facilitate simulating and analyzing a biological system, resulting in the increased efficiency for the research of systems biology. The CADLIVE toolbox is a powerful tool for constructing, simulating, and optimizing a mathematical model in biological systems and analyzing parameter space and robustness of it.

Quasi-multiparameter sensitivity analysis reveals mechanisms to enhance robustness in circadian oscillators

Kazuhiro Maeda[1] and Hiroyuki Kurata[1]

1 Department of Bioscience and Bioinformatics, Kyushu Institute of Technology
680-4 Kawazu, Iizuka, Fukuoka,820-8502, Japan

Contact: kurata@bio.kyutech.ac.jp Tel&Fax 81-948-29-7828

Many organisms ranging from cyanobacteria to mammals have evolved molecular clocks to anticipate daily changes in the environment. Although a simple transcription-translation feedback loop is sufficient for sustained oscillations, circadian clocks implement complicated feedback loops. In general, selection of types of feedback loops is suggested to affect the robustness of circadian rhythms. A current problem is to reveal the mechanism by which such a complex feedback system evolves.

Mathematical models for circadian clocks have been extensively studied. However, the simulated results of most studies depend on a particular choice of kinetic parameters, while not only network topology but also parameter values alter the system's features. To understand the exact properties of circadian clocks, it is necessary to search all plausible kinetic parameter sets that generate circadian oscillations and to characterize the features of the oscillators with them. To efficiently perform such tasks, we previously developed the two-phase search (TPS) method as a fast and non-biased search method and proposed quasi-multiparameter sensitivity (QMPS) as a fast and exact measure of robustness to uncertainty of all kinetic parameters.

By using TPS and QMPS we quantify the robustness of feedback loops with various topological features. Mathematical comparison among models with various lengths of feedback loops reveals that long feedback loops make circadian oscillations robust. We also demonstrate that the dual loop architecture has the potential to provide the most robust oscillator to multiple parameter perturbations. Interestingly, symmetry in the dual loop architecture enhances the robustness. This result is supported by the fact that kinetically symmetric dual feedback structure has been found in the *Drosophila* circadian core system.

Modeling of the metabolic regulation of microbe such as *Escherichia coli* for the transition from aerobic to anaerobic condition

Yu Matsuoka[1], Kazuyuki Shimizu[1,2], Hiroyuki Kurata[1]

[1] *Department of Bioscience and Bioinformatics, Kyushu Institute of Technology, Iizuka, Fukuoka, 820-8502, Japan*

[2]*Institute of Advanced Bioscience, Keio University, Tsuruoka, Yamagata 997-0017, Japan*

Contact: kurata@bio.kyutech.ac.jp Tel&Fax 81-948-29-7828

Escherichia coli contains several metabolic regulation mechanisms to cope with the changes in culture environment and/or genetic perturbations. These mechanisms consist of several levels such as gene level via transcription factors, enzyme level, and flux level etc. It is quite important to understand these mechanisms for the interpretation of the fermentation data. Among various types of metabolic regulations, catabolite regulation and oxygen level regulation are by far important from the practical application point of view. Although several attempts have been made for the modeling of catabolite regulation [1,2], the modeling approach for oxygen level regulation is limited. Here, we therefore, consider the modeling of oxygen level regulation as well as catabolite regulation.

Under limited oxygen level, the two global regulators such as Fnr and ArcA/B play essential roles for the metabolic regulation, where the direct oxygen sensor Fnr regulates the expressions of metabolic pathway genes under anaerobic condition, while ArcA/B regulates them under both microaerobic and anaerobic conditions. The phosphorylated ArcA represses the TCA cycle and glyoxylate pathway genes.

In the present investigation, we attempted to simulate effect of oxygen level, where we considered a mathematical model which can describe the transition from aerobiosis to anaerobiosis by taking into account the roles of global regulators such as ArcA/B and Fnr, as well as the catabolite regulation.

[1] Bettenbrock, K., Fischer, S., Klemling, A., Sauter, F.T., Gilles, E.D. 2006. A quantitative approach to catabolite repression in *Escherichia coli*. J. Biol. Chem. 281, 2578-2584.

[2] Kotte, O., Zaugg, J.B., Heinemann, M. 2010. Bacterial adaptation through distributed sensing of metabolic fluxes. Mol. Sys. Biol. 6:355.

