The Early Warning Signal of Complex Diseases Based on the Network Transition Entropy

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***Abstract*—Many evidences suggested that during the progression of complex diseases, the deteriorations are generally not smooth but abrupt, which may cause a critical transition from one state to another at a tipping point, corresponding to a bifurcation of the dynamical system for the underlying organism. A pre-disease state is assumed to exist before reaching the tipping point between a normal state and a disease state. Since the pre-disease state is defined as a limit of the normal state, which represents an early-warning signal of the disease, it is crucial to identify such a state so that remedial actions can be executed to avoid the abrupt transition to the disease state. Although most complex diseases are model free, and usually only small samples are available due to clinical limitations, we propose that an index called the network transition entropy (NTE) may serving as an early-warning indicator for predicting the critical transition. Although the theoretical deviation is based on the dynamical network biomarker (DNB), the application of NTE is DNB free.**

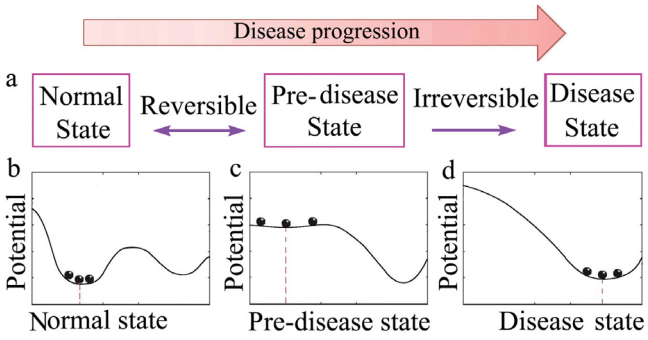

Fig. 1. | **Progression of a complex disease with sudden deterioration** A schematic illustration of dynamical features for disease progression from a normal state to a disease state through a pre-disease state by potential functions.

I. Introduction

It has been identified that a sudden change of a system state exists widely in ecosystems[1], [2], climate systems[3], [4], economics and global finance[5], [6]. The occurrence of such a change often corresponds to the critical threshold, or the so-called tipping point, at which the system shifts abruptly from one state to another. This is well known in dynamical systems theory as a bifurcation which results in a qualitative transition in states or attractors [7], [8]. Recently, evidences showed that the similar phenomena exist in clinical medicine, that is, during the progression of many complex diseases, e.g. chronical diseases such as cancers, the deteriorations are not smooth but abrupt[9]– [13]. In other words, there exists a sudden catastrophic regime shift during the process of gradual health deterioration which results in a drastic transition to the disease state. In order to describe the underlying dynamical mechanism of complex diseases, their evolutions are often modeled as time dependent nonlinear dynamical systems, in which the abrupt deteriorations are viewed as the phase transitions at bifurcation points, e.g. for prostate cancer[14], asthma attacks[9] and epileptic seizures[15]. According to the progression levels of illness, we divided the process into three stages, *i.e.* a normal state, a pre-disease state (or critical state), and a disease state (Fig.1b-d). The normal state is a steady state, representing a relatively healthy stage where the disease is under control or in an incubation period or in a chronic inflammation period. The pre-disease state is defined as a limit of the normal state just before the tipping point is reached. At this stage, the process is usually reversible to the normal state if appropriately treated, implying the instability of the pre-disease state. However, it becomes usually irreversible to the normal state if the system passes the critical point and enters another stable state, *i.e.* the disease state (Fig.1a-d). Hence, it is crucial to detect the pre-disease state so as to prevent the qualitative deterioration by taking appropriate intervention actions.

To detect the pre-disease state, we have proposed a new prediction method. Specifically, based on time-course high-throughput data, it is possible to observe many molecules at the same instant, from which we may screen out a group of observables of the following dynamical properties. Firstly, each of the molecules tends to increasingly fluctuate when the system approaches to the pre-disease state, which results in the sharply increasing standard deviation (SD). Secondly, these molecules are correlated closely when the system approaches to a critical transition point. Thirdly, the correlations between any member of the group and other molecules tends to decrease while near a critical transition point. Based on the above three generic properties, we have proposed a new indicator, the dynamical network biomarker (DNB), whose drastic change in dynamics show the imminent deterioration of complex diseases.(see [16]) Our previous work not only overcomes the difficulties due to lack of accurate models, but sheds light on the prediction even with small samples.

