Moonshot International Symposium
Dec 18, 2019, Bellesalle Tokyo Nihonbashi

DNB (Dynamical Network Biomarkers) Theory for Human Health

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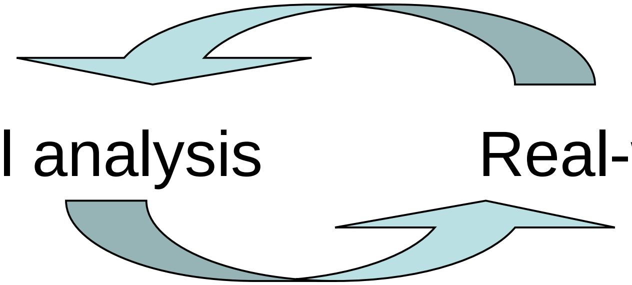
http://www.sat.t.u-tokyo.ac.jp/index.html

Mathematical Engineering

Mathematical modelling

Mathematics

Real-world



Mathematical analysis

Real-world problems

understand, solve, optimize, control, and predict

(systems with difficulty of these approaches

= complex systems)

International Research Center for Neurointelligence (IRCN), WPI

Development Study Core Unit

Rachel Wong

Kazuo Emoto

Yukiko Gotoh

Kuniyoshi Sakai

Kenichi Ohki

Director

Takao Hensch

Masanobu Kano

Technology Development Unit

Yasushi Okada

Arthur Konnerth

Haruo Kasai

Shoji Takeuchi

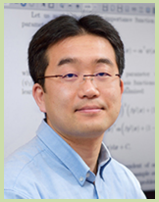
Neurodevelopmental Disorder Pathological Study Unit

Kiyoto Kasai

Takao Hensch

Mathematical Information Systems Unit

Hiroki Ueda



Masashi Sugiyama

Kazuyuki Aihara

Mathematical Modeling of NI for Novel AI and of Psychiatry and Neurological Disorders

PI (Information Science Unit): Kazuyuki Aihara

Experimntal Neuroscience

Mathematical Modeling and Analysis on Complex Neurodynamics in the Brain

Novel AI

Psychiatric and Neurological Disorders

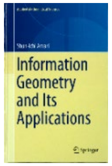
- Basic principles underlying neural circuit development and functions
- Complex six-layered structure of the cerebral cortex with recurrent connections, gap junctions, and projections from the limbic system
- Feedforward and feedback pathways between lower and higher cortical areas

- Complex systems modeling of neural circuit development and functions as well as their disorders
- Bifurcation-theoretical analysis on transitions between normal and impaired neurodynamics as well as between quasi-periodic states
- Nonlinear data analysis on spatio-temporal neuronal data
- Neuromorphic and neuro-inspired computational models and their hardware implementation

Related Historical Inheritances at Aihara's Lab in UTokyo

- J. Nagumo's neuronal circuits (1962)

- S-I. Amari's mathematical brainscience (1970s-) and information geometry (1980s-)



IRCN International Research Center for Neurointelligence

Brain/MINDS Beyond

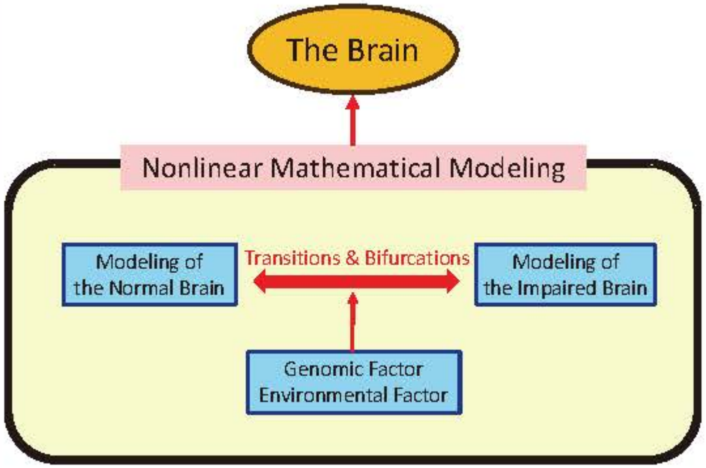
3-2. Surveys on next-generation AI technologies and development of fundamental technologies

Research and Development on Next-Generation AI and its Key Technology Based on Nonlinear Dynamics

Kazuyuki AIHARA

Ph.D., Professor, Institute of Industrial Science, The University of Tokyo

In this research project, we explore technological backgrounds of mathematical models related to information processing in the brain as well as next-generation AI based on such models, review the possibility of realization of such next-generation AI technology and trends of state-of-the-art research, and propose important tasks necessary for the realization of next-generation AI that learns from the dynamic brain particularly from the viewpoint of nonlinear dynamics with a focus on both functions of the normal brain and dysfunctions of the impaired brain. Then, we develop basic mathematical technology for innovative brain-type algorithms, and consider its applicability to robotics and mental illnesses.



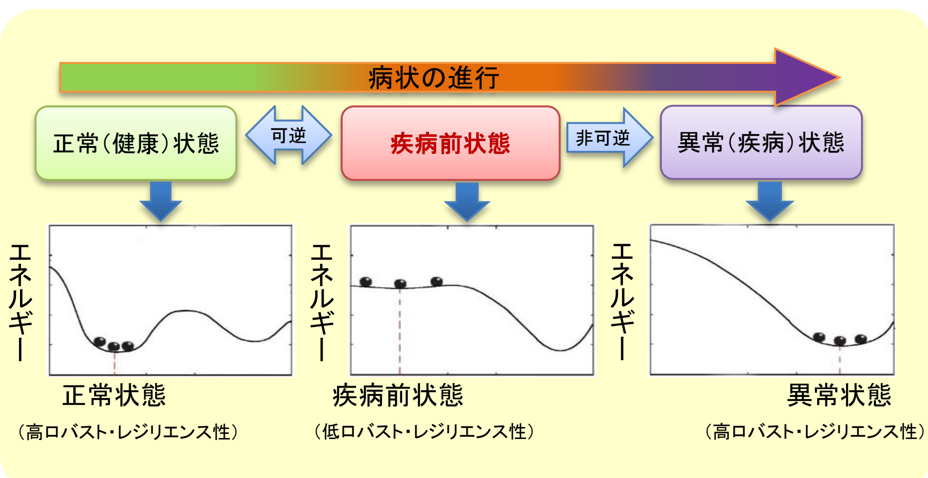
From DNA to DNB(Dynamical Network Biomarkers)

