Journal of Theoretical Biology 262 (2010) 370–380

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Signal propagation in small-world biological networks with weak noise

Dawei Hong [a,*], Shushuang Man [b]

[a] Center for Computational and Integrative Biology, Rutgers University, Camden, NJ 08102, USA
[b] Department of Mathematics and Computer Science, Southwest Minnesota State University, Marshall, MN 56258, USA

ARTICLE INFO

Article history:
Received 31 July 2009
Received in revised form
5 October 2009
Accepted 8 October 2009
Available online 24 October 2009

Keywords:
Signal propagation
Stochastic differential equation
Weak internal noise
Small-world network
Measure concentration

ABSTRACT

An emerging notion in systems biology is that biological networks have evolved to function well while their components behave stochastically. Thus, the dynamics in a biological network consist of two parts, deterministic and stochastic. A fundamental question is to find a quantitative relation between the two parts. We term such a relation as a deterministic–stochastic principle (DSP) and propose a model for a DSP with regard to signal propagation in biological networks. In this model, (i) the dynamics in a biological network is supposed to be captured by a stochastic differential equation which has been a standard approach in modeling systems with internal noise; (ii) the internal noise of a biological network is weak as is apparent in experimental observations; and (iii) a biological network is organized as small-world as suggested by recent studies. We introduce the concept of a signaling sample path. Using this concept we relate the structure of a biological network to its dynamics. The network structure characterizes the deterministic part of the dynamics, which in turn ensures a probability for a signal to propagate. The weakness of the internal noise characterizes the stochastic part of the dynamics. Analysis of the proposed model yields a quantitative description as follows: In a small-world biological network with weak internal noise, the signaling pathways (induced by the network structure) for a signal may ensure a probability near 0 for the signal propagation. Despite such a small probability, a correct response to the signal will still occur with a probability close to 1 provided that this signal propagation can take a certain amount of time. Computer simulations are performed to illustrate this result. We also discuss how a recent study on the reconstruction of a transcription network in *Saccharomyces cerevisiae* has tested the proposed model against real data.

Published by Elsevier Ltd.

1. Introduction

A unique feature found in disparate types of biological networks is that the behavior of most components of a biological network is statistical. An emerging notion in systems biology is that biological networks have evolved to function well despite the uncertain behavior of their components. Thus, the dynamics in a biological network consists of two parts, deterministic and stochastic. A fundamental question in systems biology is how to quantitatively describe a general relation between the two parts. We term such a relation as a deterministic–stochastic principle (DSP), and propose a model for a DSP with regard to signal propagation in biological networks. In this model, (i) The dynamics in a biological network is supposed to be captured by a stochastic differential equation, which has been a standard approach for decades in modeling systems with internal noise in chemistry, finance, physics, etc. (ii) The internal noise of a biological network is weak as is apparent in experimental observations. (iii) A biological network is organized as small-world as suggested by recent studies. With the proposed model we will demonstrate that utilizing the weak internal noise, robust signal propagation may be achieved through unreliable signaling pathways in a small-world biological network.

In principle, there are fundamental differences between biological and engineering networks. To describe such differences, Alon (2006) coined the term "probabilistic design", and used the following example. "Engineered devices such as a radio are designed to function with 100% probability if, say, the ON button is pressed. We would say that a probabilistic radio is a malfunctioning radio." The author further pointed out that probabilistic design is common in biology but rare in engineering, and that the study on the role of probabilistic design in biology is only at its beginning. We may interpret the term "probabilistic design" as DSP, since in most cases the deterministic and stochastic parts of the dynamics in a biological network are related to each other. In engineering, it would be wrong to claim that the hard wiring in a probabilistic radio may ensure only a probability near 0 for radio signals through the antenna to speaker, but we still can listen to such a radio with a probability close to 1. A key to understand DSP is the study of noise in

* Corresponding author.
E-mail address: dhong@camden.rutgers.edu (D. Hong).

0022-5193/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.jtbi.2009.10.019

biological networks. The interplay between resilience to and utilization of internal noise in biological networks has been at the center of research in systems biology (see Barkai and Shilo, 2007).

Let us consider two examples of how weak noise in a loosely connected biological network can be utilized to facilitate desired dynamical changes. The first is the phase synchronization in the olfactory system. Teramae and Tanaka (2004) and Nakao et al. (2005) independently proposed a stochastic differential equation model to show that a common weak noise may induce phase synchronization among oscillators. Galán et al. (2006) demonstrated the above model captured the underlying mechanism for the phase synchronization among bulb neurons in the olfactory system. Consider a group of uncoupled bulb neurons each of which is modeled as an oscillator. The initial phases in these oscillators are randomly and independently chosen. Then the noise in the olfactory system induces phase synchronization among the oscillators. However, the weakness of noise was not mathematically formulated. Hong (2007) proposed a mathematical formulation of weak noise, and analytically showed how it works. The second example is quorum sensing of bacteria. Zhou et al. (2005) demonstrated that noise induces the synchronization in a quorum sensing network in a homogenous environment where the noise is uniformly distributed. Subsequently, Hong et al. (2007) showed when the noise is weak, it may induce the synchronization in a heterogenous environment where the distribution of noise may be non-uniform.

Almost every biological network is inherently noisy, i.e., the noise in a biological network likely is internal meaning that the noise may not be switched on or off by the network. In the present paper, we consider noise in biological networks as internal. From the viewpoint of mathematics, in almost every biological network the internal noise is weak. This conclusion is based upon a well-established mathematical concept for noise—Brownian motion and observations in almost all experiments in biology. In 1905 Albert Einstein proposed a physical model for noise. For 18 years it was not clear if this physical model is mathematically sound, until Norbert Wiener proposed the Wiener process often called Brownian motion. Today, Brownian motion is a central part of a standard approach in modeling a wide variety of systems with internal noise, including chemical, ecological, financial, physical systems. Therefore, we may regard Brownian motion as a canonical form of noise. As a stochastic process, a Brownian motion is quite rough. It was proven that during any time period, almost every sample path in a 1-dimensional Brownian motion belongs to a Hölder class Λ^{α} with $0<\alpha<\frac{1}{2}$ and cannot be in such a class with $\alpha\geq\frac{1}{2}$. Recall that a function $g(t)$, $t\in[a,b]\mapsto g(t)\in\mathbb{R}$ belongs to a Hölder class Λ^{α} is defined as $|g(t_1)-g(t_2)|\leq M|t_1-t_2|^{\alpha}$ for a constant $M>0$ and for all $t_1, t_2\in[a,b]$. As a consequence, we can see that almost every sample path in a 1-dimensional Brownian motion is a function which is continuous but non-differentiable everywhere. A sample path in a Brownian motion should somehow be reflected in experimentation. However, rough functions as sample paths in a 1-dimensional Brownian motion are almost never observed in biological experiments. This strongly suggests the internal noise in a biological network is weak in the sense that the noise is restricted to a low level compared with Brownian motion.

Consider loosely connected biological networks as in the two examples mentioned earlier. We ask what additional network structures would be needed to achieve robust signal propagation through utilization of weak internal noise. Watts and Strogatz (1998) proposed a type of random network called small-world. Most biological networks appear to fit into this type (see Albert, 2005, and references therein), including the brain structural (Hagmann et al., 2008) and functional networks (Bassett et al., 2006), mammalian transcription networks (Potapov et al., 2005).

As it turns out, the concepts of weak noise and small-world are sufficient to propose a model for a DSP with regard to signal propagation in biological networks. The proposed model uses the Itô equation, a special type of stochastic differential equation, as a framework for dynamics in biological networks. This approach has been standard in modeling systems with internal noise in areas such as chemistry, finance, physics, etc (see Øksendal, 2007; Van Kampen, 2007, and references therein). We introduce a concept named signaling sample path. Using this concept we quantitatively relate the structure of a biological network to its dynamics. The network structure characterizes the deterministic part of the dynamics, and hence, it ensures a probability for a signal to propagate. (From the viewpoint of engineering, this probability must be close to 1.) The weakness of the internal noise characterizes the stochastic part of the dynamics. The weakness of noise is essentially characterized by a parameter λ. Analysis of the proposed model applies theory of stochastic differential equation and a deep result in measure concentration by Talagrand (1995) which has been successfully used in many fields such as statistical mechanics, statistics, and theoretical computer science. This indicates there are connections between systems biology and modern probability theory. The main result from the analysis is as follows. For a value that λ may take, the following holds. Suppose a signal takes N time units to propagate. If the probability for the signal to propagate ensured by the signaling pathways (induced by the network structure) is at least $\varepsilon_1(N,\lambda)$, then utilizing the weak internal noise, the probability for a correct response to the signal to occur is at least $(1-\varepsilon_2(N,\lambda))$, where $\lim_{N\to\infty}\varepsilon_1(N,\lambda)=0$ and at the same time $\lim_{N\to\infty}(1-\varepsilon_2(N,\lambda))=1$ at convergence rates sub-exponentially fast in terms of N, respectively. Mathematical expressions for $\varepsilon_1(N,\lambda)$ and $\varepsilon_2(N,\lambda)$ will be given in an explicit way.

This result suggests that in a small-world biological network with weak internal noise, although the signaling pathways may ensure a probability near 0 for a signal to propagate, a correct response to the signal will still occur with a probability close to 1 provided that the propagation of the signal can take a certain amount of time. Moreover, with the proposed model we derive five parameters, and show these five parameters in general are enough to characterize: a spatial–temporal scale for signal propagation in a small-world biological network; the weakness of the internal noise; the accuracy of the signal propagation; and a minimal probability should be ensured by the signaling pathways for a signal to propagate. Then, by Theorem 1 we synthesize these five parameters together to suggest a DSP with regard to signal propagation in small-world networks with weak internal noise. In Section 5.1 we discuss how a recent result on the reconstruction of a transcription network in *Saccharomyces cerevisiae* has tested the proposed model against real data.

2. Methods

We will use the abbreviation SBN for small-world biological network. We will frequently use $\mathcal{S}$ and $\mathcal{R}$ to refer to a signal and a response to the signal, respectively.

