Filter-based Robustness Analysis of Cellular Signaling Pathways Considering Flow Dynamics

Jian-Qin Liu

Center for Information and Neural Networks
National Institute of Information and Communications Technology
588-2 Iwaoka, Nishi-ku, Kobe 651-2492, Japan
Email: liu@nict.go.jp

Abstract–Traditional studies on the dynamics of cellular signal transmission are mainly limited to the applications of feedback control models where factors affecting the molecular signal flow, which implies the flow of molecular signals in terms of molecular concentration that expresses "information" of the dynamics of cellular functions, are not considered. But reported evidence on cellular signal transmission indicates that the accuracy and efficiency of the flow of molecular signals determines the activation of cellular signaling pathways, which is closely related to the fate of the cell. The feedback control model without considering the inevitable factor – the dynamics of the flow in signal transmission, cannot well explain the phenomenon of the feedback enhancement on the flow of molecular signals in signaling pathway networks. In this paper, a new filter-based method called the network filter in which the non-smooth state transition caused by the signal transmission in different steady states of the feedback controller is detected by a filtering mechanism that characterizes the statistical feature of molecular information channel to perform the quantitative robustness analysis of the heat shock response (HSR) network of *E. coli* is proposed. The simulation result of the robustness of the HSR network is verified by my software simulator of signal transmission processes in the cell by using a channel structure, which can quantitatively describe the characteristics of the molecular signal flow to formulate the cellular signal transmission process. The dynamics of the flow that characterizes the signal transmission process has been proven to be an adequate measurable criterion to testify the effect of feedback on robustness of signal transduction in protein folding. The results obtained demonstrate that the flow dynamics in the HSR network obeys the constructal law, which not only shows the feasibility of this method for the identification of the parameters that characterize the flow in robust cellular signaling pathway networks to find the crucial factors that affect the robustness of HSP but also shows the possibility of being used as a theoretical tool for the analysis of a broad class of dynamic networks in general because HSP determines the protein folding and the failure of the protein folding may cause neuro-degeneration.

Keywords— bioinformatics, cellular signal transmission, robustness.

1. Introduction

Cell communication [1] is the kernel physical mechanism of biological signal processing of molecular network of the cell from which the complexity of the cell can be better understood. With the advances of nanotechnology, some signaling mechanisms are able to be quantitatively described in structural biology [2], e.g., the structure of the G protein receptor acts as an antenna of the cell in the signal transmission between cells, whose discovery was highlighted in 2012 Nobel Prize in Chemistry [3]. The challenging problem is how the complex network of the cell works? i.e., how the signals cooperate [4] to sustain the biological function of the cell. In computational biology it is a problem of modeling a network called network reconstruction because biological networks, which are only unknown to us with respect to their explicit expression in cellular signal transmission [5], do exist in nature. In molecular signal processing the problem become to build a filter to create a mathematical model for a signaling pathway network whose structure can well explain the cellular function and the network filter [6] is the general method to solve the problem of the network reconstruction.

Robustness is an important attribute of staying the same, which measures the behavior of a biological system under uncertainty. Robustness of signaling pathway network is studied mainly by applying the general principles of feedback control in control theory to describe the biological system in systems biology [7]. In classical control theory, robustness of dynamics is independent of the spatial locations of involved signals, which is especially true for the central-controller based systems used in factories. But robust control models for cellular signal transmission without considering the flow of molecular signals contradicts the evidences of the dynamics of the flow caused by the molecular movement. As we know diffusion of the molecular movement results in the molecular flow within the cell. Kholodenko once introduced the diffusion process into the numerical calculation of kinase pathway [8] to demonstrate the transmission of the spatially distributed signals represented by a wave function. Two kinds of movements exist in the cell – the passive form as diffusion and the active form as cargo transportation. These molecular

movements affect the spatial distribution of the molecular concentrations in signaling pathway networks.

What kind of principles used to explain the robustness mechanism under the dynamics of the flow is a main problem trying to address in this paper. To find the characteristics of the underlying system such as minimum, maximum and optimum in result is what the conventional studies are normally carried out on the dynamics of the flow. Those characteristics only show part of the features of the dynamics of flow. One of the laws to explain the dynamics of flow in nature is the constructal law [9], a principle that describes the evolution of a complex system to survive in nature will persist in the direction of easier access of the flow. In order to study the flow dynamics in nature, a robustness model derived from a network controller structure by the integration of nonlinear control theory and communication engineering to unify the process of cellular information processing and cellular signal transmission, which is a formulated mechanism of the so-called network filter, to solve the inconsistency between the role of the feedback on the robustness in control theory and the role of the feedback on transmission rate inferred from empirical observation, is designed. Considering the principles of flow dynamics in biological networks in the cell are still unclear, using quantitative analysis of computational biology to discover the unknown law of nature in cellular signal transmission processes to understand cellular behavior in molecular level through communication theory and communication engineering is extremely important.

