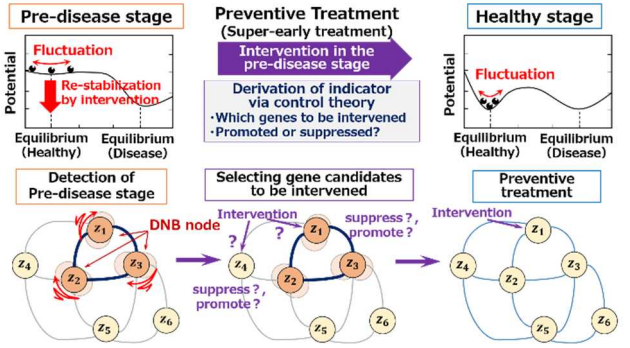
R&D Theme

Mathematical Approach to Complex Control System between Organs

Progress until FY2022

1. Outline of the project

The process to the onset of a disease is understood as rapid transition within the complex interaction network between organs, cells, and genes. A method called **Dynamical Network Biomarkers (DNB)** has been proposed to detect the pre-disease stage by focusing on the "fluctuations" in gene mRNA expression levels, hormone concentrations and others. The effectiveness of DNB has been demonstrated for various diseases. However, there is still no research on preventive treatment when such a pre-disease stage is detected. Therefore, this research has been working on a mathematical approach to establish **preventive treatment in the pre-disease stage**. It combines **DNB theory and its complementary theory with control theory** to construct a mathematical method that estimates which parts of the relevant biological network (particularly gene expression networks) should be intervened and how they should be intervened.

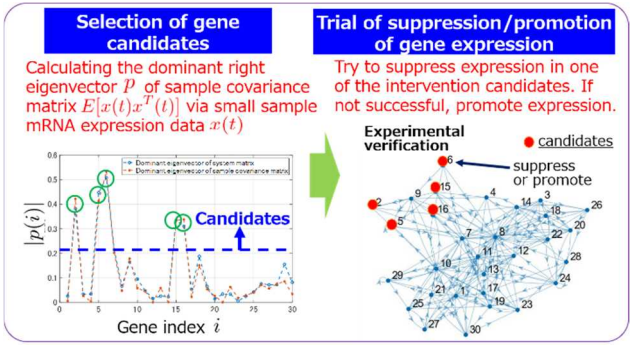


DNB Intervention theory for preventive treatment

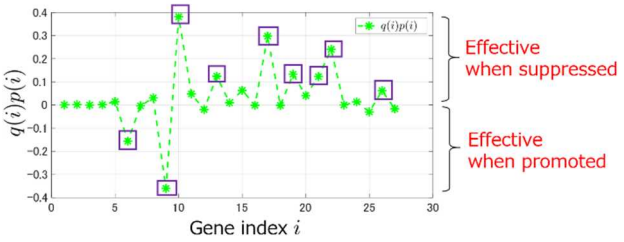
2. Outcome so far

We have developed the foundational theory of **the "DNB Intervention Theory,"** which theoretically proves a framework for interventions on gene expression networks, that was proposed last year. First, we derived rigorous solutions for preventive treatment (re-stabilization) in the pre-disease stage. We next derived an indicator called here **DNB Intervention Indicator for feasible interventions** that suppress or promote each gene expression. We proved that genes with a large absolute value of the indicator are potential candidates, and they should be suppressed if it is positive, whereas promoted if negative. As a result, we have successfully substantiated the intervention method proposed last year with rigorous theoretical foundations. We have also proposed **mathematical methods to detect warning signals of multi-stage successive transitions** and **new theory** to complement the DNB theory so that we can detect **early warning signals for deviation from healthy states** at ultra-early timing. Further, as an urgent important problem of our society, we studied **COVID-19** and found **a key gene DOCK2** for severe COVID-19 (Nature, 2022) and **optimal isolation guidelines** (Nat Comm, 2022) for COVID-19 patients.

We have collaborated **with the Saito Group at U. Toyama for experimental verification and the Fujiwara Group at U. Tokyo for the data management**. In addition to the **metabolic syndrome mouse model**, we have now taken up **the inflammatory bowel disease mouse model** with these groups. The alignment between the estimated DNB Intervention Indicators derived from mRNA data are shown below and the experimental confirmation will be a future challenge to address.