Catabolite regulation and its modulation by the specific gene mutations in *Escherichia coli* for the case of multiple carbon sources

Ruilian Yao[1], Kazuyuki Shimizu[1,2], Hiroyuki Kurata[1]

[1] *Department of Bioscience and Bioinformatics, Kyushu Institute of Technology, Iizuka, Fukuoka, 820-8502, Japan*

[2]*Institute of Advanced Bioscience, Keio University, Tsuruoka, Yamagata 997-0017, Japan*

Contact: kurata@bio.kyutech.ac.jp Tel&Fax 81-948-29-7828

The living organisms must survive in response to the variety of environmental perturbations by manipulating the cell system with sensing external and internal states, where the transcriptional control of the metabolism is of primal importance. In particular, transcription factors play essential roles for this. Among the culture environment, carbon source is by far important in practice. In particular, from the practical application point of view of utilizing lignocellulose or waste for the production of biofuels etc., it is strongly desirable to understand the catabolic regulation mechanism for the efficient use of multiple carbon sources. Most organisms consume glucose prior to consumption of other carbon sources, and exhibit diauxic growth by the so-called catabolite repression. The center for this regulation is the phosphotransferase systems (PTSs), and cAMP-Crp plays an essential role for catabolite regulation in the case of multiple carbon sources. Moreover, another global regulator Cra (catabolite repressor/activator) controls the carbon flow by sensing the cytosolic F1,6BP level in the metabolic network. In order to make clear the catabolite regulation mechanism, the effect of *crp* gene knockout (Δ*crp*) and crp enhancement (crp^+) as well as *mlc*, *mgsA*, *pgi* and *ptsG* gene knockout on the metabolism was investigated by the continuous culture at the dilution rate of 0.2 h^{-1} as well as by batch cultures. Also, the effects of *cra* gene knockout (Δ*cra*) and the enhancement of *crp* (crp^+) on the batch cultivation characteristics were investigated for a mixture of carbon sources such as glucose, fructose, and xylose under both aerobic and anaerobic conditions. The result indicates that the simultaneous consumption of multiple carbon sources such as glucose and fructose (but not glucose and xylose) can be attained with fructose to be consumed faster than glucose in *cra* mutant due to the decrease in *crp* level.

Data Preparation in Analyzing Metabolic Fluxes

Noorlin Mohd Ali[1], Tsuboi Ryo[1], Matsumoto Yuta[1], Koishi Daisuke[1], Kentaro Inoue[1], and Hiroyuki Kurata[1]

1 Department of Bioscience and Bioinformatics, Kyushu Institute of Technology
680-4 Kawazu, Iizuka, Fukuoka, 820-8502, Japan

Contact: kurata@bio.kyutech.ac.jp Tel&Fax 81-948-29-7828

A regulatory network system is formed based on the interaction of various levels, i.e. gene expression, protein-protein interaction and intracellular metabolite concentrations. The interaction of these levels is in response to the environmental and genetic changes. As for the consequence of this process, metabolic flux distribution is produced. To analyze and estimate this flux distribution, it is shown that the integration of heterogeneous data becomes important.

We have collected many metabolic pathway maps of *Escherichia coli* (*E. coli*) from original publications as a preliminary effort in creating a database. From these publications, at least one metabolite file is made according to the original experimental condition. In preparing the data for analysis task, we extracted the information on experimental condition, reactions, and metabolites from each metabolic model. All data files is prepared in same procedure for Elementary Mode (EM) analysis. Initially, 41 data files are presented and will be added timely. For the purpose of data reliability, these data are tested on Genetic Modification of Flux (GMF) [1] [2], an algorithm that predicts the flux distribution of gene knockout mutants. This algorithm is performed by utilizing the EM analysis in connecting various network levels.

We present the results by comparing the flux predictions for wild type and genetic mutants in several *E.coli* cellular metabolic network models.

Particle simulation of alveolar bone regeneration and angiogenesis -Study on basic model-

Kenta Kisu [1], Katsuya Nagayama [1], Masato Matuo [2]

1 Department of Mechanical Information Science and Technology, Kyushu Institute of Technology, Japan

2 Department of Oral Anatomy, Kanagawa Dental College, Japan

Contact: m674111k@iizuka.isc.kyutech.ac.jp Tel&Fax 0948-29-7771

Introduction

Blood vessels are required to supply the calcium for bone growth, and the movement of calcium is carried out continuously between bone and blood vessels. Also, while the blood vessels supply the calcium, bone is formed along the collagen fibers. In this way, bone and blood vessels grow due to the interaction of each other, and bone is especially classified as bone formation factor and bone absorption factor. It is difficult to observe the image from the appearance of the tooth bone regeneration and angiogenesis, so it needs to be investigated the phenomena by numerical analysis.