2.1. Dynamics in SBN

We begin with the Itô equation

$$X_t=X_0+\int_0^t f(s,X_s)\,ds+\int_0^t \sigma(s,X_s)\,dB_s,\quad t\in[0,T] \tag{1}$$

As mentioned in the introduction, (1) has been used as a standard approach in modeling a wide variety of systems with internal noise. We denote by $(\Omega,\mathcal{F},\mu)$ the underlying probability space for

(1) where $\mathcal{F}$ is a Brownian filtration $\{\mathcal{F}_t : t \in [0,T]\}$. We suppose that (1) has a unique continuous solution $\{X_t : t \in [0,T]\}$ where X_t is understood as follows. Consider an SBN as a weighted directed graph with each node labeled by a real number. Most biological networks fit into this frame. We arrange labels of the nodes and weight of the links into a vector $X_t = (x_t^{(1)} \dots x_t^{(n)}) \in \mathbb{R}^n$ such that each component $x_t^{(i)}$ $(1 \le i \le n)$ represents either the label of a node or weight of a link. At a time instant t, such a vector $X_t \in \mathbb{R}^n$ characterizes the dynamics of an SBN at that moment. We call such a vector $X_t \in \mathbb{R}^n$ a *network state*.

Eq. (1) will be kept in an abstract setting with the following assumptions on f and σ.

(A1) The drift coefficient f is determined by the network structure of an SBN. Thus, f characterizes the deterministic part of the dynamics in the SBN. We assume f is a bounded deterministic function $[0,T] \times \mathbb{R}^n \mapsto \mathbb{R}^n$, and satisfies the uniform Lipschitz condition in X_t, i.e., there are constants b_0, $K > 0$ such that $\|f(t,x)\|_\infty \le b_0$ and $\|f(t,x) - f(t,y)\|_\infty \le K\|x-y\|_\infty$ for every $0 \le t \le T$, for all $x, y \in \mathbb{R}^n$;

(A2) The diffusion coefficient σ is used to characterize the stochastic part of the dynamics in an SBN; it describes to what level the internal noise in an SBN is restricted. Thus, σ is a stochastic process adapted to the Brownian filtration $\mathcal{F}$ such that almost all sample paths in this process are uniformly bounded functions that satisfy the uniform Lipschitz condition in X_t as described in (A1). Moreover, σ constitutes the key character of the proposed model, which will be presented as Definition 1 in Section 2.3.

In what follows, by an instance of (1) we mean that f and σ are supposedly assigned with concrete (measurable) functions. By the existence and uniqueness theorem for the Itô equation, any instance of (1) that satisfies (A1) and (A2) has a unique continuous solution. In this way, we use (1) as a framework for dynamics (including signal propagation processes) in SBN.

2.2. Signal and its response

A principle in systems biology is that an SBN operates at a specific spatial–temporal scale (e.g., see Alon, 2006). Thus, during a time period shorter than the limit of this scale, no dynamical changes in the network can be measured on this scale, although beneath the scale an SBN may constantly undergo changes. Therefore, we can model the dynamics in an SBN by a continuous stochastic process $\{X_t : t \in [0,T]\}$, and then analyze the dynamics via a discrete version $\{X_{l\tau} : l = 0, \dots, N+N_0\}$ where τ is the minimum time period needed for the internal noise to possibly cause changes in the dynamics on the scale. Without loss of generality, we let $T = (N+N_0)\tau$ for some N, $N_0 \in \mathbb{Z}^+$.

A signal is defined by a spatial–temporal sequence occurring in a subnetwork at times $t = l\tau$, $l = 0, 1, \dots, N_0'$. Suppose $x_t^{(i)}$ represents the label of a node or weight of a link in this subnetwork. Then, all these sequences $\{x_{l\tau}^{(i)} : l = 0, 1, \dots, N_0'\}$ together define a *signal* $\mathcal{S}$. Given a signal, a response to this signal is defined by a spatial–temporal sequence occurring in another subnetwork at times $t = l\tau$, $l = N, (N+1), \dots, (N+N_0)$. Suppose $x_t^{(i)}$ represents the label of a node or weight of a link in that subnetwork. Then, all those sequences $\{x_{l\tau}^{(i)} : l = N, (N+1), \dots, (N+N_0)\}$ together define a *response* $\mathcal{R}$. In the proposed model, a signal $\mathcal{S}$ is considered in a general form as defined above, and our focus is the occurrence of a correct response $\mathcal{R}$ to $\mathcal{S}$. For this purpose, we introduce a notation, a subset $r_S \subseteq \{1, \dots, n\}$ defined as follows: $i \in r_S$ if and only if $x_t^{(i)}$ describes the dynamics of a node or link in the subnetwork where all possible responses to $\mathcal{S}$ are supposed to occur.

τ can be understood as the *time unit* in the propagation of $\mathcal{S}$. Accordingly, N is used to measure the total number of the time units from the beginning of $\mathcal{S}$ to the beginning of $\mathcal{R}$. That is, N is understood as *the length of propagation of a signal*. And $(N_0' + 1)$ and $(N_0 + 1)$ measure *the length of a signal* and *the length of a response*, respectively. We suppose $N_0' \le N_0$, i.e., the length of a response is longer than or equal to the length of the signal which is true in most cases. We normalize τN by 1, i.e., $\tau N = 1$. In what follows, τ will be treated as a small positive real number, and N as a large positive integer. The intuition of this arrangement is that the internal noise may affect the propagation of $\mathcal{S}$ for a number of times.

Additionally, N is used to limit the size n of the network as well as the length (N_0+1) of a response $\mathcal{R}$

$$n \le N^{\alpha_1} \text{ and } (N_0+1) \le N^{\alpha_2} \text{ for some constants } \alpha_1, \alpha_2 > 0 \tag{2}$$

2.3. Weak internal noise

Since the dynamics in an SBN is modeled by the unique continuous solution $\{X_t : t \in [0,T]\}$ of an instance of (1), the internal noise in this SBN is accordingly modeled by the martingale $\{\mathcal{M}_t : t \in [0,T]\}$ where $\mathcal{M}_t = (\mathcal{M}_t^{(1)} \dots \mathcal{M}_t^{(i)} \dots \mathcal{M}_t^{(n)}) = \int_0^t \sigma(s, X_s)\, dB_s$. Now, we formulate the weakness of the internal noise, using the diffusion coefficient σ.

Definition 1. The diffusion coefficient σ in (1) is said to be feasible, if for every $1 \le l \le N+N_0$,

(a) (smoothness) there are two constants $b_1 > 0$ and $0 < \lambda < \frac{1}{2}$ such that for every $1 \le i \le n$ and for all $s \in [(l-1)\tau, l\tau]$, $\mathcal{M}_s^{(i)} - \mathcal{M}_{(l-1)\tau}^{(i)}$ has zero mean and support in $(s-(l-1)\tau)^{(1/2)+\lambda}[-b_1/2, b_1/2]$;

(b) (average-on-scale) the process $\{\sigma(s,\cdot) - \sigma((l-1)\tau,\cdot) : s \in [(l-1)\tau, l\tau]\}$ is independent of $\mathcal{F}_{(l-1)\tau}$.

(a) characterizes a low level that the internal noise in an SBN is restricted to, reusing the idea appeared in Hong (2007) and Hong et al. (2007), respectively, for the noise in the olfactory system and quorum sensing network. In almost all experiments in biology, the dynamics of a node or link in a biological network is smooth to a certain degree. In a transcription network, the dynamics of a node (resp. link) represents the concentration level of bio-molecule (resp. the strength of regulatory function). In a neural network, the dynamics of a node (resp. link) represents the membrane potential of neuron (resp. the strength of synapse). All those dynamics are observed to posses a certain degree of smoothness. Mathematically speaking, dynamics in biological networks, including signal propagation processes, can be interpreted by functions in Hölder classes Λ^α with $\alpha > \frac{1}{2}$. In the proposed model, a signal propagation process is modeled by a continuous stochastic process $\{X_t : t \in [0,T]\}$. By (A1), (A2) and (a), it is not hard to see that each component $x_t^{(i)}$, $1 \le i \le n$, in $\{X_t : t \in [0,T]\}$ almost surely is a function in a Hölder class Λ^α with $\alpha = \frac{1}{2} + \lambda > \frac{1}{2}$. Thus, by (a) we use the smoothness of the dynamics of a node or link in an SBN to formulate a low level that the internal noise is restricted to. This opposes the roughness of one-dimensional Brownian motion where almost every sample path belongs to a Hölder class Λ^α with $\alpha < \frac{1}{2}$ and cannot be in such a class with $\alpha \ge \frac{1}{2}$.

The reason for $\lambda < \frac{1}{2}$ in (a) is as follows. By (A1), (A2) and (a) of Definition 1, we can see that for each $0 \le l \le N_0$, the range of the random variable $x_{(N+l)\tau}^{(i)}$ may well be about $\mathrm{E}[x_{(N+l)\tau}^{(i)}] \pm N^{(1/2)-\lambda}$. To let $x_{(N+l)\tau}^{(i)}$ take its possible values, we suppose $\lambda < \frac{1}{2}$. Notice that for large N, λ must be close to $\frac{1}{2}$, since in a biological network $x_{(N+l)\tau}^{(i)}$ is absolutely bounded.

(b) outlines a mechanism to achieve (a) in general. The idea is as follows. The source of the internal noise in a biological network is random activities at spatial–temporal scales finer than the spatial–temporal scale upon which the biological network operates. In transcription networks, it is the random formation and decay/death of individual molecules, irregular motion of biological particles or solutes, etc. In neural networks, it is the random fluctuations in membrane potentials or in ion channels, etc. In the proposed model, this noise source is modeled by the Brownian motion B_t in (1). Recall a principle in systems biology is that a biological network operates at a specific spatial–temporal scale. In an SBN, by definition τ is the minimum time period needed for the internal noise to possibly cause changes in the dynamics on the scale upon which the SBN operates. We suppose the internal noise in an SBN is the result of averaging a Brownian motion over each time interval of length τ. That is, in the martingale $\{\mathcal{M}_t(=\int_0^t \sigma(s,X_s)\,dB_s) : t\in[0,T]\}$, σ is supposed to average B_s over each time interval of length τ. Therefore, the behavior of σ follows the behavior of the Brownian motion B_t as described by (b).

