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REVIEW

Dynamical network biomarkers for identifying critical transitions and their driving networks of biologic processes

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Non-smooth or even abrupt state changes exist during many biological processes, e.g., cell differentiation processes, proliferation processes, or even disease deterioration processes. Such dynamics generally signals the emergence of critical transition phenomena, which result in drastic changes of system states or eventually qualitative changes of phenotypes. Hence, it is of great importance to detect such transitions and further reveal their molecular mechanisms at network level. Here, we review the recent advances on dynamical network biomarkers (DNBs) as well as the related theoretical foundation, which can identify not only early signals of the critical transitions but also their leading networks, which drive the whole system to initiate such transitions. In order to demonstrate the effectiveness of this novel approach, examples of complex diseases are also provided to detect pre-disease stage, for which traditional methods or biomarkers failed.

INTRODUCTION

Various evidences [1–5] show that many biologic processes, such as cellular differentiation processes, cellular proliferation processes and disease progression processes, involve non-smooth or abrupt state transitions, which result in drastic changes of system states or qualitative changes of phenotypes. Adipocyte differentiation is such a process. A pluripotent stem cell, with the capacity to differentiate along mesenchymal lineages of myoblast, chondroblast, osteoblast and adipocyte, initially gives rise to a preadipocyte, and then drastically undergoes clonal expansion and subsequent terminal differentiation, which result in a mature adipocyte with remarkable changes in cell morphology, cytoskeletal components and the level and type of extracellular matrix components secreted [6]. A disease progression process is also such an example, for which the system gradually moves from a normal state to a pre-disease state, and then, with further deterioration, drastically transits to a disease-state [7,8]. Generally, such a drastic transition or event can be described as a bifurcation phenomenon from a mathematical viewpoint. Figure 1 schematically shows this multistage event with the before-transition state, pre-transition state and after-transition state, where the before-transition state is a stage before the transition, during which the system is at a stable state and changes gradually or smoothly, while the pre-transition state is the limit of the before-transition state just before the imminent drastic transition, which is still reversible to the before-transition state with appropriate perturbations of system parameter. On the other hand, the after-transition state is another stable state after the transition, which is significantly different from the before-transition state. However, from the after-transition state, usually it is difficult to return to the before-transition state even by big perturbations. The pre-transition state can be considered as around a bifurcation or tipping point [9]. Note that, the normal

