Abstracts of the

# *1st* International Symposium on Aihara Moonshot Project

## June 6th – 8th, 2022

This symposium is motivated by our aim to "Realization of Ultra-Early Disease Prediction and Intervention by 2050" as the Moonshot Goal 2, which is supported by MOONSHOT Research & Development Program at the Japan Science and Technology Agency (JST). In this symposium, we would like to discuss how we can detect a "pre-disease" state, which has not yet been precisely defined but suggested as the risky state approaching the timing leaving the normal state of health. Precision medicine at a very early stage is targeted by detection of pre-disease states. For this purpose, we would like to exchange our recent research progresses, including personalized medicine, biological and mathematical modeling, control theory, and data analysis.

Organizers : Keita Iida, Koji Noshita, and Shingo Iwami

## For Registration:

https://u-tokyo-ac-jp.zoom.us/webinar/register/WN_H1l-qa12SlmanmaYsj22sQ

# Program（JST）

## 6th June

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|---|---|
| 15:00 - 15:10 | *Welcome* **Gen Sobue** |
| 15:10 - 15:20 | *Welcome* **Masato Wakayama** |
| 15:20 - 15:40 | *Opening remark* **Kazuyuki Aihara** |
| 15:40 - 16:10 | *"Identification and control of brain dynamics underpinning neuropsychiatric conditions"* **Takamitsu Watanabe** |
| | Break |
| 16:30 - 17:00 | *"Phenotyping studies using morphometric descriptors for multi-omics analysis"* **Koji Noshita** |
| | *Break* |
| 17:10 - 18:00 | *"What TDA can say about the morphology of diseased neurons"* **David Beers** |
| | *Break* |
| 19:10 - 20:00 | *"Topological Flow Data Analysis for Blood Flows Inside a Heart"* **Takashi Sakajo** |
| 20:00 - 20:50 | *"Modelling dynamics in the presence of bounded noise"* **Jeroen S.W. Lamb** |

## 7th June

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|---|---|
| 15:00 - 15:30 | *"Predicting diseases by dynamic network biomarker with network fluctuations"* **Luonan Chen** |
| | *Break* |
| 15:40 - 16:30 | *"Nonequilibrium phase transitions and critical phenomena"* **Eckehard Schöll** |
| | *Break* |
| 17:00 - 17:50 | *"Mechanisms of protective immunity in SARS-CoV-2 infection"* **Miles Davenport** |
| | *Break* |
| 18:00 - 18:30 | *"Modeling and characterizing vaccine-elicited antibody responses"* **Shingo Iwami** |
| | *Break* |
| 19:30 - 20:20 | *"From mechanisms to prediction: Designing personalised treatment strategies for eczema"* **Reiko Tanaka** |
| 20:20 - 20:50 | *"Statistical genetics, disease biology, drug discovery, and personalized medicine"* **Yukinori Okada** |

## 8th June

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|---|---|
| 15:00 - 15:50 | *"Non-genetic heterogeneity arising from biological networks"* **Mariko Okada** |
| | *Break* |
| 16:00 - 16:30 | *"Re-stabilization of gene network systems via pole placement with HDLSS data"* **Xun Shen** |
| | *Break* |
| 17:00 - 17:50 | *"Can we define attractor states in biology?"* **Kumar Selvarajoo** |
| | *Break* |
| 18:00 - 18:30 | *"Understanding the disease-triggering inter-organ crosstalk using a genetic animal model"* **Kazutaka Akagi** |
| | *Break* |
| 19:30 - 20:20 | *"Two new ideas for dynamical time-series analysis"* **Hiroshi Kokubu** |
| 20:20 - 20:50 | *"Clustering single-cell and spatial transcriptomes through multifaceted biological aspects"* **Keita Iida** |
| 20:50 - 21:00 | *Closing remark* |

*1st*
# International Symposium on Aihara Moonshot Project

*Program Director*

## Gen Sobue

Chairperson,
President, Aichi Medical University

*Sub Program Director*

## Masato Wakayama

Fundamental Mathematics Research Principal, NTT Institute for Fundamental Mathematics