DNB intervention algorithm developed



Collaborative research with Saito G and Fujiwara G: Application of gene data of IBD mouse model

3. Future plans

We have developed **a basic theory for preventive treatment based on the DNB theory (named the DNB intervention theory)**. It is our important future problem to **combine the DNB theory with its complementary theory toward a comprehensive system for ultra-early detection of many diseases.**

Here begins our new MIRAI
MOONSHOT RESEARCH & DEVELOPMENT PROGRAM

R&D Theme

Experimental Approach to Complex Control System between Organs

Progress until FY2022

1. Outline of the project

Our R&D theme has the following three objectives:

1. We are promoting the project by applying mathematical methods to our health science research on the pre-disease state **in collaboration with the Mathematical Approaches Team within the project**.
2. Based on the results of our studies, we are leading the realization of ultra-early precision medicine through **medical intervention in the pre-disease state**.
3. To elucidate and detect the pre-disease state, we are providing to a Mebyo database by acquiring temporal and comprehensive biological information of **multiple organs in animal models and in humans**.

Specifically, we are conducting validation of mathematical methods such as **dynamical network biomarkers (DNB) analysis** applied for health sciences using animal models (e.g., **metabolic syndrome model**), clinical samples (e.g., **gestational hypertension, hematopoietic tumor**), and data of **mental diseases**. Furthermore, we are providing the acquired biological information (pre-disease datasets) to GakuNin RDM **through the Mathematical Collaboration Team (Fujiwara Group, the University of Tokyo)** within the project for utilization throughout the project.

2. Outcome so far

① Ranking of the importance of DNB genes and elucidation of their functions through collaborative research within the project

Mouse gene	Human gene	Fly gene
Cst9	CST9L	CG8066, Cys, CG15369 or CG31313
Cox8C	COX8C	cox8
	X	
Tuba3b	TUBA3D	alphaTub84B
Rbakdn (RNA gene)	RBAKDN	-
Capza3	CAPZA3	cpa
Prr27	PRR27	-
Piwil1	PIWIL1	aub
Meig1	MEIG1	-
Cfap58	CFAP58	CG5882
Dusp13	DUSP13	CG7378
Asb9	ASB9	pyx
	Y	
	Z	
Lrrc46	LRRC46	CG13708

Table 1

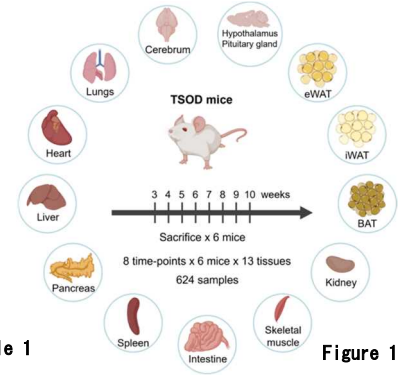


Figure 1

From 147 DNB genes in adipose tissue of spontaneously developing metabolic mice (TSOD mice), we selected 15 DNB genes (Table 1) that we considered important **from the viewpoint of Systems and Control Theory in collaboration with the Mathematical Approach Team (Tokyo Institute of Technology)**. Then at the University of Toyama, taking advantage of the genetics of Drosophila as a model organism, we conducted a rapid and comprehensive evaluation of DNB gene functions and found that **three DNB genes** (X, Y, Z) in Table 1 are involved in lipid metabolism.

② Pre-disease datasets to elucidate the inter-organ networks in metabolic syndrome mice

To detect changes in each organ that are thought to be induced before the onset of metabolic syndrome using **DNB analysis**, we obtained comprehensive gene expression information of **13 organs including adipose tissue, brain, intestine, liver, and muscle at 8 time points** from before to after the onset in TSOD mice as shown in Figure 1, and further performed DNB analysis and **detected pre-disease states in each organ**.

③ Detection of precancerous state (pre-disease state) of hematopoietic tumors using Raman microscopy

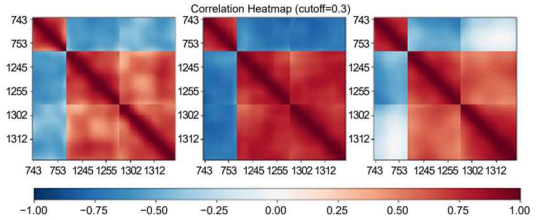


Figure 2

We are analyzing cells collected from bone marrow of patients with **hematopoietic tumors** by measuring their spectra using **Raman microscopy**. It was possible to clearly distinguish between cells from patients with hematopoietic tumors and cells from patients in precancerous states. Furthermore, **DNB analysis of Raman spectral data** showed that the DNB score of cells from patients with precancerous conditions (Figure 2 middle) was higher than that of cells from normal cases (Figure 2 left) and cells from hematopoietic tumor patients (Figure 2 right), indicating **an increased fluctuations in the cells from patients with precancerous conditions**. On the other hand, **mathematical analysis of the brain data** like mental diseases and Tokyo Teen Cohort are also progressing.