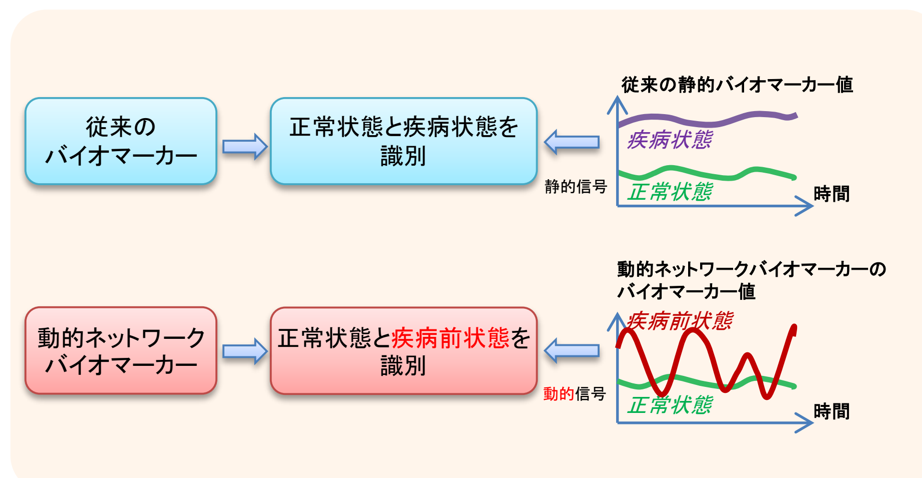
Detecting early-warning signals of complex diseases by dynamical network biomakers

DNB(Dynamical Network Biomarkers)

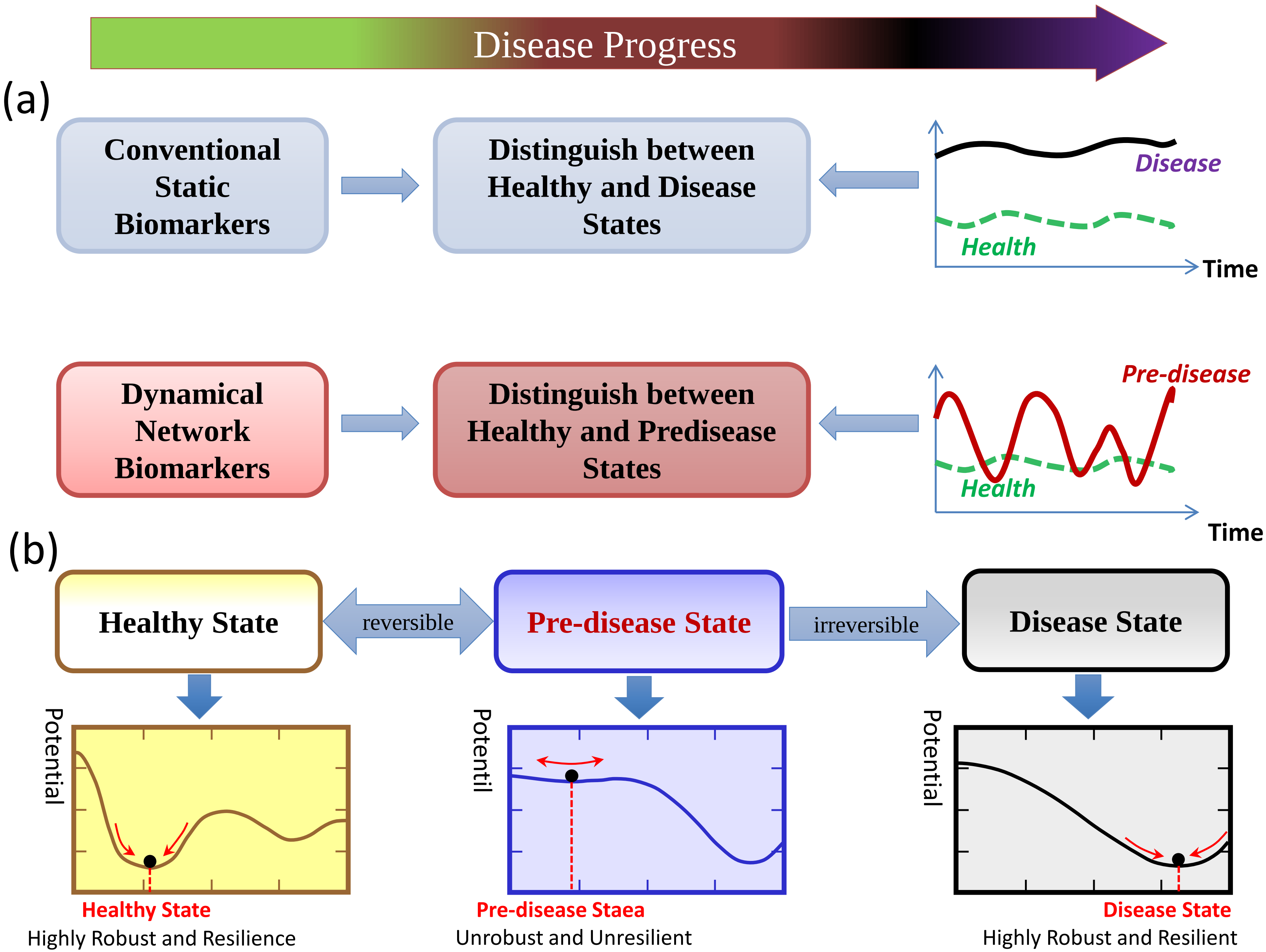
Problem: Difficulty of Finding Excellent Single Biomarkers. Impossibility of Detecting Early Warning Signals for Imminent Transitions to Disease State

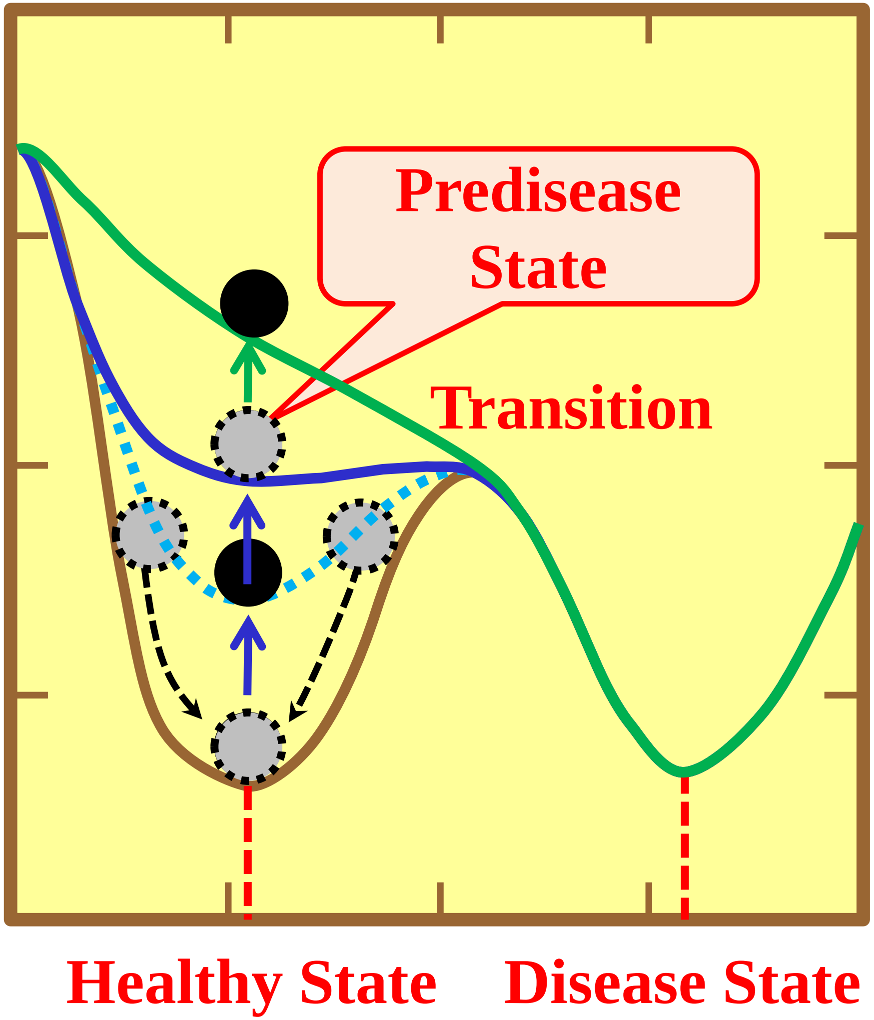
Proposal of an Entirely New Concept of Biomarkers that Provide the Early Warning Signals through Dynamics with Correlated Fluctuations（Patents2012-211921,2012-233886; *Scientific Reports*, **2**, 342, 2012; **2**, 423, 2012）。