Professor Emeritus,
Kyushu University

*Project Manager*

## Kazuyuki Aihara

University Professor,
Professor Emeritus,
The University of Tokyo

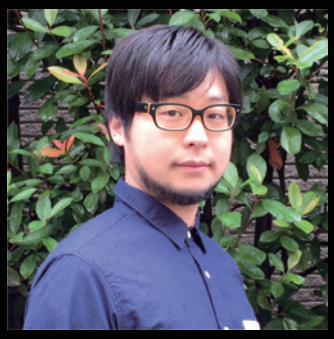
6th 15:40-

## Takamitsu Watanabe / WPI-IRCN The University of Tokyo

### *Identification and control of brain dynamics underpinning neuropsychiatric conditions*

Information processing behind a wide range of complex human cognition is considered to heavily rely on the dynamics of the whole-brain activity patterns. Also, its atypicality seen in neuropsychiatric conditions is often linked with the irregularity of such temporal properties of the macroscopic neural activity. Here, I will first talk about a data-driven manner that enables us to extract the brain dynamics from human neural data obtained by, for example, functional MRI and EEG. The method—so-called energy landscape analysis—can not only identify brain-state dynamics underpinning human intelligence but also pin down neural activity patterns specific to multiple neuropsychiatric conditions, including autism, ADHD and schizophrenia. I will also introduce a novel non-invasive brain stimulation approach that combines the energy landscape analysis with a real-time neural activity processing system. The method can track brain state dynamics almost simultaneously, which allows us to efficiently intervene in such neural dynamics with weaker stimulation and, ultimately, control typical and atypical human cognitive and behavioural tendencies.

6th 16:30-



## Koji Noshita / Kyushu University

### *Phenotyping studies using morphometric descriptors for multi-omics analysis*

The morphological traits of cells, tissues, and organs contribute to functional and disease features. Although the importance of phenotyping techniques for these morphological traits is increasing with advances in multi-omics studies, there are barriers to its advancement, including the gap between measured data and phenotypic values, low quantitativity, and low throughput caused by the lack of models for representing morphological traits.
In this talk, I introduce morphological descriptors that can be used for phenotyping morphological traits. Geometric morphometric approaches pave the way to a general-purpose method applicable to single units. Hierarchical structures composed of an indefinite number of multiple elements, which is often observed in biological structures, can be quantified in terms of their multi-scale topological characteristics. Theoretical morphological models capture specific anatomical structures if recognized. These morphological descriptors provide us with the advantages of model-based phenotyping, including robust quantification of limited datasets.

6th 17:10-

## David Beers / University of Oxford

### *What TDA can say about the morphology of diseased neurons*

The morphology of neurons is important for their function and therefore is often used to classify them. The topological morphology descriptor, a recent method developed to compare neuronal geometry, assigns a morphology descriptor called a barcode to a neuron equipped with a specified function, such as the path distance or Euclidean distance from the root of the neuron. These barcodes can be converted into matrices called persistence images, which can then be averaged across groups and to provide an interpretable summary of morphology. We show that persistence images are stable with respect to perturbations of input data, and introduce topological morphology functions, a class of functions similar to Sholl functions, that can be recovered from the associated topological morphology descriptor. To demonstrate this topological approach, we compare healthy cortical and hippocampal mouse neurons to those affected by progressive tauopathy. We find a significant difference in the morphology of healthy neurons and those with a tauopathy at a postsymptomatic age. We use persistence images to conclude that the diseased group tends to have neurons with shorter branches as well as fewer branches far from the soma.

6th 19:10-

## Takashi Sakajo / Kyoto University

### *Topological Flow Data Analysis for Blood Flows Inside a Heart*

Blood flow in the heart has complex vortex patterns, playing an important role in an efficient blood flow supply from the heart to the organs, and these patterns are disturbed by heart diseases. Recent progress in medical imaging and computer technology yields blood flow visualization tools in echocardiography and cardiac MRI. However, there are still few mathematical theories to clearly define the vortex flow structures such as size and location, or change over time in the main chamber in the heart: the left ventricle, since the flow is highly unsteady and turbulent. Therefore, the efficiency of the physiological function of the heart as a pump and pathophysiological mechanisms of cardiovascular diseases has not been fully revealed yet. Since the function of the vortex blood flow inside the left ventricle has been known to be determined by the mainstream observed in the central plane of the symmetrical anatomy of the left ventricular system, we propose a mathematical theory to extract and classify topological features of the flows in the heart in terms of symbolic graph expressions, called partially cyclically rooted COT representations. Consequently, we identify well-organized vortex flow structures as topological vortex structures, thereby characterizing healthy blood flows as well as inefficient flow patterns in the diseased heart.

