Health Intelligence Center

Division of Health Medical Data Science
健康医療データサイエンス分野

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Our mission is to utilize genomic big data and time series health medical data to realize methods for prediction and prevention of diseases and keeping/improving our health. For this purpose, we develop novel computational data analysis technologies by integrating Bayesian statistical theory and high-performance computing on supercomputer system.

1. Development of Computational Platform for Clinical Sequence and Interpretation

Shimizu E, Kasajima R, Yamaguchi K, Yokoyama K, Komura M, Saito A, Kobayashi M, Yuji K, Takane K, Shibuya T, Hasegawa T, Miyagi Y, Muto K, Tojo A, Furukawa Y, Miyano S, Yamaguchi R, Imoto S

From April 2015, Medical Genomics Research Initiative The University of Tokyo is launched. For implementing clinical sequence in the Institute of Medical Science, we formed a team of researchers and technicians who have various academic backgrounds including medicine, biology, pharmacology, genetics, statistics, computer science, ethics, etc. A highly secure infrastructure for analyzing personal genome was constructed; in the space, next generation sequencers are directly connected to a part (disconnect to internet) of supercomputer system in Human Genome Center and, for keeping traceability, laboratory information management system (LIMS) is installed to record all logs of wet experiments and computational analyses. Together with genome analysis in clinical sequence, we now intensively focus on a method for interpreting personal genome information. In July 2015, we started to use IBM Watson for cancer research to interpret the results of genome analyses. The results of genome sequence analysis including the interpretation of IBM Watson are evaluated and discussed in biweekly sequence board meeting. In 2016, we analyzed around sequence data of 100 cancer patients (more than 250 sequencing samples) with whole genome, exome, target deep sequencings. Also, multi-omics data including genome, transcriptome and epigenome were measured for integrative analysis that has the potential to achieve highly precise interpretation. This research is also performed as a part of the University of Tokyo's Center of Innovation (COI) project "Self-Managing Healthy Society".

2. Health Medical big data analysis

a. Integration of the records of health examination, microbiome and genomic data for predicting disease risks

Hasegawa T, Kakuta M, Yamaguchi R, Imoto S

Owing to increasing medical expenses, researchers have attempted to grasp clinical signs and preventive measures of diseases using electronic health record (EHR). In particular, time-series EHRs collected by periodic medical check-up enable us to

clarify the relevance among check-up results and individual environmental factors such as lifestyle. However, usually such time-series data have many missing observations and some results are strongly correlated to each other. These problems make the analysis difficult and there exists strong demand to detect clinical findings beyond them.

We focus on blood test values in medical check-up results and apply a time-series analysis methodology using a state space model. It can infer the internal medical states emerged in blood test values and handle missing observations. The estimated models enable us to predict one's blood test values under specified condition and predict the effect of intervention, such as changes of body composition and lifestyle.

We use time-series data of EHRs periodically collected in the Hirosaki cohort study in Japan and elucidate the effect of 17 environmental factors to 38 blood test values. Using the estimated model, we then simulate and compare time-transitions of participant's blood test values under several lifestyle scenarios. It visualizes the impact of lifestyle changes for the prevention of diseases. Finally, we exemplify that prediction errors under participant's actual lifestyle can be partially explained by genetic variations, and some of their effects have not been investigated by traditional association studies.

3. Computational Methods in Systems Biology and Immunology

a. Adaptive NetworkProfiler for identifying cancer characteristic-specific gene regulatory networks.

Park H[1], Shimamura T[2], Imoto S, Miyano S: [1]Faculty of Global and Science Studies, Yamaguchi University, [2]Graduate School of Medicine, Nagoya University