Although the DNB-based detection does provide the early-

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warning signal from the collective behavior of the DNB members, the accuracy of such detection highly relies on the chosen members of DNB. However, sometimes it is not easy to precisely select such DNB members due to the scale of datasets. In such cases, it requires to construct the DNB-free indicator, which may also provide early-warning signals when the system approaches to a transition point. In this paper, we propose that the network transition entropy (NTE) may serve as such DNB-free indicator. By calculating the NTE value during each sampling time period, we may obtain the dynamical tendency of system. The theoretical analysis is based on the protein-protein interaction networks, the backbone along which various biological signals can propagate in response to external stimuli and hence received particular attentions. Actually, the application of entropy is inspired by many previous works. Cover considered the random walk process on the connected graph by introducing the concept entropy rate [17]. Demetrius *et al.* proposed the concept network entropy, to describe the network topology and robustness [18],[19], see also [20] for further application. Teschendorff suggested that a metastatic cancer phenotype could be characterised by an increase in the randomness of the local information flux patterns, which is measured by entropy [21]. Wieringen *et al.* suggested cancer cells molecular entropy may increase while cancer evolves [22].

II. Preliminary

For a given regulatory network evolving along a time series, such as protein-protein interaction network, protein-DNA interaction network and global gene expression graph, the expression value of each node may vary from time to time since the regulation effects or external stimuli. It is nature to regard such variations as state transitions, that is, the whole network transit from one state to the other. Suppose there are n nodes in a regulatory network, and for node i the expression value is z_i $(i = 1, \cdots, n)$. Assume one state transition is

$$Z(t) = (z_1, \cdots, z_n) \xrightarrow{\text{transit}} Z(t+1) = (\cdots, \widehat{z_i}, \cdots, \widehat{z_k}, \cdots), \tag{1}$$

where symbol $\widehat{z_i}$ represents that the value of node i changes in the new state. There may be several reasons causing such state transition, that is, the randomly changes of some nodes regulates the others and thus drive the network into a new state. Each reason results in a possible state transitions. Therefore, we employ the transition rate to describe the probability of such "possible state transition". Without loss of generality, such state transition process represents the Markov process of the network evolution along a time series.

Suppose a transition rate matrix

$$P = (p_{i,j}),$$

which represents the probabilities of possible state transitions. Specifically, for given node index i, $p_{i,j}$ is the jth possible state transition case that involves value variation of node i. By discussing how these transition probabilities change as the system progresses from normal state to pre-disease state, we intend to construct a composite index which may reflect the underlying mechanism in dynamics and provide the early-warning signal to detect the pre-disease state.

We introduce the following notations.

For a given node i, if the jth possible transition process is presented as (1), which involves the value variation of nodes i and k, etc., then the corresponding transition probability is

$$p_{i,j} = p(\widehat{z_i}, \widehat{z_k} \mid z_k),$$

which means, while under the condition that the changes on z_k drives the network into such possible state transition, the value of nodes i and k vary in a collective manner.

Besides, assume that the state-transition graph of the network is weighted by $W_{i,j}$, the weight of the jth transition case based on node i. And denote

$$W_i = \sum_j W_{i,j}$$

as the weight of node i,

$$W = \sum_{i=1}^{n} W_i$$

as the total weight of the state-transition graph. There are the following two assumptions about the transition weight. Firstly, the total weight W is a constant. Secondly, the weight $W_{i,j}$ is positively related to the correlations of nodes.

In what follows, we use the weight of the transition to describe the the proportional probability, that is,

$$p_{i,j} = \frac{W_{i,j}}{W_i}.$$

Through such conditional probability, we are able to describe the critical behavior in dynamics of the network as it approaching to the tipping point, which is arranged in the next section.

