A Robust Controller of Dynamic Networks and Its Verification by the Simulation of the Heat Shock Response Network with Reliable Signal Transmission

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Abstract—**In this paper, a class of dynamic networks that widely exist in nature, such as signaling networks in cells, is modeled as a controller, in which the quantitative relation among principal factors is explicitly given. A reduction method with respect to the controller is proposed to transform a dynamic network into a minimum controller with only two variables and two units: a feedforward unit and a feedback unit. Here the feedforward unit is formulated as a combination of exponential functions, and the feedback unit as a polynomial function. The features of the robust controller on the aspects of non-smoothness and computational complexity are discussed. As an example to demonstrate the feasibility of the controller designed by the method proposed in this paper, the heat shock response (HSR) network of *E. coli* is simulated for its robustness to testify the effectiveness of the controller. The simulation result of the transmission process of the HSR network suggests that the designed controller is an efficient CAD (computer-aided design) tool for developing molecular communication systems using cells *in vivo*.**

Keywords-robustness; dynamic networks; heat shock response network

I. Introduction

Techniques ranging from behavior analysis to system synthesis have been developed for elucidating the behavior of complex systems, and tools derived from signal processing, control theory, and dynamical systems have been applied to complexity science, such as dynamic network analysis, to validate the results obtained from the designed models. Evidence from complexity science is often used to help us to understand various types of natural phenomena. However, the methodologies of complexity science are different from the conventional ones, especially in terms of modeling the complicated interactions that occur among many objects in a complex system. The influence of the structure on its behavior cannot be predicted only on the basis of the prior knowledge. Multiple variables are coupled in a complex system owing to the nonlinear dynamics. Therefore, we have to systematically study the relation among the variables in a complex system in order to find the causal nexus among them.

To essentially understanding the information processing mechanisms of dynamic networks through the causal nexus among the variables, robustness is a key starting point. It is still a challenging task to quantitatively analyze the robustness of dynamic networks (under discrete parameter variation) by the reduction method. In order to investigate the network constraints for sustaining robustness, in this paper, a controller involving multiple feedforwards and feedbacks where coupling exists among feedforwards and between feedforwards and feedbacks, but not among multiple feedbacks, is designed by the reduction method.

Studies on the related network dynamics mechanism are not only important for network theory in general, but also important for applications of the cellular signaling mechanism in molecular communication based on nanonetworks [1~5]. Owing to the robustness [6~15] of the heat shock response network (abbreviated as HSR) [16~22], it is helpful to study the feasibility of HSR-network based molecular communication where its information processing mechanism is the key to explore the engineered cellular signaling mechanism.

II. Reduction of Robust Dynamic Networks for a Robust Controller

A. Reduction Method for the Design of a Robust Controller

Robustness is reflected in two aspects: self-adaptation of the network structure and self-adaptation of parameters to compensate for disturbances. Robustness [6,7] is defined as a phenomenon, a measure, a kind of characteristic, or a mechanism of a system that guarantees stable states, or steady states [8], under a dynamic environment. The most observable measure of dynamic networks is stability, from which robustness is quantified. In this paper, robustness is defined as a mechanism that guarantees the stability under the condition of variation of the parameters and structure of the dynamic network of the underlying system.

Based on the state representation for a nonlinear system, a dynamic network is modeled as follows:

$$\frac{dX(t)}{dt} = f(t, X(t), U(t)), \tag{1}$$

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$$\frac{dY(t)}{dt} = g(t, X(t)), \quad (2)$$

where $U(t)$ is the input vector, $X(t)$ is the state vector, $Y(t)$ is the output vector, and $f(.)$ and $g(.)$ are functions dependent on time.

Let us consider a dynamic network formulated by (1) and (2) having multiple feedforwards denoted as $\{h_i(X)\}$ (i=0,1,…,n-1, $n \in N$) and feedbacks denoted as $\{v_j(X)\}$ (j=0,1,…,m-1, $m \in N$). In the controller, coupling exists within feedforwards, denoted as $w(\{h_i(X)\})$ (i=0,1,…, n-1, $n \in N$), and also between feedforwards and feedbacks, denoted as $s(\{h_i(X)\},\{v_j(X)\})$ (i=0,1,…,n-1, $n \in N$; j=0.1,…, m-1, $m \in N$), but multiple feedbacks are not coupled. The reduction method is as follows.