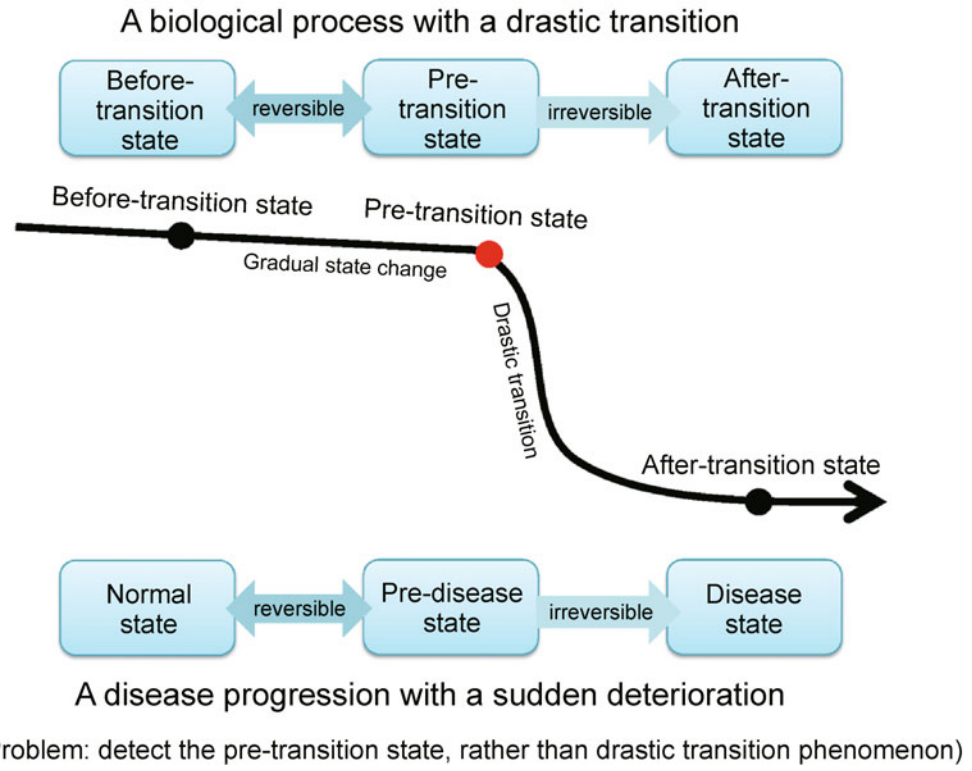

Figure 1. A biologic process with a critical transition. A state or phase change involves three stages, i.e., the before-transition stage, pre-transition stage and after-transition stage. The before-transition state is a stage before the transition, during which the system is at a stable state and changes gradually or smoothly. The pre-transition state is the limit of the before-transition state just before the imminent drastic transition, which is generally reversible to the before-transition state with appropriate perturbations of system parameters. Actually, the pre-transition state can be viewed as a part of the before-transition state. On the other hand, the after-transition state is another stable state different from the before-transition state. However, from the after-transition state, usually it is difficult to return to the before-transition state even with big perturbations. Note that, the normal state, pre-disease state and disease state during a disease progression process correspond to the before-transition state, pre-transition state and after-transition state in a general biologic process, respectively.

state, pre-disease state and disease state during a disease progression process correspond to the before-transition state, the pre-transition state and the after-transition state in this nonlinear process, respectively. In the study of state transitions, there is some previous work using the adaptive landscape or potential function to analyze biologic systems [10].

Clearly, to elucidate the molecular mechanism of such complex behavior, it is crucial to identify the pre-transition state, which is able not only to predict the state transition event but also provide information on driver molecules that initiate the critical transition. For the biomedical area, so far there are a great number of studies published in literature on classifying the normal state (or the before-transition state) and the disease state (or the after-transition state), i.e., identifying a disease phenotype by biomarkers, which includes traditional molecular biomarkers [11–17] and network biomarkers (or module biomarkers) [18–35]. Their work mainly focus on distinguishing disease samples from normal samples by comparing the distinct molecular expressions or network scores in a disease state [26]. However, traditional biomarkers fail to indicate pre-disease samples due to their static nature, i.e., either molecular expressions or network scores show little change from the normal state to the pre-disease state before the transition or tipping point is reached [7,8] due to similar phenotypes. To overcome this difficulty, recently, a new concept called "dynamical network biomarker" (DNB) [7] was developed to detect the early signals of the critical transition based on the bifurcation and center manifold theory. A DNB is composed by a group of molecules, i.e., genes or proteins, which are strongly correlated with each other but increasingly fluctuate in their expressions when the system is near a pre-transition state. This group of molecules is also proven to be the leading network [8] for

the critical transition, which makes the first move from the before-transition to the after-transition state, and thereby is causally related to driver molecules or a causal network to initiate the transition. To computationally identify the DNB from high throughput data, e.g., microarray or proteomics data, an efficient algorithm based on the state-transition local network entropy was also proposed [8]. Different from the conventional biomarkers, which are required to keep consistent values for respective samples, the DNB is a strongly correlated molecular subnetwork where the concentrations of molecules, however, dynamically fluctuate without keeping constant values in the critical state (see Figure 2). Note that DNB is to identify not the transition process but the pre-transition state just before the transition, as summarized in Figure 1.

In this paper, focusing on the dynamical features to characterize the pre-transition state from the viewpoint of dynamics and network, we review the latest work to study complex biologic processes based on DNB from both theoretical and application prospectives. We also present application examples of DNBs on detecting the pre-disease state of complex diseases, and show the differences between DNBs and traditional molecular biomarkers to illustrate why DNBs are able to distinguish pre-disease states from normal states even by a small number of samples, for which traditional molecular biomarkers failed.