For a given regulatory network, one may obtain all the possible state transitions. Generally, these state transitions could be orderly listed for each node z_i $(i = 1, 2, \cdots, n)$ respectively. As an intuitive illustration, we introduce a 6-nodes regulatory network (see Fig.2), in which nodes z_1, z_2, z_3 are supposed to compose the DNB. From this network, we could get all the possible state transition processes, which together with the corresponding transition possibilities are listed in Table 1. In order to simplify the analysis, we claim that only the direct regulation relationships (the edges between adjacent nodes) are considered as the possible reasons for state transition, that is, if there is an edge between nodes i and k, then in the state transition (1), z_j is the condition under which $p(\widehat{z_i}, \widehat{z_j} \mid z_j)$ is meaningful. Otherwise, $p(\widehat{z_i}, \widehat{z_j} \mid z_j) \equiv 0$.

III. Main results

In this section, we appeal to certain ideas from ergodic theory and statistical mechanics to characterize the critical properties of the transition graph in terms of an n-nodes network, which is often used to describe the regulation relationship among genes or proteins. Suppose that the basic regulation is represented by the undirected links between

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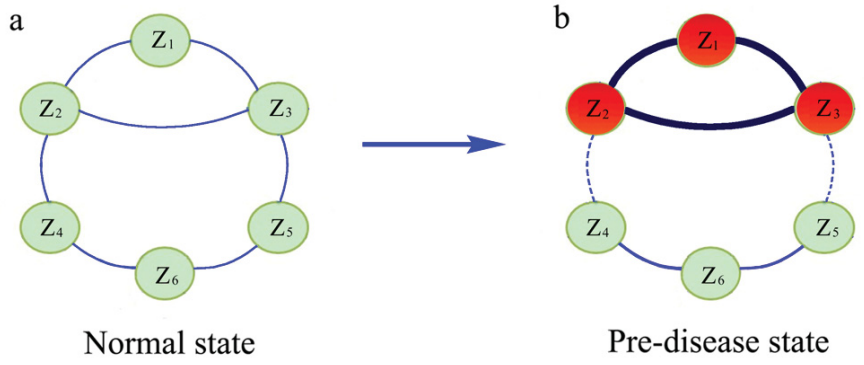

Fig. 2. | **A 6-nodes illustrative network** Each node represents a molecule in the biochemical regulation process. The undirected links between adjacent nodes show the regulation relationship between them. In this network, nodes z_1, z_2, z_3 are supposed to compose the dynamical network biomarker (DNB).

TABLE I
THE TABLE OF THE STATE TRANSITION RATE.

Nodes	States number	State transition rate	Conditional probabilities	
z_1	1	$p_{1,1}$	$p(\ \text{none} \mid \text{none}\ )^*$	$\sum_j p_{1,j} = 1$
	2	$p_{1,2}$	$p(\ \widehat{z_1}, \widehat{z_2} \mid z_2\ )$	
	3	$p_{1,3}$	$p(\ \widehat{z_1}, \widehat{z_3} \mid z_3\ )$	
	4	$p_{1,4}$	$p(\ \widehat{z_1}, \widehat{z_2}, \widehat{z_3} \mid z_2, z_3\ )$	
z_2	1	$p_{2,1}$	$p(\ \text{none} \mid \text{none}\ )$	$\sum_j p_{2,j} = 1$
	2	$p_{2,2}$	$p(\ \widehat{z_1}, \widehat{z_2} \mid z_1\ )$	
	3	$p_{2,3}$	$p(\ \widehat{z_2}, \widehat{z_3} \mid z_3\ )$	
	4	$p_{2,4}$	$p(\ \widehat{z_2}, \widehat{z_4} \mid z_4\ )$	
	5	$p_{2,5}$	$p(\ \widehat{z_1}, \widehat{z_2}, \widehat{z_3} \mid z_1, z_3\ )$	
	6	$p_{2,6}$	$p(\ \widehat{z_1}, \widehat{z_2}, \widehat{z_4} \mid z_1, z_4\ )$	
	7	$p_{2,7}$	$p(\ \widehat{z_2}, \widehat{z_3}, \widehat{z_4} \mid z_3, z_4\ )$	
	8	$p_{2,8}$	$p(\ (\widehat{z_1}, \widehat{z_2}, \widehat{z_3}, \widehat{z_4} \mid z_1, z_3, z_4\ )$	
z_3	the case of z_3 is similar to case z_2			$\sum_j p_{3,j} = 1$
z_4	1	$p_{4,1}$	$p(\ \text{none} \mid \text{none}\ )$	$\sum_j p_{4,j} = 1$
	2	$p_{4,2}$	$p(\ \widehat{z_2}, \widehat{z_4} \mid z_2\ )$	
	3	$p_{4,3}$	$p(\ \widehat{z_4}, \widehat{z_6} \mid z_6\ )$	
	4	$p_{4,4}$	$p(\ \widehat{z_2}, \widehat{z_4}, \widehat{z_6} \mid z_2, z_6\ )$	
z_5	the case of z_5 is similar to case z_4			$\sum_j p_{5,j} = 1$
z_6	1	$p_{6,1}$	$p(\ \text{none} \mid \text{none}\ )$	$\sum_j p_{6,j} = 1$
	2	$p_{6,2}$	$p(\ \widehat{z_4}, \widehat{z_6} \mid z_4\ )$	
	3	$p_{6,3}$	$p(\ \widehat{z_5}, \widehat{z_6} \mid z_5\ )$	
	4	$p_{6,4}$	$p(\ \widehat{z_4}, \widehat{z_5}, \widehat{z_6} \mid z_4, z_6\ )$	

