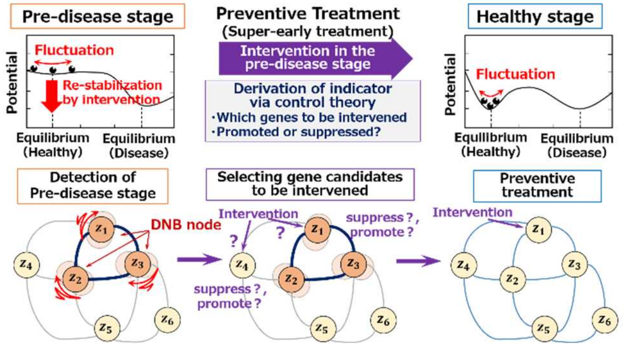
R&D Theme

# 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.

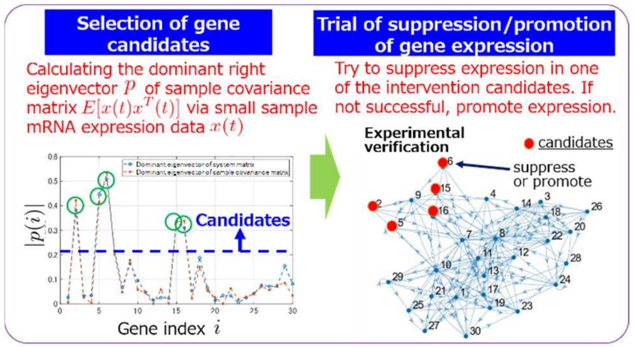



DNB Intervention theory for preventive treatment

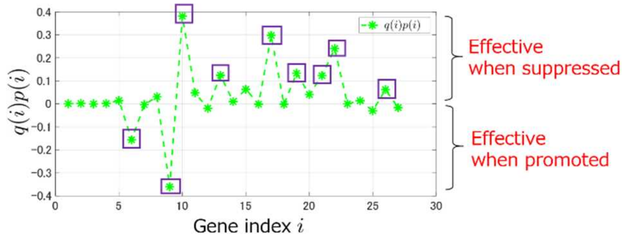
### 2. Outcome so far

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.