First, make the reduction from the system (1) formulated by $\{h_i(X)\}$ and $\{v_j(X)\}$ for the following controller

$$\frac{d}{dt}h = f'_1(h, v), \quad (3)$$

and

$$\frac{d}{dt}v = f'_2(h, v). \quad (4)$$

Here h and v are selected from $\{h_i(X)\}$ and $\{v_i(X)\}$, respectively.

Second, formulate a feedforward-centered unit as a combination of exponential functions and a feedback-centered unit as a polynomial function. Through the above method, a class of dynamic networks can be reduced to a minimum controller, and robustness under parameter variation can thus be observed. A formulation of two variables for the feedforward unit is developed as follows:

$$\frac{d}{dt}h = \sum_{i=0}^{l} a_i \exp(b_i(h,t)) e_i(h,v), \quad (5)$$

where $l \in N$, $b_i(h,t)$ and $e_i(h,v)$ are polynomial terms.

As we can see from the minimum model, existing control theory is available for constructing the feedback unit because of its polynomial form (e.g., the Lyapunov function). It is opposed to the situation for the feedforward unit. In contrast to the well-known S-system, which transforms a combination of multiplication terms into a logarithm form in order to use matrix operators, the non-polynomial structure of the controller proposed here is applicable to those units whose mathematical representation is not an S-system and is an extension of the S-system to model dynamic networks.

B. *Feature of the Robust Controller under Discrete Parameter Variation*

In the above robust controller, two features – non-smoothness of the state transition processes and the computational complexity – are directly related to the network structure.

1) Non-smooth Characteristics of a Robust Controller under Discrete Parameter Variation

Since it is necessary to know the characteristics of the analytic model that has been briefly discussed above, here we need discrete representation in theory because different areas of stability are not connected in the parametric space, which differs from the assumption that the variation of the parameters is a continuous function. According to the notation in [23], the basic object of a dynamical system in the control theory can be given as follows

$$\frac{d}{dt}X(t) = f(X(t), v(t)) \text{ a.e. } 0 \le t \le T, \quad (6)$$

where the measurable control function $v(\cdot)$ is chosen subject to the constraint

$$v(t) \in V \text{ a.e. } 0 \le t \le T, \quad (7)$$

Here, V denotes a set in a Euclidean space R_n. (The notation "a.e." refers to "almost everywhere" [23].)

In the robustness of a dynamic network under a discrete variation of parameters, the variable $X(\cdot)$ is defined as $X_k(\cdot)$ (k=0,1,…, K-1, $K \in N$) without loss of generality, and $U(t)$ is defined as the indication function for the parameters that sustain the robustness of $X(t)$ in a dynamic network, which is not necessarily smooth; i.e., it can be non-smooth. "Non-smooth" means that the function is not differentiable, i.e., $U(t) \notin C^l$. In the case where noise is exerted on the input variable (signal node) of a dynamic network, the variable $X_k(t)$ (k=0,1,…, K-1, $K \in N$) and parameter $U(t)$ have non-smooth characteristics.

In non-smooth control, the problem is given as

To find a control function $U(\cdot)$ that guarantees that $X_k(t)$ converges to 0.

It can be redefined as

To find a set of values of function $U(\cdot)$ that guarantee that $X_k(t)$ converges to a stable state (including 0).

As concluded in [23], the issue of controllability for a non-differentiable control function is transformed to the issue of optimality of the function with the observation on a trajectory of $X(\cdot)$ with respect to $s < t$:

$$T(X(t)) - T(X(s)) \geqq s - t, \quad (8)$$

where the functions $T(X(t))$ and $T(X(s))$ are the convergence times of the states $X(t)$ and $X(s)$ under the indexes t and s, respectively.

The minimum of $v(t)$ in the paper is to minimize the supermartingale measure that shows the moment for the arrival of the steady state when the probability is sufficient to converge before we can make a decision on the arrival of stable states, which corresponds to non-smooth transitions among different stable areas and smooth or non-smooth transitions within the same areas. The corresponding parameters are found by using the model check method.

2) Computational Complexity of the Feedback Unit

Since (5) includes multiple coefficients, the search space for the parameter set that satisfies the robustness becomes huge. This situation is different from the one of the continuous function of the parameter variation used to study the influence of the parameters on the robustness behavior. As we know, the Monte Carlo approach is the basic way to validate the parameter setting of the network, and parameter tuning for the entire parameter space which guarantees robustness is an NP problem; therefore, analysis of the computational complexity of the parameter tuning process is required.