Analysis model

We investigated using the particle model on phenomena due to the interaction of bone regeneration and angiogenesis. Particle model is a method of analyzing particles by moving the calculation points to track the movement of the particles. Here the particles has a broad meaning until tissue pieces from individual cells or groups of cells, both treated particles containing particles that do not contain blood vessels and blood vessels.

Results and future work

In this study, we established each basic model of bone formation and angiogenesis.

As a result, we have confirmed that the angiogenesis blood vessels extend toward the maximum value in the region of attraction clot, vascular network is not joined to each other while branching blood vessels are formed. Furthermore, in the process of bone regeneration tooth, pattern of bone formation in alveolar bone after tooth extraction was confirmed by introducing dynamics factors of the reaction-diffusion, bone morphogenetic protein, bone absorption factors. In the future, consider a model that takes into account the influence of VEGF concentration and calcium to perform coupled analysis of angiogenesis and bone formation inside the alveolar bone after tooth extraction, and interaction with vascular bone and teeth. We will also perform verification and comparison with the real image of the alveolar bone.

Numerical simulation of epidermal skin formation using particle model

Takahiro Uehara[1] , Katsuya Nagayama[1] , Yasuko Amano[2] , Masanori Tanahashi[2]
1 Kyushu Institute of Technology, 2 Kao Corporation

Skin is the largest organ of the human body. We can check for an epidermis condition and provide appropriate care, especially since epidermis is the most outside part of the skin. In recent years, concern about the cosmetics field is increasing very much regardless of man and woman, and researches on anti-aging therapy or cosmetics were done briskly.

The epidermis consists of four layers of various differentiation statues. A basal layer, one of the layer which comprises epidermis, plays a role in providing new cells.

The divided cells move toward the skin surface, differentiated into stratum corneum and finally detached from skin surface. Skin cells are not only changing its shape but also physical properties during this process. In order to further understand the mechanisms of skin development, computational simulation can be useful. It was difficult by the conventional analysis technique to change parameters in the middle of analysis once values were set in the beginning. A particle model, with which each particle follows designated algorisms, is suitable method to simulate skin formation. Therefore, we applied the particle model in simulating three-dimensional skin formation accompanied by proliferation and cornification of skin cells. Algorisms were set in consideration of the influences of the cells of different physical properties and the structural changes of the cell. Simulated results could visualize and predict the phenomenon of turnover of the epidermis. The model will be expected as a diagnostic tool of the beauty of skin.

Particle simulation of cancer growth and angiogenesis -based on the image of rabbit ear-

Yuki Oshiumi[1] and Katsuya Nagayama[1] and Ichiro Miura[2]
1 Division of Mechanical Information Science and Technology, Kyushu Institute of Technology
680-4 Kawazu, Iizuka, Fukuoka,820-8502, Japan
2 Department of Human Pathophysiology, Faculty of Medicine, Juntendo University

Contact: nagayama@mse.kyutech.ac.jp Tel&Fax 81-948-29-7778

The purpose of this study is to elucidate of cancer growth phenomenon and to support to the development of treatment. The paper presents the development of a simulator that can be expressed in a short period of time the tumor growth observed over long time and difficult. In order to tumor growth, it is necessary to produce new blood vessels to supply nutrients. Tumor angiogenesis has stimulated the production of vascular endothelial growth factor by cells. In this way, there is a close relationship between tumor growth and angiogenesis, the growth by interaction. In this study, we analyze for cancer growth and angiogenesis using the particle model. Particle model is analysis method that .Particle is treated as cancer cells or blood vessels; phenomenon is expressed by the interaction of the particles.

The paper suggests that particle simulation of cancer growth and angiogenesis based on the image. The particle of cancer cells is arranged in the initial vessel shape obtained from two-dimensional X-ray CT images that were observed in the ears of the rabbit cultured tumor (Keiji Umetani, Kentaro Uesugi, Makito Kobatake, Akira Yamamoto, Takenori Yamashita, Shigek iImai Synchrotron radiation microimaging in rabbit models of cancer for preclinical testing, A609(2009)38–49). Cancer growth and angiogenesis were analyzed simultaneously to predict the tumor growth to the present from the initial state. This author compared and evaluated the analysis and the actual phenomenon.

