Dynamic Network Biomarkers
~ A System to discover Novel Biomarkers to detect Pre-Diseased States! ~

KEY INVENTION

A system to discover the novel biomarkers, so-called "*Dynamic Network Biomarkers (DNBs)*" to detect "*Pre-Diseased States*" has been developed.

What's DNBs?

- DNBs are the biomarkers to detect "Pre-Diseased States" by analyzing the changes in the correlation of several gene expressions using mathematical and statistical methods.
- The existing biomarkers detect "Diseased States". However, DNBs can detect *"Pre-Diseased States"*.

SUMMARY of INVENTION

[Process to discover DNBs]

The correlation and standard deviation of each factor are equal and medium in the healthy stage (A).

The factor group (Z1 to Z3) that indicates remarkably more specific properties than the others appears in the pre-diseased stage (B).

➡ This factor group is "Dynamic Network Biomarker (DNB)".

The correlation of the factor group goes down up to the equal to the others although the standard deviation of the group is slightly bigger than the others (Specific properties disappear) in the diseased stage (C).

As the factor group indicating specific properties is usable as a "Warning Signal" of "Pre-Diseased States", DNB is a biomarker to detect "Pre-Diseased States".

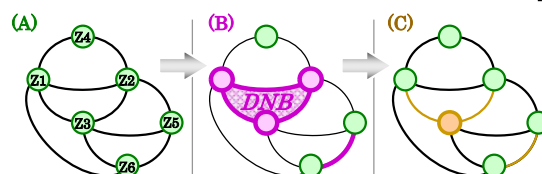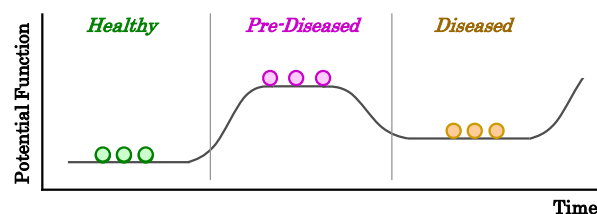Diagram of System Stability expressed by Potential Function

Diagram of System Network
- ◎ Z1 to Z6 : Factors related to Biomolecules such as Genes or Proteins
- ◎ Connection Lines of each Factor : Correlation of each Factor
- ◎ Circle Lines : Standard Deviation (SD) of each Factor

EFFECT of INVENTION

[Method to measure DNB Intensity]

- DNBs appear under the following two (2) conditions.
    - a. The SD of gene expression quickly goes up.
    - b. The correlation of expression of each gene goes up.
- DNBs are measurable by the following formula.

$$\text{Comprehensive Index (I)} = \frac{SDd \times PCCd}{OPCCd}$$

- SDd : The average of the SD of the factors in DNB
- PCCd : The average of the absolute value of the Pearson Correlation Function of each factor in DNB
- OPCCd : The average of the absolute value of the Pearson Correlation Function between the factors in DNB

[Case Study of DNB Discovery]

1. The DNBs for the diabetes and obesity have been discovered in the mouse models.
   ⇒ 147 genes have been identified as the DNB for metabolic syndrome.

   SCIENTIFIC REPORTS, **9**, 8767 (2019)

2. CALML3 has been discovered as a gene for the suppression of hepatocellular carcinoma metastasis in the mouse models.
   ⇒ The CALML3 gene expression has been confirmed to be different between in the lung metastasis and no lung metastasis mice.

   Nature Communications, **9**, 678 (2018)

APPLICATION expected

- ◎ Application for the system to discover novel biomarkers
- ◎ Application for the disease prevention technologies by the diagnostics of pre-diseased states

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