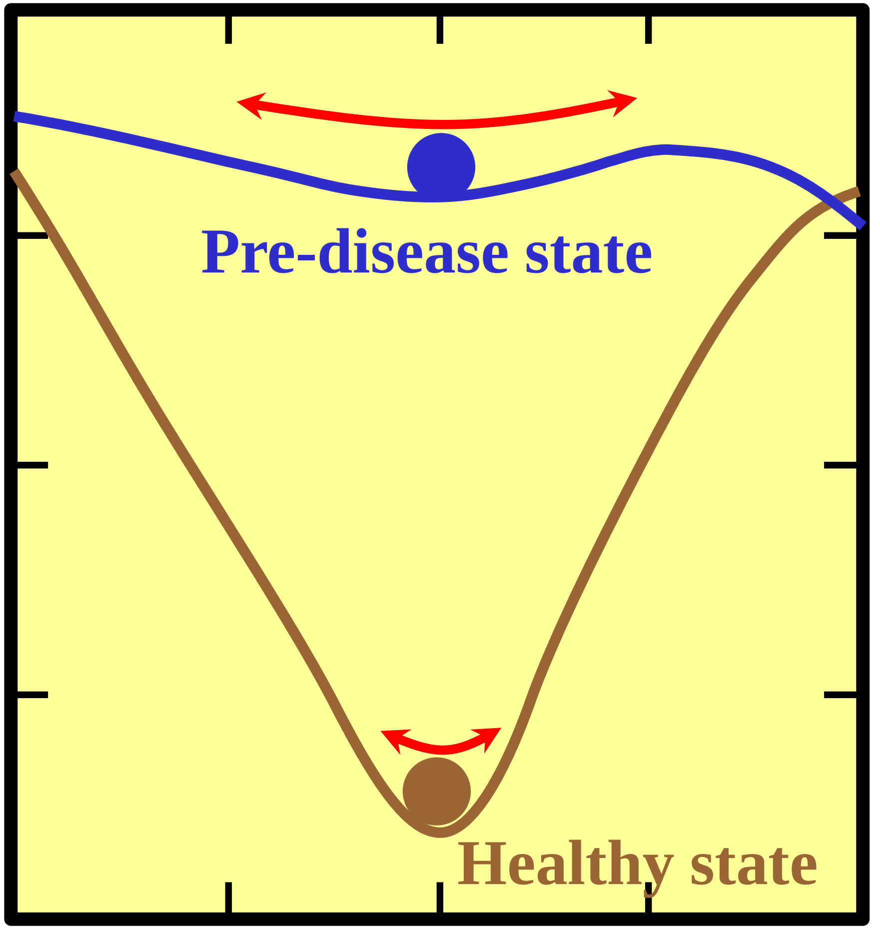


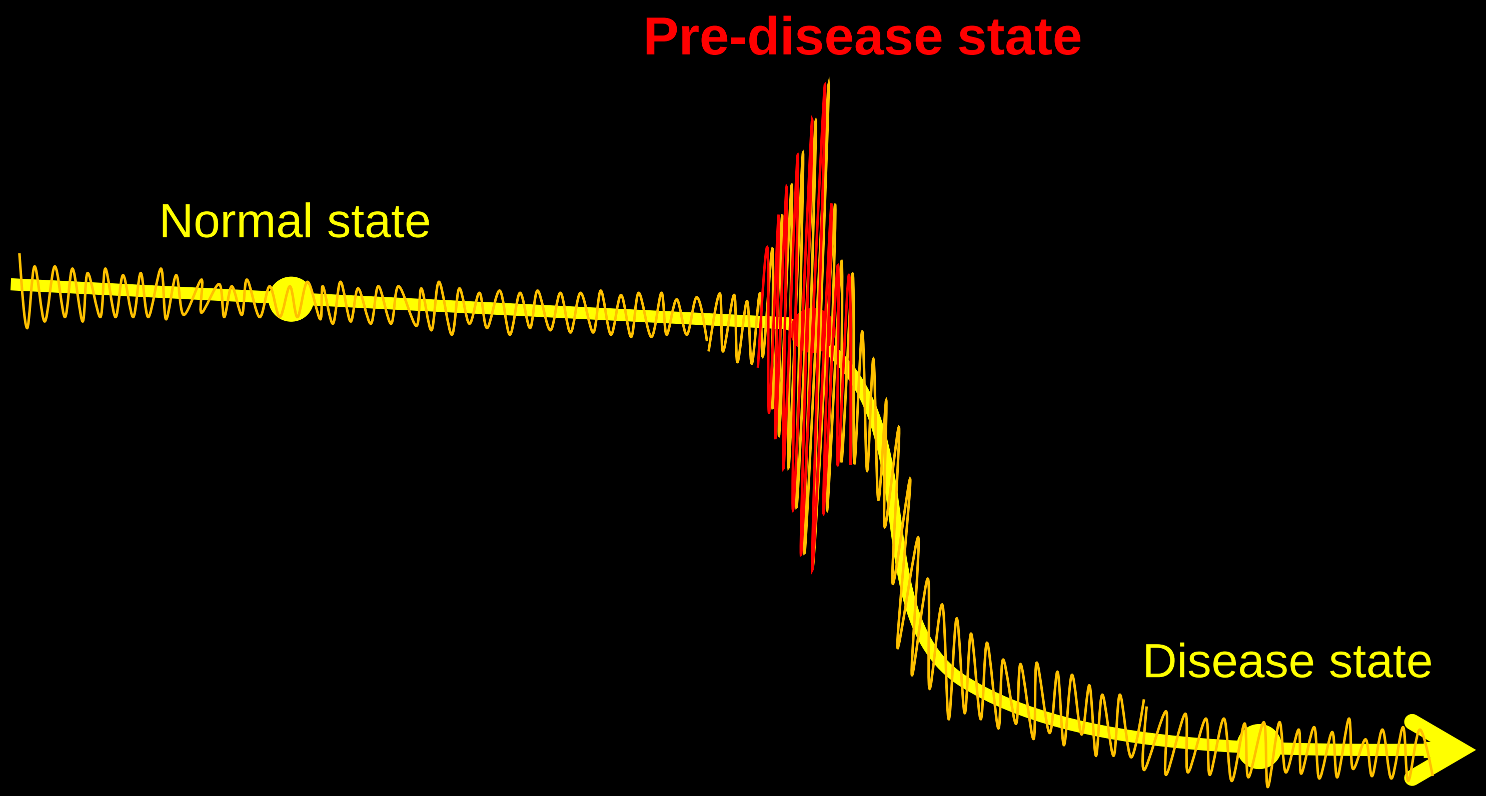


Applications to Power Grids with large Renewable Energy, Complex Engineering Systems, and Economical Data.