Numerical simulation of liver cell proliferation – basic model

Yusuke Tsuji[1], Masayuki Yumita[1], Katsuya Nagayama[1], Nana Shirakigawa[2] and Hiroyuki Ijima[2]

1 Kyushu Institute of Technology

2 Kyushu University

Contact: nagayama@mse.kyutech.ac.jp Tel&Fax 81-948-29-7778

In recent years, Japanese patients of the viral hepatitis are more than 3 million people. Furthermore, viral hepatitis is said to the people disease in the 21st century. because the patients are increasing. The hepatitis is the state that the cell of the liver was destroyed. The main cause is a virus and a drug, drinking. When a serious organ disease or malfunction are caused by suffering from hepatitis, only cure is organ transplantation at present. Therefore the rebuilding of the liver based on tissue engineering attracts attention now. However, the rebuilding technology is developing, the mechanism is unclear. Our simulation of the organ rebuilding aims at supporting a study of the regenerative medicine in this study. As the first step, we build the analysis model using the particle method this time. The analysis object is a cell of 10μm in diameter in the $1mm^3$.A purpose of this analysis is to elucidate the condition of an increase process and the increase of the cell in the micro range. The parameters such as diffusivity, nourishment density, the nourishment consumption speed of the cell use the parameter obtained from the experiment. At first we compared the theory type (nourishment diffusion equation) with the analysis result of the nourishment diffusion and inspected validity of nourishment diffusion and the nourishment consumption of this analysis. Furthermore, I built an analysis model of the cell proliferation by incorporating an increase, extinction in this model. We will build construction prediction analysis of organ by analyzing more extensive range using this analysis result and model in future.

Numerical simulation of hair formation using particle model

Shogo Matsuoka[1], Katsuya Nagayama[1], Hiroyuki Taguchi[2]
[1]*Kyushu Institute of Technology, 680-4 Kawazu, Iizuka City, Fukuoka, Japan*
[2] *Kao Corporation, 2606 Akabane, Ichikai-machi, Haga-gun Tochigi, Japan*

Contact: nagayama@mse.kyutech.ac.jp Tel&Fax 81-948-29-7778

In recent years, anti-aging, health and beauty, cosmetic and hair diseases attract attention. In particular, the hair has been very important in determining the human appearance. It is hoped that the formation mechanism in the root of hair will be clarified.

Hair repeats the cycle of anagen, telogen and decay with a fixed cycle. In anagen, hair is formed through multiplication and specialization of a cell. This process of hair formation is considered to have affected to elongation rate, thickness, intensity, and form of hair. Therefore, there are many articles of the observation and experiment for skin and hair. However, it is difficult to observe process of formation which happens in hair. This study developed an analysis method of formation of the formative process in roof of hair using a particle model in a 3D domain. Based on this model, numerical simulation on formation process that includes cell division, transformation of cell, and keratinization was carried out. The validity of the analysis was verified comparing with the actual structure of the hair.

This analysis model is considered using the particle model. Particle model treats particles as moving calculation points and the movements of the particles are traced. This method is suitable for analysis with the large deformation or the number of calculation point is changing. The cellular particles move in response to the influence of pressure and spring force. The pressure works to keep the distance of particles. The spring force works to make the continuum of the cellular particles structural.
We inspect the validity of the model by comparison between volume of the analysis model with the change of the particle shape and theoretical value, comparison of the growth rate with the real hair and comparison with the photograph of the cross-section.

Development of image registration techniques and its application to medical fields

Hyoungseop Kim, Joo Kooi Tan, Seiji Ishikawa
Department of Mechanical and Control Engineering, Kyushu Institute of Technology
1-1, Sensui, Tobata, Kitakyushu, Fukuoka, 804-8550 Japan

Contact: kim@cntl.kyutech.ac.jp, Tel: +81-93-884-3185, Fax: +81-93-861-1159

Introduction

Image processing is one of key technologies in biomedical engineering, computer vision, computer graphics etc. In recent years, with the increasing interest in the field of computer vision and image processing, the development of an efficient recognition system for abnormalities in the medical fields has become an indispensable part of the intelligent systems. There are two main streams, 2-D and 3-D (or 4-D) on medical image processing fields. Especially, there are many applications such as 3-D computer graphics which is used a 3-D representation of geometric data by using rending and 3-D modeling techniques.

On the other hand, medical staffs can easily observe human subject as real images in 2-D and/or 3-D. They want to know the patient's subject by observation based on CT (Computed Tomography), MRI (Magnetic Resonance Imaging), US (Ultra Sound) image. Especially, 3-D image has progressively developed and its application is being more and more widely used in the clinical fields. The 3-D image processing technique can give the powerful and flexible tools for 3-D image processing, analysis and visualization tools to radiologists. There are many software vendors to contribute tools for simulation, surgical planning, visualization and quantitative analyzing. It has been developed and implemented in almost every modern tomographic modality such as, CT, MRI, and US image etc.

