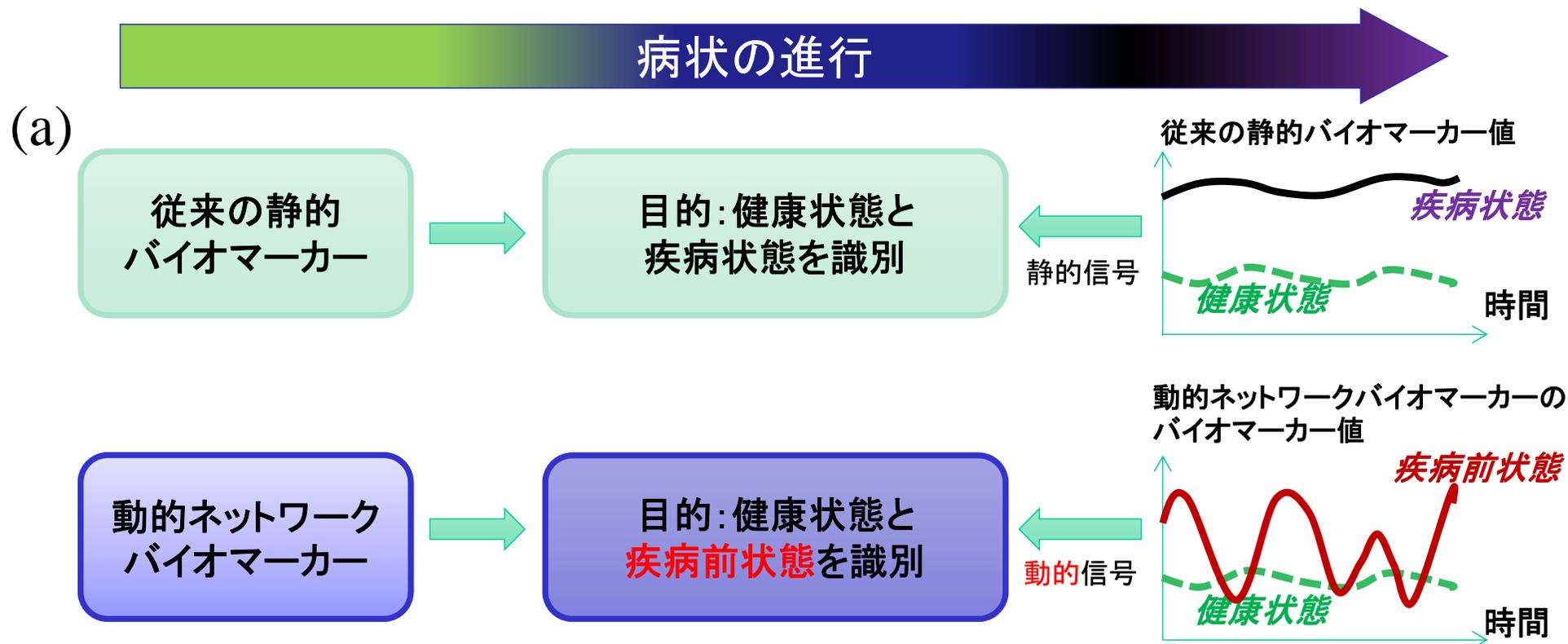
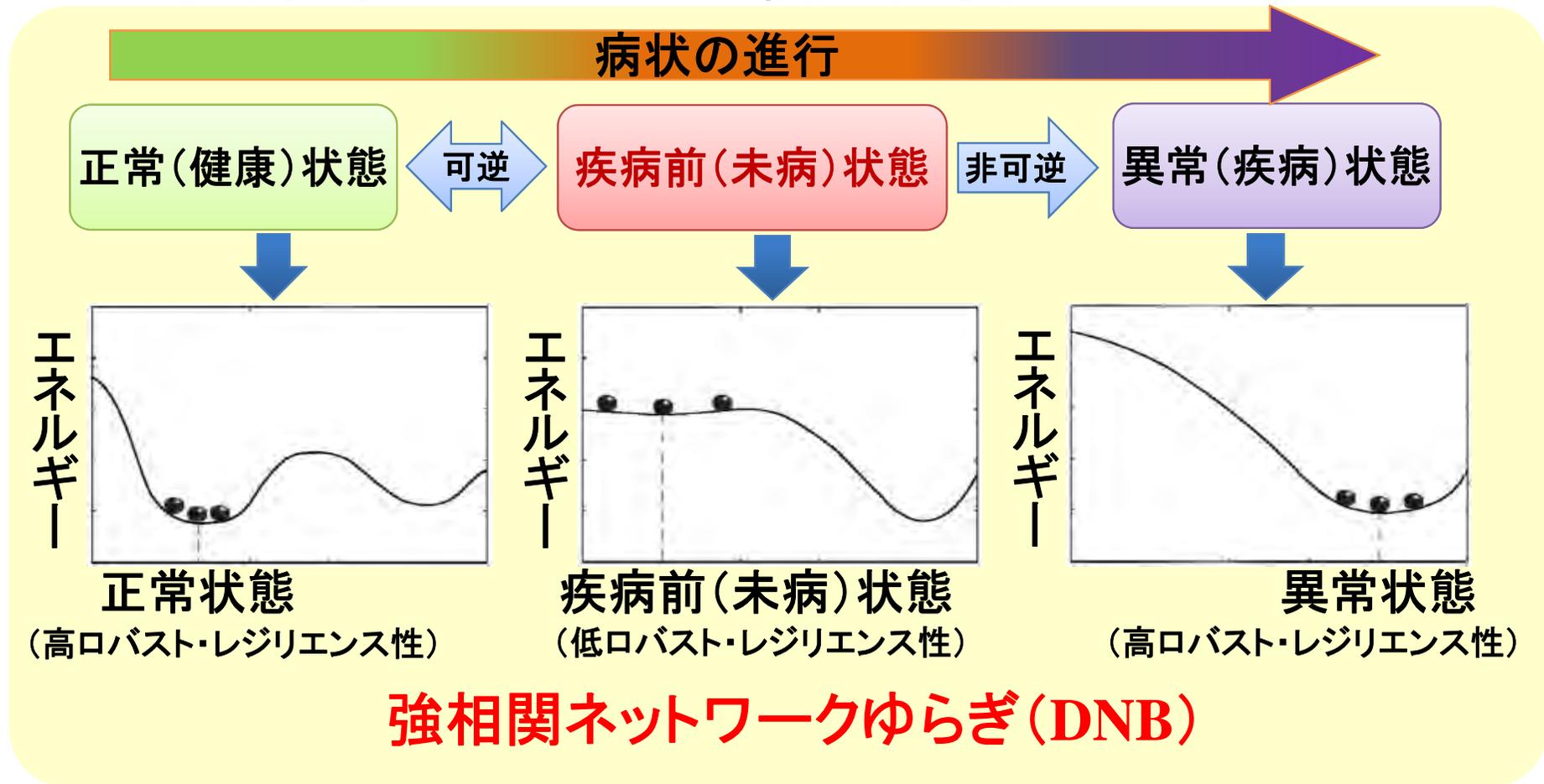