Disease Progress
(a)
Conventional Static Biomarkers
Distinguish between Healthy and Disease States
Disease
Health
Time
Dynamical Network Biomarkers
Distinguish between Healthy and Predisease States
Pre-disease
Health
Time
(b)
Healthy State
reversible
Pre-disease State
irreversible
Disease State
Potential
Potentil
Potential
Healthy State
Highly Robust and Resilience
Pre-disease Staea
Unrobust and Unresilient
Disease State
Highly Robust and Resilient


Predisease State
Transition
Healthy State
Disease State


Pre-disease state
Healthy state



Disease progression

Local Codim-1 Bifurcations

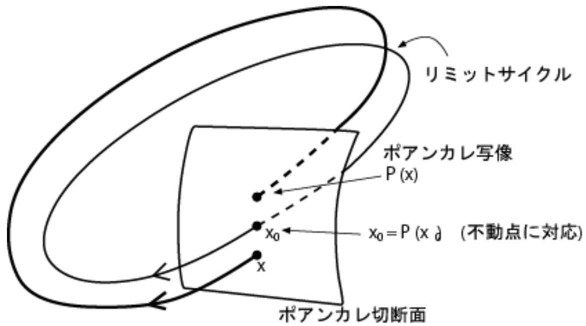
$$\frac{dX(t)}{dt} = F(X(t)) \xrightarrow[\text{Poincare Section}]{} x(t+1) = f(x(t)) \xrightarrow[\text{Linearization}]{} \xi(t+1) = \frac{\partial f}{\partial x} \cdot \xi(t)$$

$t \in R$ $\qquad\qquad\qquad\qquad$ $t \in Z$

$\downarrow$

Linearization

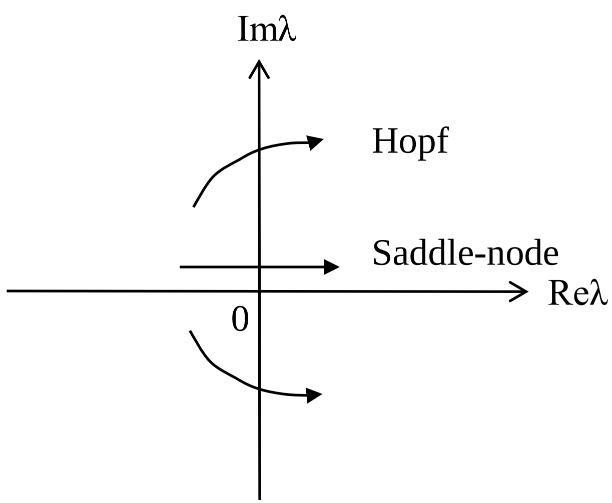
$$\frac{d\xi(t)}{dt} = \frac{\partial F}{\partial X} \cdot \xi(t)$$