There is currently much discussion about sample (patient)-specific gene regulatory network identification, since the efficiently constructed sample-specific gene networks lead to effective personalized cancer therapy. Although statistical approaches have been proposed for inferring gene regulatory networks, the methods cannot reveal sample-specific characteristics because the existing methods, such as an L1-type regularization, provide averaged results for all samples. Thus, we cannot reveal sample-specific characteristics in transcriptional regulatory networks. To settle on this issue, the NetworkProfiler was proposed based on the kernel-based L1-type regularization. The NetworkProfiler imposes a weight on each sample based on the Gaussian kernel function for controlling effect of samples on modeling a target sample, where the amount of weight depends on similarity of cancer characteristics between samples. The method, however, cannot perform gene regulatory network identification well for a target sample in a sparse region (i.e., for a target sample, there are only a few samples having a similar characteristic of the target sample, where the characteristic is considered as a modulator in sample-specific gene network construction), since a constant bandwidth in the Gaussian kernel function cannot effectively group samples for modeling a target sample in sparse region. The cancer characteristics, such as an anti-cancer drug sensitivity, are usually nonuniformly distributed, and thus modeling for samples in a sparse region is also a crucial issue. We propose a novel kernel-based L1-type regularization method based on a modified k-nearest neighbor (KNN)-Gaussian kernel function, called an adaptive NetworkProfiler. By using the modified KNN-Gaussian kernel function, our method provides robust results against the distribution of modulators, and properly groups samples according to a cancer characteristic for sample-specific analysis. Furthermore, we propose a sample-specific generalized cross-validation for choosing the sample-specific tuning parameters in the kernel-based L1-type regularization method. Numerical studies demonstrate that the proposed adaptive NetworkProfiler effectively performs sample-specific gene network construction. We apply the proposed statistical strategy to the publicly available Sanger Genomic data analysis, and extract anti-cancer drug sensitivity-specific gene regulatory networks.

b. Bayesian model for analyzing human leukocyte antigen regions

Hayashi S, Yamaguchi R, Mizuno S[3], Komura M, Miyano S, Nakagawa H[4], Imoto S: [3]Center for Advanced Medical Innovation, Kyushu University, [4]RIKEN Center for Integrative Medical Sciences

Although human leukocyte antigen (HLA) genotyping based on amplicon, whole exome sequence (WES), and RNA sequence data has been achieved in recent years, accurate genotyping from whole genome sequence (WGS) data remains a challenge due to the low depth. Furthermore, there is no method to identify the sequences of unknown HLA types not registered in HLA databases. We developed a Bayesian model, called ALPHLARD, that collects reads potentially generated from HLA genes and accurately determines a pair of HLA types for each of HLA-A, -B, -C, -DPA1, -DPB1, -DQA1, -DQB1, and -DRB1 genes at 3rd field resolution. Furthermore, ALPHLARD can detect rare germline variants not stored in HLA databases and call somatic mutations from paired normal and tumor sequence data. We illustrate the capability of ALPHLARD using 253 WES data and 25 WGS data

from Illumina platforms. By comparing the results of HLA genotyping from SBT and amplicon sequencing methods, ALPHLARD achieved 98.8% for WES data and 98.5% for WGS data at 2nd field resolution. We also detected three somatic point mutations and one case of loss of heterozygosity in the HLA genes from the WGS data. ALPHLARD showed good performance for HLA genotyping even from low-coverage data. It also has a potential to detect rare germline variants and somatic mutations in HLA genes. It would help to fill in the current gaps in HLA reference databases and unveil the immunological significance of somatic mutations identified in HLA genes.

c. An *in silico* automated pipeline to identify tumor specific neoantigens from next generation sequencing data

Hasegawa T, Hayashi S, Shimizu E, Mizuno S, Yamaguchi R, Miyano S, Nakagawa S, Imoto S:

Recent progress of massive parallel sequencing technology enables us to detect somatic mutations in each of cancer patients. It is known that some mutated peptides produced from missense mutations binds to the major histocompatibility complex (MHC). Since MHC presents mutated peptides to anti-tumor T cells, understanding this process is important in cancer immunotherapy. In this paper, we introduce a computational pipeline to predict binding affinity between mutated peptides and MHC molecules to detect neoantigens. We have implemented this pipeline on our supercomputer system. With nonsynonymous substitutions, frameshift insertions and deletions detected and intron retentions from whole-genome or exome sequencing data, we utilize RNA sequencing data and annotation data to make neoantigen detection pipeline more accurate.

4. Metagenome Analysis of Intestinal Microbiome

a. Analysis of intestinal microbiome.