The transition of the states can be formulated as an automaton, where the transition of the stable states from the current stable state to the next stable state is triggered by parameter variation. Here, the steps of the transition represent the computational cost, namely computational complexity. The stable and unstable steady states of the dynamic network are classified into two classes of samples, from which the corresponding point probability can be calculated.

It is obvious that the current state only depends on the previous one. Consequently, the Markov process (chain) is applicable here, and the resultant logical inference obeys the Bayesian rule of a decision-making process that shows that the estimation of the related probability is the maximum likelihood estimation.

The transition processes within the classes and between the classes give rise to the complexity issue. An efficient way of realizing the transition process is realistic-cost computing, meaning a low order of computational complexity, i.e., to guarantee that the computing process is finished in a limited time. Here we limit the state transition to the case where only one transition process exists between two nodes.

Let $N_1(i)$ and $N_2(i,j)$ be the number of states of *class (i)* and the number states of *class (i)* and *class (j)*. We have

$$N(n,m) = \sum\nolimits_{i=0}^{n} N_1(i) + \sum_{i=0}^{n} \sum_{j=0}^{m} N_2(i,j), \tag{9}$$

where $N(n,m)$ refers to the total number of transition steps, n refers to the number of stable areas, and m refers to the number of samples in each stable state. According to (9), linear complexity is possible if the transition processes among different states are controlled through connecting each pair of nodes by only one route. This will reduce the combinatorial form of C_n^2 into $O(n)$; i.e., any node can be reached by a random route at one time. The advantage of this scheme is avoiding the exponential increase in the number of connected links and nodes of the underlying dynamic network.

III. Response Network and Its signal Transmission

A. Related Works on Robutsness in Heat Shock Response

In the study of robustness related to bioinformatics [6,8-22], a core method is to model the dynamic network in terms of control theory (i.e., to describe the network in terms of feedforward/amplifiers, feedback, and actuators). Examples demonstrating robustness can be found in bacterium *E. coli*, frog *Xenopus*, budding yeast *S. cerevisiae* and other species. Here, in this paper the heat shock response (HSR) network of *E. coli* is selected because it has been investigated for more than twenty years in biology as a target system to study the robustness of dynamic networks.

The methods applied in robustness research on heat shock response [16-22] mainly come from control theory, in which the PID (Proportional, Integral, Derivative) controller is still a general form of controllers in biological systems. For example, El Samad et al. [16] suggested three derivative types of PID to model the HSR network. Kurata et al. [17] proposed a module-based method to analyze robustness of HSR networks. Chen et al. [15] applied the linear matrix inequality (LMI, the most advanced mathematical tool in robust control theory) in robustness analysis of gene regulatory networks. The dynamic model described by Chen et al. [9] is a good example to design models for the analysis of HSR network [22]. According to the results reported in recent years [16–22], almost all the major methods from control theory have been applied to the analysis of HSR network. On the overview and representative processes of integration of control theory and systems biology, readers are suggested to refer [24] and [25], respectively.

B. Verification of the Robust Controller by the Heat Shock Response Network

As a complex system, the HSR network (see Fig.1) consists of multiple variables. The direct relation between two factors of σ^{32} and DnaK is under the conditions that

(1) the process on *mRNA*(σ^{32}) is a constant process of feeding to σ^{32} that activates the HSR network;
(2) the binding states of DNAP and σ^{32} are approximated by the linear function of σ^{32};
(3) the partial differential equation of σ^{32} is approximated by a differential equation of σ^{32} dependent on time;
(4) the integration of σ^{32} is approximated by the linear function of σ^{32}.

A formulation based on two variables is developed as follows:

$$\begin{aligned}\frac{d}{dt}\sigma &= b_0 \exp(-t) - b_1\sigma - b_2\sigma(\exp(-a_1 t) + a_3\sigma) \\ &\quad - b_3\sigma[Dnak](\exp(-a_1 t) + \exp(-a_2 t) + a_5\sigma) + c,\end{aligned} \tag{10}$$

where $\sigma = \sigma^{32}$.

A robust controller is designed where the gain part of the controller is the signaling process centered on σ^{32}, which decides the output for protein folding. The signaling process centered on DnaK gives the negative-feedback signal to the signaling process centered on σ^{32} with the heat shock signal as a reference. In the HSR network, the feedback directly from the outside - protein folding process is estimated by the signaling process from DnaK to σ^{32}. The notation "[ ]" refers to the concentration of signaling molecules. The stability of [σ^{32}] can be sustained in the simulation using the two-variable formulation of [σ_{32}] and [DnaK] even by setting [Dnak] as a random signal, and the two exponential terms $\exp(-a_1 t)+\exp(-a_2 t)$ in (10) are approximated by one exponential term $\exp(-a_4 t)$ where $a_4 > 0$. Thus, we have that

$$\frac{d}{dt}\sigma = b_0\exp(-t) - b_1\sigma - b_2\sigma(\exp(-a_1 t) + a_3\sigma) - b_3\sigma[Dnak](\exp(-a_4 t) + a_5\sigma) + c, \quad (11)$$

where $\sigma = \sigma^{32}$.