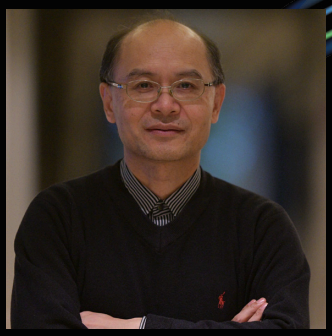
6th 20:00-

## Jeroen S.W. Lamb / Imperial College London

### *Modelling dynamics in the presence of bounded noise*

Mathematical models of dynamics that include "noise" often include rather strong assumptions on the nature of the noise. In particular, a common assumption is that the noise is de facto unbounded. While common assumptions on the nature of noise may facilitate the mathematical analysis, it may also give rise to unrealistic and incorrect models. In this talk, I will discuss ways in which bounded noise may be implemented and what kind of analysis and results can be obtained in this context, specifically in the context of bifurcation.

7th 15:00-



## Luonan Chen / The University of Tokyo

### *Predicting diseases by dynamic network biomarker with network fluctuations*

We develop a DNB (dynamic network biomarker) method with the criterion of network fluctuations, i.e., temporal network flow entropy (TNFE) to detect the critical states of complex diseases on the basis of each individual. By applying this method to a simulated dataset and various real diseases, including respiratory viral infections and tumors with omics data, the critical states before deterioration were detected and their dynamic network biomarkers (DNBs) were identified successfully. The results on the simulated dataset indicate that the TNFE method is robust under different noise strength, and is also superior to the existing methods on detecting the critical states. Moreover, the analysis on the real datasets demonstrated the effectiveness of TNFE for providing early-warning signals on various diseases. In addition, we also predicted disease deterioration risk and identified drug targets for cancers based on stage-wise data.

7th 15:40-

## Eckehard Schöll / Technische Universität Berlin

### *Nonequilibrium phase transitions and critical phenomena*

Phase transitions in nonlinear dynamical systems far from thermodynamic equilibrium have been investigated since the 1970s and 1980s, and concepts from thermodynamics and statistical physics have been applied to describe self-organization, spatio-temporal pattern formation, phase coexistence, critical phenomena, and first and second order nonequilibrium phase transitions [1,2]. Much more recently, phase transitions and critical phenomena have been studied in dynamical networks, where synchronization transitions may arise, giving birth to a plethora of partial synchronization patterns and complex collective behavior, with applications to many physical, chemical, biological, physiological, and technological systems [3,4,5,6].

[1] Haken, H., Synergetics, An Introduction: nonequilibrium phase transitions and self-organization in physics, chemistry, and biology, Springer (1978).

[2] Schöll, E., Nonequilibrium Phase Transitions in Semiconductors, Springer (1987).

[3] Schöll, E., Chimeras in Physics and Biology: Synchronization and Desynchronization of Rhythms, Nova Acta Leopoldina 425, 67 (2020).

[4] Schöll, E., Partial synchronization patterns in brain networks, Europhys. Lett. 136, 18001 (2021).

[5] Berner, R., Yanchuk, S. and Schöll, E., What adaptive neuronal networks teach us about power grids, Phys. Rev. E 103, 042315 (2021).

[6] Berner, R., Sawicki, J., Thiele, M., Löser, T. and Schöll, E., Critical parameters in dynamic network modeling of sepsis, arXiv:2203.13629 (2022).

7th 17:00-

## Miles Davenport / UNSW Sydney

### *Mechanisms of protective immunity in SARS-CoV-2 infection*

Infection with or vaccination against SARS-CoV-2 elicits a variety of immune responses. Identifying which responses predict or mediate protection from reinfection or moderate the severity of infection is an important priority to support future vaccine strategies and to assist in pandemic planning. This requires the integration of data from immunological assays and epidemiological studies to understand mechanisms of immune protection. Neutralising antibodies have been shown to be an important correlate of protection from symptomatic SARS-CoV-2 infection. In addition, passive antibody studies show that antibodies can directly mediate immune protection from severe SARS-CoV-2 infection. Studies are ongoing to identify whether T cell effector mechanisms may also contribute to protection. Meta-analysis and modelling of clinical and experimental data provide an important approach to understanding immunity to SARS-CoV-2 infection.

7th 18:00-

## Shingo Iwami / Nagoya University

### *Modeling and characterizing vaccine-elicited antibody responses*

Recent studies have provided insights into the effect of vaccine boosters on recall immunity. Given a limited global supply of the vaccinations, identifying vulnerable populations with lower sustained vaccine-elicited antibody titers is important to decide target individuals for the booster. Here we investigated longitudinal data among the cohort of the same individuals of 2,526 people in Fukushima, Japan from April 2021 to December 2021. Antibody titers following a two-dose SARS-CoV-2 vaccination were repeatedly monitored along with the information on lifestyle habits, comorbidities, adverse reactions, and medication. By employing mathematical modeling and machine learning, we characterized the elicited immune response following a two-dose SARS-CoV-2 vaccination.