In (b) the average-on-scale mechanism is defined upon the existence of feasible σ which also satisfy (A2). By the martingale representation theorem, it is not hard to see such σ exist if N and τ are both fixed numbers. In a concrete SBN, N and τ may well be considered as fixed numbers. Also, recall the martingale representation theorem is an existence theorem. This indicates that without knowing the details of how the internal noise in an SBN is restricted, we can safely take what has been observed—the noise is restricted to a low level as characterized by (a). That is, the martingale representation theorem assures, given a martingale $\mathcal{M}_t$, there is mechanism that averages the Brownian motion B_t to yield the martingale.

2.4. Deterministic vs. stochastic

In a biological network, the network structure specifies how the nodes and links are put together, and hence, it characterizes the deterministic part of the dynamics. There are a number of papers and monographs on this subject. We refer the reader to Alon (2006) and Palsson (2006) for comprehensive surveys and references.

We introduce a concept named signaling sample path. Using this concept we relate the network structure of an SBN to its dynamics. In what follows, as in the literature on biological networks, by "a signaling pathway" we mean a path in a biological network along which a signal is passed from node to node to yield a response that correctly corresponds to the signal, and as in theory of stochastic process, by "a sample path" we mean a function $X_t(\omega)$ for a fixed $\omega\in\Omega$ which represents network states at time instances t for all $t\in[0,T]$.

Recall that with (A1) and (A2) we use the Itô equation (1) as a framework for dynamics in biological networks. This implies that the differential equation $X_t = X_0 + \int_0^t f(s,X_s)\,ds$, $t\in[0,T]$, is used to characterize the deterministic part of the dynamics in an SBN, and the term $\int_0^t \sigma(s,X_s)\,dB_s$ in the stochastic differential equation $X_t = X_0 + \int_0^t f(s,X_s)\,ds + \int_0^t \sigma(s,X_s)\,dB_s$, $t\in[0,T]$, characterizes the stochastic part of the dynamics in the same SBN.

As far as signal propagation in an SBN is concerned, the above differential equation may have multiple solutions, each of which describes how a given signal may propagate in the SBN. When the stochastic part is added, the solution of the above stochastic differential equation is a stochastic process, which is fundamentally different from multiple solutions for the differential equation even if this stochastic process is the unique continuous solution for the stochastic differential equation. It is crucial to recognize that a solution of the differential equation becomes a sample path in the unique continuous solution of the stochastic differential equation. This suggests properties of the stochastic process—the unique continuous solution of the stochastic differential equation may play an important role in signal propagation. As we will see, the result of the present paper shows this is indeed the case.

We call a sample path $X_t(\omega)$ in $\{X_t : t\in[0,T]\}$ a *signaling sample path* with respect to $\mathcal{S}$, if this sample path is from a solution of the differential equation as discussed in the previous paragraph. That is, following the deterministic part of the dynamics, the network states along this sample path exhibit how $\mathcal{S}$ is passed from node to node to yield a response $\mathcal{R}$ that correctly corresponds to $\mathcal{S}$. We define

$$A_{\mathcal{S}} = \{\omega\in\Omega : X_t(\omega) \text{ is a signaling sample path}\} \tag{3}$$

Since the underlying probability space for $\{X_t : t\in[0,T]\}$ is $(\Omega,\mathcal{F},\mu)$, in terms of probability $\mu(A_{\mathcal{S}})$ measures the deterministic part of the dynamics with regard to the propagation of $\mathcal{S}$.

Since an SBN is organized as small-world, the network structure of an SBN would likely provide a minimum value for $\mu(A_{\mathcal{S}})$. Indeed, we may suppose $\mu(A_{\mathcal{S}})$ has a lower bound

$$\mu(A_{\mathcal{S}}) \geq \exp\left(-\frac{N^{2\lambda_2}}{4}\right) \text{ for a constant } \lambda_2 \text{ with } 0<\lambda_2<\lambda<\frac{1}{2} \tag{4}$$

The idea behind this inequality is as follows. The propagation of $\mathcal{S}$ is viewed as a chain of cascading events. Since the biological network is organized as small-world network, by definition the length of such a chain is almost surely poly-logarithmic of the network size n. Thus, by the first inequality (2) we may write this length as $k_1\log^{k_2} N$ for some constants $k_1,k_2>0$. We assume that with probability at least $\exp(-N^{2\lambda_2}/4k_1\log^{k_2} N)$ (<1 for large N), an event correctly triggers the next event, which leads to the inequality in (4).

Notice that the hypothesis made by (3) and (4) is quite weak so that the lower bound on the right-hand side of the inequality is near 0 for large N.

2.5. SBN suitable for signal propagation

By definition, a signaling sample path $X_t(\omega)$ with respect to a signal $\mathcal{S}$ exhibits a correct response to $\mathcal{S}$. Thus, any response $\mathcal{R}$ that deviates not far from a response observed along a signaling sample path should be a correct response to $\mathcal{S}$. The following definition is a realization of this idea. Let λ_1 be a constant, with $0<\lambda_2<\lambda_1<\lambda<\frac{1}{2}$. We define

Definition 2. A response $\mathcal{R}$ to a signal $\mathcal{S}$ is said to be correct, if for every $x_t^{(i)}$, $i\in r_{\mathcal{S}}$, and for each $0\leq l\leq N_0$, there is $X_t(\omega)\in A_{\mathcal{S}}$ such that

$$|x^{(i)}_{(N+l)\tau} - x^{(i)}_{(N+l)\tau}(\omega)| \leq \frac{1}{N^{\lambda-\lambda_1}}\left(\frac{b_0}{N^{(1/2)-\lambda}}+b_1\right) \tag{5}$$

There is a minor complication in Definition 2. That is, for different $i\in r_{\mathcal{S}}$ or $0\leq l\leq N_0$, in (5) we may have different $x^{(i)}_{(N+l)\tau}(\omega)$, $\omega\in A_{\mathcal{S}}$. This issue will be resolved by Corollary 1 in Section 4.2.

We are now ready to define the proposed model by a class of SBN in which weak internal noise can be utilized for signal propagation.

Definition 3. An SBN is said to be suitable for a signal $\mathcal{S}$ to propagate, if

(i) the propagation of $\mathcal{S}$ can be captured by the unique continuous solution of an instance (1) in which the drift coefficient f satisfies (A1), and the diffusion coefficient σ satisfies (A2) and is feasible as in Definition 1;
(ii) the correctness of a response $\mathcal{R}$ to $\mathcal{S}$ is defined by Definition 2 with $\mu(A_{\mathcal{S}})$ satisfying (4);

(iii) the network size as well as the length of $\mathcal{R}$ is bounded as expressed in (2).

Except in simulations in Section 2.5, in what follows, a signal is considered in a general form as defined in Section 2.2 so that the proposed model may be applied to disparate types of SBN. We will frequently say an SBN is suitable whenever there is no confusion about what signal is being considered.

3. Results

3.1. The theorem

Definition 3 indicates that as far as signal propagation in biological network is concerned, only five parameters, $\tau, N, \lambda, \lambda_1$ and λ_2, essentially need to be adjusted.

- τ and N are paired together to specify a spatial–temporal scale for signal propagation as discussed in Section 2.2.
- λ, λ_1 and λ_2 satisfy a relation $0<\lambda_2<\lambda_1<\lambda<\frac{1}{2}$. The parameter λ is basic. The constraint $\lambda\in(0,\frac{1}{2})$ is to formulate the weakness of noise as in Definition 1.
- N, λ and λ_1 together characterize the accuracy of signal propagation as given in Definition 2.
- N and λ_2 together describe a basis for the robustness of signal propagation, namely a minimum probability provided by network structure for signal propagation as expressed in (4).

Given a signal $\mathcal{S}$, we let {a correct response $\mathcal{R}$ to $\mathcal{S}$ occurs} denote the event where the response $\mathcal{R}$ in the sample path $X_t(\omega)$ is correct. That is, $X_t(\omega)$ models an experimental trial in which a correct response $\mathcal{R}$ to $\mathcal{S}$ is observed. Then, μ {a correct response $\mathcal{R}$ to $\mathcal{S}$ occurs} represents the probability for a correct response to the signal to occur. The following theorem synthesizes the five parameters together, suggesting a DSP with regard to signal propagation in suitable SBN.

Theorem 1. *In an SBN that is suitable for a signal $\mathcal{S}$ to propagate*

$$\mu\{\text{a correct response } \mathcal{R} \text{ to } \mathcal{S} \text{ occurs}\} \geq 1-\frac{N^{\alpha_1+\alpha_2}}{\mu(A_{\mathcal{S}})}\exp\left(-\frac{N^{2\lambda_1}}{4}\right)\geq 1-N^{\alpha_1+\alpha_2}\exp\left(-\frac{N^{2\lambda_1}-N^{2\lambda_2}}{4}\right) \tag{6}$$

A mathematical proof for this theorem can be found in Section 4.3. In regard to signal propagation, (6) quantitatively describes a general relation between the deterministic and stochastic parts of the dynamics in suitable SBN. Indeed, let $\varepsilon_1(N,\lambda)=\exp(-N^{2\lambda_2}/4)$ and $\varepsilon_2(N,\lambda)=N^{\alpha_1+\alpha_2}\exp(-(N^{2\lambda_1}-N^{2\lambda_2})/4)$. Then, $\varepsilon_1(N,\lambda)$ can be viewed as the minimum probability should be ensured by the signal pathways for a signal $\mathcal{S}$ to propagate. Corresponding to such a $\varepsilon_1(N,\lambda)$, $1-\varepsilon_2(N,\lambda)$ is a lower bound for a correct response $\mathcal{R}$ to $\mathcal{S}$ to occur.

3.2. The illustration

We use computer simulations to illustrate Theorem 1. For simplicity, we assume the lengths of a signal $\mathcal{S}$ and its response $\mathcal{R}$ are the same. In Section 4.3, with Corollary 2 we will show in general that the length of $\mathcal{R}$ can be longer than the length of $\mathcal{S}$.