従来の静的バイオマーカーと動的バイオマーカー

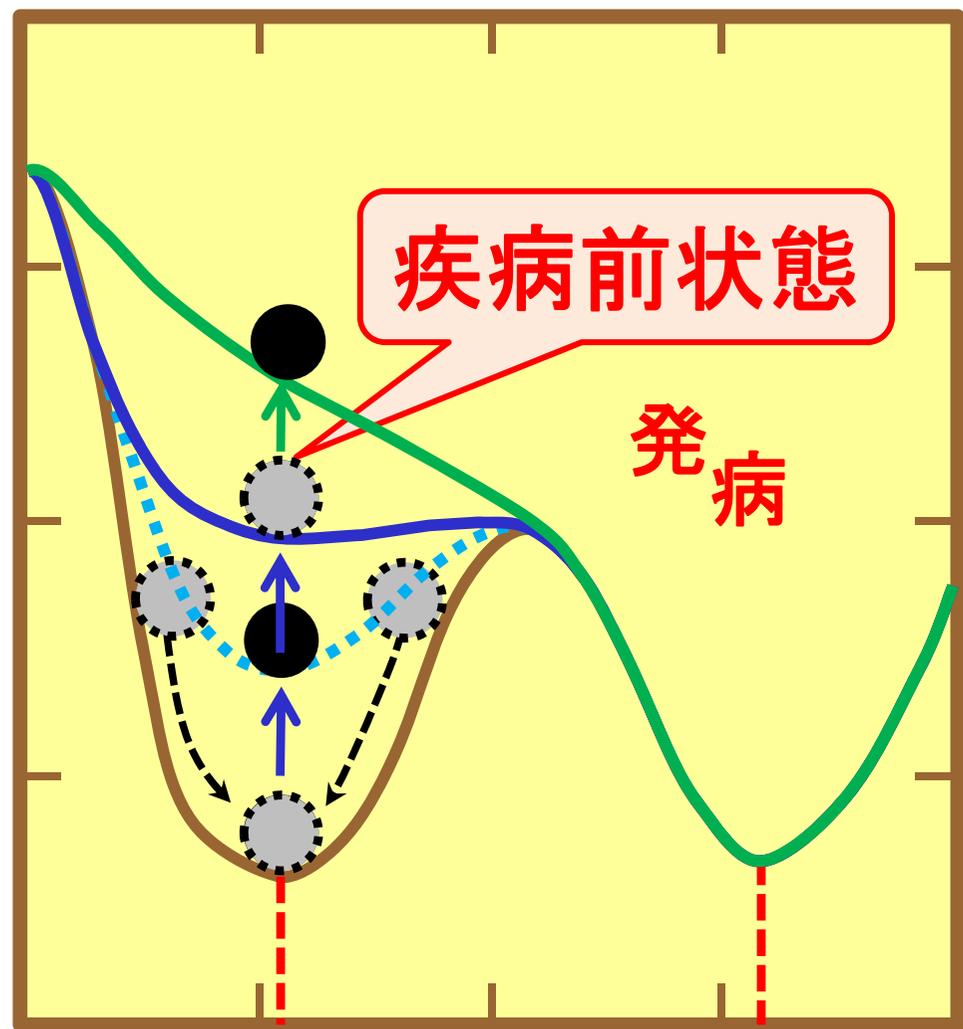


DNB: 平均値 → ゆらぎ

DNB理論：全体構造が未知の複雑臓器ネットワークの疾病前状態を、観測ビッグデータのみを基にして、数理モデルの仮定は一切なしにデータ駆動で重要因子を網羅的に取り出すことによって検出する。