We had developed some application software for computer aided diagnosis (CAD) system based on image registration technique. and it application for medical imaging software. In this paper, we show two registration techniques: rigid and non-rigid image registration method.

Temporal subtraction technique

Lung cancer has become the primary cause of cancer related deaths in the world, and its early diagnosis and detection are important for improving the chances of survival. In order to detect the lung cancer a temporal subtraction technique has been introduced in the medical field. The temporal subtraction image is obtained by subtraction of a previous image from a current one. It can be used for enhancing the interval changes such as formation of new lesions and changes in existing abnormalities on medical images by removing most of the normal structures. Moreover, some CAD systems with temporal subtraction of time series in chest radiographs have been developed [1]. Despite of these efforts, subtraction artifacts are still remains on the temporal subtraction images. To achieve a temporal subtraction image with high accuracy, we propose a new image registration method based on generalized gradient vector flow (GGVF) [2] and convergence index filter algorithms.

In this paper, we show a new registration method to remove subtraction artifacts on temporal subtraction image which is obtained previous and current CT image set. Our computerized scheme for image registration form differential two image serious included five steps, mainly: 1) applying preprocessing techniques including normalization of the voxel size and segmentation of lung region on each image serious, 2) global matching by gravity point of lung region, 3) local matching by vector convergent image based on GGVF, 4) smoothing of shift vectors by using a 3-D elastic matching technique, and 5) create a warping image based on voxel matching technique [1]. In this paper, we applied the GGVF and convergence index filter algorithms to remove subtraction artifacts. The voxel matching technique, on the other hand, is a method for enhancing temporal changes. It can detect nodule candidates from the temporal subtraction image.

Optimal image registration for Cyberknife based on ICP algorithm

Image registration is the most important problem and a fundamental task in medical image analysis, computer vision, etc. Medical doctor can analyze and detect the abnormalities and register the image by use of human expert knowledge employing their anatomical knowledge even if complex and difficult problem. In the medical image processing field, some image registration techniques are proposed to find a geometrical transformation that relates the points of an image to their corresponding points of another image.

When multi modal images are used in same patient determining the transformation to register the images is necessary. It is difficult to align the different image. To improve the accuracy and efficiency of registration many researchers introduced their methods on the image processing and computer vision. There are two types of registration method which are obtained from same modality and different modality. In recent years, multi-modal image registration techniques are

proposed for analyzing the different modal images. Especially, CT and MR imaging of the head for diagnosis and surgical planning indicate that physicians and surgeons gain important information from these modalities. In general, in order to register two images, physicians segment the volumes of interest from each set of slices manually. However, manual segmentation of the object area may require several hours for analyzing. Therefore, manual segmentation and registration method cannot be applied for clinical application of the head CT and MR images.

In order to register the two types of images, many automatic and/or semi-automatic image registration methods have been proposed. Fitzpatrick *et al.*[3] proposed a visual assessment of accuracy of retrospective registration techniques. Ding *et al.*[4] proposed the volume image registration by template matching. Furthermore, the mutual information methods have appeared as one of the important technique as multi modal registration (CT and PET, CT and MRI) in medical image processing. Also Maes *et al.* [5] proposed an image registration method by use of maximization of mutual information. The method employed the multi direction set method (Powell's method) [6] request transformation parameters for image registration in three dimension (3-D). But the method needed long processing time for image registration. The other methods also required processing time for registration or manual operation, too. To overcome those problems, we propose an automatic image registration technique.

In this paper, we show a new method for automatic registration of head CT and MR images by using ICP (iterative closest point) algorithm [7] in several extracted data and maximization of mutual information. One of the benefits of using the ICP algorithm is that computational costs can be reduced on the registration. The primary objective of this study is to increase the registration accuracy and reduce the computational processing time. The technique is applied to five real image sets which are obtained from the two different modalities and the satisfactory results are obtained. We believe this registration system makes it possible to improve the registration accuracy to align the CT and MR image of head.

Conclusion

In summary, we had presented image registration methods based on rigid and non-rigid image processing techniques and its application to medical fields. We believe that the proposed image registration techniques and displayed abnormalities on to screen for supporting to radiologists is useful tools for early diagnosis in CAD system.

Acknowledgement

This work is partly supported by the Biomedical Informatics R&D Center from Kyushu Institute of Technology Japan.

Reference

[1] Itai et al., “Development of a voxel matching technique for substantial reduction of subtraction artifacts in temporal subtraction images obtained from thoracic MDCT”, *J Digital Imaging*, **23**(1), pp.31-38, 2010.