In simulation Fig. 1, we consider a signal $\mathcal{S}$ as a deterministic temporal sequence $\{h_{\mathcal{S}}(l\tau): l=0,\ldots,N_0\}$ at a node u, and a correct response $\mathcal{R}$ to $\mathcal{S}$ as a temporal sequence $\{h_{\mathcal{R}}((l+N)\tau): l=0,\ldots,N_0\}$ at another node v. The link (u,v) is to mimic the only signaling pathway from u to v which ensures a probability $\mu(A_{\mathcal{S}})=\exp(-N^{2\lambda_2}/4)$ for $\mathcal{S}$ to propagate. In simulation Fig. 2, we consider a signal $\mathcal{S}$ consisting of two branches propagating in parallel from u_1 and u_2 to v_1 and v_2, separately and independently. Two links (u_1,v_1) and (u_2,v_2) are to mimic the only signaling pathways, each of which ensures the same probability $\exp(-N^{2\lambda_2}/4)$ for a branch of $\mathcal{S}$ to propagate. The two responses to the two branches at v_1 and v_2 must be synchronized.

An algorithm used for the simulations is as follows. Following the (sample) path-wise definition of stochastic integration, the Itô equation (1) is viewed as an operator $\mathcal{I}$ that transforms a signal $\mathcal{S}$ to a correct response $\mathcal{R}$. Given $\mathcal{S}$, using (N_0+1) functions $w_l(t), t\in[l\tau,(l+N)\tau]$, $\mathcal{I}$ transforms $h_{\mathcal{S}}(l\tau)$ to $h_{\mathcal{R}}((l+N)\tau)$ where all $w_l(t)$ are functions in a Hölder class Λ^{α} with $\alpha>\frac{1}{2}$, and satisfy $w_l(l\tau)=h_{\mathcal{S}}(l\tau)$ and $w_l((l+N)\tau)=h_{\mathcal{R}}((l+N)\tau)$, $l=0,\ldots,N_0$.

Algorithm 1. $\mathcal{A}_h$:

{1} for $l=0$ to N_0
{2} $h_{\mathcal{C}}((l+N)\tau):=h_{\mathcal{S}}(l\tau)$;
{3} for $g=1$ to N
{4} with probability $(\mu(A_{\mathcal{S}}))^{1/N}$,
$h_{\mathcal{C}}((l+N)\tau):=h_{\mathcal{C}}((l+N)\tau)+[w_l((l+g)\tau)-w_l((l+g-1)\tau)]$;
{5} $h_{\mathcal{C}}((l+N)\tau):=h_{\mathcal{C}}((l+N)\tau)+\delta(l,g)$ where $\delta(l,g)$ is a random number with zero mean and support in $\tau^{(1/2)+\lambda}\left[-\frac{b_1}{2},\frac{b_1}{2}\right]$;
{6} output $h_{\mathcal{C}}((l+N)\tau)$ (as if it is $h_{\mathcal{R}}((l+N)\tau)$);
{7} check the error $(h_{\mathcal{C}}((l+N)\tau)-h_{\mathcal{R}}((l+N)\tau))$;

The algorithm $\mathcal{A}_h$ consists of two loops, an outer loop line {1}−{7} and an inner loop line {3}−{5}. A signal $\mathcal{S}$ is a temporal sequence of (N_0+1) elements. Through the outer loop, these (N_0+1) elements are transformed in temporal order.

Recall the time unit for the propagation of $\mathcal{S}$ is τ, and we take the normalization $\tau N=1$ (Section 2.2). Thus, the inner loop claims each element in $\mathcal{S}$ takes N time units to propagate. During the time unit $((l+g-1)\tau,(l+g)\tau]$, line {4} asserts with probability $(\mu(A_{\mathcal{S}}))^{1/N}$, $h_{\mathcal{C}}((l+N)\tau)$ has an increment $[w_l((l+g)\tau)-w_l((l+g-1)\tau)]$. This mimics the transform of the element is along the signaling pathway which is overall ensured as $\mu(A_{\mathcal{S}})$ by the network structure. Line {5} indicates in any case the internal noise always affects the transform. It is crucial to recognize the importance of line {5}: In the case when $h_{\mathcal{C}}((l+N)\tau)$ does not have the increment in line {4}, i.e., the propagation is disrupted, the internal noise can be viewed as holding the element momentarily which describes how the noise helps the propagation. This is consistent with observations in most cases: the decay of a biological signal takes a much longer period than τ.

The transform without help from the internal noise is simulated as follows. In the algorithm $\mathcal{A}_h$, line {3} to {5} are replaced by one line

{⋄} with probability $\mu(A_{\mathcal{S}}), h_{\mathcal{C}}((l+N)\tau):=h_{\mathcal{R}}((l+N)\tau)$, else, null;

where "null" is to simulate no output in plotting. Line {7} is removed. That is, the link is simulated as an unreliable channel so that each element in a signal is transformed with probability $\mu(A_{\mathcal{S}})$.

For the simulation Figs. 1 and 2, the values assigned to the five parameters are: $\tau=10^{-6}$; $N=10^6$; $\lambda=0.49$; $\lambda_1=0.2$; and $\lambda_2=0.1105$. The τ and N are paired together to specify a spatial–temporal scale seen in neural networks. According to Schröder et al. (2005), the minimum time period needed for the internal noise in a neural network to possibly cause changes in the dynamics can be measured in microseconds. The duration from the beginning of a signal to the beginning of its response in a neural network can usually be measured on a scale of seconds.

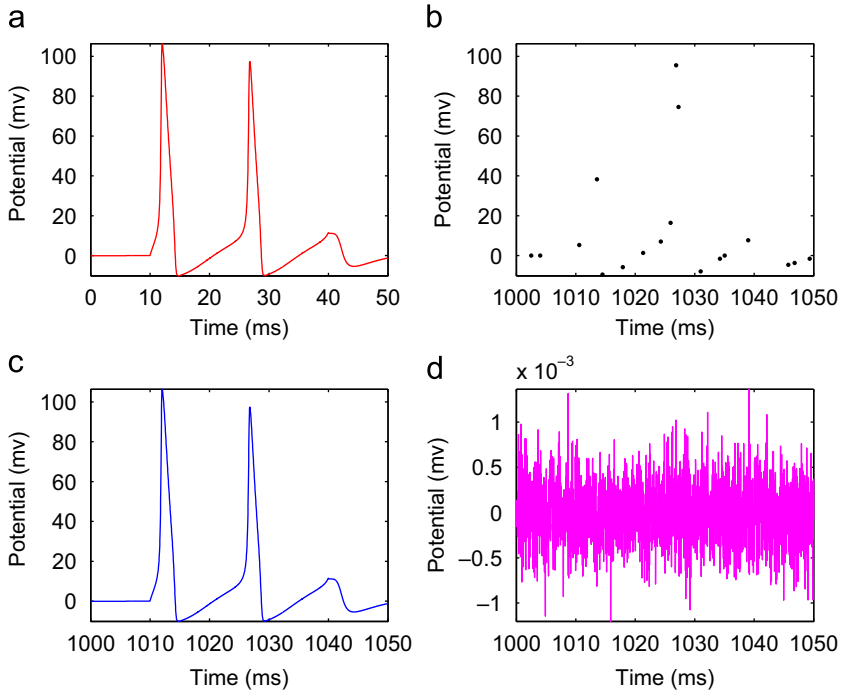

Fig. 1. (a) A numerical solution from the Hodgkin–Huxley equation (a standard model for electrical characteristics of neurons or cardiac myocytes) is taken as a signal $\mathcal{S}$. It should be noted that the signal is used in a general setting and is not meant to represent a specific biological situation. We suppose a correct response $\mathcal{R}$ is essentially a duplicate of $\mathcal{S}$. (b) With $N=10^6$ and $\lambda_2=0.1105$, the link (u,v) ensures a probability $\mu(\mathcal{A}_{\mathcal{S}})=\exp(-N^{2\lambda_2}/4)=0.005012$ for $\mathcal{S}$ to propagate, i.e., the link is an unreliable channel so that each $h_C((l+N)\tau)$, $l=0,\ldots,N_0$, is transformed with probability 0.005012. With no help from the internal noise, the response is disrupted: only a few elements of $\mathcal{S}$ were transformed. It should be noted that the disrupted response is only for illustration. In a concrete biological network, such a disrupted response may well look differently, e.g., missing spikes in a train in a neural network. (c) With help of the internal noise, a correct response $\mathcal{R}$ occurs. This response is $\{h_C((l+N)\tau) : l=0,\ldots,N_0\}$ obtained by the algorithm $\mathcal{A}_h$. (d) The result from the error checking in the algorithm $\mathcal{A}_h$ shows the internal noise causes errors over the entire period. Since the internal noise is restricted at a low level, these errors are small. Importantly, through the 10^6−dimensional product probability space induced by the internal noise, a correct response is shown in (c) as predicted by Theorem 1.

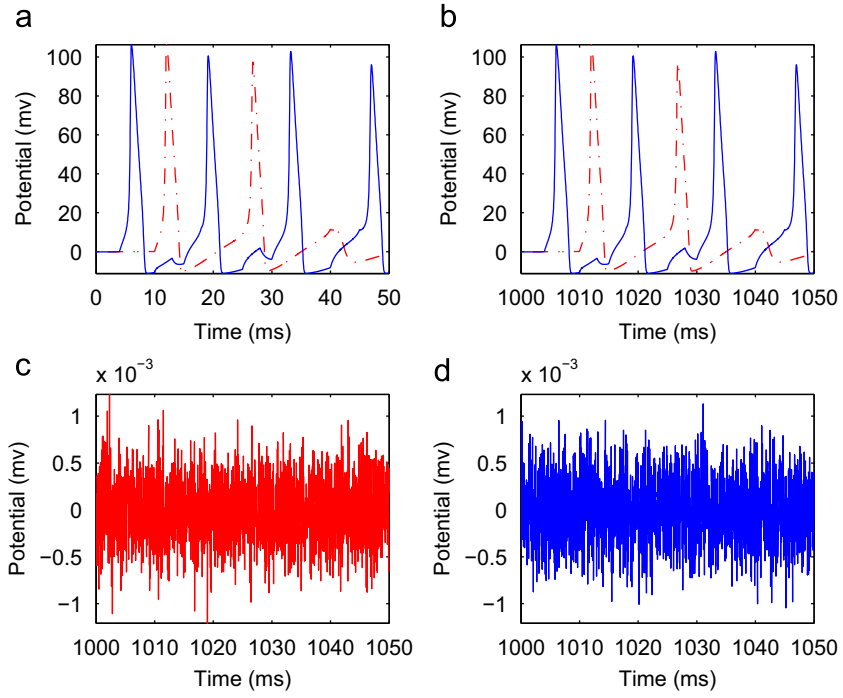

Fig. 2. (a) A signal $\mathcal{S}$ consists of two branches represented respectively by a solid and dash–dot curve. We suppose a response to a branch is essentially a duplicate of the branch. The algorithm $\mathcal{A}_h$ transforms each branch to its response, separately and independently. (b) As in simulation Fig. 1, each of the two links (u_1,v_1) and (u_2,v_2) ensures probability 0.005012 for the branch of $\mathcal{S}$ to propagate. Two responses to the two branches are synchronized in 10^6 μs = 1000 ms. This type of synchronization is predicted by (24) in the proof of Theorem 1. (c) and (d) The results obtained by the algorithm $\mathcal{A}_h$ in the error checking respectively for transforming the two branches of $\mathcal{S}$. The patterns of errors are different in transforming the two branches. Nevertheless, the internal noise synchronizes the occurrence of two correct responses shown in (b).