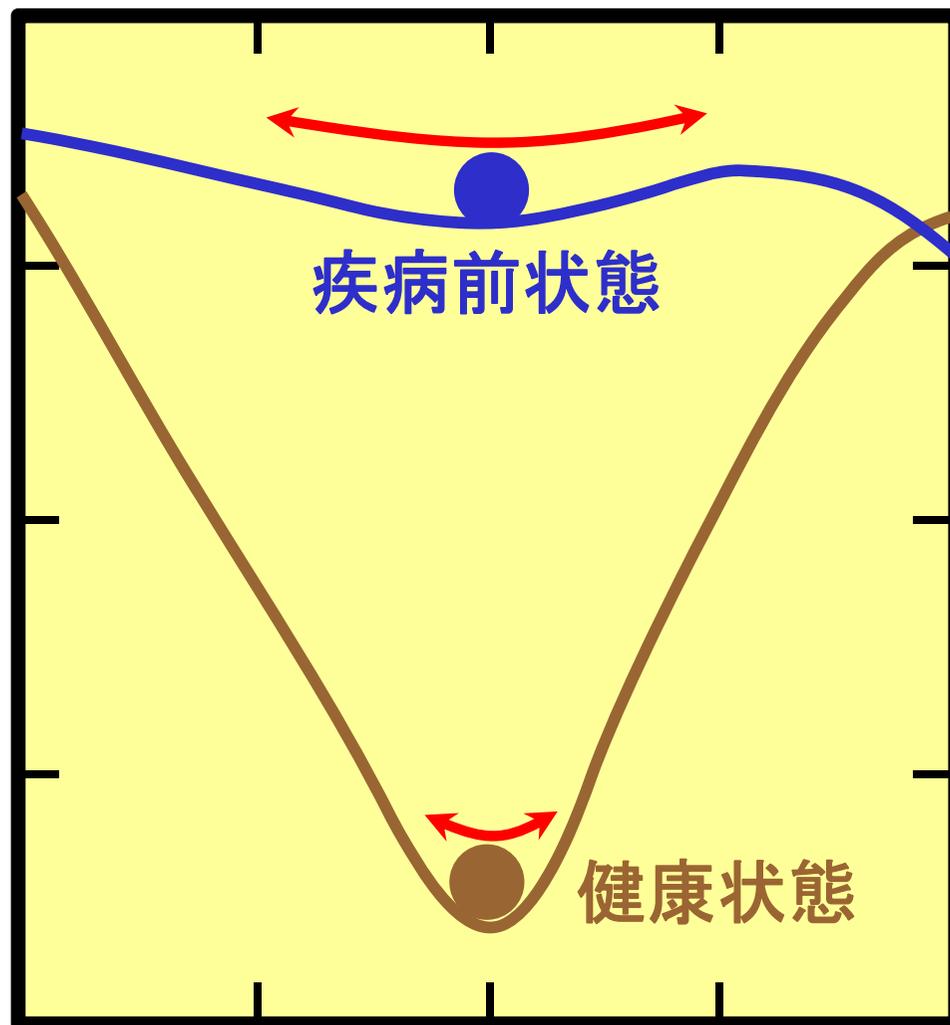


分岐理論に基づく健康状態から疾病状態への疾病前(未病)状態を介した状態遷移の模式図

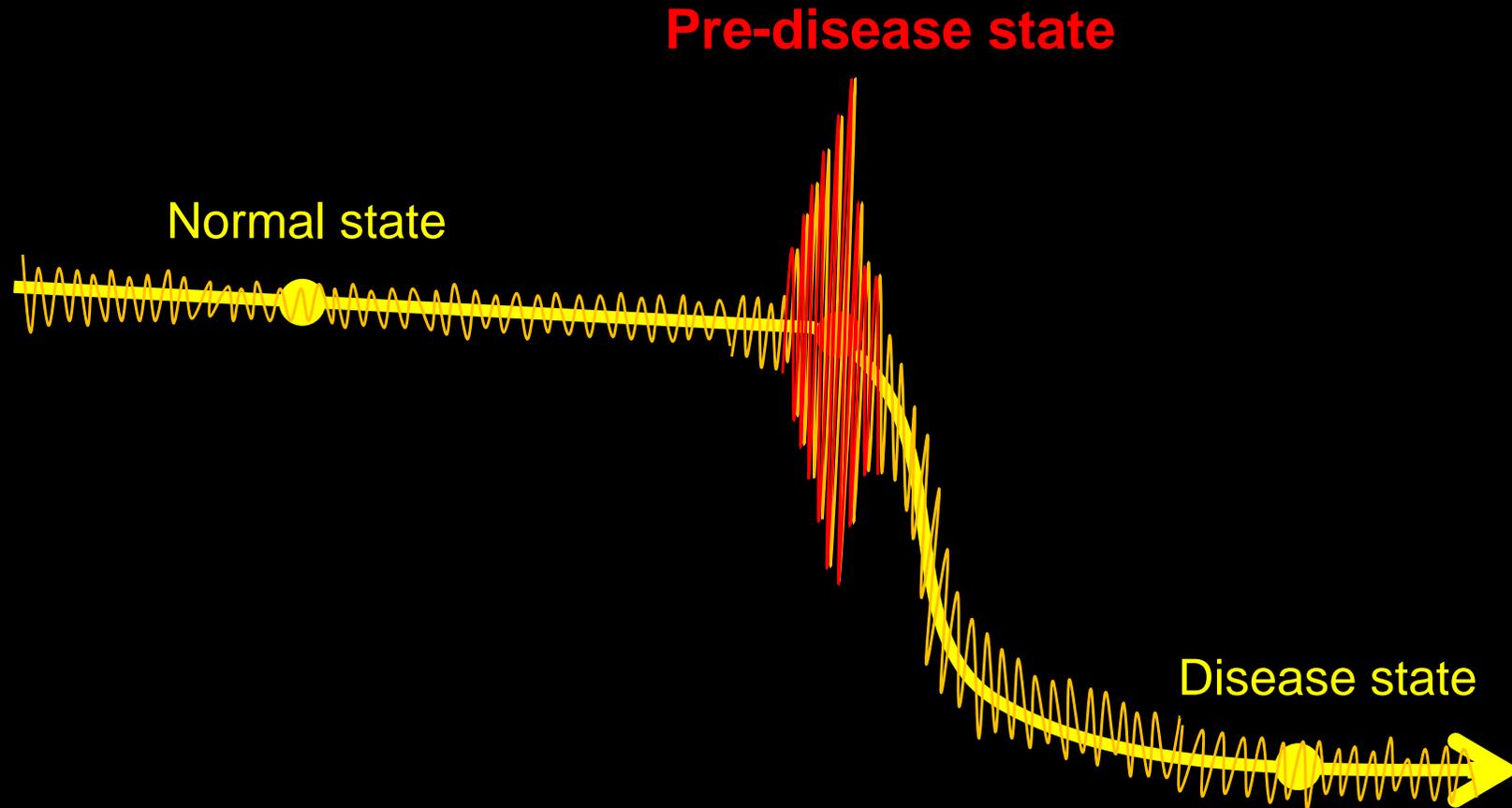


健康状态

病气状态



Signal not from statistics but from dynamics



Disease progression

Information on

×

Average values

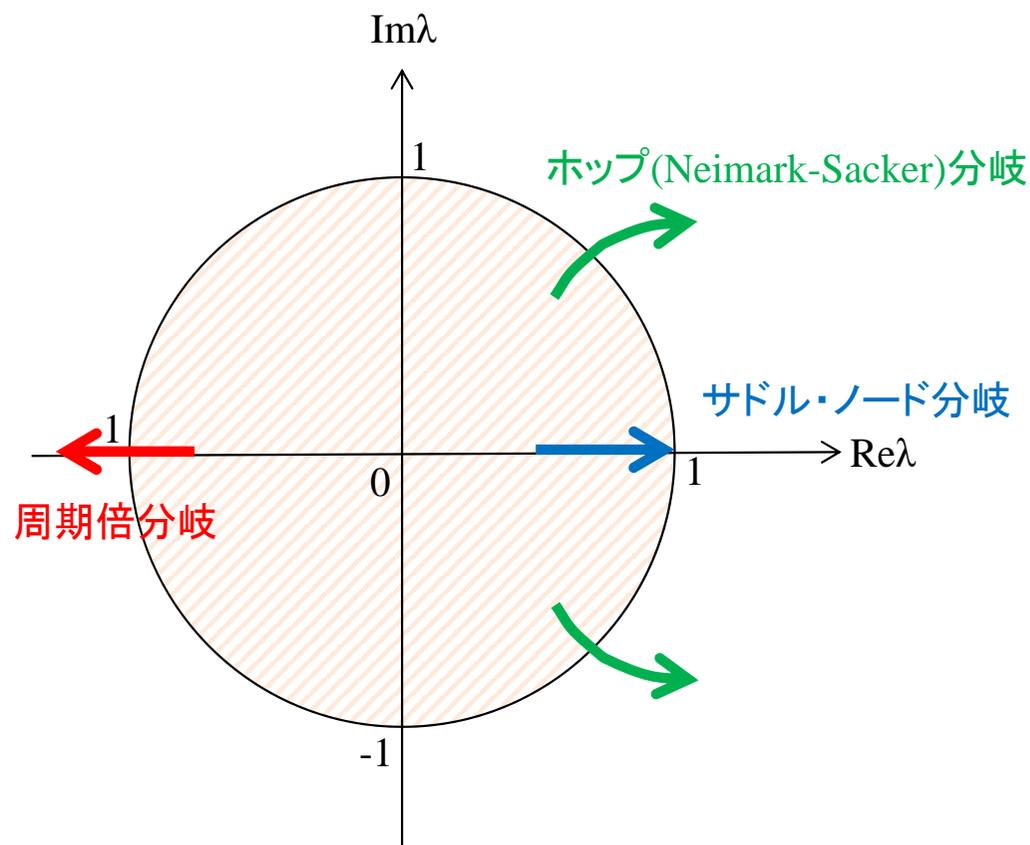
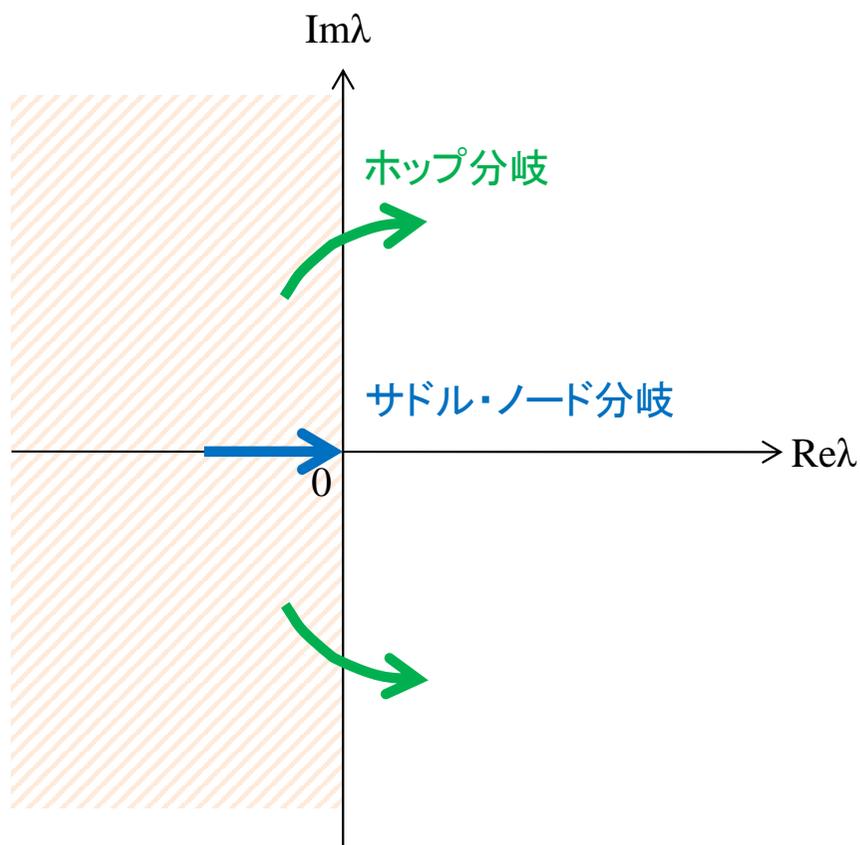
√

Individual variations

非線形システムの余次元1局所分岐

連続時間力学系の平衡点の分岐

離散時間力学系の不動点, 周期点の分岐

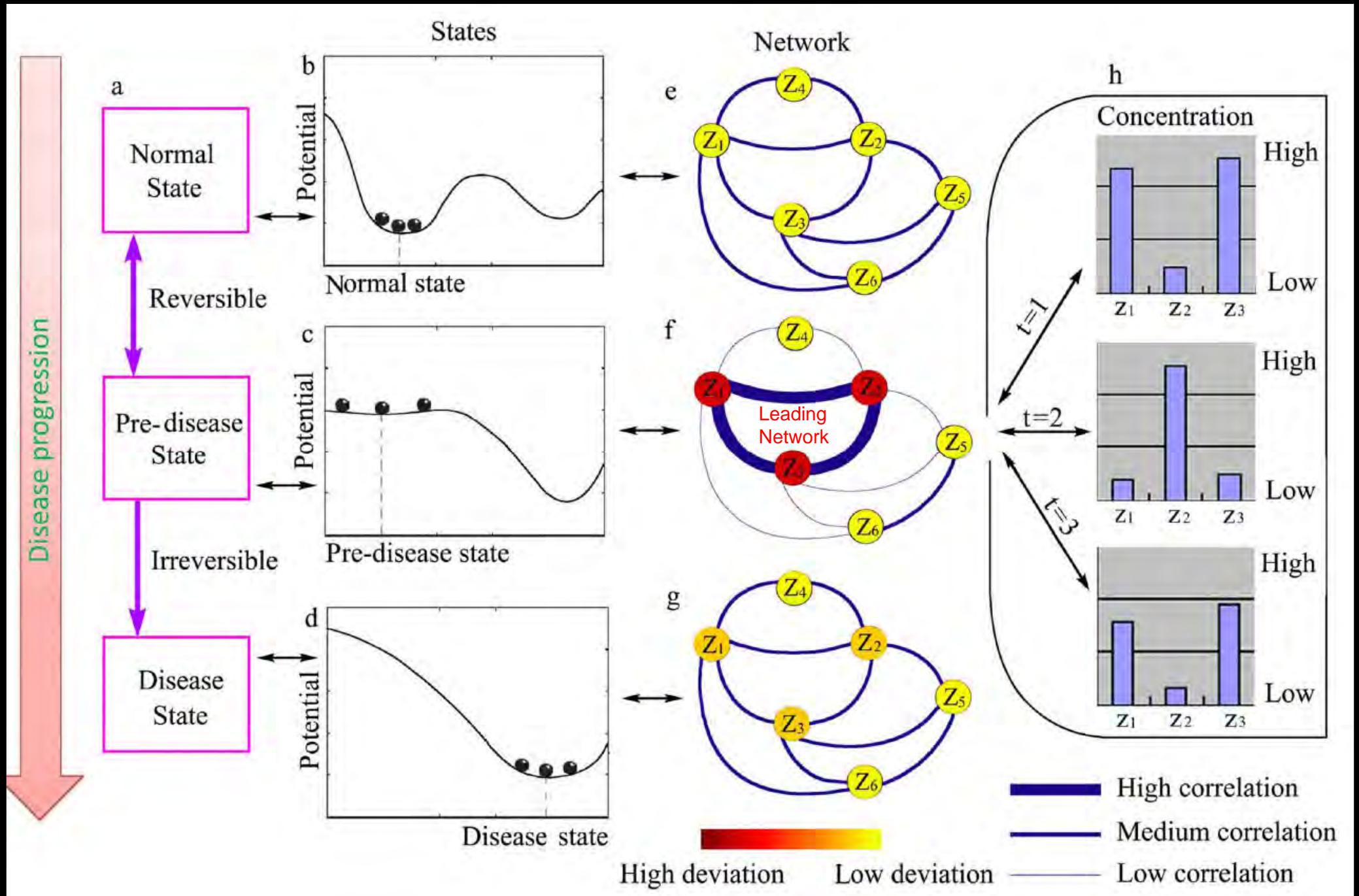


平衡点, 不動点 \Leftrightarrow homeostasis,

課題: **homeodynamics**

Dynamical Network Biomarker (DNB)

(L.Chen et al., Sci. Rep., 2012)



DNBインデックス (Sci. Rep., 2012 他; 特許第5693198号 他)

$$I = SD_d \cdot PCC_d,$$

ここで,

SD_d : DNB要素の平均標準偏差,

PCC_d : DNB要素間のPCC (Pearson's Correlation Coefficient) の絶対値の平均値.