The robustness analysis of bio-molecular networks under discrete state transition is mainly discussed in this paper. As we know, among the major characteristics of the cell, specificity is the key to understand the cellular signaling mechanism that sustains the robustness of the cell. Through some specific molecular signals for cellular functions, the methods of system identification and signal estimation are used to quantitatively analyze the signaling dynamics of pathways in the cell. Considering the stochastic characteristics of the object in this study, the signaling mechanism of state transitions among different areas of steady states via non-smooth analysis, which is in contrast to the widely applied analysis methods for signaling pathways in continuous form, is first analyzed. To the best of my knowledge, there are no reports on applying non-smooth mathematical methods to robustness analysis of biological networks although the non-smooth mathematics methods have been applied in optimal control engineering. There is no optimality in cellular signal transmission processes considering that flow dynamics in cellular signaling pathway networks is caused by molecular movement. In this paper, the study of the quantitative analysis of signaling pathway networks formulated by the network filter is presented from the viewpoint of network simulation based on the feasibility, especially the reliability related to the capability of the signaling pathways to transmit special molecular signals. This quantitative analysis of cellular signaling networks

can well explain why and how the robustness can be sustained under the dynamics of flow. The channel unit that describes the flow caused by the signal transmission is introduced into the dynamic model of cellular signaling pathway so the joint temporal and spatial dynamics can be investigated. Using the supporting technology from communication engineering, the effect of the channel capacity of cellular signaling processes with dynamic characteristics is studied. Also based on the factors of the channel, a network filter, which can integrate the nonlinear signaling dynamics and the signal transmission process to formulate the flow phenomenon, is designed for the modulation of the dynamics of the flow. The conclusion that the flow dynamics within the cell helps to sustain the robustness of signaling pathways is consistent with the constructal law – a governing principle in nature. The simulation results show the proposed method is efficient for the bioinformatics analysis of signaling pathway networks as one of the basic principles of nano-scale communication networks though the study in this paper is only limited to the robustness of cellular signaling pathways. The originality of the theoretical model of the network filter is that it embeds the dynamics of the flow into the controlling process to unify both the active and passive movement of signaling molecules in a cell. The theoretical model for molecular drug delivery is only limited to the diffusion mechanism of molecular movement [10]. Here there is a need to mention that it is the first time that the existence of the constructal law in the simulated cellular signaling dynamics of the HSR pathway, which is an instance of HSP (heat shock proteins) for protein folding, is testified. The research presented here is to establish a rigorous and unified theoretic framework for the cellular signaling transmission process in order to explain the phenomena observed in the empirical study of signaling pathway networks [11], and to provide a direct window for potential molecular drug design and delivery to prevent the neuro-degeneration.

2. Quantitative Analysis of the Dynamics of Flow in Signaling Pathway Networks

As we know, the non-smooth state transition is caused by the information flow transmitted through the channel exists. This fact shows the limitation of the traditional controller, i.e., the stochastic variation of the transmitted signals is not taken into the consideration in control design scheme. So, the channel is introduced into the controller structure to formulate it as a network filter so as to perform the quantitative analysis of the flow dynamics.

Before discussing the simulation, the communication mechanism of the cell is depicted as the formalization of cellular signal transmission process in terms of the communication protocols of communication networks, where the structure of the signal transmission represented by chemical concentration of signaling molecules in the cell is mapped to an overlay network structure of

communication networks designed according to the concept of "software-defined networks", which obeys the "OpenFlow" principle [12]). That spatial dynamics of the signaling pathways of the cell is able to be quantitatively analyzed by using the channel representation and transmission operations is one of the most obvious merits of the communication network models being applied in bio-informatics. With this, it becomes feasible to simulate and analyze the joint temporal and spatial dynamics of the cellular signaling process. The modules of my simulation software for signaling and network configuration is described in terms of software engineering and have been introduced into the bio-informatics analysis based on autonomic network architecture in communication engineering.