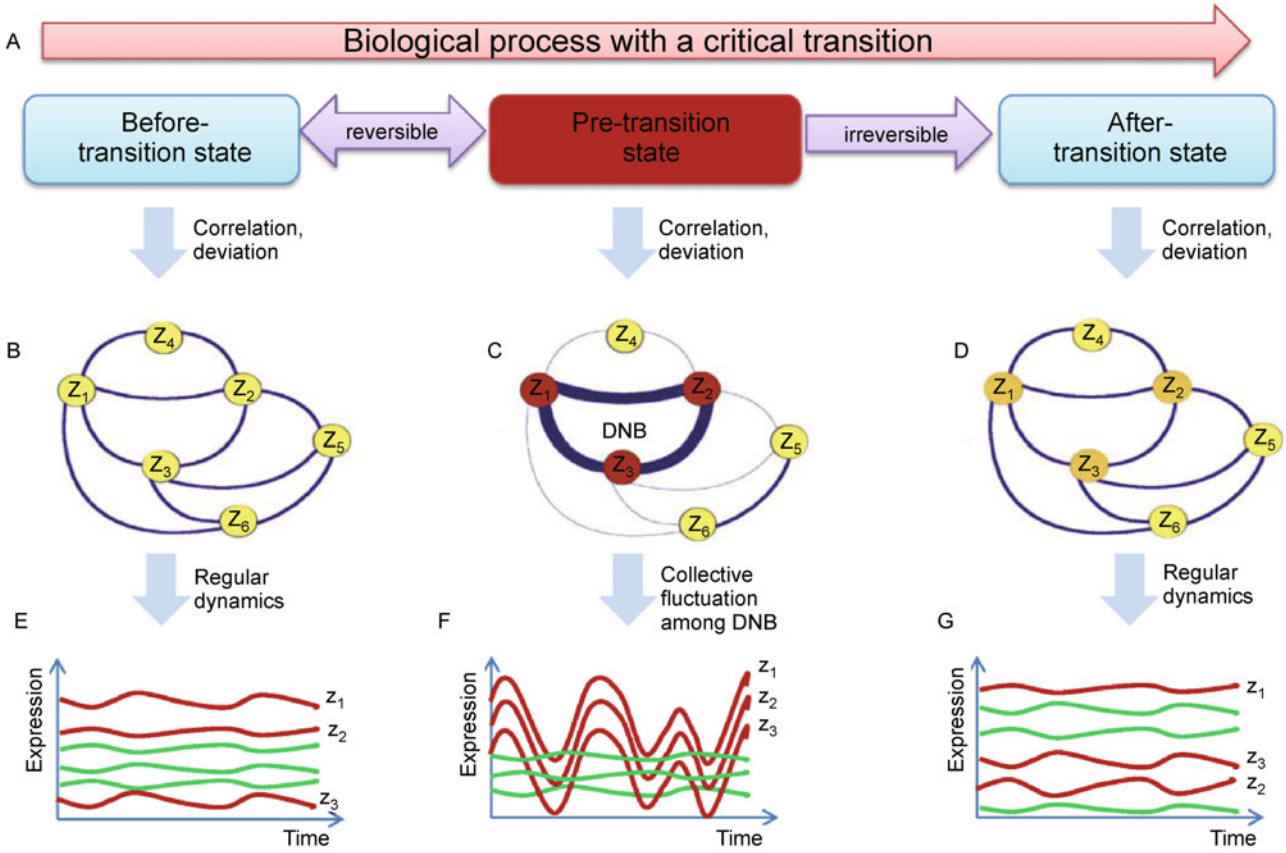

Figure 2. Dynamical network biomarkers. A schematic illustration of a dynamical network biomarker (DNB) or the leading network during a biologic process. (A) Three states during a biologic process with a state transition. (B,E) The before-transition state is a steady state, during which the expressions of the molecules are almost consistent (E). Molecules are regulated by each other, thus forming a biomolecular network (B).(C,F) The pre-transition state is defined as a limit of the before-transition state and situated before the imminent state transition point is really reached. At this stage, a group of molecules are strongly correlated among themselves but lose the correlation with the remaining molecules (C). This group of molecules are also highly fluctuated (F), and are called a DNB (i.e., Fz_1, z_2, z_3G) or the leading network of the transition. (D,G) The after-transition state is another steady state, during which the expressions of the molecules remain consistent again. The traditional biomarker can be used to distinguish the before-transition state from the after-transition state, but fails to distinguish the pre-transition state. In (B–D), the color of nodes represents the strength of the standard deviation (SD) and the thickness of edges represents the value of the Pearson's correlation coefficient (PCC). The green lines in (E–G) represent the dynamics of z_4, z_5, and z_6, i.e., non-DNB molecules, and the red lines represent that of DNB molecules.

THREE STAGES FOR A STATE TRANSITION

As shown in Figure 1, a biologic process with a state transition can be divided into three stages, i.e., the before-transition state, pre-transition state and after-transition state. Note that similar partition of a biologic process has also been employed in a lot of previous work (e.g., [36]). The sudden change occurs at a pre-transition state, or the so-called tipping point, at which the system shifts abruptly from one state to another. To describe the underlying dynamical mechanism of complex biologic systems, their evolutions are modeled as time dependent nonlinear dynamical systems or networks, in which the abrupt state change is often viewed as the state transition at a bifurcation point [37]. This is well known in dynamical systems theory as a bifurcation that results in a qualitative transition in dynamical structure or attractors [38,39]. Clearly, elucidating such a critical transition at the network level holds the key to understanding the fundamental mechanism of biologic processes.

However, for many biologic processes, it is not easy to identify a pre-transition state because the state of the system may change little before the pre-transition state is reached. In other words, there may be little difference between the before-transition state and the pre-transition states, as shown in Figure 1. That is also why traditional techniques based on snapshot static measurements of biomarkers (e.g., differential expressions) fail to distinguish a pre-transition state from a before-transition state.