DNBの特性

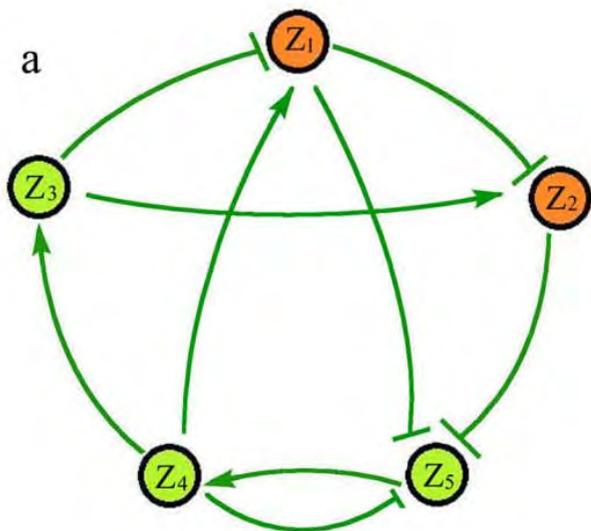
DNBの要素 x_i, x_j に関して, 分岐点(発病点)に近づく時,

$$PCC(x_i, x_j) \rightarrow \pm 1,$$

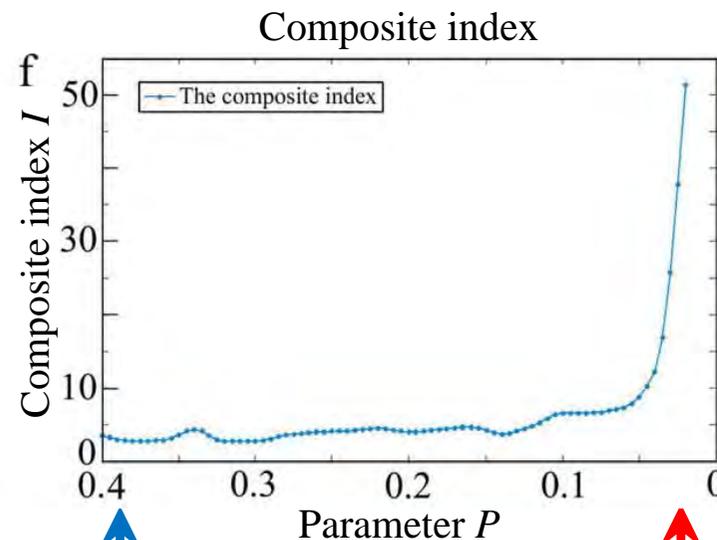
$$SD(x_i) \rightarrow \infty,$$

$$SD(x_j) \rightarrow \infty.$$

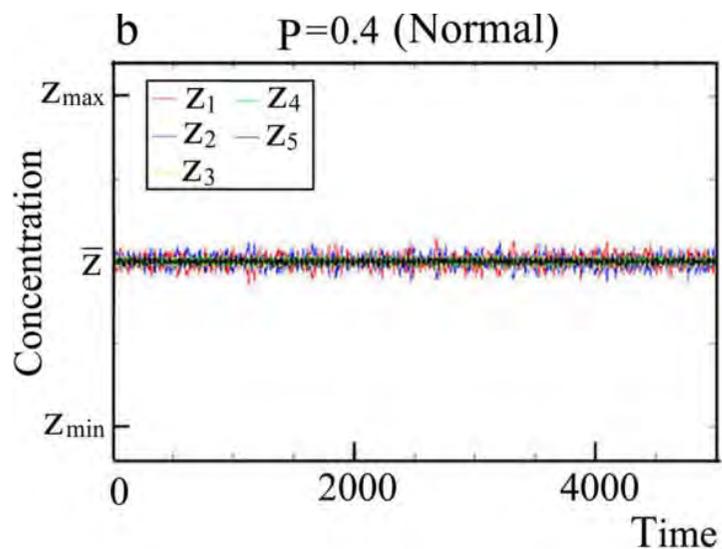
遺伝子ネットワークモデルを用いたDNB理論の説明 (L.Chen et al.,Sci. Rep.2012)



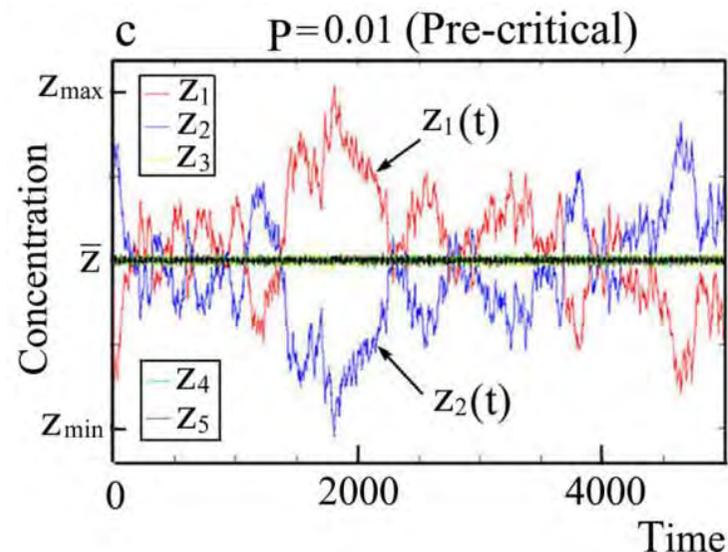
遺伝子ネットワークモデル



健康状態 疾病前状態 発病



健康状態のゆらぎ



疾病前状態のゆらぎ

Once disease occurs, difficult to be cured

《黄帝内经》 紀元前**221**年

《*Yellow Emperor's Medicine*》 **221 BC**

上医治未病， 中医治欲病， 下医治已病

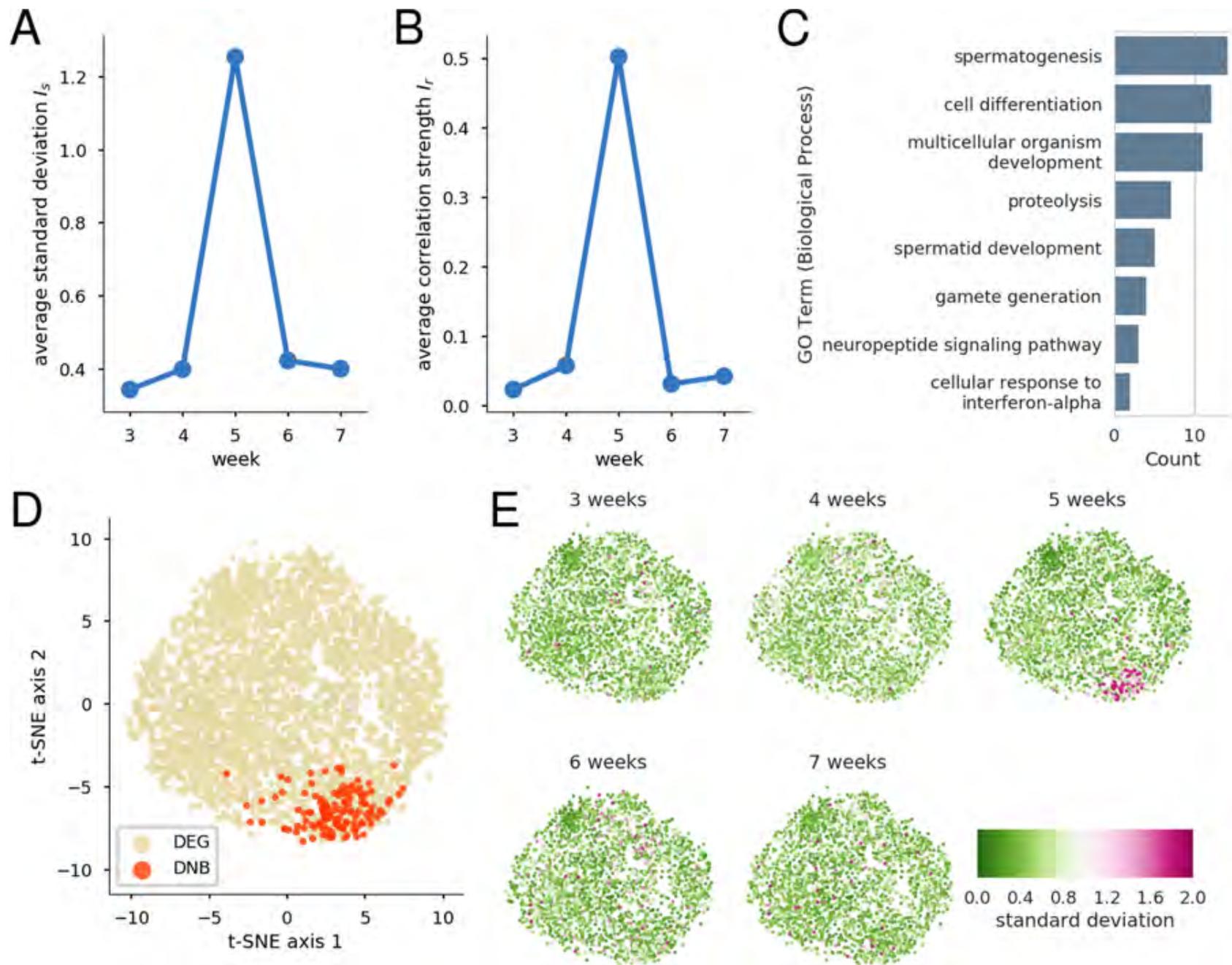
the best doctor
treats
diseases that have
not occurred

the better doctor
treats
occurring diseases

the inferior doctor
treats
diseases that have
occurred.