[2] C. Xu et al., “Generalized Gradient Vector Flow External Forces for Active Contours”, Signal Processing, **71**(2), pp.131-139, 1998.

[3] J. M. Fitzpatrick, D. L. G. Hill, Y. Shyr, J. West, C. Studholme and C. R. Maurer, Jr., “Visual Assessment of the Accuracy of Retrospective Registration of MR and CT Images of the Brain”, *IEEE Transactions on Medical Imag*., vol.17, no.4, pp.571-585, 1998.

[4] L. Ding, A. Goshtasby and M. Satter, “Volume Image Registration by Template Matching”, *Image and Vision Computing*, vol.19, no.12, pp.821-832, 2001.

[5] F. Maes, A. Collignon, D. Vandermeulen, G. Marchal and P. Suetens, “Multimodality Image Registration by Maximization of Mutual Information”, *IEEE Trans. on Medical Imaging*, vol.16, no.2, pp.187-198, 1997.

[6] W. H. Press, S. A. Teukolsky, W. T. Vetterling and B. P. Flannery, *Numerical Recipes in C*, 2nd Ed, Cambridge Univ. Press, pp.412-419, 1993.

[7] Paul J. Besl, et al. “A Method for Registration of 3-D Shapes”, *IEEE Transactions on pattern analysis and machine intelligence*, vol.14, no.2, 1992.

Enzyme- and DNA-assisted natural computing approaches for simple polynomial algebra over fields

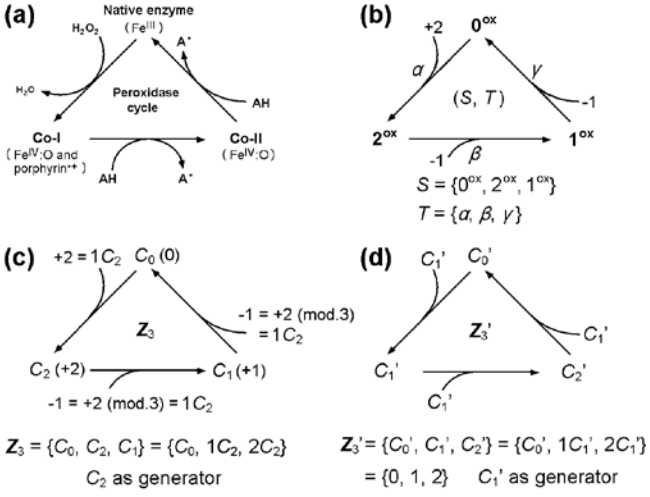
Tomonori Kawano[1,2]

1 Faculty of Environmental Engineering, The University of Kitakyushu, Kitakyushu 808-0135, Japan.

2 University of Florence LINV Kitakyushu Research Center (LINV@Kitakyushu), Kitakyushu 808-0134, Japan.

Contact: kawanotom@kitakyu-u.ac.jp Tel 81-93-695-3207 Fax 81-93-695-3304

Biocomputing is a recently growing and highly interdisciplinary field of research that investigates models and computational techniques inspired by biology and related sciences. Here, cyclic behavior (redox cycling) of purified horseradish peroxidase protein among native enzyme and its two electron-oxidized and single electron-oxidized intermediates known as Compounds I and II was algebraically expressed as a cyclic additive group $\boldsymbol{Z}_3 = \{C_0, C_2, C_1\} = \{C_0, 1C_2, 2C_2\} = \{0, 2, 1\}$, and a cyclic multiplicative group $\boldsymbol{Z}_3^* = \{C_1, C_2\} = \{C_1, C_2^1\} = \{1, 2\}$, with C_2 as the common generator. Above algebraically expressed features of the enzyme's redox cycle was applied to help determining the coefficients in polynomials formed after additive and/or multiplicative operations between polynomial rings $f(x)$ and $g(x)$ over a coefficient field derived from $\boldsymbol{Z}_3$. Similarly, use of a pair of small DNA molecules was proposed for determining the coefficients for additively and multiplicatively obtained polynomials over F, $(\boldsymbol{Z}_2; +, \times)$; where $\boldsymbol{Z}_2 = \{C_0, C_1\} = \{0, 1\}$. Discussion include the required designs of two distinct DNA molecules for performing binary logical conjunction (AND) and exclusive disjunction (XOR), upon polymerase-chain reactions.