To overcome this problem, a general indicator was recently developed based on a model free concept with the theoretical foundation on bifurcation theory, i.e., a dynamical network of biomarkers, or a dynamical network biomarker (DNB), which can distinguish a pre-transition state from other states [7] even with a small number of samples. The DNB can be obtained based on three observable conditions, and is actually an observable subnetwork of molecules, which is able to detect the signals of the pre-transition state, or a critical stage just before the sudden change, with only a few samples provided that high-throughput data are available for each sample. A DNB is a generic signal for the pre-transition state regardless of the differences of biologic systems, and therefore it can be widely applied to study various biologic processes. Moreover, DNBs have been shown theoretically to be the leading biomolecular networks (or leading networks) in critical transitions, which make the first move from a before-transition state to an after-transition state. In other words, the leading network is the first subnetwork that breaks down the initial regime, which means that it is strongly related to the causal (or driving) genes, in contrast to the differential gene expression that usually results from the transition rather than causing the transition. Therefore, identifying the leading network during a critical transition not only provides important information on driver molecules on this nonlinear dynamical process but also can indicate the occurrence of a pre-transition state in a dynamical point of view [8], and thus is of significance from both biologic and medical viewpoints [8,40]. Next, we review this method as well as the related works mainly based on the references [7,8].

DYNAMICAL NETWORK BIOMARKER (DNB)

Generally, a mathematical model for describing a biologic process may include a large number of parameters and variables. In particular, the dynamics for a transition is in fact very complicated either before or after a sudden change, and therefore the state equations are generally constructed in a high-dimensional phase space with a large number of variables and parameters (e.g., over thousands) [41–44]. However, when the system approaches the pre-transition state or tipping point, surprisingly we can show that whole dynamics is generally constrained only to one- or two-dimensional center manifold, which can be exploited to analyze the complex transition phenomenon, regardless of the differences of systems as well as the size of the system (e.g., number of variables). This is the key idea for the DNB.

Specifically, from a theoretical view of point, provided that the system driven by some known or unknown parameters approaches to the critical point that is a very special phase during the whole dynamical process, the system can be expressed in a very simple form, i.e., generally it can be expressed by one- or two-variable dynamical equations in an abstract phase space around a codimension-one bifurcation point [45,46]. This is generally guaranteed by the bifurcation theory and center manifold theory [47,48]. Thus because of this special feature, during this special phase, unlike during other periods (i.e., the before-transition stage, and after-transition stage), it is possible to detect its signal. On the other hand, rapid advancements on high-throughput technologies have enabled us to observe gene expressions or even protein expressions at the genome-wide scale [42], i.e., with over thousands of measurements in one sample. Such high-dimensional big data not only provide a global view with rich information on the concerned system, but also represent the accumulated effects of its long-term dynamics [41], which implies that even a small number of samples may characterize the dynamical features of a living organism.

To derive a DNB, we use the following dynamical system to represent a general biologic process.

$$Z(k+1) = f(Z(k); P). \tag{1}$$

$Z(k)=(z_1(k),...,z_n(k))$ represent observed data, i.e., concentrations of molecules (e.g., gene expressions or protein expressions) at time $k(k=0,1,...)$, e.g., hours or days, which are the variables describing the dynamical state of the system. P are parameters representing slowly changing factors, including genetic factors (e.g., SNP and CNV) and epigenetic factors (e.g., methylation and acetylation), which drive the system from one state (or an attractor) to another (see Figure 3). $f=(f_1,...,f_n)$ are generally nonlinear functions of $Z(k)$ with a fixed point $Z=\overline{Z}$, such that $\overline{Z}=f(\overline{Z};P)$. Assume that there is a value P_c such that at least one of the eigenvalues of the Jacobian matrix $\frac{\partial f(Z;P_c)}{\partial Z}\big|_{Z=\overline{Z}}$ equals 1 in modulus, which implies that the system undergoes a bifurcation at $\overline{Z}$ when P reaches the threshold P_c. Following the standard way [9,49], we can linearize the dynamical equations of (1) near a fixed point $\overline{Z}$ as follows:

$$Z(k+1)=\overline{Z}+\frac{\partial f(\overline{Z};P)}{\partial Z}(Z(k)-\overline{Z})$$

By introducing new variables $Y(k)=(y_1(k),...,y_n(k))$ and a transformation matrix S satisfying $Y(k)=S^{-1}(Z(k)-\overline{Z})$, the linearized system in the abstract space with the perturbations of noise is given as follows when all the eigenvalues are real and different:

$$Y(k+1)=\Lambda(P)Y(k)+\xi(k), \tag{2}$$

where $\Lambda(P)$ is the diagonalized matrix of $\frac{\partial f(Z;P)}{\partial Z}\big|_{Z=\overline{Z}}$, and $\xi(k)=(\xi_1(k),...,\xi_n(k))$ are Gaussian noises with zero means and covariances $k_{ij}=\mathrm{Cov}(\xi_i,\xi_j)$. Without loss of generality, it is supposed that $Y(k)$ have zero means and $\Lambda(P)=\mathrm{diag}(\lambda_1(P),...,\lambda_n(P))$ with each $|\lambda_i|$ between 0 and 1 due to the stable fixed point at the before-transition state and the pre-transition state. Among the eigenvalues, the largest one in modulus, say λ_1, first approaches 1 when parameter $P\to P_c$. This eigenvalue characterizes the system's rate of change around the fixed point and is called the dominant eigenvalue. The covariance and PCC at the abstract space are respectively represented as in Ref. [7]:

$$\mathrm{Cov}(y_i,y_j)=\frac{k_{ij}}{1-\lambda_i\lambda_j},$$

$$PCC(y_i,y_j)=\frac{k_{ij}}{\sqrt{k_{ii}k_{jj}}}\frac{\sqrt{(1-\lambda_i^2)(1-\lambda_j^2)}}{1-\lambda_i\lambda_j}.$$

Clearly, it holds that $\mathrm{Var}(y_1)=\mathrm{Cov}(y_1,y_1)\to+\infty$, when the dominant eigenvalue $|\lambda_1|\to 1$ because of the change in the parameter values, but $\mathrm{Cov}(y_i,y_j)$ for $i\neq j$ and $\mathrm{Var}(y_i)$ for $i\neq 1$ have no drastic change (bounded) because of $0<|\lambda_i|<|\lambda_1|<1(i=2,...,n)$. Also, $PCC(y_1,y_j)\to 0$ for any $j\neq 1$ when $|\lambda_1|\to 1$.

Now, we study the statistic properties for the original variables Z whose values are directly measured as high-throughput data, by $z_i=\sum_{j=1}^{n}s_{ij}y_j+\overline{z}_i$ where s_{ij} is the (i,j)-element of the linear transformation S. It follows

$$\mathrm{Cov}(z_i,z_j)=s_{i1}s_{j1}\mathrm{Var}(y_1)+\cdots+s_{in}s_{jn}\mathrm{Var}(y_n)+\sum_{k,m=1,k\neq m}^{n}s_{ik}s_{jm}\mathrm{Cov}(y_k,y_m),$$

$$PCC(z_i,z_j)=\frac{\mathrm{Cov}(z_i,z_j)}{\sqrt{\mathrm{Var}(z_i)\mathrm{Var}(z_j)}},$$

where $\mathrm{Var}(z_i)=\mathrm{Cov}(z_i,z_i)$. Then, with the results from the abstract space Y, we have the following statistical conclusion on the observable space Z.

1. If a variable z_i is related to y_1, that is, $s_{i1}\neq 0$, then the standard deviation $SD(z_i)=\sqrt{\mathrm{Var}(z_i)}$ increases to infinity (drastic change) as $\lambda_1\to 1$.

2. If both variables z_i and z_j are related to y_1, that is, both s_{i1} and s_{j1} are nonzero, then $\mathrm{Cov}(z_i, z_j)$ tends to infinity (drastic change) as $\lambda_1\to 1$. Moreover, $|PCC(z_i,z_j)|\to 1$ (drastic change) as $\lambda_1\to 1$.

3. If $s_{i1}\neq 0$ but $s_{i1}=0$, then $|PCC(z_i,z_j)|\to 0$ (drastic change) as $\lambda_1\to 1$.

4. If $s_{i1}=0$, then $SD(z_i)$ is bounded (non-drastic change) as $\lambda_1\to 1$.

5. If both s_{i1} and s_{j1} are vanishing, i.e., $s_{i1}=s_{j1}=0$, then $|PCC(z_i,z_j)|\to a$ (non-drastic change) with $a\in(0,1)$ as $\lambda_1\to 1$.

Since variable y_1 is related to the dominant eigenvalue λ_1, all variables z_i with nonzero s_{i1} form a group, called the dominant group, that will make the first move to transit to the after-transition state from the before-transition state through the pre-transition state. The dominant group characterizes the dynamical features of the underlying system, and the molecules in the group are strongly and dynamically correlated in the pre-transition state. These molecules in the dominant group are expected to form a subnetwork or functional module from a network viewpoint. Hence, they are defined as a DNB group. When the system approaches the pre-transition state, the five conditions above can be also expressed in terms of expression of molecules as follows.

1. There is a dominant group appearing when the system approaches the pre-transition state. The standard deviation of each molecule in the group sharply increases.