* $p(\ \text{none} \mid \text{none}\ )$ represents the probability of the invariant state while under condition "none of the nodes changes".

adjacent nodes. And we claim that the discussions below are in the ideal cases.

Definition For a gene regulatory network with n nodes $(z_1, z_2, \cdots, z_n)$, the network transition entropy is defined as index

$$H = \sum_{i=1}^{n} \mu_i H_i,$$

and

$$H_i = -\frac{1}{T_i} \sum_j p_{i,j} \log p_{i,j},$$

where $T_i = \text{SD}(z_i)$ is the standard deviation, $\mu = (\mu_1, \cdots, \mu_n)$ is the stationary distribution satisfying $\mu_j = \sum_i \mu_i p_{i,j}$ for all j.

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This index is based on the system changes among many possible states, called network transition entropy (NTE) on account of the formal similarities with various entropic concepts which arise in ergodic theory. It is worthy noting that although the NTE index relates to the network, it is different from the "network entropy" mentioned in [18], in which the network entropy is actually based on the random walk on the network, from nodes to nodes. The NTE reflects the possible transitions among different states of the network. Through the variation of conditional transition rate $p_{i,j}$, the NTE tendency describes the collective changes of nodes in dynamics when the system approaches to the tipping point.

According to the theoretical derivation of [16], we know that when the system approaches to the tipping point, or equivalently, is in pre-disease state, there are the following generic properties:

- If both z_i and z_j are in the dominant group (or DNB), then
$$\mathrm{PCC}(z_i, z_j) \to \pm 1,$$
while $\mathrm{SD}(z_i) \to \infty$ and $\mathrm{SD}(z_j) \to \infty$,
- if z_i is in the dominant group but z_j is not, then
$$\mathrm{PCC}(z_i, z_j) \to 0,$$
while $\mathrm{SD}(z_i) \to \infty$, and $\mathrm{SD}(z_j)$ approaches to a bounded value,
- if neither z_i nor z_j is in the dominant group, then
$$\mathrm{PCC}(z_i, z_j) \to a, \quad a \in (-1, 1) \setminus \{0\}$$
while both $\mathrm{SD}(z_i)$ and $\mathrm{SD}(z_i)$ approach to bounded values respectively,

where PCC is short for the Pearson's correlation coefficient, SD for the standard deviation.

In the light of the above generic properties when near the transition point, the nodes in a regulatory network could be divided into four groups according to the network structural features: **(1)**. DNB nodes which are linked with DNB nodes only, e.g. z_1 (see Fig.2). **(2)**. DNB nodes which are linked with outside nodes, e.g. z_2 and z_3). **(3)**. Non-DNB nodes which has linkage with DNB nodes, e.g. z_4 and z_5. **(4)**. Non-DNB nodes that has no linkage with DNB nodes, e.g. z_6.

Although under the stochastic perturbation, the expression of each node z_i may differ from instant to instant, we illustrate that the index H_i for each node z_i progresses steadily as the system approaching to the critical tipping point as following cases.