Qualitative Concept → Quantitative Indexes

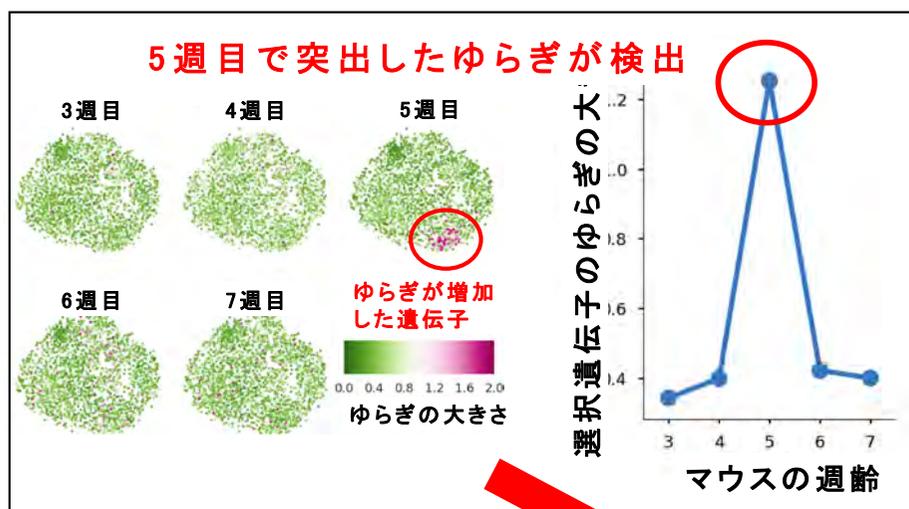
**Early diagnosis by
dynamical network biomarkers**



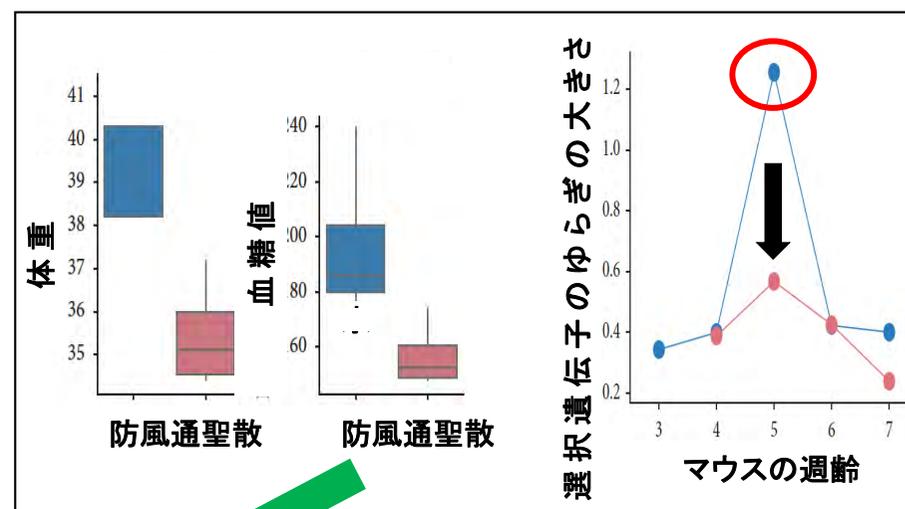
メタボリックシンドロームマウスの未病状態の検出
(K. Koizumi et al., Sci. Rep., 2019)

メタボリックシンドロームの未病の検出と治療の可能性

未病の検出に成功



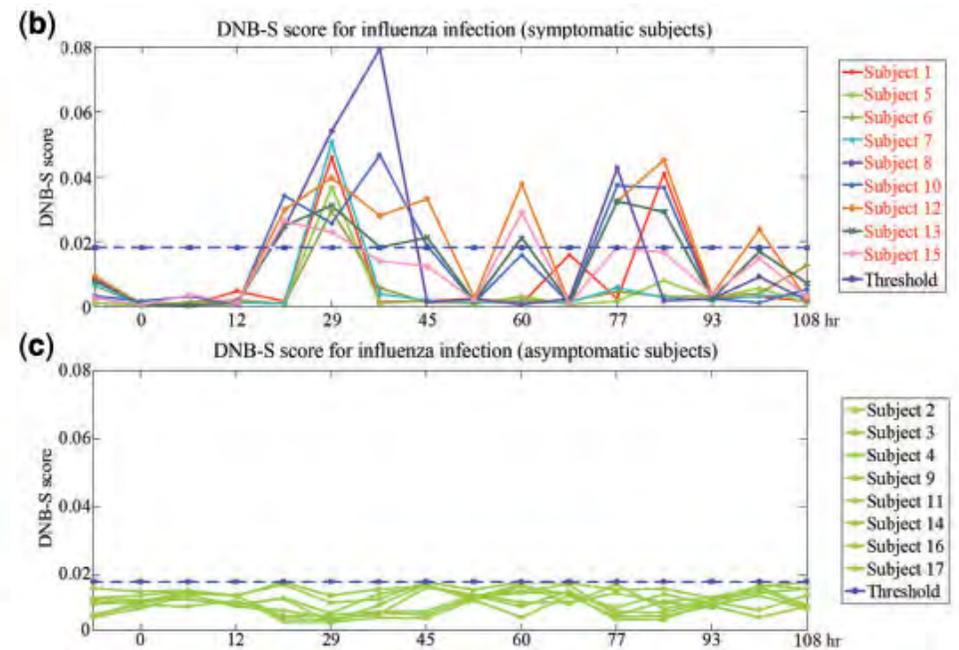
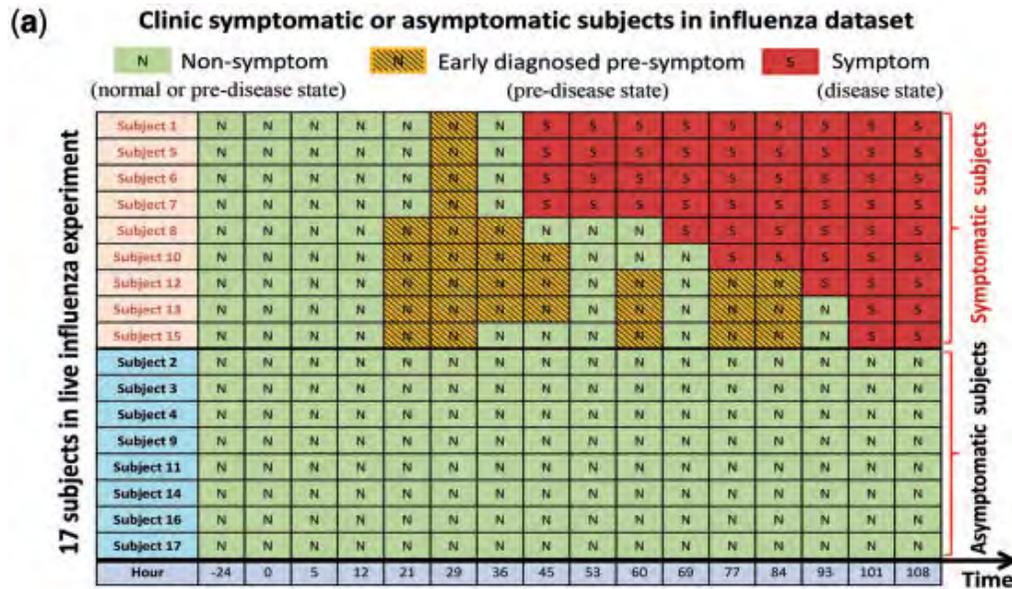
漢方薬による未病の改善が示唆