2. The correlation for each pair of molecules among the

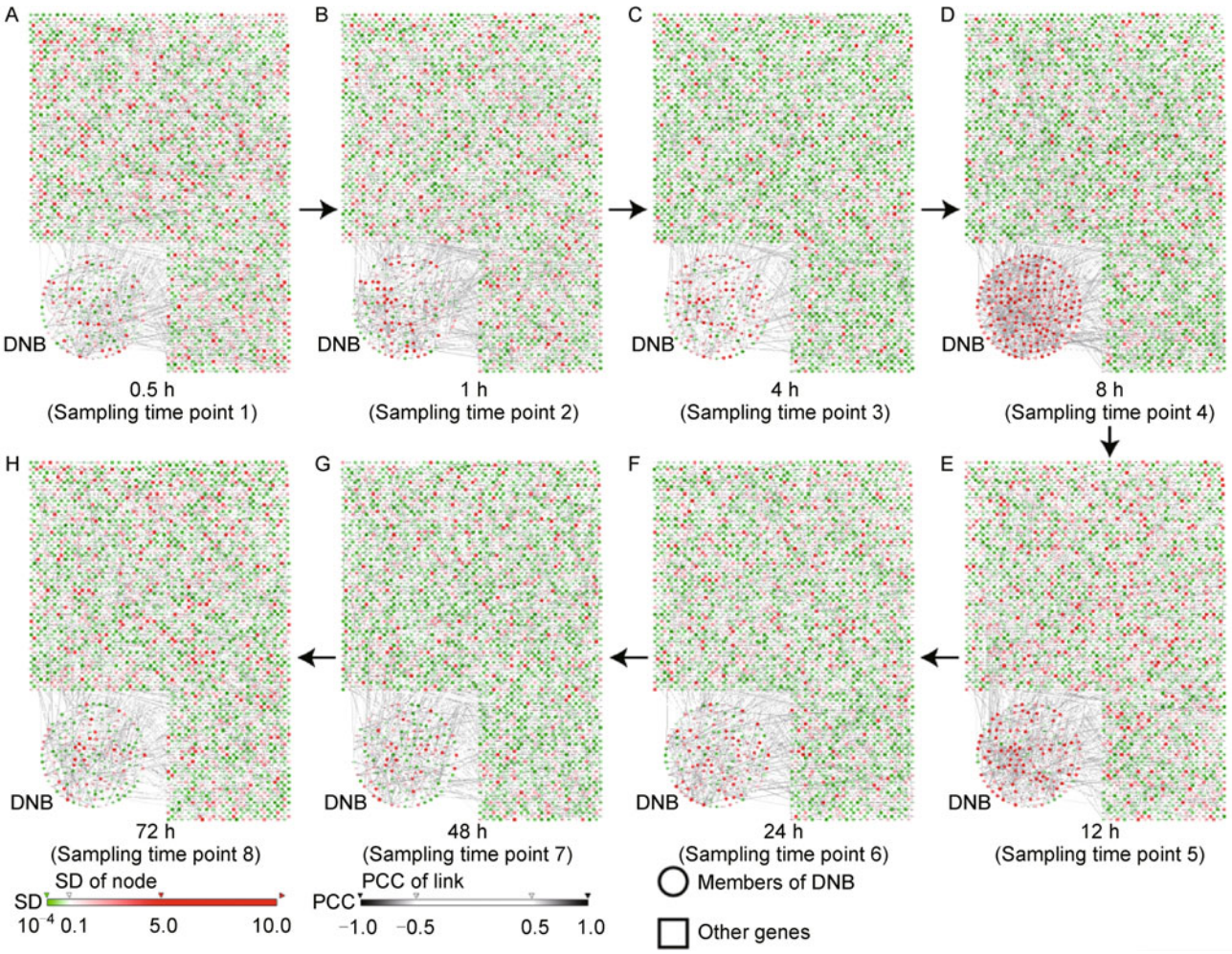

Figure 3. Identifying early signals of acute lung injury by DNB we show the dynamic evolution of the whole mouse network structure (3452 genes and 9238 links) with the identified DNB (220 genes and 1167 links). (A) The whole mouse network at 0.5 h; (B) The whole mouse network at 1 h; (C) The whole mouse network at 4 h; (D) The whole mouse network at 8 h (the pre-disease state); (E) The whole mouse network at 12 h; (F) The whole mouse network at 24 h; (G) The whole mouse network at 48 h; (H) The whole mouse network at 72 h.

group drastically increases.

3. The correlation between one molecule in the group and another outside of the group drastically decreases.

4. There is no drastic change for the standard deviation of each molecule outside of the group.

5. There is no drastic change for the correlation among each pair of the molecules outside the group.

These DNB members obviously satisfy the first three conditions above. Therefore, the first three conditions are considered as three criteria to detect the DNB or signals of the pre-transition state. Besides, since the three criteria are in fact the generic properties of the DNB members in dynamics whenever the system approaches a critical tipping point, these properties should lie in many complex biologic processes with sudden transition phenomena. Such critical behavior coincides with the phenomenon described by the so-called "critical slowing down" theory [9], but is described in a network form in DNB theory.