7th 19:30-

## Reiko J. Tanaka / Imperial College London

### *From mechanisms to prediction: Designing personalised treatment strategies for eczema*

Atopic dermatitis (or eczema, AD) is the most common inflammatory skin disease characterised by inflamed, dry and itchy skin leading to substantial quality of life impairment and significant socioeconomic impact. Designing personalised treatment strategies for AD is challenging, given the apparent unpredictability and large variation in AD symptoms and treatment responses within and across individuals. A first step toward developing personalised treatment strategies is to better predict the consequences of possible treatments at an individual level, rather than at population level, to deal with the variability across patients.

We developed a mechanistic model of AD pathogenesis which provided a coherent mechanistic explanation of the dynamic onset, progression, and prevention of AD, as a result of interactions between skin barrier, immune responses and environmental stressors. Model predictive control using the mechanistic model suggested a possibility for designing personalized treatment strategies. We also adapted the structure of the mechanistic model to real patient data and developed a Bayesian mechanistic model tailored to each individual, that can predict the next day’ s AD severity score given their score and treatments used on that day.

These works presented hopes and challenges in designing personalized treatment strategies for AD, for which detailed dynamic data is not often available.

7th 20:20-

## Yukinori Okada / Osaka University / The University of Tokyo / RIKEN Center for IMS

### *Statistical genetics, disease biology, drug discovery, and personalized medicine*

Statistical genetics is a research field that evaluates causality of human genetic variations on diseases, using statistical and bioinformatics approaches. Recent developments of sequencing technologies have provided human disease genome data of hundreds of thousands of the subjects, and successfully identified comprehensive catalogues of genetic susceptible loci. However, little is known regarding how to develop methodology to integrate large-scale human genome data with diverse biological resources. We have developed such methods and applied to a pioneering example of large-scale genetic association studies on a variety of human complex traits. Tran-layer omics analysis identified the cell types and microbiomes implicated in disease biology. Network analysis between the disease risk genes and the drug target genes could identify novel candidates of drug repositioning. Integration of cell type-specific gene expression profiles estimated from GWAS with compound perturbation databases can pinpoint novel therapeutic targets and compounds. Application of the machine learning methods into population genome data can classify the samples without prior biological information. These results should empirically show the value of statistical genetics to dissect disease biology, novel drug discovery, and personalized medicine. Finally, we would like to introduce our activity on young researcher developments ( “Summer school of statistical genetics” in Osaka Univeristy).

8th 15:00-

## Mariko Okada / Institute for Protein Research, Osaka University

### *Non-genetic heterogeneity arising from biological networks*

Signaling networks play an important role in connecting the extracellular environment with intracellular genetic information. NF-kappa B is a transcription factor that regulates the expression of a wide variety of genes in inflammation, cancer and immune systems in response to the environmental changes, and is also known for its threshold and oscillatory dynamics, which are attracting theoretical and experimental attentions. We quantitatively study the dynamics of NF-kappa B and its target gene expression using epigenetic data, live cell imaging and mathematical modeling. Our study reveals that NF-kappa B activates enhancers for gene expression in immune B cells in both cooperative and non-cooperative manners. The cooperative mechanism requires lineage-specific open chromatin DNA regions of B cells for all-or-none gene responses. Imaging analysis together with single RNA-sequence analysis suggests that the enhanced heterogeneity in expression of NF-kappa B target genes is associated with higher-order of macromolecular assembly similar to the mechanism of liquid-liquid phase separation. We propose that this is the one of the origins of non-genetic heterogeneity contributing to clonal expansion of B cells. We also introduce patient-specific modeling that allows us to understand the patient heterogeneity resulting from a cancer signaling network.

8th 16:00-

## Xun Shen / Tokyo Institute of Technology

### *Re-stabilization of gene network systems via pole placement with HDLSS data*

The Dynamical Network Biomarkers (DNBs) theory has been proposed to detect early-warning signals of critical transitions in gene network systems only with High-Dimension Low-Sample-Size (HDLSS) data of the system state. Besides, recent experimental results have shown that the manipulation of multiple DNB gens immediately before critical transitions leads to remarkable changes in malignant phenotypes of lung cancer. Towards giving a theoretical foundation for ultra-early medical treatment, this paper proposes the re-stabilization of gene network systems by pole placement with HDLSS data, where the dominant eigenvector of the system matrix is focused. In addition, we conduct an approximation to decrease the number of assigned inputs for the pole placement. The feasibility and effectiveness have been investigated by theoretical analysis and numerical simulations.

