Goal2 Realization of ultra-early disease prediction and intervention by 2050. Comprehensive Mathematical Understanding of the Complex Control System between Organs and Challenge for Ultra-Early Precision Medicine



R&D item

1. Mathematical Approach to Complex Control System between Organs

Progress until FY2023

1. Outline of the project

The process to the onset of a disease is understood as state transition of the complex interaction network between organs, cells, and genes. A method called Dvnamical Network Biomarkers (DNB) has been proposed to detect the pre-disease states by focusing on the "fluctuations" in gene mRNA expression levels. hormone concentrations and others. The effectiveness of DNB has been demonstrated for various diseases. On the other hand, there is no research on preventive treatment when such a pre-disease state is detected. Our goal is to expand DNB theory to multi-stage transitions. develop its complementary theory like spatiotemporal information transformation learning and energy landscape analysis, and then establish preventive network treatment in the pre-disease states by combining DNB theory and control theory.



Development of the detection of pre-disease state and preventive treatment based on DNB theory

2. Outcome so far

In 2022, we developed the basic theory of DNB intervention based on a mathematical model of mRNA expression. In 2023, for more practical applications. we extended it to include the process from mRNA expression to protein production based on a model mRNAs and proteins. hierarchical of Specifically, we theoretically derived an index (the DNB intervention index) to identify candidate genes in the gene expression network that are highly effective for intervention from the mRNA or protein level to prevent diseases (re-stabilization). The relationship between mRNA intervention and the corresponding protein intervention was clarified and an approximation (a reference value) of the DNB intervention index was successfully derived even when only mRNA expression levels could be measured.

We have also proposed mathematical methods to detect warning signals of multi-stage successive transitions (Nat Comm, 2024) and new theory to complement the DNB theory so that we can detect early warning signals for small 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 applied the developed theory to the inflammatory **bowel disease (IBD) mouse model** with these groups, and derived the reference values for the DNB intervention indicators shown in the figure below. Experiments conducted by the Saito group for protein intervention on the relevant mice confirmed the effectiveness of the method.



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

Furthermore, we have successfully observed multistage state transitions in lung cancer mice. On the basis of the results from these mouse models, our experimental group is currently working on extending the analysis to human data.

3. Future plans

We have expanded the DNB intervention theory to include protein interventions, in addition to mRNA. Future challenges include extending this theory to hierarchical networks of genes and cells and adapting it for single-cell sequencer data. It is also our important future problem to combine the DNB theory with its complementary theory toward a comprehensive system for ultra-early medicine of many diseases.