Usui Y, Kimura Y, Satoh T, Takemura N, Ouchi Y, Ohmiya H, Kobayashi K, Suzuki H, Koyama S[5], Hagiwara S, Tanaka H, Imoto S, Eberl G[6], Asami Y[5], Fujimoto K, Uematsu S: [5]Food Science Research Laboratories, R&D Division, Meiji Co., Ltd, [6]Institut Pasteur, Microenvironment and Immunity Unit

The gut is an extremely complicated ecosystem where micro-organisms, nutrients and host cells interact vigorously. Although the function of the intestine and its barrier system weakens with age, some probiotics can potentially prevent age-related intestinal dysfunction. Lactobacillus delbrueckii subsp. bulgaricus 2038 and Streptococcus thermophilus 1131, which are the constituents of LB81 yogurt, are representative probiotics. However, it is unclear whether their long-term intake has a beneficial influence on systemic function. Here, we examined the gut microbiome, fecal metabolites and gene expression profiles of various organs in mice. Although age-related alterations were apparent in them, long-term LB81 yogurt intake led to an increased Bacteroidetes to Firmicutes ratio and elevated abundance of the bacterial family S24-7 (Bacteroidetes), which is known to be associated with butyrate and propanoate production. According to our fecal metabolite analysis to detect enrichment, long-term LB81 yogurt intake altered the intestinal metabolic pathways associated with propanoate and butanoate in the mice. Gene ontology analysis also revealed that long-term LB81 yogurt intake influenced many physiological functions related to the defense response. The profiles of various genes associated with antimicrobial peptides-, tight junctions-, adherens junctions- and mucus-associated intestinal barrier functions were also drastically altered in the LB81 yogurt-fed mice. Thus, long-term intake of LB81 yogurt has the potential to maintain systemic homeostasis, such as the gut barrier function, by controlling the intestinal microbiome and its metabolites.

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Health Intelligence Center

Division of Health Medical Computational Science
健康医療計算科学分野

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The mission of this division is to develop computational science for transforming biomedical data to knowledge. By making full use of supercomputers, we are now focusing on annotation, translation and interpretation of genomic data including RNA sequences for supporting cancer research and clinical sequence.

1. Computational Science for Cancer Research

a. A temporal shift of the evolutionary principle shaping intratumor heterogeneity in colorectal cancer

Saito T[1,3], Niida A, Uchi R[1], Hirata H[1], Komatsu H[1], Sakimura S[1], Hayashi S[2], Nambara S[1], Kuroda Y[1], Ito S[1], Eguchi H[1], Masuda T[1], Sugimachi K[1], Tobo T[1], Nishida H[3], Daa T[3], Chiba K[2], Shiraishi Y[2], Yoshizato T[4], Kodama M[3], Okimoto T[3], Mizukami K[3], Ogawa R[3], Okamoto K[3], Shuto M[3], Fukuda K[3], Matsui Y[5], Shimamura T[5], Hasegawa T[6], Doki Y[7], Nagayama S[8], Yamada K[9], Kato M[10], Shibata T[10,11], Mori M[7], Aburatani H[12], Murakami K[3], Suzuki Y[13], Ogawa S[4], Miyano S, Mimori K[1]: [1]Kyushu University Beppu Hospital, [2]Laboratory of DNA Information Analysis, Human Genome Center, Institute of Medical Science, The University of Tokyo, [3]Oita University Hospital, [4]Kyoto University, [5]Nagoya University Graduate School of Medicine, [6]Division of Health Medical Data Science, Health Intelligence Center, Institute of Medical Science, The University of Tokyo, [7]Osaka University, [8]Cancer Institute Hospital, [9]Takano Hospital, [10]National Cancer Center Research Institute, [11]Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, The University of Tokyo, [12]Research Center for Advanced Science and Technology, The University of Tokyo, [13]Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, The University of Tokyo