Spectroscopic analysis of the model color filters used for CIELAB-based optical logic gate demonstrations

Kiyoshi Moritaka[1] and Tomonori Kawano[1]

1 Faculty and Graduate School of Environmental Engineering, The University of Kitakyushu, Kitakyushu, 808-0135, Japan

Contact: kawanotom@kitakyu-u.ac.jp Tel 81-93-695-3207 Fax 81-93-695-3304

In recent decades, a number of researchers have been engaged in the study of natural computing systems which employ physical, chemical and biological phenomena as the direct media for manifesting the computation. Among such attempts, the studies focusing on the use of lights as key components of computation attracted the attention by researchers and engineers since these studies are potentially applicable to the signal processing through optical interconnections between electronic devices. The team of authors has been engaged to development of CIELAB-based printable and computable color codes possibly used for novel optical logic gate system as one of natural computing approaches. Our recent works include the use of CIELAB-coded colors for Boolean conjunction (AND operations) with color codes printed on papers and transparent films. In addition, colored reflectors were also used for conjunction, disjunction and/or masking of colors printed on the films. Above approaches provide an interesting unplugged color computing models by which Boolean operation of colors can be achieved simply by overlaying a color code-printed film over colored films, paper or reflectors. Here, we have spectroscopically analyzed the modes of color-conjunction using a pair of films with model color codes. Finally, future developments of enhanced noise-tolerant color codes are discussed.

Micro-robotic approach for development of photo-responsive micro-particle transportation system using the living cells of green paramecia

Kohei Otsuka[1] and Tomonori Kawano[1]

1 Faculty and Graduate School of Environmental Engineering, The University of Kitakyushu, Kitakyushu, 808-0135, Japan

Contact: kawanotom@kitakyu-u.ac.jp Tel 81-93-695-3207 Fax 81-93-695-3304

Recently, the areas of micro-robotic studies have been expanded to cover the use of living microorganisms as model target materials controllable within the micro-sized systems. Some researchers have described the cells of *Paramecium* species as “swimming sensory cells” or “swimming neurons” applicable to micro-biorobotics. We employed the cells of green paramecia (*Paramecium bursaria)* as a working model for micro-robotic study. Green paramecia can be found in fresh water environments such as rivers, ponds, and lakes. Cells of green paramecia may fulfill two key criteria to be used as the photo-controllable micro-particle carriers. Firstly, the green paramecia can be attracted or repelled by light stimuli. Secondly, into a single cell of green paramecia, micro-particles (sized *ca.* 2-10 μm in diameter) can be loaded to and packed within, by replacing the natural symbiotic green algae. The types of cellular behaviors positively and negatively responsive to light, are known as phototactic and photorepellent responses, respectively. Here, we report on our novel demonstration of the photo-driven micro-particle transportation using green paramecia.

A study on real-time finger character recognition using Kinect

Kai Inoue[1] and Takeshi Saitoh[1]

1 Department of Systems Design and Informatics, Kyushu Institute of Technology

680-4 Kawazu, Iizuka, Fukuoka, 820-8502, Japan

Contact: saitoh@ces.kyutech.ac.jp Tel&Fax 81-948-29-7713

It has been reported that there are 70 million hearing-impaired persons in the world, and 276,000 hearing-impaired persons in Japan. These persons use a sign language as the communication method. However, many hearing persons do not use sign language. In order to support the smooth communication between a hearing-impaired person and a hearing person, our goal is to develop a sign language recognition system. In this research we propose a finger character recognition method using Microsoft Kinect. Finger character is a method of spelling words using hand shape and its movements. Kinect is a motion sensing input device by Microsoft.

In our proposed method, we automatically extract the right hand region from depth image which captured by Kinect. Next, we calculate six features of number of finger, aspect ratio, area ratio between bounding rectangle and hand region, roundness, range ratio, and Fourier descriptors. These features are fed to SVMs. In order to prevent wrong recognition in a real-time process, we implement two functions of motionless judge process and voting process.

We set 41 Japanese finger characters without a motion as the recognition target as shown in Figure 1, and the evaluation experiments were carried out with five subjects. As the results, we obtained the recognition rate of 95% of person dependent recognition, and 53% of person independent recognition.

Figure 1: 41 Japanese finger characters.

Gaze point detection using inside-out camera

Junki Iwagami[1] and Takeshi Saitoh[1]
1 Department of Systems Design and Informatics, Kyushu Institute of Technology
680-4 Kawazu, Iizuka, Fukuoka, 820-8502, Japan

Contact: saitoh@ces.kyutech.ac.jp Tel&Fax 81-948-29-7713

First Person Vision, which attempts to understand a user's behavioral intention, requires information on the user's state and on what the person is looking at. We propose an inside-out camera that simultaneously obtains image of the user's eye and image of that user's visual field, and propose a method for estimating the user's gaze point based on the configuration of the camera.