3. Future plans

We are working on more detailed single cell analysis and intercellular network analysis of visceral adipose tissues from **high-fat diet-induced metabolic syndrome mice and humans**. **We are also improving the Raman microscope for** developing a clinical examination device that can be applied to detect the pre-disease state of human hematopoietic tumors.

国立研究開発法人 科学技術振興機構
Japan Science and Technology Agency

Here begins our new MIRAI
MOONSHOT RESEARCH & DEVELOPMENT PROGRAM

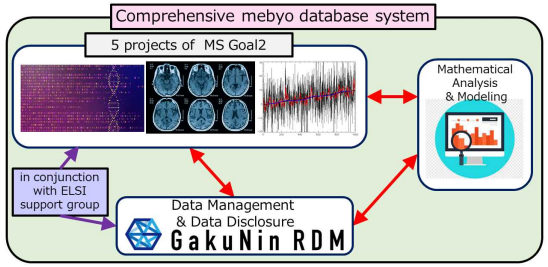
R&D Theme

Mathematical Collaboration with Other Moonshot Projects, Development of Data Base, and ELSI Supporting System

Progress until FY2022

1. Outline of the project

This R&D theme can be divided into two sub-themes: one is **"Mathematical Collaboration with other Moonshot Projects"** and the other is **"Database Construction"**. Mathematical collaboration involves the construction of **a mathematical analysis infrastructure** that can be used across the entire Moonshot Goal 2, as well as mathematical collaboration on disease data obtained in Goal 2. In particular, we will construct **a comprehensive mathematical analysis method** for detecting the state of Mebyo just before the transition from a healthy state to a diseased state.



Conceptual diagram of the construction of a comprehensive Mebyo database system

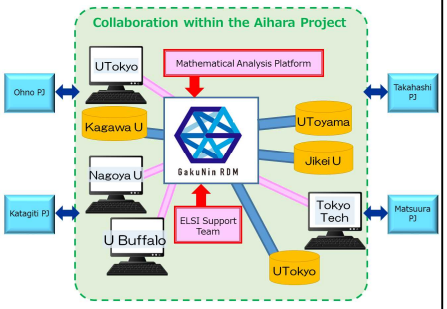
In addition, the database construction aims to compile the results of the entire project, construct **a comprehensive Mebyo database of complex organ regulatory systems**, and make it widely available to society. **In collaboration with all the projects in Moonshot Goal 2**, we will construct a comprehensive Mebyo database based on experimental data, clinical data, and cross-sectional mathematical analysis data related to each disease.

Through these efforts, we will contribute not only to the project's goals of comprehensive mathematical understanding of complex organ regulatory systems and early precision medicine, but also to the realization of **a society capable of predicting and preventing diseases in the ultra-early stages**, which is **the goal of Goal 2 as a whole**.

2. Outcome so far

In the mathematical collaboration, the construction of mathematical analysis methods and the development of mathematical analysis software have begun in order to start mathematical analysis using artificial data generated by mathematical models and existing open data, etc., in anticipation of data analysis of experimental and clinical data that will be obtained in **the 5 projects in MS Goal 2**. For example, software has been developed and released for each of the Aihara Project's original mathematical analysis methods, such as **DNB analysis and ASURAT**. The released software has been tested on **the GakuNin RDM**, and it has been verified that the software can be used for the entire MS Goal 2. Thus, the construction of the mathematical analysis platform is steadily progressing.

In addition, in database construction, **the Goal 2 database** was designed. For example, database construction is steadily progressing with metadata design and database mock-up creation, and is getting ready for data collection and sharing across the MS Goal 2. The database working group has started concrete work toward the use of the database for the entire Goal 2 project.



In addition, we are working closely with **the ELSI support team** to consider appropriate responses to ethical, legal, and social issues (ELSI) that may arise in comprehensive Mebyo database construction.

3. Future plans

In mathematical collaborative research, we will continue to build **a data sharing system to continue to promote mathematical collaboration with each project under Goal 2**. In addition, we will continue to construct a mathematical analysis platform that can be used **across the entire Goal 2**. By releasing various mathematical analysis methods as software that can be used by anyone in Goal 2, it is expected that mathematical collaboration will be promoted.

As for the database construction, the database design will be completed and data sharing within Goal 2 will be promoted as soon as possible. To this end, we will resolve issues related to data sharing and promote data storage by taking **a leading role within Goal 2**. In addition, we will work with **the ELSI support team in our project** to create a database white paper in order to establish common usage methods and rules for the comprehensive Mebyo database construction.

国立研究開発法人 科学技術振興機構 Japan Science and Technology Agency