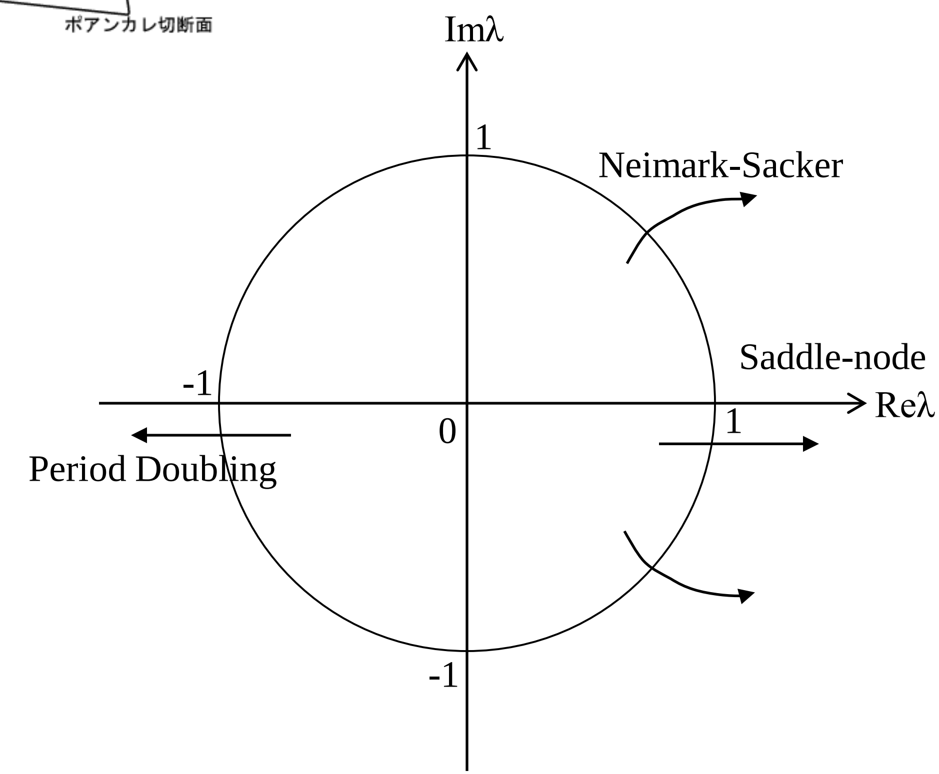


$\downarrow$

Bifurcation Analysis

Bifurcation Analysis





Main Theorem

1. If both i and j are in DNB,

Pearson Correlation $pcc(x_i, x_j) \rightarrow \pm 1$

Standard Deviation $sd(x_i)$ and $sd(x_j) \rightarrow \infty$

2. If only i is in DNB,

Pearson Correlation $pcc(x_i, x_j) \rightarrow 0$

Standard Deviation $sd(x_i) \rightarrow \infty$ but $sd(x_j) = \mathit{bounded}$

3. If both i and j are not in DNB,

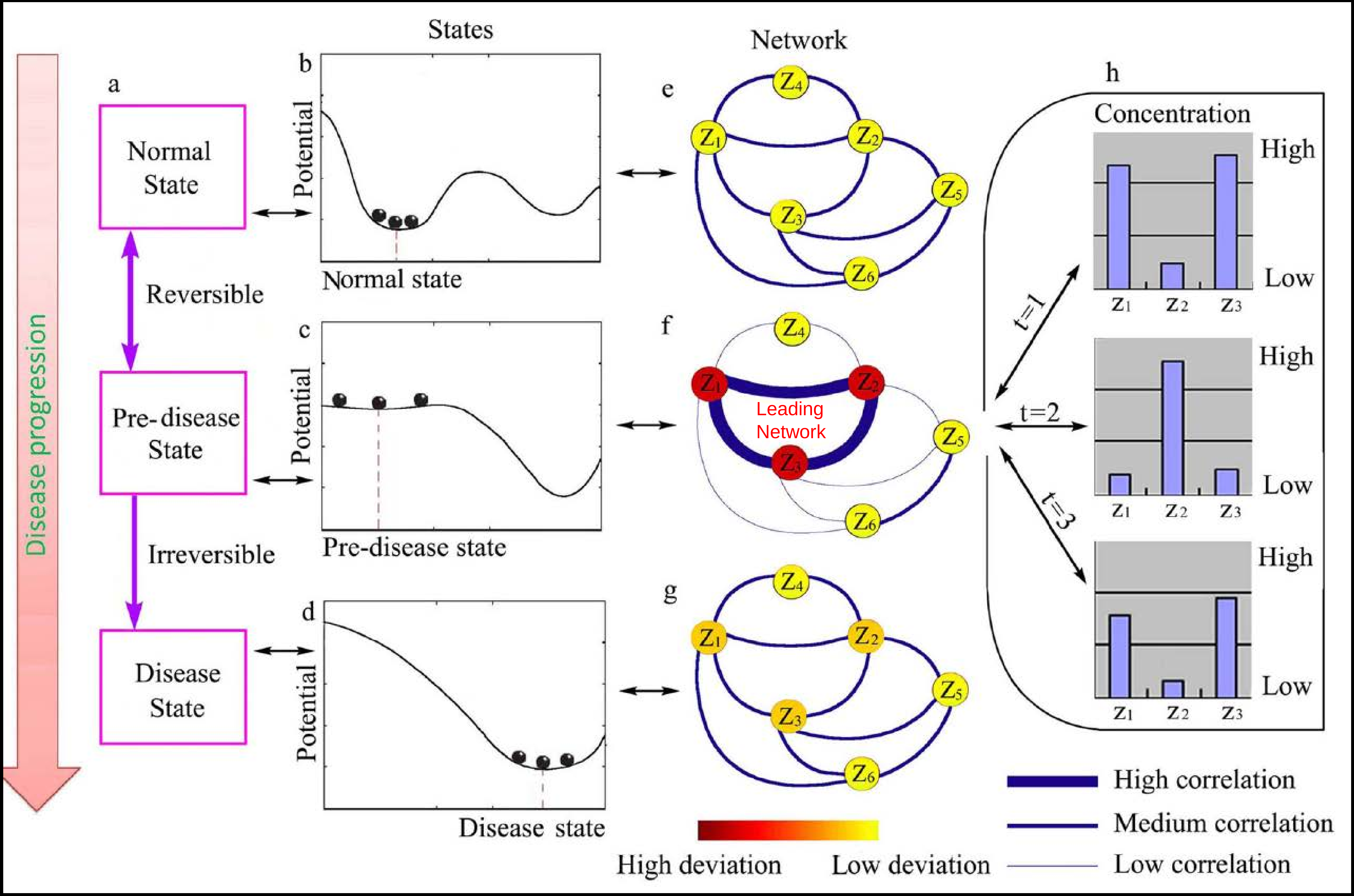
Pearson Correlation $|pcc(x_i, x_j)| \rightarrow a \quad (0 < a < 1)$

Standard Deviation $sd(x_i)$ and $sd(x_j) = \mathit{bounded}$

Three Measurable Conditions → **Critical State**

Dynamical Network Biomarker (DNB)

（Chen et al., Sci. Rep.,2:342,2012)