The λ is chosen to be close to $\frac{1}{2}$ as discussed in Section 2.3. Once τ, N and λ are determined, values for λ_1 and λ_2 can be chosen in certain ranges, all of which will demonstrate the robustness of signal propagation. Here, we made the above choice only for the purpose of illustration. The choice of w_l used in the simulations will be discussed in Section 5.2.

As in (2), we use N to limit N_0, letting $(N_0+1)=10^5$, i.e., $\alpha_2=\frac{5}{6}$ such that $(N_0+1)=(10^6)^{5/6}=10^5$. This means the length of a signal as well as its response is measured on a scale of seconds. In the simulation, when $(N_0+1)=10^5$, the computer program takes hours to produce one set of output. To perform computations in a reasonable amount of time, we used $(N_0+1)=2000$ to run the computer program, and got output similar to what obtained with $(N_0+1)=10^5$. Despite this change we still use $(N_0+1)=10^5$ for theoretical prediction made by Theorem 1.

We let $b_0=1$ in (A1) and $b_1=2$ in Definition 1. Having values assigned to all the parameters, using Theorem 1 we can make some theoretical predictions about the outcome of the simulations Figs. 1 and 2. According to (5), the accuracy of signal propagation is characterized by an error bound of ≈ 0.034 for these chosen parametric values, which is indeed larger than the errors $\pm 2\times 10^{-3}$ found in our simulations; the probability for a correct response $\mathcal{R}$ to $\mathcal{S}$ to occur should always be at least $1-3\times 10^{-13}$ as supported by the outcomes of multiple runs in our simulations.

The MATLAB programs used for the simulations are available on request.

4. Analysis

We first analyze a special case when the length N_0' of a signal equals the length N_0 of its response. Then, at the end of Section 4.3 we extend the analysis to a general case where $N_0'\le N_0$.

4.1. The average-on-scale

By Definition 3, in a suitable SBN the propagation of a signal is supposedly captured by the unique continuous solution $\{X_t: t\in[0,T]\}$ of an instance (1). Projecting such a solution on every single dimension of X_t, we have for every $1\le i\le n$

$$\begin{aligned} x_t^{(i)} &= x_0^{(i)}+\int_0^t f_i(s,x_s^{(1)},\ldots,x_s^{(n)})\,ds \\ &\quad +\sum_{j=1}^{k}\int_0^t \sigma_{ij}(s,x_s^{(1)},\ldots,x_s^{(n)})\,dB_s^{(j)} \\ &= x_0^{(i)}+\int_0^t f_i(s,x_s^{(1)},\ldots,x_s^{(n)})\,ds+\mathcal{M}_t^{(i)} \quad t\in[0,T] \end{aligned} \tag{7}$$

We show the average-on-scale in Definition 1 results in $\{x_{l\tau}^{(i)}: l=0,\ldots,(N+N_0)\}$, $i=1,\ldots,n$, being stochastic processes with *independent increments*. In general, these processes as a discrete version of the unique continuous solution of an instance of (1) are Markovian not necessarily with independent increments. For $1\le i\le n$, define $\pi_l^{(i)}=x_{l\tau}^{(i)}-x_{(l-1)\tau}^{(i)}$, $l=1,\ldots,N+N_0$. Then,

Lemma 1. *For every $1\le i\le n$, the increments $\pi_l^{(i)}$ of $x_t^{(i)}$, $l=1,\ldots,N+N_0$, are independent.*

Proof. Recall that when an instance of (1) meets the conditions for the existence and uniqueness theorem, the unique continuous solution $\{X_t: t\in[0,T]\}$ can be obtained by an iteration procedure. For the proposed model, for each $1\le i\le n$, let $x_t^{(i)}(0)\equiv x_0^{(i)}$, and then with (7) inductively define

$$\begin{aligned} x_t^{(i)}(h+1) &= x_0^{(i)}+\int_0^t f_i(s,x_s^{(1)}(h),\ldots,x_s^{(n)}(h))\,ds \\ &\quad +\sum_{j=1}^{k}\int_0^t \sigma_{ij}(s,x_s^{(1)}(h),\ldots,x_s^{(n)}(h))\,dB_s^{(j)}, \quad t\in[0,T] \end{aligned}$$

For each $1\le i\le n$, we have a sequence of continuous stochastic processes $\{x_t^{(i)}(h): t\in[0,T]\}$, $h=0,1,2,\ldots$ All these stochastic processes are defined on the probability space $(\Omega,\mathcal{F},\mu)$ such that for almost all $\omega\in\Omega$

$$\lim_{h\to\infty} x_t^{(i)}(h)=x_t^{(i)} \quad \text{uniformly for } t\in[0,T] \tag{8}$$

Moreover, by the uniqueness, the iteration may begin at any time $t\in[0,T]$. Recall that $T=(N+N_0)\tau$ (Section 2.2). For any $1\le l\le N+N_0$, if we take the random variable $x_{(l-1)\tau}^{(i)}$ from the solution, and for $t\in[(l-1)\tau,T]$, define $x_t^{(i)}(0)\equiv x_{(l-1)\tau}^{(i)}$ and

$$\begin{aligned} x_t^{(i)}(h+1)-x_{(l-1)\tau}^{(i)} &= \int_{(l-1)\tau}^t f_i(s,x_s^{(1)}(h),\ldots,x_s^{(n)}(h))\,ds \\ &\quad +\sum_{j=1}^{k}\int_{(l-1)\tau}^t \sigma_{ij}(s,x_s^{(1)}(h),\ldots,x_s^{(n)}(h))\,dB_s^{(j)} \end{aligned} \tag{9}$$

then (8) holds uniformly for $t\in[(l-1)\tau,T]$. With harmless notation abuse, we will use the same symbol $x_t^{(i)}(h)$ for iterations starting at different times.

$(x_t^{(i)}-x_{(l-1)\tau}^{(i)})$ is the increment of $x_t^{(i)}$ during the period $[t,l\tau]$, $(l-1)\tau\le t\le l\tau$. Let us first consider a simple case when $l=2$ and the random vector $(x_\tau^{(1)}\ldots x_\tau^{(n)})$ takes a single value $(a_\tau^{(1)}\ldots a_\tau^{(n)})$.

Claim: For every $1\le i\le n$, for every $t\in(\tau,2\tau]$, we have for each $h\ge 0$, the random variable $(x_t^{(i)}(h)-a_\tau^{(i)})$ is independent of $\mathcal{F}_\tau$.

We prove this claim by induction on h, using (9). For $h=0$, $(x_t^{(i)}(0)-a_\tau^{(i)})\equiv 0$, and hence, it is independent of $\mathcal{F}_\tau$. For $h>0$, on the right hand side of (9), under the induction hypothesis we have: the first term is independent of $\mathcal{F}_\tau$ because by (A1) f_i is deterministic; and (ii) the second term is also independent of $\mathcal{F}_\tau$ by (b) in Definition 1. From this, the claim follows.

Let $h\to\infty$ in (9). Then, with the claim, the uniform convergence in (8), (A1) and (A2), and the continuity of measure, we have for a given $a_\tau^{(i)}$, the random variable $(x_t^{(i)}-a_\tau^{(i)})$ is independent of $\mathcal{F}_\tau$. Because $(a_\tau^{(1)}\ldots a_\tau^{(n)})$ can be chosen according to the probability distribution of $(x_\tau^{(1)}\ldots x_\tau^{(n)})$, we have that $(x_t^{(i)}-x_\tau^{(i)})$, in particular, $(x_{2\tau}^{(i)}-x_\tau^{(i)})$ is independent of $\mathcal{F}_\tau$. The lemma follows from repeating the above argument for $l=3,\ldots,N+N_0$. □

4.2. Measure concentration I

In Section 2.2, we formulated a signal as a spatial–temporal sequence occurring in a subnetwork at times $t=l\tau$, $l=0,1,\ldots,N_0$. A signal is deterministic; that is, for $x_t^{(i)}$ representing the label of a node or weight of a link in the subnetwork, the sequence $\{x_{l\tau}^{(i)}: l=0,1,\ldots,N_0\}$ as a branch of the signal is deterministic. In the analysis followed, we consider the sequence of network states $\{X_{l\tau}: l=0,1,\ldots,N_0\}$ as deterministic, i.e., all sequences $\{x_{l\tau}^{(i)}: l=0,1,\ldots,N_0\}$, $i=1,\ldots,n$, are deterministic. This is to resolve a major concern in the study of signal propagation in biological networks, namely the retention of the background activity of a signal. When a signal is propagating, other processes taking place during the same time, often called the background activity in literature, should be retained as well. The background activity of a signal is generally unknown to the signal. In Section 2, signal propagation is modeled in a quite general way: signal and

response, noise, and suitable SBN are all formulated without specifications such that signal propagation in disparate types of biological networks may fit into the proposed model. Now, we let the sequence of network states $\{X_{l\tau} : l = 0, 1, \ldots, N_0\}$ be deterministic without specifications. That is, given a signal we consider all possible background activities. And we show in a suitable SBN, a correct response to the signal will occur no matter what the background activity may be. Also, notice that the supposition of the sequence of network states $\{X_{l\tau} : l = 0, 1, \ldots, N_0\}$ being deterministic does not require changes on the proposed model.