未病医療・未病創薬
の構築に向けて

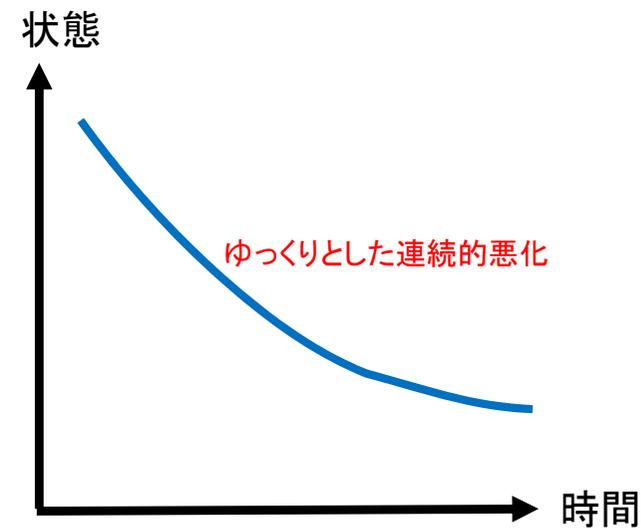
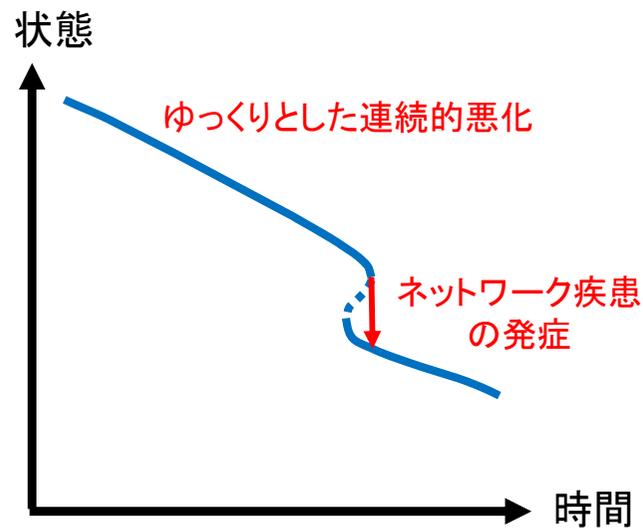
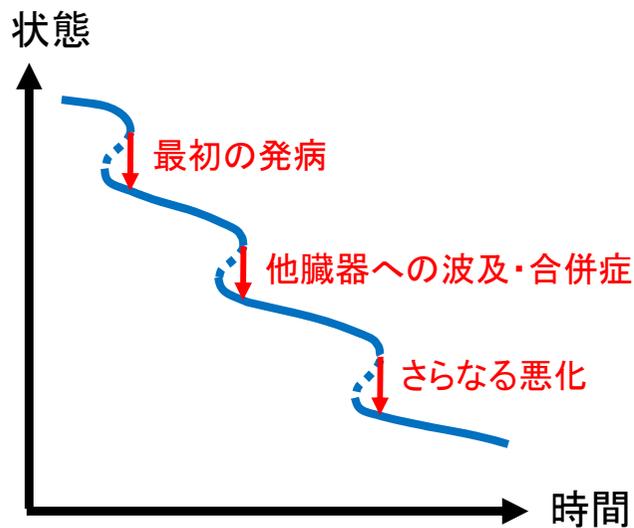
K. Koizumi, et al., Scientific Reports,
Vol.9, Article No.8767, pp.1-11 (2019).