A$^\diamond$ For the Type 1 nodes (e.g. DNB member z_1, which is linked with other DNB members z_2 and z_3 only), since in the pre-disease state, the correlations among the DNB members (e.g. z_1, z_2, and z_3) increase sharply, the expressions of these nodes fluctuate in strongly collective manner, inferring that if any one of them changes, then most probably the other two nodes change accordingly. Therefore, the state transition that all the expression of DNB members changes collectively, takes the most probability, while the other possible state transitions are unlikely to happen. For the specific example,

$$p_{1,4} = p(\ \widehat{z_1}, \widehat{z_2}, \widehat{z_3} \mid z_2, z_3\ ) \to 1,$$

while other $p_{1,i} \to 0$. Besides, $T_1 = \mathrm{SD}(z_1) \to \infty$, which leads to

$$H_1 = -\frac{1}{T_1} \sum_j p_{1,j} \log p_{1,j} \to 0.$$

B$^\diamond$ We focus on the Type 2 nodes, e.g. DNB member z_2 (and z_3), which not only linked with DNB members z_1 and z_3 (z_2) but also with non-DNB node z_4 (z_5). In the pre-disease state, since the correlations between DNB members and non-DNB nodes decrease drastically, it is unlikely that perturbations on non-DNB nodes would influence the DNB members. It follows

$$p_{2,4} = p(\ \widehat{z_2}, \widehat{z_4} \mid z_4\ ) \to 0.$$

The same case holds for $p_{2,6}$,$p_{2,7}$ and $p_{2,8}$. Besides, $p_{2,1}$,$p_{2,2}$ and $p_{2,3}$ are also approaching to 0 due to the same reason in **A**$^\diamond$. The exception is

$$p_{2,5} = p(\ \widehat{z_1}, \widehat{z_2}, \widehat{z_3} \mid z_1, z_3\ ) \to 1$$

due to the strongly collective behavior of DNB (z_1, z_2, z_3) in dynamics, while others approaches to 0. Considering $T_2 = \mathrm{SD}(z_2) \to \infty$, we have

$$H_2 = -\frac{1}{T_2} \sum_j p_{2,j} \log p_{2,j} \to 0.$$

Obviously, the same case holds for z_3 and H_3.

C$^\diamond$ Then we discuss the Type 3 nodes, e.g. z_4 (and z_5) which is outside the DNB but has linkage with DNB member z_2 (z_3). In the pre-disease state, since the correlations between DNB members and Type 3 nodes decrease drastically, it is unlikely that the variation of DNB members would influence the Type 3 nodes. It follows

$$p_{4,2} = p(\ \widehat{z_2}, \widehat{z_4} \mid z_4\ ) \to 0.$$

On the other hand, since there are no significant changes in the correlations among non-DNB nodes, the probability of the state transition that perturbations on some non-DNB nodes drive the other non-DNB nodes change, is no less than that in normal state, e.g. $p_{4,1}$, $p_{4,3}$ are no less than their values in normal state. Considering $p_{4,1} + p_{4,3} + p_{4,4} = 1$, and $T_4 = \mathrm{SD}(z_4)$ has little changes comparing with its value in normal state on account of $\mathrm{SD}(z_4)$ approaching to a bounded value, it infers that the value of H_4 in pre-disease state is no larger than that in normal state. Moreover, we can estimate the upper bound of H_4, that is, when the system is in the pre-disease state, it holds

$$\begin{aligned} H_4 &= -\frac{1}{T_4} \sum_j p_{4,j} \log p_{4,j} \\ &= -\frac{1}{T_4} (p_{4,1} \log p_{4,1} + p_{4,3} \log p_{4,3} + p_{4,4} \log p_{4,4}) \\ &< -\frac{1}{T_4} \log \left(\frac{1}{3}\right). \end{aligned}$$

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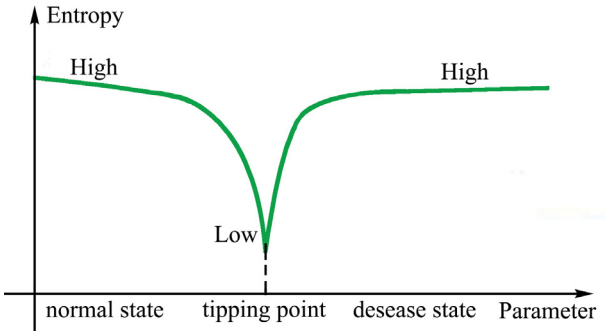

Fig. 3. | **Sketch of the network transition entropy** As the disease progressing, the NTE changes from high level (the normal state), to low level (pre-disease state), then back to high level again (disease state). The sketch shows that the sudden change in NTE may serve as an early-warning signal to detect the pre-disease state.