For $1 \le i \le n$, for $0 \le l \le N_0$

$$x^{(i)}_{(N+l)\tau} = \sum_{j=1}^{N} (x^{(i)}_{(j+l)\tau} - x^{(i)}_{(j+l-1)\tau}) + x^{(i)}_{l\tau} = \sum_{j=1}^{N} \pi^{(i)}_{j+l} + x^{(i)}_{l\tau} \tag{10}$$

Since $x^{(i)}_{l\tau}$, $0 \le l \le N_0$, are deterministic, we have

$$\mathrm{E}[x^{(i)}_{(N+l)\tau}] = \sum_{j=1}^{N} \mathrm{E}[\pi^{(i)}_{j+l}] + x^{(i)}_{l\tau} \tag{11}$$

Lemma 2. *For $1 \le i \le n$, we have for $0 \le l \le N_0$*

$$\mu\left(|x^{(i)}_{(N+l)} - \mathrm{E}[x^{(i)}_{(N+l)}]| \le \frac{1}{N^{\lambda-\lambda_1}}\left(\frac{b_0}{N^{(1/2)-\lambda}} + b_1\right)\right) \ge 1 - 2\exp\left(-\frac{N^{2\lambda_1}}{2}\right) \tag{12}$$

Proof. For $1 \le i \le n$, for $0 \le l \le N_0$, let $\theta^{(i)}_{j+l} = \pi^{(i)}_{j+l} - \mathrm{E}[\pi^{(i)}_{j+l}]$, $j = 1, \ldots, N$. Using (10) and (11), we have

$$\sum_{j=1}^{N} \theta^{(i)}_{j+l} = x^{(i)}_{(N+l)\tau} - \mathrm{E}[x^{(i)}_{(N+l)\tau}] \tag{13}$$

We observe $|\theta^{(i)}_{j+l}| = |\pi^{(i)}_{j+l} - \mathrm{E}[\pi^{(i)}_{j+l}]| = |(x^{(i)}_{j+l} - x^{(i)}_{j+l-1}) - \mathrm{E}[x^{(i)}_{j+l} - x^{(i)}_{j+l-1}]|$ $\le 2\sup_{\omega \in \Omega} |x^{(i)}_{j+l}(\omega) - x^{(i)}_{j+l-1}(\omega)|$. Using this and (7), by (A1) and (a) in Definition 1 we have

$$|\theta^{(i)}_{j+l}| \le 2\left(b_0\tau + b_1\tau^{(1/2)+\lambda}\right) = \frac{2}{N^{(1/2)+\lambda}}\left(\frac{b_0}{N^{(1/2)-\lambda}} + b_1\right) \quad (N\tau = 1) \tag{14}$$

By Lemma 1, $\theta^{(i)}_{j+l}$ are independent random variables with zero mean. Combining this with (13) and (14), by Hoeffding's (1963) inequality, we have for $\delta > 0$, for $1 \le i \le n$, and for $0 \le l \le N_0$

$$\mu(|x^{(i)}_{(N+l)} - \mathrm{E}[x^{(i)}_{(N+l)}]| \le \delta) \ge 1 - 2\exp\left(-\frac{\delta^2 N^{2\lambda}}{2\left(\frac{b_0}{N^{(1/2)-\lambda}} + b_1\right)^2}\right)$$

Let

$$\delta = \frac{1}{N^{\lambda-\lambda_1}}\left(\frac{b_0}{N^{(1/2)-\lambda}} + b_1\right).$$

The lemma follows. □

This lemma demonstrates that in a suitable SBN where the internal noise is restricted to a low level as in Definition 1, the noise brings the stochastic stability to the overall dynamics as described by (12): at times $t = (N+l)\tau$, $l = 0, \ldots, N_0$, every $x^{(i)}_t$, $1 \le i \le n$, concentrates on its expectation, i.e., the network states X_t at these times are stochastically stable.

A corollary of Lemma 2 explains a correct response to a signal is related to the stable network states X_t at times $t = (N+l)\tau$, $l = 0, \ldots, N_0$, as observed in most experiments. Let $\mu(\star|A_S)$ denote the conditional probability that under condition $\omega \in A_S$, the inequality

$$|x^{(i)}_{(N+l)} - \mathrm{E}[x^{(i)}_{(N+l)}]| \le \frac{1}{(N^{\lambda-\lambda_1})}\left(\frac{b_0}{N^{(1/2)-\lambda}} + b_1\right)$$

holds for $i \in r_S$ and $0 \le l \le N_0$ in the sample path $X_t(\omega)$. Then,

Corollary 1.

$$\mu(\star|A_S) \ge 1 - 2N^{\alpha_1+\alpha_2}\exp\left(-\frac{2N^{2\lambda_1} - N^{\lambda_2}}{4}\right) \tag{15}$$

Proof. Denote by $\mu(\star \cap A_S)$ the probability of the intersection of the following two events: $\omega \in A_S$; and the inequality

$$|x^{(i)}_{(N+l)} - \mathrm{E}[x^{(i)}_{(N+l)}]| \le \frac{1}{N^{\lambda-\lambda_1}}\left(\frac{b_0}{N^{(1/2)-\lambda}} + b_1\right)$$

holds for $i \in r_S$ and $0 \le l \le N_0$ in the sample path $X_t(\omega)$. Then, by (2) and (12) we have

$$\mu(\star \cap A_S) \ge \mu(A_S) - 2N^{\alpha_1+\alpha_2}\exp\left(-\frac{N^{2\lambda_1}}{2}\right)$$

The corollary follows from this and (4). □

This corollary resolves the complication in Definition 2: for different $i \in r_S$ or $0 \le l \le N_0$, in Definition 2 we can use different $x^{(i)}_{(N+l)\tau}(\omega)$, $\omega \in A_S$ in (5), since (15) indicates they all highly concentrate on $\mathrm{E}[x^{(i)}_{(N+l)\tau}]$ as long as N is large enough.

4.3. Measure concentration II

Lemma 1 claims the dynamics $x^{(i)}_t$ in each component (a node or link) in a suitable SBN exhibits independent increments for time intervals $[(l-1)\tau, l\tau]$, $l = 1, \ldots, N+N_0$. This is consistent with observations in most biological experiments. During a time interval $[(l-1)\tau, l\tau]$, the value of $x^{(i)}_t$ changes from $x^{(i)}_{(l-1)\tau}(\omega)$ to $x^{(i)}_{l\tau}(\omega)$ where $x^{(i)}_{l\tau}(\omega)$ may well correlate to $x^{(i)}_{(l-1)\tau}(\omega)$. However, in most biological experiments, it has been observed: (i) the expectations $\mathrm{E}[(x^{(i)}_{l\tau} - x^{(i)}_{(l-1)\tau})]$, $l = 1, \ldots, N+N_0$, are determined, i.e., the dynamics is predicable over time; (ii) for $1 \le l' < l \le N+N_0$, how $(x^{(i)}_{l\tau}(\omega) - x^{(i)}_{(l-1)\tau}(\omega))$ deviates from $\mathrm{E}[(x^{(i)}_{l\tau} - x^{(i)}_{(l-1)\tau})]$ are independent of how $(x^{(i)}_{l'\tau}(\omega) - x^{(i)}_{(l'-1)\tau}(\omega))$ deviates from $\mathrm{E}[(x^{(i)}_{l'\tau}(\omega) - x^{(i)}_{(l'-1)\tau}(\omega))]$. The proof for Lemma 1shows the cause of this independency is the internal noise. Thus, this lemma is sound from the perspective of mathematics as well as biology.

Upon Lemma 1 we prove Theorem 1 stated in Section 3.1. The technique idea behind the proof is as follows. For a signal $\mathcal{S}$, in a general way, we extend the subset $A_S \subseteq \Omega$ (it may be the case $\mu(A_S) = \exp(-N^{2\lambda_2}/4) \approx 0$) to almost entire Ω such that a correct response to $\mathcal{S}$ will occur in sample paths $X_t(\omega)$ with high probability. To achieve this, we may use a refined martingale argument. However, the isoperimetric theorem by Talagrand (1995), a deep result in measure concentration, is much more powerful. This theorem provides a general way to extend a given subset to almost the entire domain in a product probability space. Talagrand proposed a distance often called Talagrand's convex distance with which we can do so. The origin of this distance can be traced back to probability in Banach spaces (Ledoux and Talagrand, 1991).

Proof of Theorem 1. Given a signal $\mathcal{S}$, we fix $1 \le i \le n$ and $0 \le l \le N_0$. Denote by $\pi^{(i,l)}$ the random vector $(\pi^{(i)}_{l+1} \ldots \pi^{(i)}_{l+N})$ which takes points in $\mathbb{R}^N$ as its values. With harmless notation abuse, we also denote such a point by $\pi^{(i,l)}$. We will call $\pi^{(i,l)}$ a point whenever it is treated in this way.

We say that a point $\pi^{(i,l)}$ is induced by a sample path $X_t(\omega)$ if $x^{(i)}_{j\tau}(\omega) - x^{(i)}_{(j-1)\tau}(\omega) = \pi^{(i)}_j$ for all $j = l+1, \ldots, l+N$. Accordingly, we say that a set $H^{(i,l)}_{\Sigma}$ of points $\pi^{(i,l)}$ is induced by an event $\Sigma \in \mathcal{F}$ if

each point in this set is induced by a sample path $X_t(\omega)$ with $\omega \in \Sigma$. Different events may induce the same set of points. In what follows, for a given $H_{\Sigma}^{(i,l)}$ we consider Σ as the union of all events that induce $H_{\Sigma}^{(i,l)}$. We can see that such an union is still in $\mathcal{F}$ under the conditions of the proposed model.

We construct a probability space with domain $H_{\Omega}^{(i,l)}$, the set of points induced by Ω. It is not hard to verify: all these unions Σ mentioned above form a sub $\sigma-$algebra of $\mathcal{F}$; all these subset $H_{\Sigma}^{(i,l)} \subseteq H_{\Omega}^{(i,l)}$ form a $\sigma-$algebra of $H_{\Omega}^{(i,l)}$; and the one-to-one correspondence $\Sigma \leftrightarrow H_{\Sigma}^{(i,l)}$ induces a probability measure $v^{(i,l)}$ on $H_{\Omega}^{(i,l)}$ with

$$v^{(i,l)}(H_{\Sigma}^{(i,l)}) = \mu(\Sigma) \tag{16}$$

By Lemma 1, this probability space is a product space. In what follows, we simply denote this product probability space by $H_{\Omega}^{(i,l)}$.