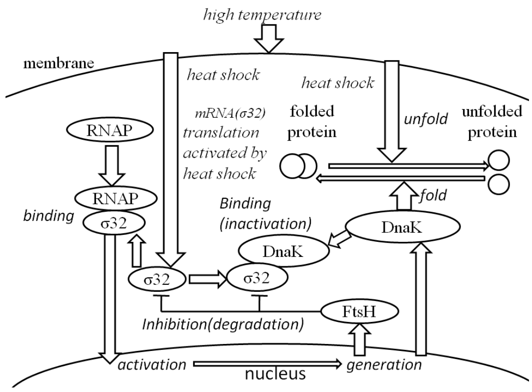

Figure 1. The schematic description of the HSR network

The parameter set as {b_0 = 0.1, b_1 = -0.00003, b_2 = 0.4, b_3 = 0.5, a_1 = 0.2, a_3 = 0.03, a_4 =0.2, a_5 = 0.3, c = 0.00182} have been identified under the condition that [Dnak] is assumed to be Gaussian noise.

When [σ^{32}] = 0.002, it has

$$\frac{d}{dt}\sigma^{32} = 0. \quad (12)$$

Thus, robustness in the HSR network is achieved.

In order to study the characteristics of the controller formulated by (11), that is, the quantitative relation between DnaK and σ^{32}, the feedback of factor DnaK on σ^{32} is polynomial gotten by the reduction of the related signaling process. The effect of factor σ^{32} on DnaK is nonlinear. The module-based simulation for the variables DnaK and σ^{32} is realized by using the software tool Cell Illustrator Professional Version 4. Figure 2 shows the robustness of σ^{32} by the simulation, which is consistent with the one indicated by (11) and (12). Here the unit nM refers to nanomolar. As we can see, the simulation results have verified the robustness behavior of the controller. It is noticeable that the value of the steady state of the designed controller matches the simulated one, where the overshoot of the designed controller is suppressed greatly owing to the efficiency of its structure.

Though benchwork studies on cellular signaling processes of the HSR network have a relatively long history, wet experiments are not available yet for fine-grained analysis of the HSR network, especially where the local concentration of the signaling molecules of the cells is unknown. According to the current state-of-the-art of biotechnology and experimental protocols, new findings from the simulation of the HSR network with respect to its robustness will extend the existing theory of HSR networks and provide a computer-aided means for experimental study of HSR networks.

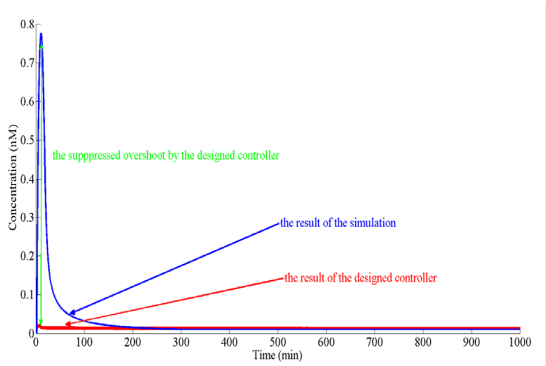

Figure 2. Robustness performance comparison with respect to σ^{32} (curve of concentration versus time)