The last inequality holds as a result of the conditional extreme value. Actually, denote $f = f(a_1, a_2, a_3) = -\sum_k a_k \log(a_k)$, where $\sum_k a_k = 1$. From

$$\begin{cases} f_{a_1} = \log(a_1) - \log(1 - a_1 - a_2) = 0, \\ f_{a_2} = \log(a_2) - \log(1 - a_1 - a_2) = 0, \end{cases}$$

we know that $a_1 = a_2 = a_3$ is the necessary condition for the minimal value of f, which with the boundary condition leads to the above inequality. Obviously, the same case holds for z_5 and H_5.

D$^\diamond$ For the Type 4 nodes (e.g. non-DNB node z_6 which has no linkage with any DNB member), since even in the pre-disease state, there are no significant changes in correlations between Type 4 nodes and other nodes, the probability of each possible state transition remain invariant, e.g. probabilities $p_{6,j}$ have no large-scale fluctuates. Besides, in view of $T_6 = \mathrm{SD}(z_6)$ approaching to a bounded value, $H_6 = -\frac{1}{T_6}\sum_j p_{6,j} \log p_{6,j}$ has the similar value as its expression in the normal state and could be viewed as an invariant.

Now we consider the stationary distribution μ, which possesses the following expression

$$\mu_i = \frac{W_i}{W},$$

since

$$\begin{aligned} \sum_i \mu_i p_{i,j} &= \sum_i \frac{W_i}{W}\frac{W_{i,j}}{W_i} \\ &= \sum_i \frac{1}{W} \cdot W_{i,j} \\ &= \frac{W_j}{W} \\ &= \mu_j. \end{aligned}$$

The stationary probabilities are proportional to the transition weights. Remind the assumptions that the total weight W is a constant, while the weight $W_{i,j}$ is positively related to the correlations of nodes. We now have the qualitative changes in W_i as the system progressing into pre-disease state, that is, W_1 increases because the average correlation of z_1 with other nodes increase sharply, inferring μ_1 increases; W_4 decreases because the correlation of z_4 with z_2 approaches to 0, while the correlations of z_4 with other nodes have no significant changes and remain low levels, inferring μ_4 decreases (the same case holds for W_5 and μ_5); W_6 keeps invariant since no significant changes occur in the correlations of z_6 with its neighbors, inferring μ_6 keep invariant. Cases for W_2 and W_3 are complex, since there are correlations decreased ($\mathrm{corr}(z2, z4)$, $\mathrm{corr}(z3, z5)$, etc.), while other correlations increased ($\mathrm{corr}(z2, z1)$, $\mathrm{corr}(z3, z2)$, etc.). However, since $H_2 \to 0$ and $H_3 \to 0$ as the system approaching to the tipping point, it is simple for the pre-disease state.

Considering all the discussions above, we have

$$\begin{aligned} H_{\mathrm{pre-disease}} &= \sum_{i=1}^{6} \mu_i H_i \\ &\to \mu_1 \cdot 0 + \mu_2 \cdot 0 + \mu_3 \cdot 0 + \mu_4 \cdot H_4 + \mu_5 \cdot H_5 + \mu_6 \cdot H_6, \end{aligned}$$

and thus $H_{\mathrm{pre-disease}} < H_{\mathrm{normal}}$, which provides the early-warning signal we need (see Fig.3).