K. Koizumi, et al., Evidence-Based
Complementary and Alternative Medicine,
Vol.2020, Article No.9129134, pp.1-9 (2020).

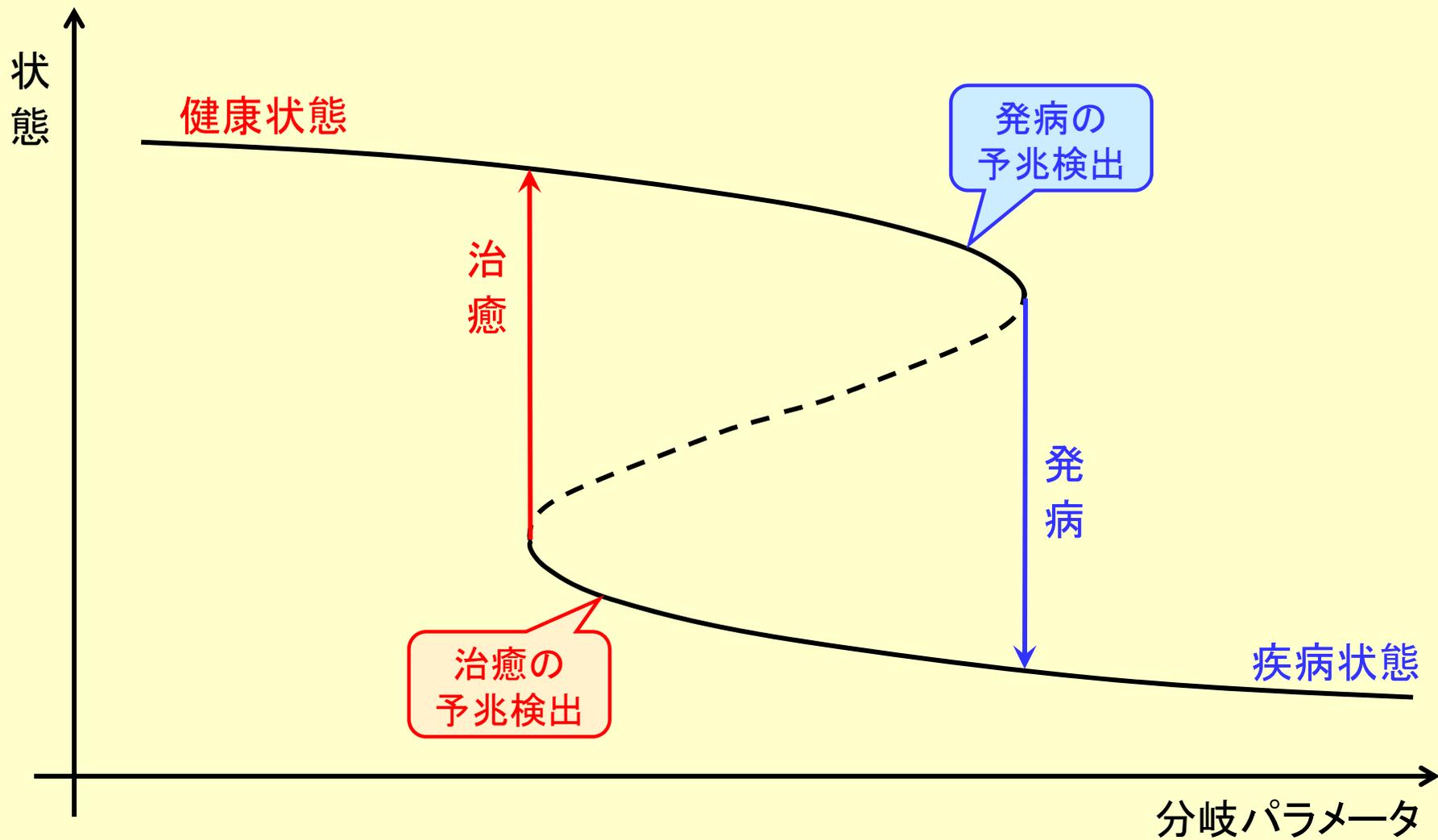


ヒトのH3N2型インフルエンザの未病状態の検出

R. Liu, X. Yu , X. Liu, D. Xu, K. Aihara, and L. Chen, Bioinformatics, Vol.30, No.11, pp.1579-1586 (2014).

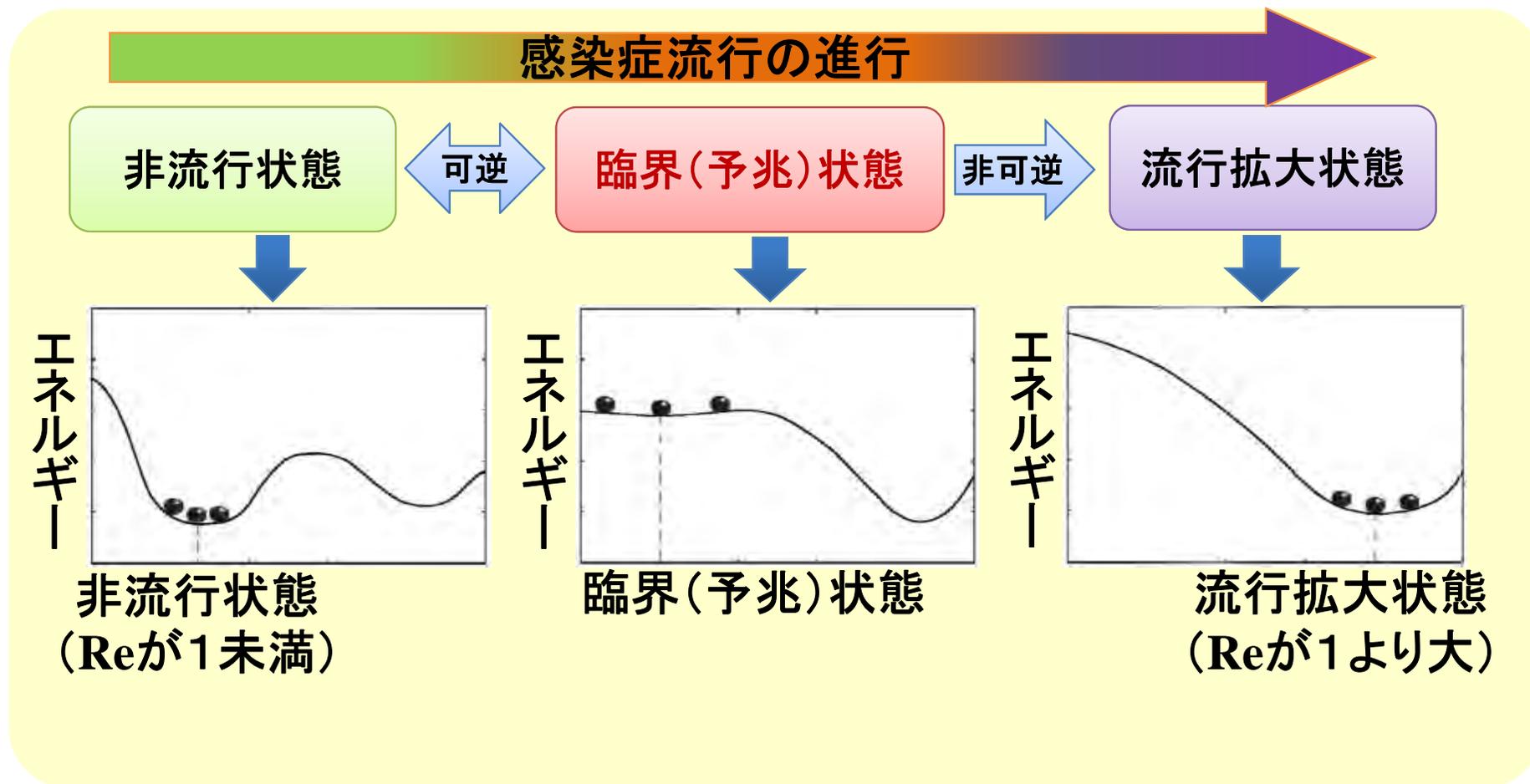


単独臓器疾患を越えた、他臓器への波及・合併症、多臓器不全等の悪化過程の解明

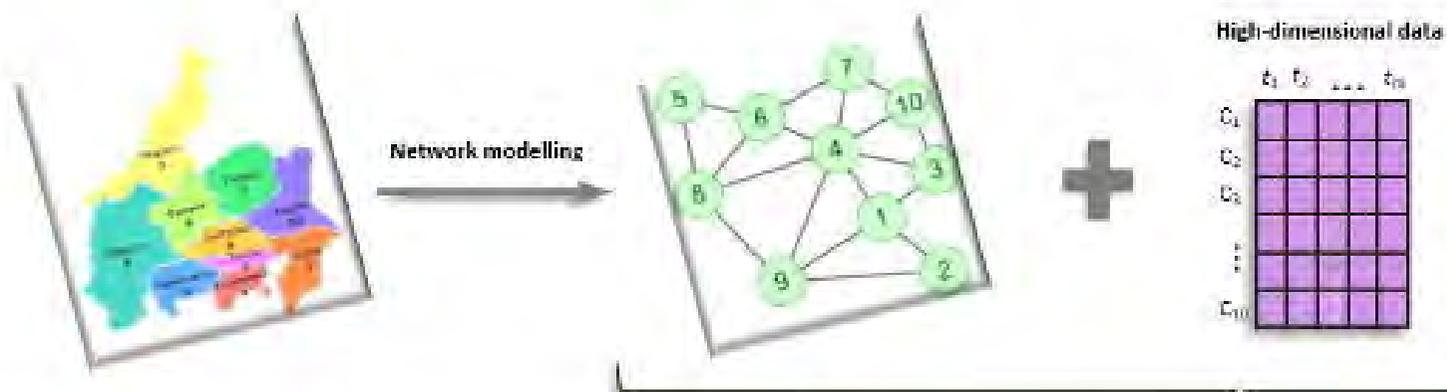


DNBの2つの応用

DNB理論の新型コロナウイルスの流行予兆検出への応用 (Science Bullitin, 2021)



非流行状態から流行状態への
臨界(予兆)状態を介した状態遷移の模式図

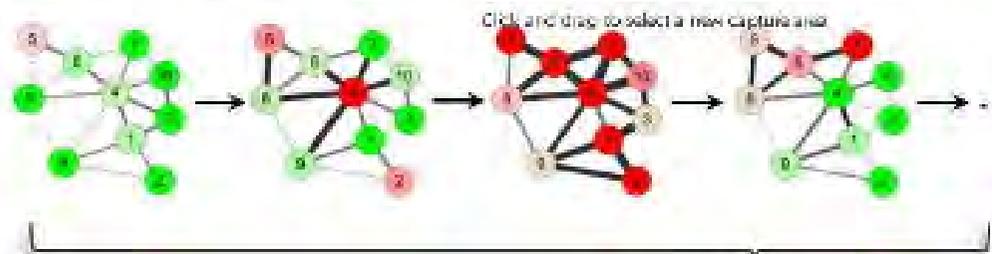


Calculating the LNE index for each local network

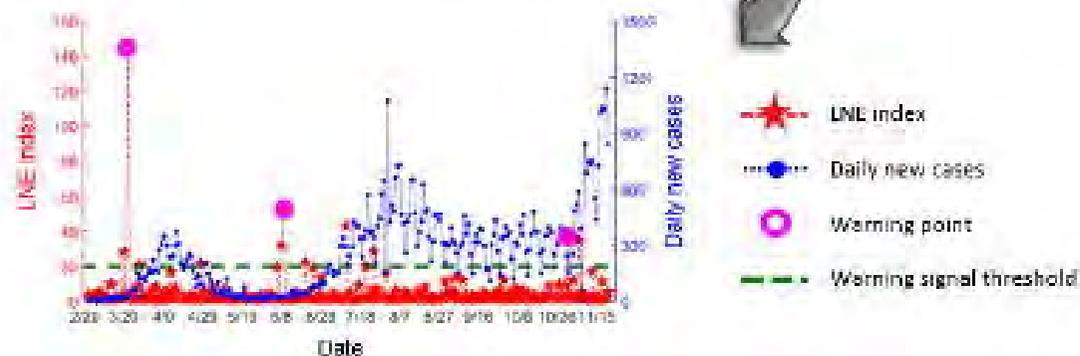
$$H_k(t) = -\frac{|SD(\bar{k}(t)) - SD(\bar{k}(t-1))|}{\log(L)} \sum_{i=1}^L p_i(t) \log(p_i(t))$$

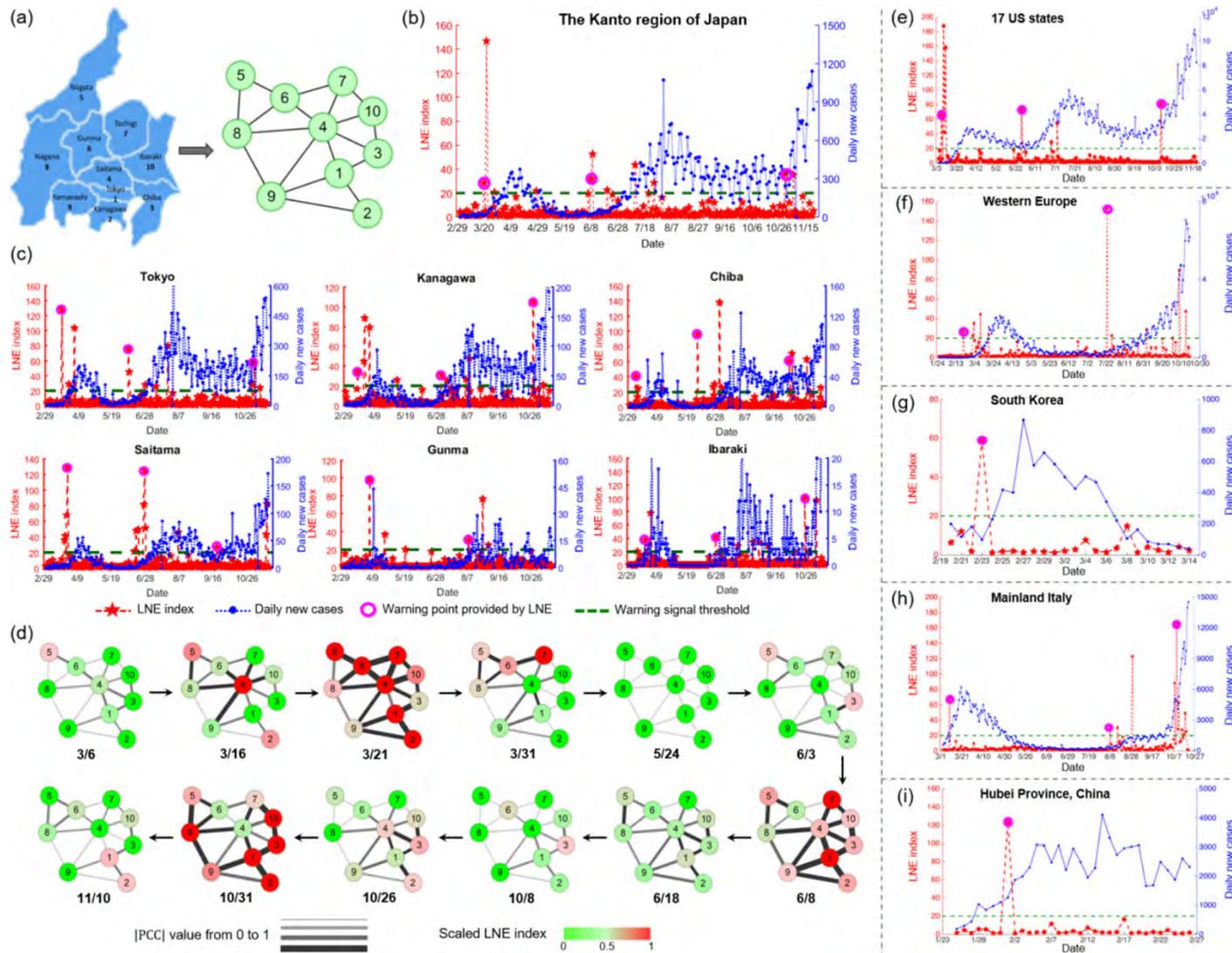
$$\text{with } p_i(t) = \frac{|PCC(\bar{k}_i(t), \bar{k}(t))|}{\sum_{j=1}^L |PCC(\bar{k}_j(t), \bar{k}(t))|}$$