Through the product probability space $H_{\Omega}^{(i,l)}$, we analyze the behavior of $x_{l+N}^{(i)}$. Consider $H_{A_{\mathcal{S}}'}^{(i,l)}$ where $A_{\mathcal{S}}'$ is the union of all events in $\mathcal{F}$ that induce the same set of points $\pi^{(i,l)}$ as $A_{\mathcal{S}}$ does. By (16) we have

$$v^{(i,l)}(H_{A_{\mathcal{S}}'}^{(i,l)}) = \mu(A_{\mathcal{S}}') \geq \mu(A_{\mathcal{S}}) \tag{17}$$

Define

$$H_{B_{\mathcal{S}}(i,l)}^{(i,l)} = \left\{ \overline{\pi}^{(i,l)} \in H_{\Omega}^{(i,l)} : |\{j : (l+1 \leq j \leq l+N) \wedge \exists \pi^{(i,l)} \in H_{A_{\mathcal{S}}'}^{(i,l)} (\pi_j^{(i)} \neq \overline{\pi}_j^{(i)})\}| \leq N^{(1/2)+\lambda_1} \right\} \tag{18}$$

Claim:

$$v^{(i,l)}(H_{B_{\mathcal{S}}(i,l)}^{(i,l)}) \geq 1 - \frac{1}{v^{(i,l)}(H_{A_{\mathcal{S}}'}^{(i,l)})} \exp\left(-\frac{N^{2\lambda_1}}{4}\right) \tag{19}$$

We prove this claim by Talagrand's isoperimetric theorem. In the product probability space $H_{\Omega}^{(i,l)}$, Talagrand's convex distance $d_{\mathcal{T}}$ can be expressed as

$$d_{\mathcal{T}}(\overline{\pi}^{(i,l)}, H_{A_{\mathcal{S}}'}^{(i,l)}) = \sup_{\beta \in \mathbb{R}^N} \left\{ z(\beta) : z(\beta) = \inf_{\pi^{(i,l)} \in H_{A_{\mathcal{S}}'}^{(i,l)}} \left\{ \sum_{j=l+1}^{l+N} \beta_j \mathbf{1}(\pi_j^{(i)} \neq \overline{\pi}_j^{(i)}) \right\} \right.$$
$$\left. \text{and} \quad \sum_{j=l+1}^{l+N} \beta_j^2 \leq 1 \right\}$$

where

$$\mathbf{1}(\pi_j^{(i)} \neq \overline{\pi}_j^{(i)}) = 1 \quad \text{if } \pi_j^{(i)} \neq \overline{\pi}_j^{(i)}, \ 0 \text{ otherwise} \tag{20}$$

By Theorem 4.1.1 in Talagrand (1995), we have

$$v^{(i,l)}(d_{\mathcal{T}}(\overline{\pi}^{(i,l)}, H_{A_{\mathcal{S}}'}^{(i,l)}) < N^{\lambda_1}) \geq 1 - \frac{1}{v^{(i,l)}(H_{A_{\mathcal{S}}'}^{(i,l)})} \exp\left(-\frac{N^{2\lambda_1}}{4}\right) \tag{21}$$

Indeed, letting $\beta_j = N^{-1/2}$ for $j = l+1, \ldots, l+N$ in (20), we can see that if a point $\overline{\pi}^{(i)} \in H_{\Omega}^{(i,l)}$ satisfies $d_{\mathcal{T}}(\overline{\pi}^{(i)}, H_{A_{\mathcal{S}}'}^{(i,l)}) < N^{\lambda_1}$ then $\overline{\pi}^{(i)} \in H_{B_{\mathcal{S}}(i,l)}^{(i,l)}$ by (18). From this and (21), the claim follows.

Consider $B_{\mathcal{S}}(i,l) \subseteq \Omega$ obtained by extending $A_{\mathcal{S}}' \subseteq \Omega$, as implied in (18). By definition, for every $\omega' \in A_{\mathcal{S}}'$ there is $\omega \in A_{\mathcal{S}}$ such that the two sample paths $X_t(\omega')$ and $X_t(\omega)$ exhibit the same increments $\pi_j^{(i)} = x_{j\tau}^{(i)} - x_{(j-1)\tau}^{(i)}$, $j = l+1, \ldots, l+N$. On the other hand, (18) indicates for every $\omega'' \in B_{\mathcal{S}}(i,l)$ there is $\omega' \in A_{\mathcal{S}}'$ such that the two sample paths $X_t(\omega'')$ and $X_t(\omega')$ disagree on at most $N^{(1/2)+\lambda_1}$ of the increments $\pi_j^{(i)} = x_{j\tau}^{(i)} - x_{(j-1)\tau}^{(i)}$, $j = l+1, \ldots, l+N$. Hence, for every $\omega'' \in B_{\mathcal{S}}(i,l)$ there is $\omega \in A_{\mathcal{S}}$ such that the two sample paths $X_t(\omega'')$ and $X_t(\omega)$ disagree on at most $N^{(1/2)+\lambda_1}$ of the increments $\pi_j^{(i)} = x_{j\tau}^{(i)} - x_{(j-1)\tau}^{(i)}$, $j = l+1, \ldots, l+N$. This implies that by (A1), (A2), (a) in Definition 1, and (6), we have for every $\omega'' \in B_{\mathcal{S}}(i,l)$ there is $\omega \in A_{\mathcal{S}}$ such that in the two sample paths $X_t(\omega'')$ and $X_t(\omega)$

$$|x_{l+N}^{(i)}(\omega'') - x_{l+N}^{(i)}(\omega)| \leq \frac{1}{N^{\lambda-\lambda_1}} \left(\frac{b_0}{N^{(1/2)-\lambda}} + b_1 \right) \tag{22}$$

Now, let us revisit (19). Applying (16) to the left hand side, we have

$$v^{(i,l)}(H_{B_{\mathcal{S}}(i,l)}^{(i,l)}) = \mu(B_{\mathcal{S}}(i,l))$$

while, for the right hand site, by (17) we have

$$1 - \frac{1}{v^{(i,l)}(H_{A_{\mathcal{S}}'}^{(i,l)})} \exp\left(-\frac{N^{2\lambda_1}}{4}\right) \geq 1 - \frac{1}{\mu(A_{\mathcal{S}})} \exp\left(-\frac{N^{2\lambda_1}}{4}\right)$$

Putting the above two and (19) together, we have that given a signal $\mathcal{S}$, for fixed $1 \leq i \leq n$ and $0 \leq l \leq N_0$,

$$\mu(B_{\mathcal{S}}(i,l)) \geq 1 - \frac{1}{\mu(A_{\mathcal{S}})} \exp\left(-\frac{N^{2\lambda_1}}{4}\right) \tag{23}$$

By Definition 2 and (22) we have

$$\cap_{i \in r_{\mathcal{S}}} \cap_{0 \leq l \leq N_0} B_{\mathcal{S}}(i,l) \subseteq \{\text{a correct response } \mathcal{R} \text{ to } \mathcal{S} \text{ occurs}\} \tag{24}$$

The theorem follows from $|r_{\mathcal{S}}| \leq n$, (2), (23) and (24). □

Corrollary 2. *In a suitable SBN, for a signal $\mathcal{S}$, (6) holds when the length of a response $\mathcal{R}$ is longer than the length of $\mathcal{S}$, provided that the length of $\mathcal{R}$ is less than or equal to N^{α_2}.*

Proof. Consider the case where a signal $\mathcal{S}$ is a spatial–temporal sequence occurring in a subnetwork at times $t = l\tau$, $l = 0, 1, \ldots, N_0'$, while, its response $\mathcal{R}$ is a spatial–temporal sequence occurring in a subnetwork at times $t = l\tau$, $l = N, N+1, \ldots, N+N_0$ with $N_0 > N_0'$. It is not hard to verify the proof of Theorem 1 can be applied to this case with care as follows. For $N_0' < l \leq N_0$, the product probability space $H_{\Omega}^{(i,l)}$ has dimension $N+(l-N_0')$ higher than N as in the proof of Theorem 1. Since the measure concentration introduced by Talagrand's isoperimetric theorem behaves better in a product probability space with higher dimension, the N_0 in Theorem 1 can be any integer as long as this integer is less than or equal to N^{α_2}. □

5. Discussions

Remarking on the results of this paper, we discuss some possible directions for future research.

5.1. Reconstruction of biological network

In the reconstruction of biological networks, we are asked to construct a biological network based upon experimental data. This is a fast growing interdisciplinary field (see Chen et al., 2009). When reconstructing a biological network, a mathematical model that correctly captures the dynamics in the network is crucial.

Let us examine a basic problem in the reconstruction of biological networks as an example. Given a target gene and a group of possible regulatory genes, construct a network that demonstrates the regulatory mechanism and identifies which genes are regulators of the target gene. The experimental data used to construct this network are collected in microarrays. Experiments have confirmed that the dynamics in such a transcription network are statistical. Chen et al. (2005) proposed a stochastic differential equation model for a transcription network in *Saccharomyces cerevisiae*. The test results of this model fit a set of standard testing data better than other proposed models do. The stochastic differential equation used was an instance of the Itô equation. The maximum likelihood estimator used was proposed by Akaike (1974) as a general purpose

estimator that has been used in many other models. The transcription network has only a few nodes, and hence, it can be viewed as a small-world network. The authors implemented the noise as a weak noise modeled by a Brownian motion. Both the test and the analysis were carried out using computer simulations of the model. A computer program can only simulate a truncated normal distribution, which results in a weak noise as characterized by Definition 1.

The above stochastic differential equation model provides a concrete example that a suitable SBN may capture the signal propagation in a transcription network in *Saccharomyces cerevisiae*. This allows the use of a general purpose maximum likelihood estimator to select the regulators of the target gene correctly. As the authors pointed out, the methodology used in their study appears applicable to reconstruction of other biological networks, if advanced techniques from theory of stochastic differential equations are applied.