COMPOSITE CRITERION FOR DNB

To obtain a strong signal of the pre-transition state, the following composed index is proposed by combining the three criteria [7]:

$$I =: \frac{SD_d \cdot PCC_d}{PCC_o},$$

where PCC_d is the average Pearson's correlation coefficient of the dominant group in absolute value; PCC_o is the average Pearson's correlation coefficient of the dominant group with other molecules in absolute

value; SD_d is the average standard deviation of the dominant group. Although the expression of each observable z_i may stochastically change at any time instant because of the perturbation, this composite index is expected to increase sharply whenever the system approaches a critical transition point, and therefore, it can serve as an effective early-warning signal to identify the pre-transition state and its leading network. Figure 2 illustratively shows the dynamical features of the DNB and the leading network during a biologic process.

EARLY-WARNING SIGNALS FOR COMPLEX DISEASES

Differences between DNB and traditional biomarkers

There usually exists sudden health deterioration during gradual progression of many chronic diseases. Such a critical phenomenon generally results in a drastic or a qualitative transition of the concerned network system from the normal state to the disease state. As shown in Figure 1, a disease progression can be divided into three stages, i.e., the normal state, the pre-disease state and the disease state, which correspond to the before-transition state, the pre-transition state and the after-transition state respectively in a general biologic process. The normal state is a steady state, representing a relatively healthy stage during which the disease is under control, in an incubation period or in a chronic inflammation period. The pre-disease state is defined as the limit of the normal state immediately before the tipping point is reached. In this pre-disease stage (see Figure 1), the process is usually reversible to the normal state if appropriately treated. However, it usually becomes irreversible to the normal state even by using advanced treatment if the system passes the critical point and enters another stable state or the attractor. Hence, it is crucial to detect the pre-disease state so as to prevent qualitative deterioration by taking early intervention actions.

As summarized in Figure 4 and Table 1, rather than identifying the pre-disease state before the critical transition, the traditional molecular biomarkers aim to distinguish disease samples from normal samples, and thus are unable to detect early signals of the complex diseases before the catastrophic deterioration, which is actually a common phenomenon in many complex disease, such as prostate cancer [15], asthma attacks [1],

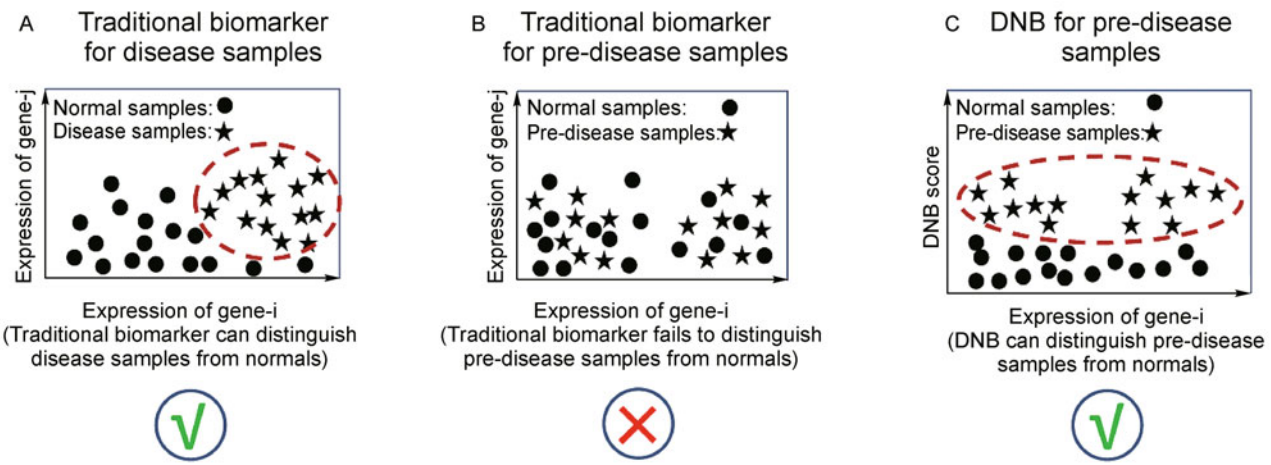

Figure 4. Difference between DNB and traditional biomarkers. Traditional molecular biomarkers and network biomarkers are able to identify the disease state from the normal state (A), but fail to distinguish the pre-disease state from the normal state (B). In contrast, DNB can distinguish the pre-disease state from the normal state by using high throughput data even with a small number of samples (C).