The stress signal of the cell means the signal from the environment goes irregularly beyond the normal threshold. As a kind of response to stress, heat shock response (HSR) refers to a cellular function in which the cell can sustain the protein folding when the temperature is higher than the normal temperature. The heat shock response pathway network of *E. coli* is selected to study robustness. In the simulation experiment, signaling molecule DnaK in the HSR pathway is used as the indicator of the robustness of the heat shock response pathway of *E. coli.* Figure 1 (a) ~ (c) give the simulation results of the robustness of the signal transmission process. Different channel capacity of signal transmission is used in order to compare the stochastic effect on the flow under the condition of non-selection and selection mechanisms for the flow. Channel capacity with uniform as well as Gaussian distributions is used in the simulation to investigate the influence of different ranges of the channel capacity on the changes of flow. From Figure 1 (a) ~ (c), we can see that flow dynamics of the signal transmission process is greatly affected by the variation of the channel capacity. Figure 1 (d) shows the effect of channel on the signals, the flow dynamics where channel capacity is set as uniform distribution and Gaussian distribution. From the simulation experiment, it has been found that the channel configured by the Gaussian distribution has a higher efficiency of information transmission than the one by the uniform distribution.

Fig. 1 (d) gives the result of a comparative study on flow dynamics with respect to two groups of parameter settings – a non-selective mechanism for the flow formulated by a uniform distribution and a selective mechanism for the flow formulated by a Gaussian distribution. The result is obtained by using the different configurations where the non-selective mechanism and selective mechanism correspond to the diffusion process and non-diffusion process, respectively. By simulating the network filtering mechanism of a robust cellular signaling pathway network that characterizes the flow, that the robustness of the HSR pathway (an instance of HSP [13])
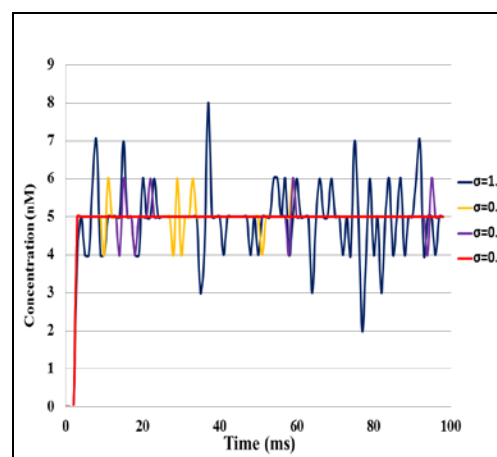
for protein folding is affected by the channel parameters regulating the flow is observed.
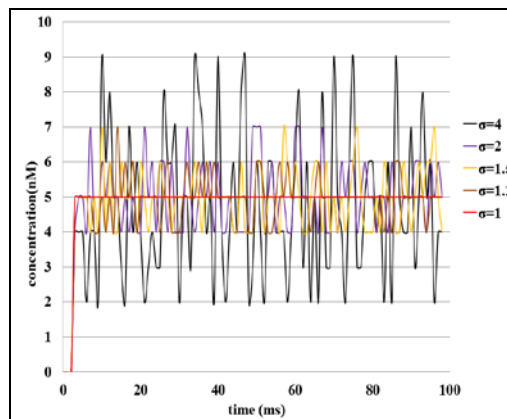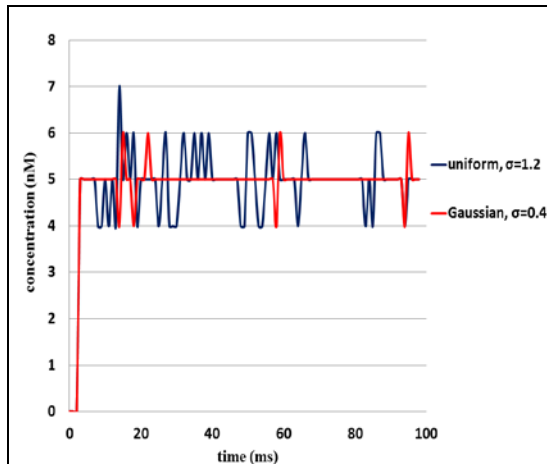

(a) Channel capacity is set as a uniform distribution with the mean 5nM/ms and different variances sampled within [1, 4] nM/ms.
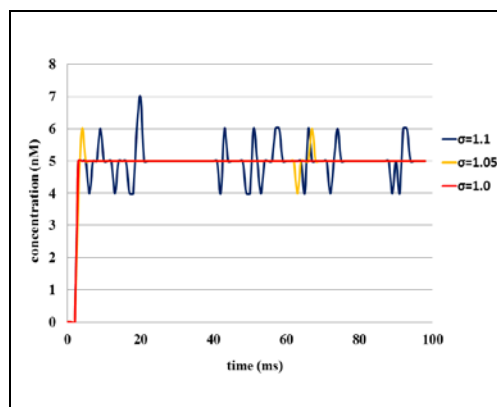
(b) Channel capacity is set as a uniform distribution with the mean 5nM/ms and different variances sampled within [1.0, 1.1] nM/ms.