Advanced colorectal cancer harbors extensive intratumor heterogeneity shaped by neutral evolution; however, intratumor heterogeneity in colorectal precancerous lesions has been poorly studied. We perform multiregion whole-exome sequencing on ten early colorectal tumors, which contained adenoma and carcinoma in situ. By comparing with sequencing data from advanced colorectal tumors, we show that the early tumors accumulate a higher proportion of subclonal driver mutations than the advanced tumors, which is highlighted by subclonal mutations in KRAS and APC. We also demonstrate that variant allele frequencies of subclonal mutations tend to be higher in early tumors, suggesting that the subclonal mutations are subject to selective sweep in early tumorigenesis while neutral evolution is dominant in advanced ones. This study establishes that the evolutionary principle underlying intratumor heterogeneity shifts from Darwinian to neutral evolution during colorectal tumor progression.

Simulation methodology is employed in this

study by using supercomputers.

b. Cancer evolution and heterogeneity

Mimori K[1], Saito T[1], Niida A, Miyano S

Undoubtedly, intratumor heterogeneity (ITH) is one of the causes of the intractability of cancers. Recently, technological innovation in genomics has promoted studies on ITH in solid tumors and on the pattern and level of diversity, which varies among malignancies. We profiled the genome in multiple regions of nine colorectal cancer (CRC) cases. The most impressive finding was that in the late phase, a parental clone branched into numerous subclones. We found that minor mutations were dominant in advanced CRC named neutral evolution; that is, driver gene aberrations were observed with high proportion in the early - acquired phase, but low in the late-acquired phase. Then, we validated that neutral evolution could cause ITH in advanced CRC by super - computational analysis. According to the clinical findings, we explored a branching evolutionary process model in cancer evolution, which assumes that each tumor cell has cellular automaton. According to the model, we verified factors to foster ITH with neutral evolution in advanced CRC. In this review, we introduce recent advances in the field of ITH including the general component of ITH, clonal selective factors that consolidate the evolutionary process, and a representative clinical application of ITH.

c. Neutral theory in cancer cell population genetics

Niida A, Iwasaki WM[14], Innan H[14]: [14]The Graduate University for Advanced Studies

Kimura's neutral theory provides the whole theoretical basis of the behavior of mutations in a Wright-Fisher population. We here discuss how it can be applied to a cancer cell population, in which there is an increasing interest in genetic variation within a tumor. We explain a couple of fundamental differences between cancer cell populations and asexual organismal populations. Once these differences are taken into account, a number of powerful theoretical tools developed for a Wright-Fisher population could be readily contribute to our deeper understanding of the evolutionary dynamics of cancer cell population.

2. Implementation of Cancer Clinical Sequence

In collaboration with Professor Yoichi Furukawa (Division of Clinical Genome Research, Advanced Clinical Research Center), Professor Arinobu Tojo (Division of Molecular Therapy, Advanced Clinical Research Center), Research Associate Professor Koichiro Yuji (Project Division of International Advanced Medical Research), IMSUT Research Hospital, and Human Genome Center, we have been implementing cancer genomic medicine since 2011. Some reports are published [1,4,8, 11-12]. Use of IBM Watson for Genomics assisted experts who are responsible for diagnosis and therapy.

a. Artificial Intelligence for Cancer Genomic Medicine: Understanding Cancer is Beyond Human Ability

Miyano S

We have been running cancer clinical sequence based on whole genome, whole exome, panels, RNA sequencing and epigenetic analysis at our institute. When focused on hematology/oncology, it takes four days for a patient from signing informed consent (IC) to receiving diagnosis. This five-day process consists of IC, specimen collection, whole exome sequencing, whole exome sequence data analysis, interpretation/translation of mutations by oncologists, determining the diagnosis combined with all pathological data and returning the result (therapy if any) to the patient. Therapies are not only drugs but also hematopoietic stem cell transplantation. A pipeline Genomon for analyzing cancer genomes and RNA sequences by next-generation sequencers plays one of the key roles. It is running on the supercomputer system SHIROKANE at our Human Genome Center. The bottleneck of interpretation/translation was drastically resolved by employing IBM Watson for Genomics in harmony with our in-house human curation pipeline. We report how our system works as a conglomerate of oncologists, cancer biologists, bioinformaticians augmented with Watson and Genomon.

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