IV. Numerical Simulation

To demonstrate the effectiveness and applicability of NTE, we carried out numerical simulation. We propose the following equations representing gene regulations among a five-gene network:

$$\begin{cases} \frac{\mathrm{d}z_1(t)}{\mathrm{d}t} = (90|P| - 1236) + \frac{240-120\ |P|}{1+z_3(t)} + \\ \qquad \frac{1488 z_4(t)}{1+z_4(t)} - 30|P|\ z_1(t) + \zeta_1(t), \\ \frac{\mathrm{d}z_2(t)}{\mathrm{d}t} = (75|P| - 150) + \frac{60-30\ |P|}{1+z_1(t)} + \\ \qquad \frac{(240-120\ |P|)z_3(t)}{1+z_3(t)} - 60\ z_2(t) + \zeta_2(t), \\ \frac{\mathrm{d}z_3(t)}{\mathrm{d}t} = -1056 + \frac{1488\ z_4(t)}{1+z_4(t)} - 60 z_3(t), + \zeta_3(t) \\ \frac{\mathrm{d}z_4(t)}{\mathrm{d}t} = -600 + \frac{1350\ z_5(t)}{1+z_5(t)} - 100 z_4(t) + \zeta_4(t), \\ \frac{\mathrm{d}z_5(t)}{\mathrm{d}t} = 108 + \frac{160}{1+z_1(t)} + \frac{40}{1+z_2(t)} + \frac{1488}{1+z_4(t)} - \\ \qquad 300\ z_5(t) + \zeta_5(t), \end{cases},$$

where P is a scalar control parameter, $\zeta_i(t)\ \ (i = 1, 2, \cdots, 5)$ are Gaussian noises with zero means and covariances $\kappa_{ij} = \mathrm{Cov}(\zeta_i, \zeta_j)$. $z_i\ \ (i = 1, \ldots, 5)$ respectively represents the concentration of mRNA-i. The gene regulations are represented by the Michaelis-Menten form except degradation rates, which are linearly proportional to the concentrations of the corresponding genes. The degradation rates for mRNAs are $(30P, 60, 60, 100, 300)$.

For the calculation of conditional probability

$$p(\vec{X}|\vec{Y}) = \frac{p(\vec{X}, \vec{Y})}{p(\vec{Y})},$$

where both $\vec{X}$ and $\vec{Y}$ are vectors, we employ the Gaussian Kernel Estimator. Specifically, if $\vec{Y} = (y_1, \cdots, y_n)$ and there

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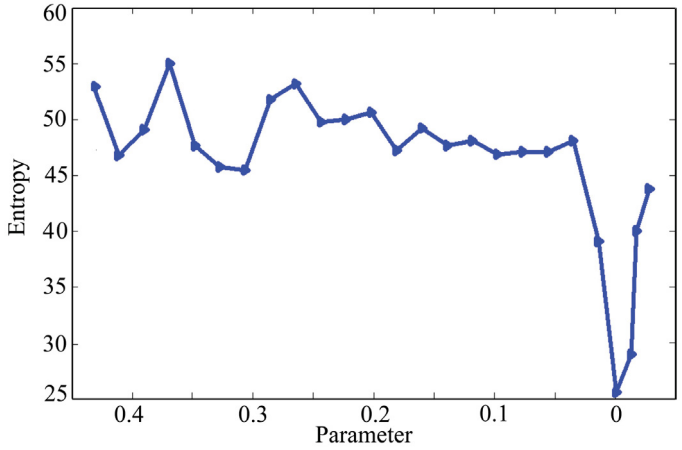

Fig. 4. | **Numerical simulation** The horizontal axis represents the control parameter P, which varies from 0.44 to -0.04 and the critical threshold is $P = 0$ corresponding to the bifurcation point. The vertical axis is the network transition entropy. From the simulation curve, when the system approaches to the tipping point ($P = 0$), the NTE decreases sharply.

are N samples $(\vec{S}_1, \cdots, \vec{S}_N)$ for Y, then

$$p(\vec{Y}) = \frac{1}{N}\sum_{i=1}^{N} \frac{1}{(2\,\pi)^{n/2}|C|} \cdot \exp\left(-\frac{1}{2}(S_j - S_i)^T\, C^{-1}\,(S_j - S_i)\right),$$

where C is the covariance matrix of S_i $(i = 1, \cdots, N)$, each S_i is an n-dimensional vector.

From the numerical simulation, we see that the change in index NTE indicates the approaching of tipping point. Therefore, NTE may serve as an early-warning signal for detecting the abrupt catastrophic change of the network (see Fig.4).