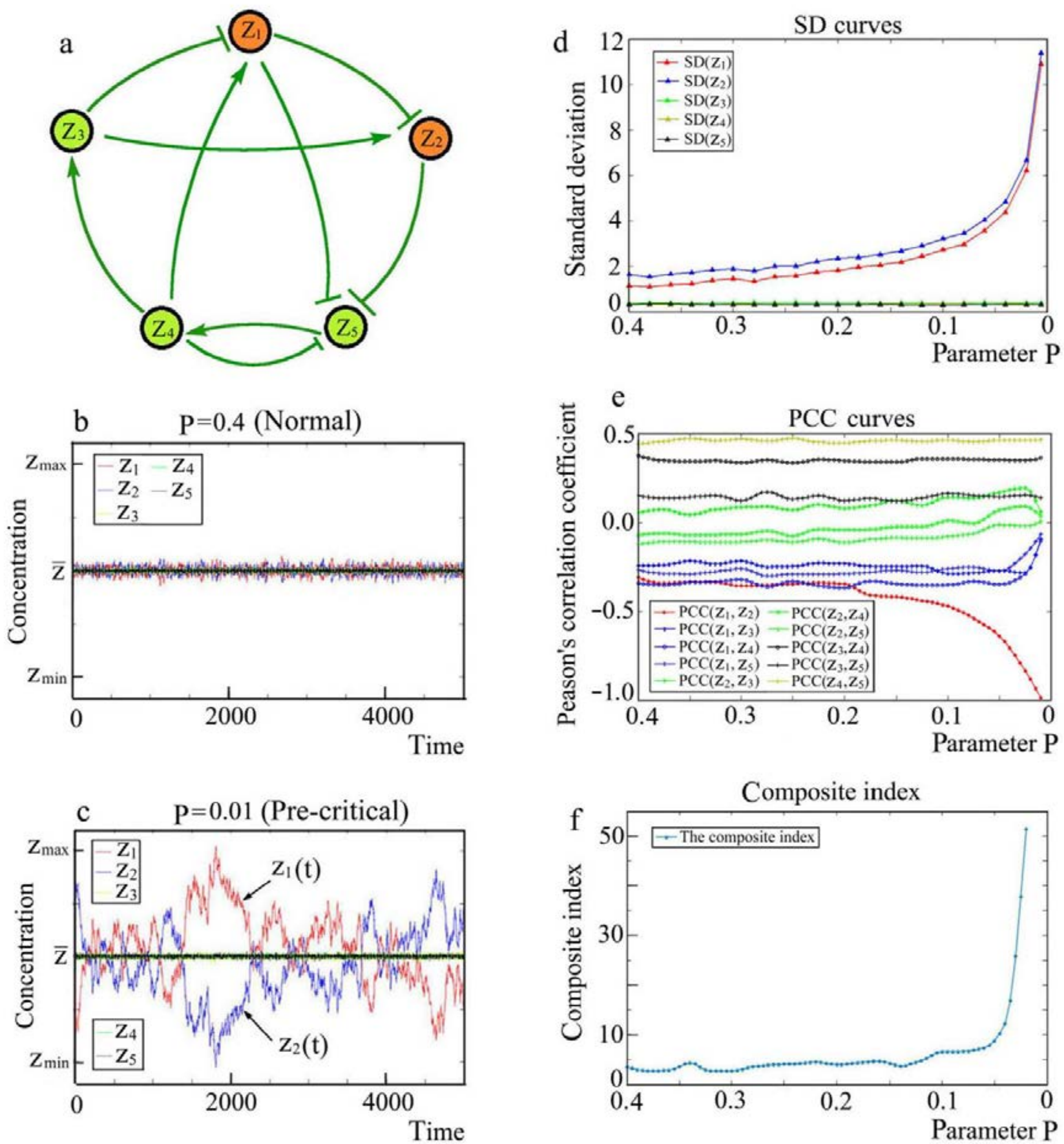


Composite Indicator based on DNB

$$I =: SD_d \cdot PCC_d$$

PCC_d : *average PCC of DNB in absolute value*
SD_d : *average SD of DNB*

Based on the two conditions



Numerical validation of theoretical results. (a) A five-gene model for a DNB and an early-warning signal. The network model and detailed background are described in Supplementary Information B. The tipping point is at P50 in the theoretical model, at which the system undergoes a critical transition or a bifurcation detected by z_1 and z_2. (b)–(c) When the system approaches the tipping point (P50), z1 and z2 become closely correlated with increasingly strong deviations from P50.4 to P50.01. (d)–(e) Figures show the curves of SDs and PCCs for the variables against the parameter P, which clearly indicate the tendency of z_1 and z_2, i.e., their fluctuations ($SD(z_1)$ and $SD(z_2)$) and correlation ($|PCC(z_1, z_2)|$) increase drastically whereas their correlations with other nodes ($|PCC(z_1, z_3)|$), $|PCC(z_1, z_4)|$, $|PCC(z_1, z_5)|$, $|PCC(z_2, z_3)|$, $|PCC(z_2, z_4)|$, and $|PCC(z_2, z_5)|$) decrease drastically when the system approaches the tipping point, which satisfies all three criteria for the DNB. (f) The curve shows the clear tendency of the composite index near the
tipping point for the DNB composed of (z_1, z_2), which can be used as the early-warning signal for predicting the imminent change in the concerned system.

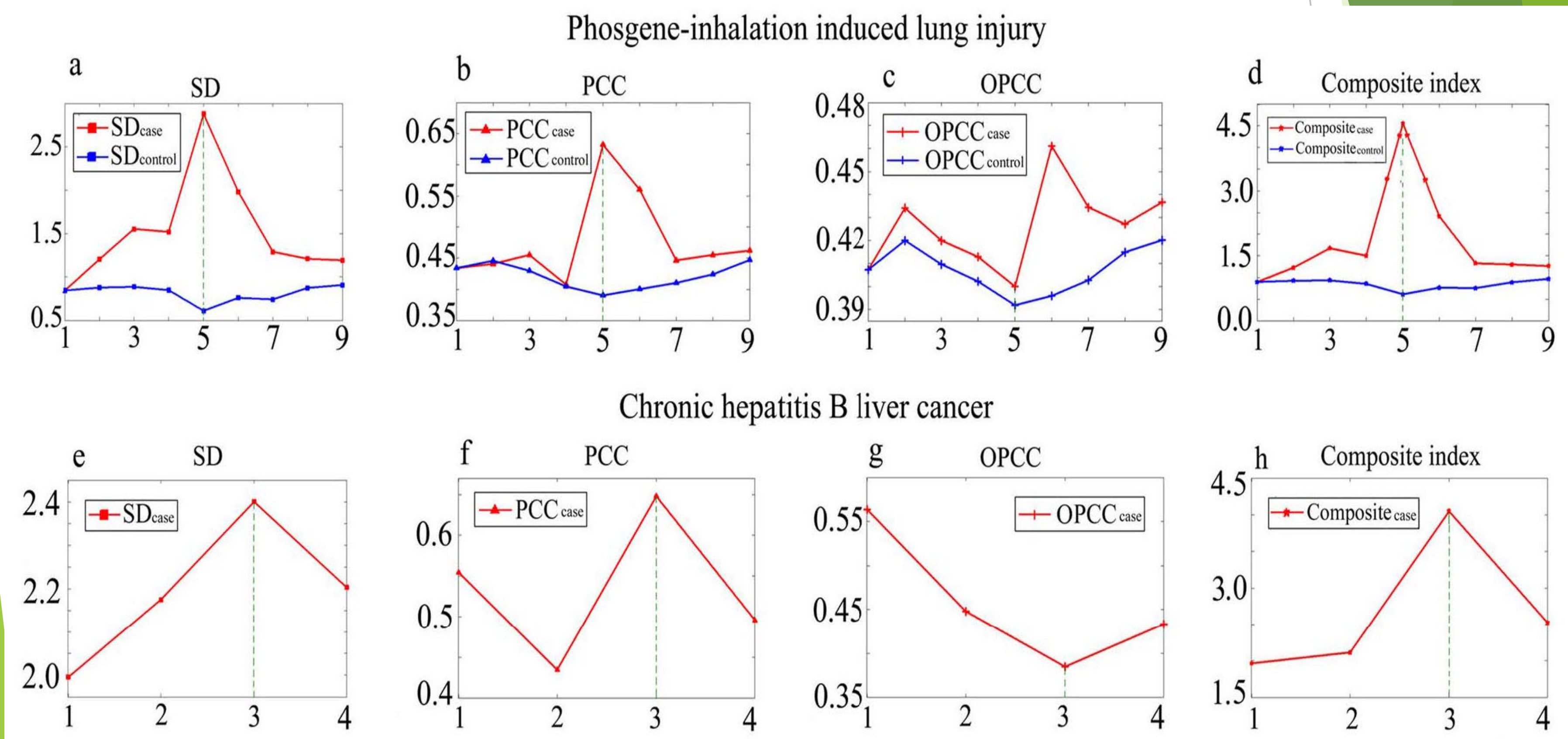
（Chen et al.,Sci.Rep.,2:342,2012)

Three Diseases

- Acute Lung Injury — Mouse
- Liver Cancer (HBV, HCV) — Human
- Lymph Cancer — Human

Chen, et al., Scientific Reports, 2, 342, 2012
Liu, et al., Scientific Reports, 2, 813, 2012
Liu, et al., Medicinal Research Reviews, 2013

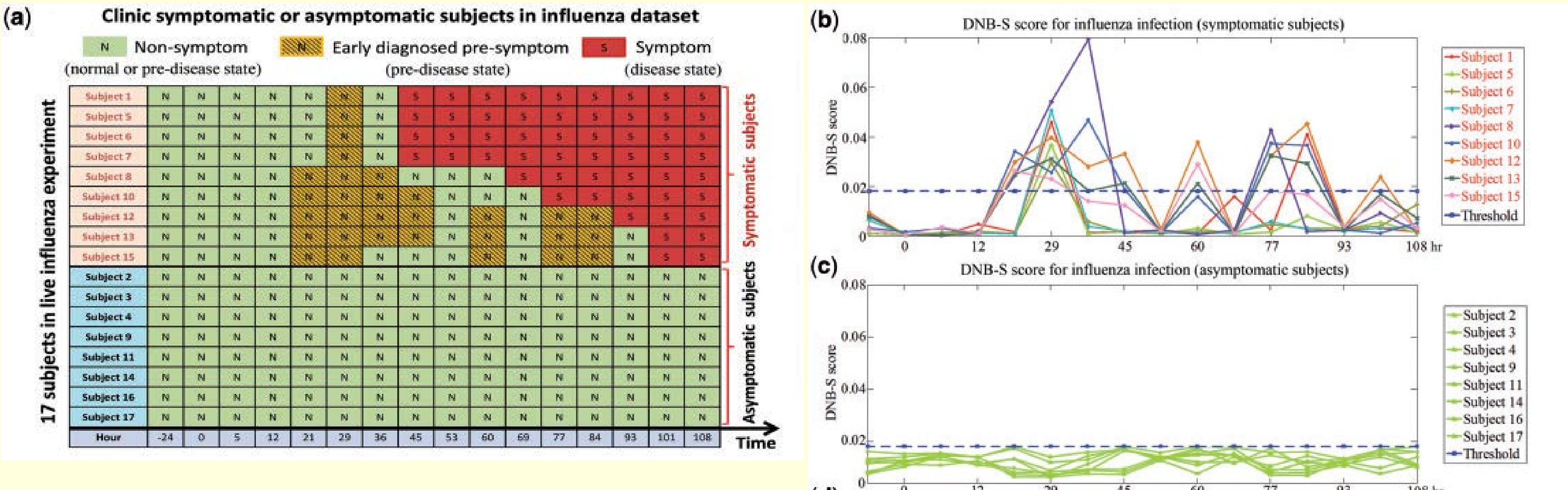
Application: prediction of lung injury and liver cancer(from hepatisis to cirrhosis)



（Chen et al., Sci. Rep.,2:342,2012)

17 healthy human volunteers received intranasal inoculation of flu H3N2(Huang et al,PLoS Genetics,2011).