(c) Channel capacity is set as a Gaussian distribution with the mean 5nM/ms and different variances sampled within [0.3, 1.0] nM/ms.

(d) Comparison of two cases where channel capacity is set as a uniform distribution with the mean 5nM/ms and variance 1.2nM/ms and a Gaussian distribution with the mean 5nM/ms and variance 0.4 nM/ms.

Figure 1 Simulation results of dynamics of the flow in cellular signal transmission

Since the flow dynamics greatly affects the activation of the HSP signaling network of protein folding under stress, the regulation of the pathway on the protein folding mechanism is significant for the cell-intrinsic function, i.e., the function of the so-called "self-regulation", which prevents the neuronal degeneration caused by the mis-folding of protein. The result of the flow dynamics in the simulation, which is designed based on biologically faithful model of cellular signaling pathway networks, fits the contructal law. Here, what should be emphasized is when <u>empirical experimental results obtained from the software simulation is in consistent with the theoretical principle of a scientific law</u> it in turn proves the correctness of the simulation in which the selective mechanism of the channel reinforce the strength of the flow towards the direction of "easier access of the flow" to survive. Survivability of the HSR pathway is represented by the robustness in this paper.

3. Conclusion

In this paper, the dynamics of information flow within the cell, which sustains the robustness of signaling pathways is discussed. The stress response pathway in the cell, a robust system in nature is used to specify the robustness requirements under non-smooth state transition and a filter is designed to explain the observed phenomenon in order to capture the true nature of the robustness. The robustness of a cellular signal transmission process modeled by the filter is formulated and the effect of the flow dynamics of cellular signaling processes is simulated based on the formulated mathematical model of the filtering mechanism. The results from the quantitative analysis of the robust cellular signal transmission process show that the flow dynamics

of the signal transduction of stress response network of protein folding in *E. coli* obeys the "constructal law". By testifying this dynamical feature through the simulation of the robust cellular signaling process of the HSP pathway, it has been found that the flow dynamics greatly affects the activation of the HSP signaling network of protein folding under stress, which can prevents the neuronal degeneration caused by protein mis-folding, a generalized mechanism of cellular signaling processes under an external stress because of the conservativeness among different species.

References

[1] A. Bruce, A. Johnson, J. Lewis, M. Raff, K. Roberts, & P. Walter, *Molecular Biology of the Cell*, New York: Garland Science, Fourth Edition, 2002.
[2] Q. C. Zhang, D. Petrey, L. Deng, "Structure-based prediction of protein–protein interactions on a genome-wide scale," *Nature*, vol.490, pp.556–560, October 2012.
[3] [Online] Available: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2012/advanced-chemistryprize2012.pdf
[4] E. D. Levy, C. R. Landry, S. W. Michnick, "Signaling through cooperation," *Science*, vol.328, no.5981, pp.983-984, May 2010.
[5] M. J. Herrgård, et al, "A consensus yeast metabolic network reconstruction obtained from a community approach to systems biology," *Nature Biotechnology*, vol.26, pp.1155 – 1160, 2008.
[6] X.-M. Zhang, Q.-L. Han, "Network-based H ∞ filtering for discrete-time systems," *IEEE Transactions on Signal Processing*, vol.60, no.2, pp.956-961, February 2012.
[7] P. A. Iglesias and B. P. Ingalls, Eds., Control theory and systems biology, Cambridge: MIT Press, 2010.
[8] B. N. Kholodenko, Cell-signalling dynamics in time and space, *Nature reviews: Molecular cell biology*, vol.7, no.3, 2006, 165-176.
[9] A. Bejan, Constructal Law, online available at: http://www.mems.duke.edu/bejan-constructal-theory
Also see: http://en.wikipedia.org/wiki/Constructal_law
[10] Y. Chahibi, M. Pierobon, S. O. Song and I. F. Akyildiz, "A Molecular Communication System Model for Particulate Drug Delivery Systems," *IEEE Transactions on Biomedical Engineering*, vol. 60, no. 12, pp. 3468-3483, December 2013..
[11] R. C. Yu, et al., Negative feedback that improves information transmission in yeast signalling, *Nature*, vol.456, pp.755-761, December 2008.
[12] http://www-06.ibm.com/systems/jp/networking /openflow/
[13] V. Prahlad, R. I. Morimoto, "Integrating the stress response: lessons for neurodegenerative diseases from *C. elegans*," *Trends in Cell Biology*, vol.19, no.2, February 2009, pp.52–61.