V. Conclusion

In this work, from both view of theoretical analysis and numerical simulation, we proposed that the drastic change in network transition entropy (NTE) may provide an early-warning signal as the system approaching to the critical tipping point (see Fig.3 and Fig.4). Since the decrease of NTE index occurs when the system approaching to the tipping point, the critical decrease is sudden and may be abrupt, which makes the signal distinguishable. Besides, we point out that the application of NTE could be straightforward, by simply calculating H_i corresponding to each node z_i. Therefore, the application of NTE is DNB-free, although the theoretical derivation is based on the characteristics of DNB members. Clearly, this work is merely a first step towards accurately detecting pre-disease state through NTE, since calculating the state transition probability is still a tough task when there are massive regulation relationships.

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References

[1] M. Scheffer,*et al.*, Catastrophic shifts in ecosystems Nature **413**, 591–596(2001).
[2] M.J. Drake and D.B. Griffen, Early warning signals of extinction in deteriorating environments, Nature **467**, 456–459(2010).
[3] V. Dakos,*et al.*, Slowing down as an early warning signal for abrupt climate change, Proc. Natl Acad. Sci. USA **105**, 14308–14312(2008).
[4] T.M. Lenton, *et al.*, Tipping elements in the Earth's climate system, Proc. Natl Acad. Sci. USA **105**, 1786–1793(2008).
[5] J. Kambhu, S. Weidman and N. Krishnan, *New Directions for Understanding Systemic Risk: A Report on a Conference Cosponsored by the Federal Reserve Bank of New York and the National Academy of Sciences* The National Academies Press, 2007.
[6] R.M. May, S.A. Levin and G. Sugihara, Ecology for bankers, Nature **451**, 893–895(2008).
[7] R. Gilmore, *Catastrophe Theory for Scientists and Engineers*, Dover, 1981.
[8] J.D. Murray, *Mathematical Biology*, Springer, 1993.
[9] J.G. Venegas, *et al.*, Self-organized patchiness in asthma as a prelude to catastrophic shifts, Nature **434**, 777–782(2005).
[10] P.E. McSharry, L.A. Smith and L. Tarassenko, Prediction of epileptic seizures: are nonlinear methods relevant? Nature Med. **9**, 241–242(2003).
[11] P.B. Roberto, G. Eliseo and C. Josef, Transition models for change-point estimation in logistic regression. Statist. Med., **22**, 1141–1162(2003).
[12] S. Paek,*et al.*, Hearing preservation after gamma knife stereotactic radiosurgery of vestibular schwannoma, Cancer **104**, 580–590(2005).
[13] J.K. Liu, R.L. Rovit and W.T. Couldwell, Pituitary Apoplexy, Seminars in Neurosurgery **12**, 315–320(2001).
[14] Y. Hirata, N. Bruchovsky and K. Aihara, Development of a mathematical model that predicts the outcome of hormone therapy for prostate cancer, J. Theor. Biol. **264**, 517–527(2010).
[15] B Litt,*et al.*, Epileptic seizures may begin hours in advance of clinical onset: a report of five patients, Neuron **30**, 51–64 (2001).
[16] L.N. Chen, R. Liu, *et al.*, Detecting early-warning signals for sudden deterioration of complex diseases by dynamical network biomarkers, submitting.
[17] T. Cover and J. Thomas, *Elements of information theory*, Wiley, New Jersey, 2005.
[18] L. Demetrius, V. Gundlach and G. Ochs, Complexity and demographic stability in population models, Theoretical Population Biology **65**, 211C225 (2004).
[19] L. Demetrius and T. Manke, Robustness and network evolutionłan entropic principle, Physica A **346**, 682C696 (2005).
[20] T. Manke, L. Demetrius and M. Vingron, An entropic characterization of protein interaction networks and cellular robustness, J. R. Soc. Interface **30**, 51–64 (2001).
[21] A. Teschendorff and S. Severini, Increased entropy of signal transduction in the cancer metastasis phenotype, BMC Systems Biology **4**, (2010).
[22] W. Wieringen and A. Vaart, Statistical analysis of the cancer cells molecular entropy using high-throughput data, Bioinformatics Advance Access **20**, (2010).

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