Gene-expression profiles of peripheral blood were analysed by DNB.



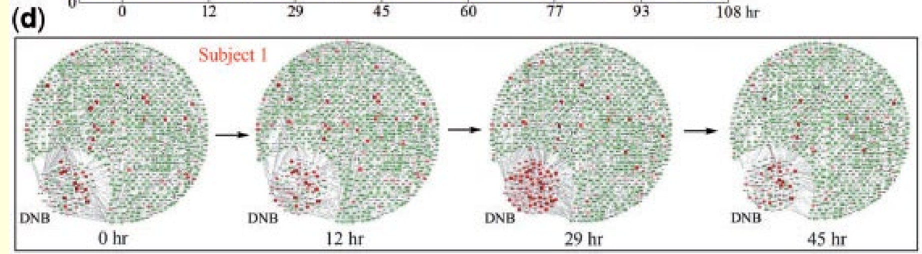
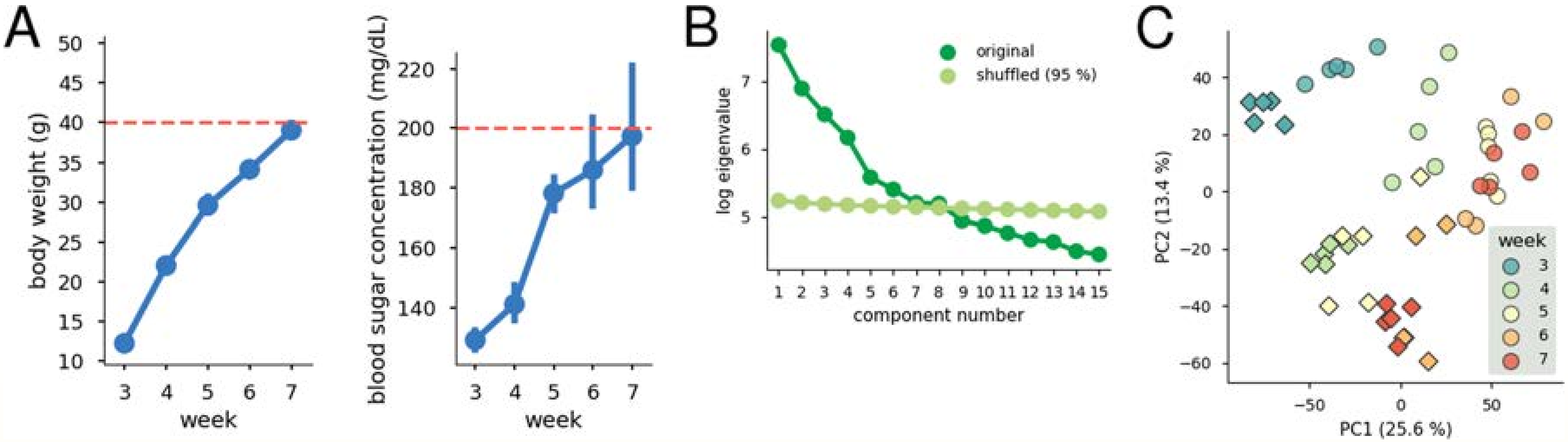


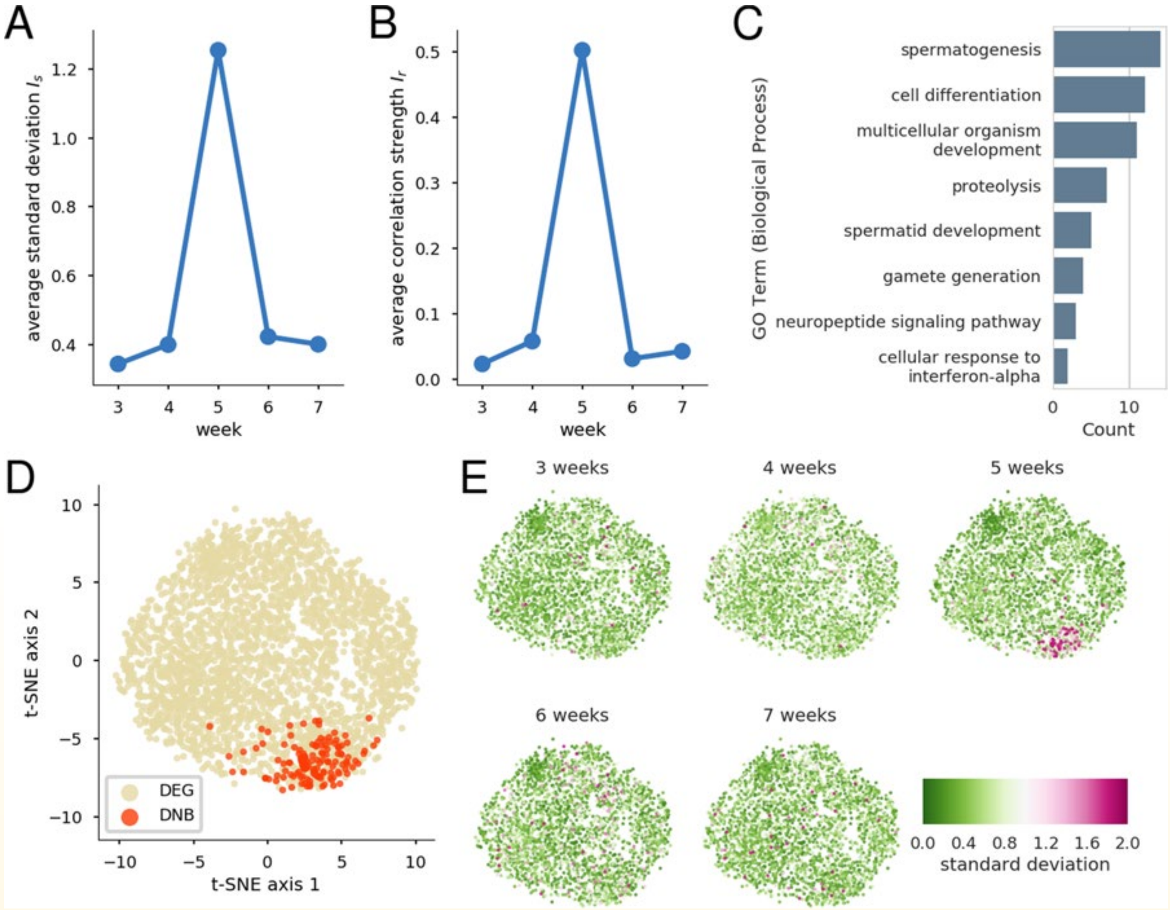
Fig. 4. Identifying the pre-disease state for live influenza infection of 17 humans based on a single sample. We demonstrate early diagnosis of live influenza infection in 17 humans using a real biomedical dataset. (a) The clinic symptoms (S) and non-symptoms (N) at different time points among the 17 subjects with live influenza infection based on real clinic tests. (b)-(c) show the DNB-S scores of nine single-sample symptomatic subjects (humans) and eight asymptomatic subjects (humans) for influenza infection resulting from H3N2 virus. The pre-disease states or presymptom for influenza infection occurred around 29 h (i.e. 29, 36 and 45 h), whereupon the DNB-S scores became respectively higher than the threshold shown in (b). All symptomatic subjects were correctly identified before the clinical diagnosis of the disease state (b), whereas all asymptomatic subjects showed no signals of the pre-disease states and were also correctly classified (c). (d) The dynamic changes in the molecular network of a single-sample subject (Subject 1) at 0, 12, 29 and 45 h (sliding window) with the corresponding DNB, where the color of the nodes represents the fluctuation strength of molecular expressions, and each edge represents the correlation between two nodes. It can be seen that at 29 h, there is a strong signal to indicate the pre-disease state or pre-symptom