8th 17:00-

## Kumar Selvarajoo / Agency for Science, Technology and Research / National University of Singapore / Nanyang Technological University

### *Can we define attractor states in biology?*

Living systems are known to display complex and non-linear behaviors, such as self-organization, cell fate decisions and emergent properties. Commonly, biologists look at a very small subset of genes, proteins or metabolites to investigate such behaviors. These are often selected based on setting arbitrary threshold values relying mostly on very highly expressed or variable ones. Here, I will share our works on transcriptome-wide data analyses of immune, cancer and microbial cells without setting any threshold but still adopting a rigorous way to remove technical noise or variation. Our analyses, based on sound statistical laws, led us to define statistical density plots where we observed a fractal-like subset of genes' dynamic response to fall into global cell fate trajectories. These localizations may well define a way to investigate attractor states in biology.

8th 18:00-

## Kazutaka Akagi / University of Toyama

### *Understanding the disease-triggering inter-organ crosstalk using a genetic animal model*

Consumption of unhealthy Western diets is associated with the prevalence of type 2 diabetes and obesity, which have risen drastically for decades. These disorders are linked with disruption of metabolic homeostasis that leads to chronic inflammation. Moreover, the morbidity associated with long-standing type 2 diabetes results from serious complications including nephropathy, cancer and cardiovascular diseases. The current therapeutics for diseases including type 2 diabetes are targeted to after its onset, but it' s often starting too late. Hence, we need to develop the new therapeutic approaches that targeting the pre-disease state in the context of each disease. However, the definition of the pre-disease state and its biomarkers have not well characterized.

We have successfully detected a pre-disease state in the mouse model of metabolic syndrome before the disease onset using the dynamical network biomarkers (DNB) theory. We have also identified 147 genes, which represent this pre-disease state from adipose tissue. To investigate the underlying biological mechanisms responsible for these DNB genes, we took advantage of the *Drosophila* model system. Due to their short lifespan and ease of genetic manipulation; invertebrate models continue to be useful as models for understanding human diseases. In particular the conservation of biological processes and signaling pathways between mammals and *Drosophila* provides a unique opportunity to understand the common biological mechanisms across species. In this talk, I will summarize our strategy to unveil the biological functions of DNB genes.

8th 19:30-

## Hiroshi Kokubu / Kyoto University

### *Two new ideas for dynamical time-series analysis*

The method of time-delay coordinate embedding due to Floris Takens is a now classical idea for inferring information of unknown dynamics from its time-series data by observation. It gives a mathematical basis of reconstructing an attractor of the unknown dynamics under a mild condition, and has been used in many application problems.

The purpose of this talk is to propose two new ideas on the dynamical time-series analysis which may improve some insufficiencies of the Takens method. One idea is the Conley-Morse decomposition of the global dynamics, and the other is the reservoir computing. The former uses many short time-series data from different points of the phase space of the unknown dynamical system, from which one can obtain a Morse decomposition of the global structure of the dynamics including unstable invariant subsets. The latter provides us with a model of time evolution constructed in the reservoir phase space that mimics the dynamics of the unknown system. An advantage of having a concrete model for unknown dynamics is that one can learn unseen information of the target dynamics. We will give several examples that show such advantages of these ideas.

8th 20.20-

**Keita Iida** / Osaka University

# *Clustering single-cell and spatial transcriptomes through multifaceted biological aspects*

Single-cell transcriptomics have deepened our knowledge of biological complexity in terms of molecular heterogeneity in cell populations. However, conventional signature gene-based approaches may be insufficient in capturing such complexity as genes can interact with each other to regulate a certain biological function. Here, we introduce ASURAT, a computational tool for simultaneous cluster analysis and interpretation of single-cell data in terms of cell type, disease, biological function, and signaling pathway activity. Mimicking Saussure' s idea for defining "meaning" in semiology, we introduce correlation structures into annotated gene sets defined in knowledge-based databases, such as Cell Ontology, Disease Ontology, Gene Ontology databases, and Kyoto Encyclopedia of Genes and Genomes. Then, we apply a novel correlation graph decomposition to each gene set, producing a triplet we term "sign" containing biological description, subset of genes, and correlation structure, which is the central concept of our analysis. To validate usability and clustering performance, we apply ASURAT on single-cell RNA sequencing and spatial transcriptome datasets of human pancreatic ductal adenocarcinoma (Moncada et al., Nat. Biotechnol. 38, 2020). We demonstrate that ASURAT is able not only to cluster spatial transcriptomic data into functionally distinct tissue regions but also identify de novo atypical regions.

MOONSHOT RESEARCH & DEVELOPMENT PROGRAM

Brain/MINDS Beyond