Inferring the dynamic evolution of disease spread in the district-network



Detecting the early-warning signals of the infectious disease outbreaks





Real-time monitoring of COVID-19 spreads and outbreaks in the Kanto region of Japan and other regions. (a) A ten-node network of the Kanto region. (b) The LNE index (the red curve) and the number of daily new cases (the blue curve) in the Kanto region. (c) The district-specific (local) LNE indices (the red curves) and the number of daily new cases (blue curves) for six districts. (d) The dynamic evolution of the district-network during the epidemic. (e–i) The results of other five regions. For all the LNE indices, the fuchsia circles represent the early warning points, which are ahead of the drastic increases in daily new cases. In the case of multiple warning points appearing within a short period of time, the first warning signal is marked.

数理モデルの変遷

I. The Newtonian paradigm (17世紀～)

方程式: Given

解: Solved

II. The Poincaré-Runge-Kutta paradigm (19世紀末～)

方程式: Given

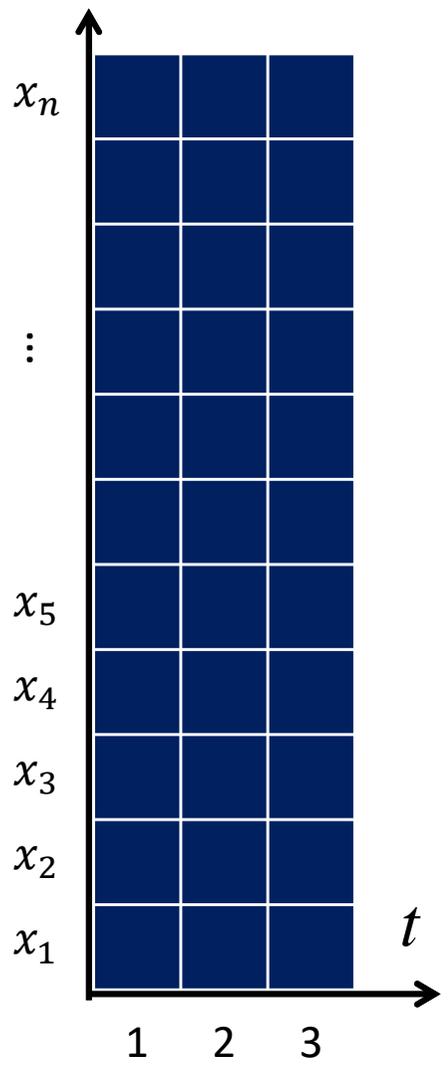
解: × (the geometric and qualitative theory, numerical calculation)

III. The algorithmic (computer-aided) modelling paradigm (1981年～)

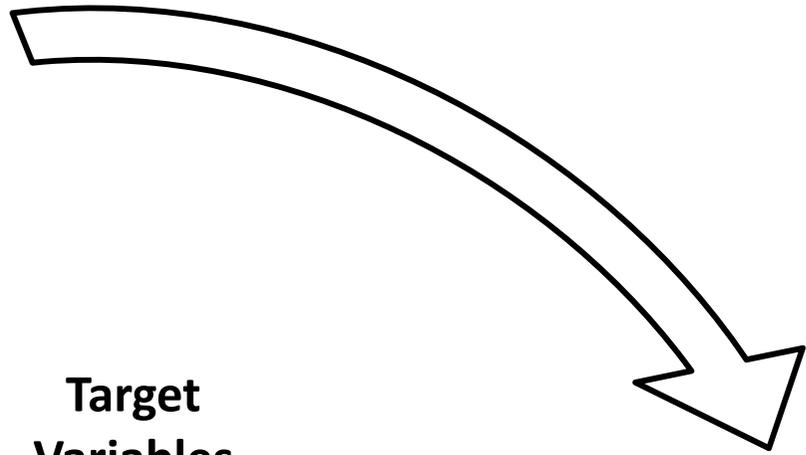
方程式: Not given (the embedding theory)

解: × (computer-aided approximation)

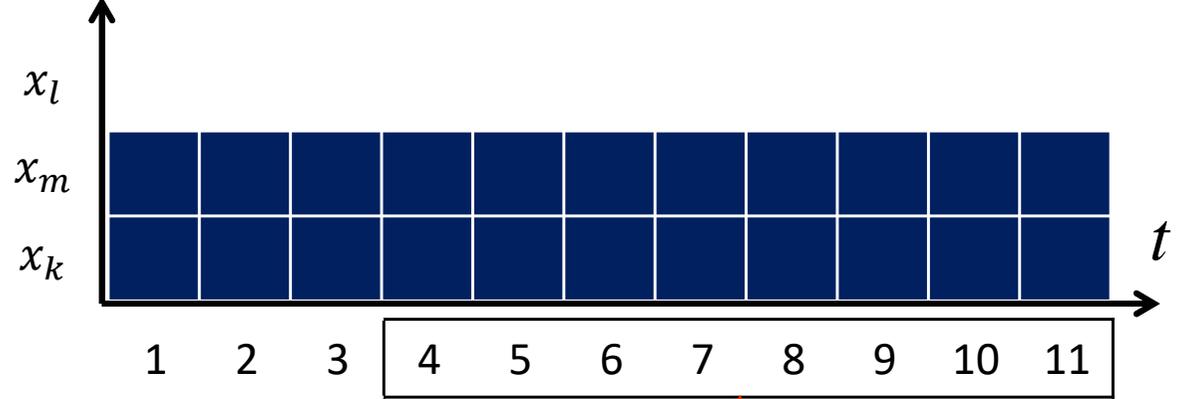
埋め込み (embedding) 定理に基づき, **時系列データ**から数理モデルを構築.



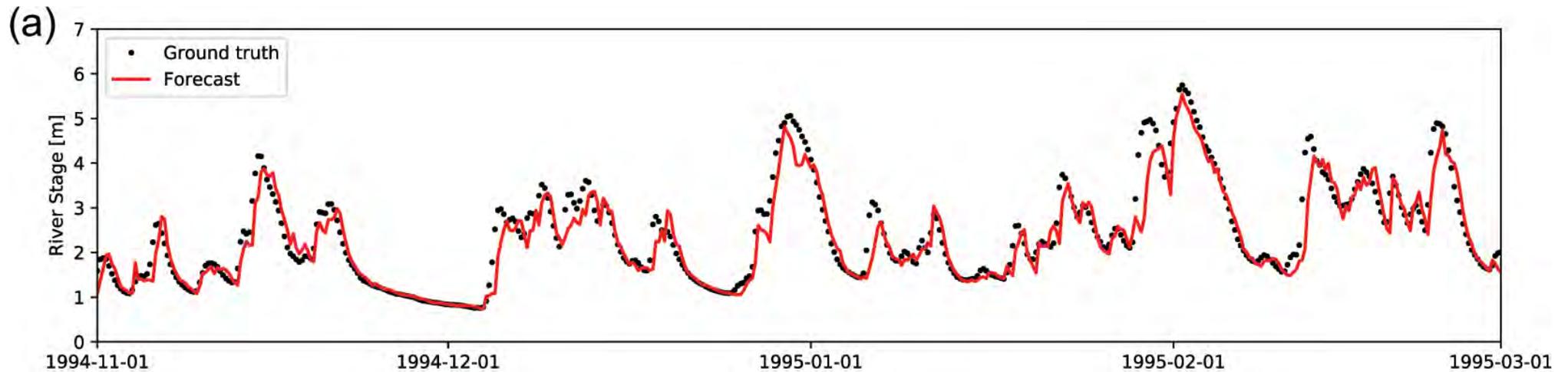
**Short-term High-dim
Measurements**



**Target
Variables**



Prediction



Forecast results for the flood dataset. Panel (a) shows a comparison of the ground truth and the proposed 24-h-ahead forecast. The proposed forecast did not underestimate the maximum river stage, which is the maximum value of the whole dataset.