Rui Liu, Xiangtian Yu, Xiaoping Liu, Dong Xu, Kazuyuki Aihara, and Luonan Chen
Identifying critical transitions of complex diseases based on a single sample
Bioinformatics first published online February 10, 2014, doi:10.1093/bioinformatics/btu084



Body weights, blood sugar concentrations, and PCA of the transcriptome data. (A) Body weights and blood sugar concentrations measured from TSOD mice. Error bars show 95% confidence intervals. Red dashed lines show the suggested thresholds for defining obesity in TSOD mice (body weight ≥40 g) and prediabetes in rodents (blood glucose level ≥200 mg/dL). (B) Scree plot of the largest 15 components. The number of meaningful PCs is estimated to be the number of eigenvalues calculated from the original transcriptome data larger than the 95 percentiles of eigenvalues calculated from shuffled data. For more details, see Dimensionality reduction in Materials and Methods. © PCA plot of the transcriptome of TSOD mice (circles) and TSNO mice (diamonds). The numbers in parentheses denote explained variance ratios corresponding to each PC. Regarding results of other meaningful components, see Supplementary Fig. S1. PC: principal component.

Koizumi et al., Scientific Reports, 9, 8767 (2019).



Characteristics of 147 DNB genes. (A) The average standard deviation Is. (B) The average correlation strength Ir. (C) Enriched GO annotations. No KEGG pathway was enriched in the DNB genes. (D) A t-SNE plot of the union set of the DNB genes and 2665 DEGs. The overlapping genes were colored as DNB genes. For more details, see Dimensionality reduction in Materials and Methods. (E) Spatio-temporal fluctuation patterns of the DNB genes and DEGs. The color scale shows the standard deviation.

Koizumi et al., Scientific Reports, 9, 8767 (2019).

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

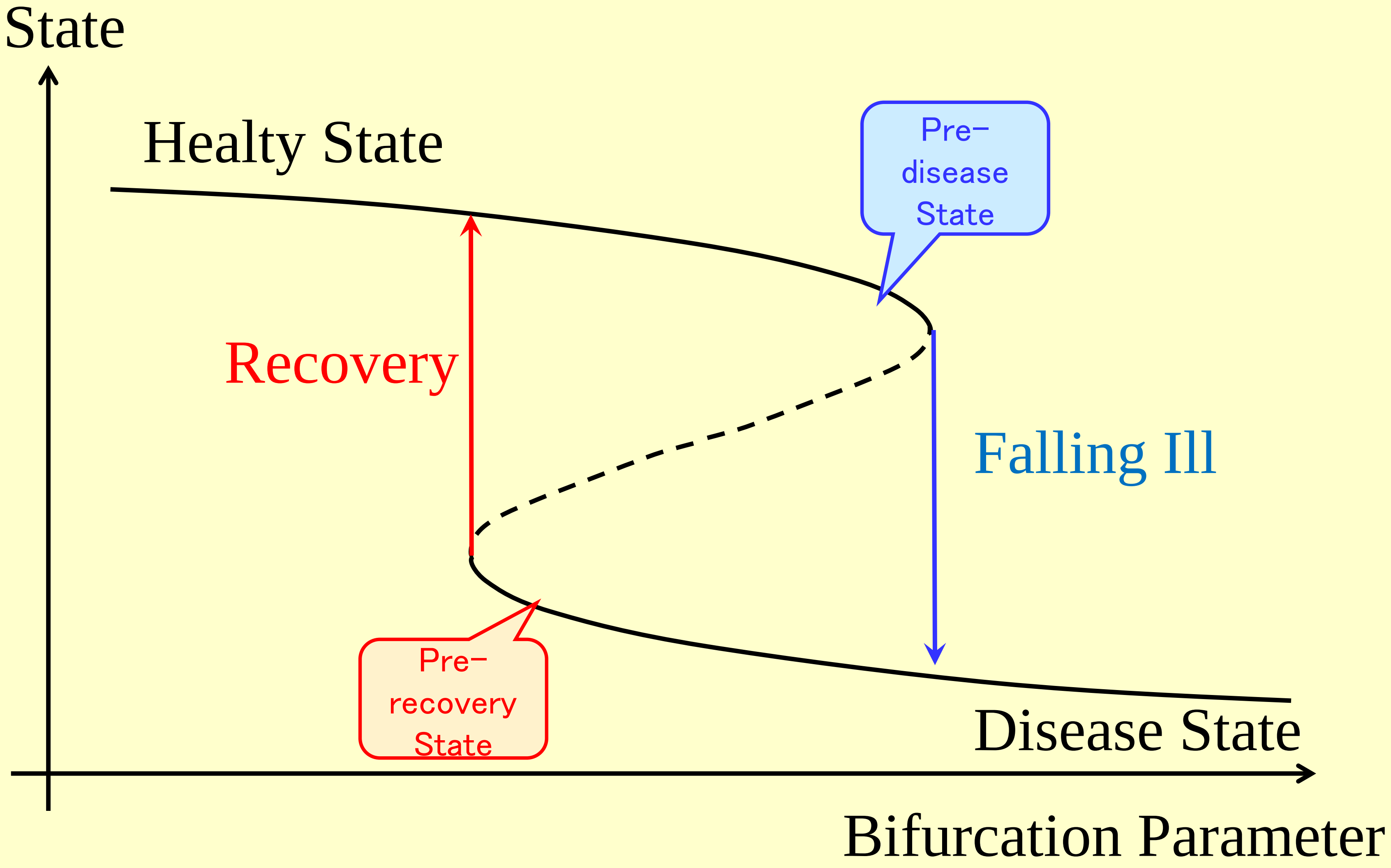
Early diagnosis by dynamical network biomarkers

DNB:

Common Components

+

Individual Components



Two Applications of DNB Theory

Conclusion

- Harness of High-Dimensional Data for Detecting Early-Warning Signals of State Transitions like Complex Diseases.