The inside-out camera uses two USB cameras, one is called the eye camera which captures the user's eye and the other is called the scene camera which captures the user's visual field. The left image of figure 1 shows a photo that a user wears developed the inside-out camera.

In the proposed method, we first extract a center point P_E of the pupil from an image of the eye camera. The middle image of figure 1 shows the eye image overlaid the extracted pupil. Next, we estimate a gaze point G_o using P_E. To estimate G_o, our method requires a calibration task for user, and calculate the relationship between P_E and G_o. After estimating G_o, scene camera image is emphasized using G_o. The right image of figure 1 shows the scene camera image.

We have not evaluate our method quantitatively yet. Thus, our future work is to evaluate our method with various experiments, and indicate the effectiveness of our method.

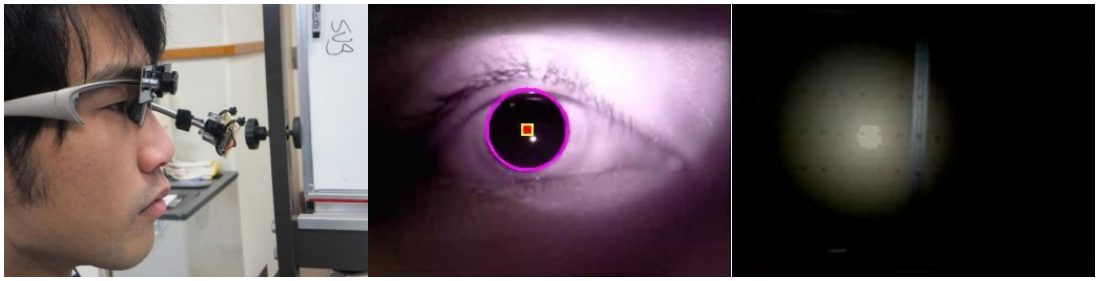


Figure 1: Left: developed the inside-out camera, middle: eye camera image overlaid the extracted pupil, right: scene camera image emphasized the gaze point.

Neuronal rhythm and long-term potentiation modulated by the circadian cycle in rat hippocampal slices

Hiroki Nakatsuka [1] and Kiyohisa Natsume [1]

1 Graduate School of Life Science and Systems Engineering, Kyushu Institute of Technology, 2-4Hibikino, Kita-Kyushu, Fukuoka, 808-0196, Japan

Contact: natume@brain.kyutech.ac.jp, Tel & Fax 81-93-695-6094

Brain has circadian rhythm and the rhythm affects the neuronal activities. Cholinergic receptor agonist carbachol induces β oscillation intermittently in rat hippocampal slices. In the present paper, whether the carbachol-induced β oscillation is modulated in the light- and dark-phase or not was studied. First, we checked if long-term potentiation (LTP) induced by theta burst stimulation was altered in the light and dark phases. LTP of population spike (PS) amplitude at CA1 synapse in hippocampal slices which were derived from the rat brains in the dark phase was larger than that in the light phase. Next, we recorded carbachol induced β oscillations in slices from both phases. The frequency, duration and amplitude of the oscillations in the light- and dark-phase slices are not significantly different. On the other hand, the inter-burst interval (IBI) in the dark-phase slices was significantly shorter than that in the light-phase slices. A $GABA_A$ receptor antagonist SR95531 significantly shortened IBI of the oscillation in the light-phase slices, while it did not change it in the dark-phase slices. Melatonin also shortened IBI in the light-phase slices. Because carbachol-induced β oscillation generates in CA3 neuronal network, these results suggest that the activity of inhibitory interneurons in hippocampal CA3 will increase in the light phase by melatonin secreted from pineal gland, and melatonin can modulate the neuronal rhythm induced in hippocampus accompanying the modulation of LTP.

At CA1 region, there are two types of inhibitory neurons, one is feed-forward type, and the other is feedback type. Which type of inhibitory neurons can be modulated by the circadian rhythm was clarified by induction of long-term potentiation (LTP). From CA1 region LTPs of population spike (PS) and population excitatory postsynaptic potential (pEPSP) are recorded, and feedback and feed-forward inhibitory neurons are involved in the modulation of PS and pEPSP LTP, respectively. From our results, PS LTP was modulated by circadian rhythm while pEPSP LTP was not. The results suggest that the feedback inhibitory neurons in CA1 can be modulated by the circadian rhythm.

Index

T

U

V

Y

Z