Table 1 Comparison of traditional molecular biomarker, network biomarker and dynamical network biomarker

Biomarker type	Diagnosis	Markers	Features	Causality of disease
Molecular biomarker	Disease state	Individual molecules	Static signal	Unclear
Network biomarker	Disease state	Molecular network	Static signal	Unclear
Dynamical network biomarker	Pre-disease state	Molecular network	Dynamical signal	Leading network, driver network

Note: Molecular biomarker distinguishes disease state from normal state; Network biomarker distinguishes disease state from normal state; Dynamical network biomarker distinguishes pre-disease state from normal state.

and epileptic seizures [2,50]. On the other hand, recent advances on network medicine provide a new way to identify the disease state by using network biomarkers [18–25]. Although a network biomarker is considered as a stable form to characterize the disease state in contrast to individual molecule biomarkers, it is also to use the static information for distinguishing disease samples from normal samples. Completely different from the traditional biomarkers, the DNB exploits dynamical features of disease progression to distinguish not disease samples but pre-disease samples from the normal samples.

Application to early diagnosis of complex diseases

The DNB method has been applied to real data [7,8], and has successfully identified critical transitions as well as DNBs or the leading networks for lung injury disease, HCC-induced liver cancer, HBV-induced liver cancer and lymphoma cancer based on their microarray data. Figure 3 shows the result on acute lung injury [51]. By the experiment for phosgene-inhalation induced lung injury of mice, the gene expressions for nine time points were measured, and then were used to detect the early signals of the lung injury. As shown in the figure, from the beginning there is no significant difference between the DNB and remaining genes before 8 h. The significant signal implies the pre-disease state at 8 h (although there was still no identified damage on the lung at that moment). However, it was found that the phenotypic change for the lung injury occurred at next time point (12 h), which validated the theoretical prediction. Interestingly, there is no significant difference again between the DNB and other genes when the lung was deeply damaged at 72 h (at disease state). This fact indicates that DNB is not to distinguish the disease state but to distinguish the pre-disease state from the normal state.

As shown in Figure 4 and Table 1, unlike the traditional molecular biomarkers in medicine, whose expressions reflect the severity or presence of some disease state and which are required to have different but consistent (or constant) values either in normal samples or abnormal ones, to distinguish a disease state from a normal state, a DNB is a strongly correlated molecular network in which the concentrations of molecules, however, dynamically change without keeping constant values in the pre-disease state. In other words, the concentrations of molecules in the DNB tend to increasingly fluctuate when the system approaches the pre-disease state, although they change in a strongly collective manner, which is the key feature of a DNB. Hence, the existence of the DNB indicates that the system is in the pre-disease state. It is noteworthy that each individual patient may not have exactly the same DNB even for the same disease, that is, some molecule members in the DNB may differ from person to person. Unlike traditional biomarkers, a DNB is not composed of a group of fixed molecules even for the same disease and might have different members depending on individual variations that are detected by individual high-throughput data. Compared with the traditional molecular and network biomarker, the DNB shows obvious advantages. First, the DNB is used for detecting a pre-disease state rather than a disease state, which is usually irreversible to a normal state. Second, since the DNB is obtained by using high-throughput data at a few sampling time points, it meets the sampling requirements of clinical medicine, that is, only a small number of samples available. Third, although a DNB subnetwork is for capturing the signals of the pre-disease state, some DNB members may be considerably relevant to the traditional disease biomarkers, which were actually verified by the functional analysis in Refs [7,8], that is, some reported disease-related genes are actually in the DNB. The other unreported molecules may be considered as the novel candidates for causing the disease. From this point of view, the DNB subnetwork also provides a clue to finding new potential drivers of diseases.

CONCLUSION

Biomarkers are useful in characterizing biologic features and diagnosing diseases in the biologic and medical areas, respectively. However, the traditional biomarkers including molecular biomarkers and network biomarkers are mainly designed to distinguish two (multiple) different states, rather than to identify the transition point or pre-transition state. In contrast, the DNB or leading network is a new concept and method aiming at detecting the pre-transition state just before the critical transition even with a small number of samples. Hence, the DNB has obvious advantages when applied to analyzing complex biologic processes or diseases with sudden change phenomena. It also opens a new way to analyze big biomedical data. The major features of the DNB are summarized as follows.

- The DNB is a general model-free approach to identify early-signal before critical transitions by small samples of high-throughput data, with theoretical background on nonlinear dynamics (bifurcation and center manifold theory).
- The DNB is the leading network of the drastic state change, and thus is closely related to the causal network to initiate the transition. This feature is considered as the first such theoretical result to ensure the causality of a biologic event.
- The DNB detects the pre-disease state of a disease progression in a dynamical manner, in contrast to static traditional molecular or network biomarkers.
- The DNB can handle personal variations (e.g., genetic or epigenetic factors) due to its generic properties,

and therefore the DNB opens a new way for personalized medicine.

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CONFLICT OF INTERESTS

The authors declare no competing financial interests.

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