C. Reliable Signal Transmission by the HSR Network

In addition to the importance of the robustness of the HSR networks in biology, the study on its application in molecular communication which has been extended to nanonetwork communication [1~4] is also important. Integrated with the molecular signaling process of inter-cell (i.e., cell-to-cell) communication, the molecular signaling process of intra-cell (i.e., within-the-cell) communication carried out by the signaling pathway networks provides us powerful tools to design and simulate the protocol of molecular communication. For the purpose of investigating the reliability of the transmission process in intra-cell communication, the signal transmission of intra-cell communication built by the HSR network in cells *in vivo* is modeled and simulated. On the general principle of molecular communication and the architecture of nanonetworks, readers are suggested to refer to [1~3]. In the simulation, both the sender *Tx* and receiver *Rx* are designated as σ^{32} that is spatially distributed in the cell and the channel between them located in the cell is controlled by the HSR network to transport the signaling molecules σ^{32} and DnaK. In the simulation, the related parameters are set as follows in accordance with Fig. 2. Considering the noise caused by thermodynamics [26], the bandwidth of the channel is set as a random signal defined by a uniform distribution whose mean is 0.0025nM for unicasting owing to the structure of the cell *in vivo* that includes enormous organelles such as Golgi apparatus, ER (endoplasmic reticulum), and others. The delay caused by the active and passive transportation is set as a uniform distribution whose mean is 5min. The loss of the channel mainly caused by non-specific interactions of signaling molecules is set as a uniform distribution whose mean is with the range of [0.1, 1.1] in the unit of 0.0005nM considering the resolution effect.

The I/O relation between *Tx* and *Rx* and the reliability performance of the transmission process are illustrated in Fig. 3 and 4. As shown in Fig. 3, the *Rx* signal matches well with the *Tx* signal when the mean of the channel loss is 0.1 in the unit of 0.0005nM where the reference signal is DnaK as a measure to characterize the RTT (round trip time). We can see that the concentration values at the receiver and the sender are identical except several cases where the concentration values at the receiver are lower than the ones at the sender. Owing to the fact that Dnak is a global signal of the HSR network and coupled with σ^{32}, the concentration of DnaK is the major measure for *Tx* used to perceive the transmission effect of the signal σ^{32} at *Rx*. Because the signals of the simulated transmission process are periodically sampled, the curves of Fig. 3 and 4 are illustrated in discrete values. In Fig. 4, the performance of the transmission is briefly outlined where the signal of *Rx* varies with respect to the channel loss. With the robustness of HSR, the received signal in general can be sustained at certain level. The transmission process whose controller can be used to design the physical layer of intracellular molecular communication protocol is reliable under the noisy environment of the cell *in vivo*, and is compatible with the robust codes of signaling pathway networks within the cell [27] with low computing cost [28] by harnessing the robustness of molecular signaling process of cells [29].

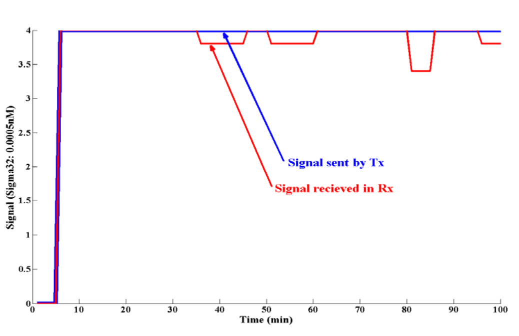

Figure 3. Signals of the sender and the receiver

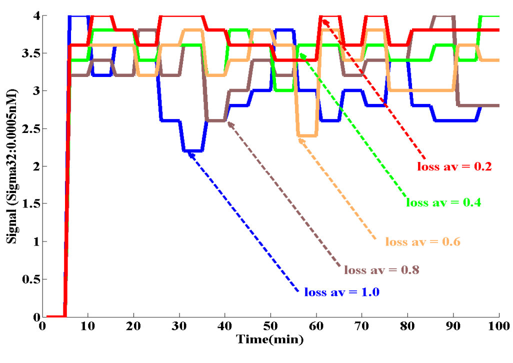

Figure 4. The reliability performance of *Rx* on channel loss

IV. Conclusion

In this paper, a reduction method for a class of dynamic networks is proposed, from which a two-variable minimum controller is derived, and corresponding non-smooth characteristics and the related computational complexity is discussed. The heat shock response (HSR) network of *E. coli* is simulated to validate the controller designed by the reduction method. With respect to the minimum controller of a dynamic network that consists of feedback and feedforward, the feasibility of the proposed reduction method in the simulation of the HSR network is testified and the reliability of the signal transmission process for intra-cell molecular communication by the HSR network is clarified by simulation.

Acknowledgment

The authors sincerely thank Hiroyuki Kurata for his important help on the heat shock response pathways; Chen Li, Masao Nagasaki and Satoru Miyano for their help on checking the simulation model, Hiroaki Kojima on checking the chemistry aspect of the model; Makoto Naruse on physics aspect of the model; Masayuki Murata and Kenji Leibnitz on network engineering; and the Biological ICT group of NICT-KARC on molecular biology. The comments by the anonymous referees are also appreciated, which are helpful to improve the readability of the paper.

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