In our opinion, in the reconstruction of biological networks, it may be natural to set a stochastic differential equation backward in time. That is, taking suitable SBN as a framework for dynamics in biological networks, we look at the Itô equation backward in time. Backward (or more general, forward–backward) stochastic differential equation is a field initiated by Pardoux and Peng (1990); efficient numerical methods were also proposed (e.g., Ma et al., 2002). Although backward stochastic differential equations bring challenges in mathematical terms, it has found numerous applications in finance (see El Karoui et al., 1997). In our case, a good numerical solution (say, with a strong convergence property) for a backward stochastic differential equation would in theory exhibit the evolving process of a biological network backward in time, which could be useful in reconstruction of the network from incomplete data.

5.2. Simulation of signal propagation in suitable SBN

Theorem 1 indicates signal propagation in suitable SBN can in principle be simulated by numerical solution for a special type of stochastic differential equation, the Itô equation. The simulations we carried out in Section 3.2 follows this principle. In general, to find a numerical solution for a stochastic differential equation can be difficult (see Kloeden and Platen, 1999). However, applying theory of stochastic integration, we can have a simple algorithmic scheme for simulations of signal propagation in suitable SBN. This scheme was expressed by the algorithm $\mathcal{A}_h$ in Section 3.2. A realization of this scheme is to assign concrete functions to w_l, $l=0,\ldots,N_0$; that is, for a suitable SBN, we may assign appropriate functions to w_l in $\mathcal{A}_h$ and then simulate the signal propagation process by this realization of $\mathcal{A}_h$.

A signal propagation process in a suitable SBN is supposed to be captured by the unique continuous solution of an instance of the Itô equation (1). By (7) we project such a solution on single dimensions. In the proof of Theorem 1, our analysis is localized on single dimensions according to (7), and then these localized analyses are synthesized simply by an intersection in (24). This approach enables us to consider suitable SBN in general without detailed network structures. A localized analysis focuses on the dynamics of a component, node or link. We notice that in a biological network, the dynamics of a link may be critical, e.g., in a transcription (or neural) network, it represents the dynamics of a regulatory function (or a synapse) which may influence the dynamics of the entire network. For a fixed component, by (7) we have a fixed $1\leq i\leq n$ and the dynamics of this component is characterized by

$$x_t^{(i)}=x_0^{(i)}+\int_0^t f_i(s,x_s^{(1)},\ldots,x_s^{(n)})\,ds+\sum_{j=1}^{k}\int_0^t \sigma_{ij}(s,x_s^{(1)}\ldots,x_s^{(n)})\,dB_s^{(j)} \tag{25}$$

which is an Itô integral over $t\in[0,T]$. It is not hard to verify in a suitable SBN (i.e., under the conditions of the proposed model), (25) can be obtained as a sample path-wise Riemann–Stieltjes integral (Chung and Williams, 1990), that is, for almost every $\omega\in\Omega$ and for all $1\leq N^*\leq N+N_0$

$$\begin{aligned}x_{N^*\tau}^{(i)}(\omega)=x_0^{(i)}(\omega)&+\lim_{N\to\infty}\tau\sum_{l=1}^{N^*}f_i((l-1)\tau,x_{(l-1)\tau}^{(1)}(\omega),\ldots,x_{(l-1)\tau}^{(n)}(\omega))\\&+\lim_{N\to\infty}\sum_{l=1}^{N^*}\sum_{j=1}^{k}\sigma_{ij}((l-1)\tau,x_{(l-1)\tau}^{(1)}(\omega),\ldots,x_{(l-1)\tau}^{(n)}(\omega))(B_{l\tau}^{(j)}(\omega)-B_{(l-1)\tau}^{(j)}(\omega))\end{aligned} \tag{26}$$

where $N\tau=1$. With Lemma 1 we showed the right hand side of (26) can be understood as a sum of random variables as expressed in (10). Then, we can see that the expectations of these random variables determine w_l. In simulation Fig. 1 as well as Fig. 2, for simplicity we let each w_l, $l=0,\ldots,N_0$, be a Hill function often used to characterize input–output relation in biological network.

Finding w_l for a suitable SBN may bring challenges. However, it would ease computer simulation for the signal propagation. By definition, the diameter of a small-world network almost surely is poly-logarithmic in terms of the network size. It is natural to expect in a small-world network for efficient information processing, the length of each signaling pathway for a given signal should be poly-logarithmic in terms of the network size. But, the computational cost of using such signaling pathways may be very high, if the network does not have a central control over signal propagation which is the case for most biological networks. For such case, Kleinberg (2000) proposed a family of small-world networks and proved the following. Except for some members in this family, no computer algorithms can guide a signal to propagate along these signaling pathways of poly-logarithmic length; and even for these members, at each step the proposed computer algorithm needs the information of the geometric location of the current node, which can hardly be justified in biological terms. This result suggests signal propagation in a small-world biological network may be more complex than any computer algorithm, when the signal propagation uses signaling pathways with length poly-logarithmic of the network size. On the other hand, it is observed that signal propagation in most small-world biological networks, e.g., the brain functional networks (Bassett et al., 2006), does use signaling pathways with length poly-logarithmic of the network size. Thus, a question is how to use computer simulation in the study of signal propagation in suitable SBN. With the result of this paper, we suggest using w_l to resolve the issue, i.e., applying a mathematical procedure to find w_l to reduce the complexity of computer simulation. It seems worthwhile to investigate this method in the future.

Acknowledgments

The authors are grateful to Michel Talagrand for his encouragement over many years. The authors' thanks go to Joseph V. Martin for helpful discussions, to Michael A. Palis for the support, and to Joseph Procell who carefully read through the manuscript and made corrections. The authors thank the three referees for their inspiring and instructive comments which greatly improved the presentation of this paper.

With love the authors dedicate the present paper in memory of Fangran Hong.

References

Akaike, H., 1974. A new look at the statistical model identification. IEEE Transactions on Automatic Control 19, 716–723.

Albert, R., 2005. Scale-free networks in cell biology. Journal of Cell Science 118, 4947–4957.

Alon, U., 2006. An Introduction to Systems Biology: Design Principles of Biological Circuits. CRC Press, Boca Raton.

Barkai, N., Shilo, B.-Z., 2007. Variability and robustness in biomolecular systems. Molecular Cell 28, 755–759.

Bassett, D.S., Meyer-Lindenberg, A., Achard, S., Duke, T., Bullmore, E., 2006. Adaptive reconfiguration of fractal small-world human brain functional networks. Proceedings of the National Academy of Sciences of the United States of America 103, 19518–19523.

Chen, K.-C., Wang, T.-Y., Tseng, H.-H., Huang, C.-Y.F., Kao, C.-Y., 2005. A stochastic differential equation model for quantifying transcriptional regulatory network in *Saccharomyces cerevisiae*. Bioinformatics 21, 2883–2890.

Chen, L., Wang, R.-S., Zhang, X.-S., 2009. Biomolecular Networks: Methods and Applications in Systems Biology. Wiley, New York.

Chung, K.L., Williams, R.J., 1990. Introduction to Stochastic Integration, second ed. Birkhäuser, Basel.

El Karoui, N., Peng, S., Quenez, M.C., 1997. Backward stochastic differential equations in finance. Mathematical Finance 7, 1–71.

Galán, R.F., Fourcaud-Trocmé, N., Ermentrout, G.B., Urban, N.N., 2006. Correlation-induced synchronization of oscillations in olfactory bulb neurons. Journal of Neuronscience 26, 3646–3655.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., Sporns, O., 2008. Mapping the structural core of human cerebral cortex. PLoS Biology 6, e159.

Hoeffding, W., 1963. Probability inequalities for sums of bounded random variables. Journal of the American Statistical Association 58, 13–30.

Hong, D., 2007. Analysis of noise-induced phase synchronization in nervous systems: from algorithmic perspective. Information Processing Letters 105, 35–39.

Hong, D., Saidel, W.M., Man, S., Martin, J.V., 2007. Extracellular noise-induced stochastic synchronization in heterogeneous quorum sensing network. Journal of Theoretical Biology 245, 726–736.

Kleinberg, J., 2000. The small-world phenomenon: an algorithmic perspective. In: Proceedings of 32nd ACM Symposium on Theory of Computing, pp. 163–170.

Kloeden, P.E., Platen, E., 1999. Numerical Solution of Stochastic Differential Equations. Springer, Berlin.

Ledoux, M., Talagrand, M., 1991. Probability in Banach Spaces. Springer, Brlin.

Ma, J., Protter, P., San Martin, J., Torres, S., 2002. Numerical method for backward stochastic differential equations. Annals of Applied Probability 12, 302–316.

Nakao, H., Arai, K.-S., Nagai, K., Tsubo, Y., Kuramoto, Y., 2005. Synchrony of limit-cycle oscillators induced by random impulses. Physical Review E 72, 026220.

Øksendal, B., 2007. Stochastic Differential Equations: An Introduction with Applications, sixth ed. Springer, Berlin.

Palsson, B.Ø., 2006. Systems Biology: Properties of Reconstructed Networks. Cambridge University Press, Cambridge.

Pardoux, E., Peng, S., 1990. Adapted solution of a backward stochastic differential equation. Systems & Control Letters 14, 55–61.

Potapov, A.P., Voss, N., Sasse, N., Wingender, E., 2005. Topology of mammalian transcription networks. Genome Informatics 16 (2), 270–278.

Schröder, I., Harlfinger, P., Huth, T., Hansen, U.P., 2005. A subsequent fit of time series and amplitude histogram of patch-clamp records reveals rate constants up to 1 per microsecond. The Journal of Membrane Biology 203, 83–99.

Talagrand, M., 1995. Concentration of measure and isoperimetric inequalities in product spaces. Publications Mathématiques de l'Institut des Hautes Etudes Scientifiques 81, 73–205.

Teramae, J.-N., Tanaka, D., 2004. Robustness of the noise-induced phase synchronization in a general class of limit cycle oscillators. Physical Review Letters 93, 204103.

Van Kampen, N.G., 2007. Stochastic Processes in Physics and Chemistry, third ed. North-Holland, Amsterdam.

Watts, D.J., Strogatz, S.H., 1998. Collective dynamics of small-world networks. Nature 393, 440–442.

Zhou, T.S., Chen, L.N., Aihara, K., 2005. Molecular communication through stochastic synchronization induced by extracellular fluctuations. Physical Review Letters 95, 178103.