Competitive Memory Functions in Gene Regulatory Network

A B M Shamim Ul Hasan[1], Hiroyuki Kurata[2]
Email: o794042s@bio.kyutech.ac.jp[1], kurata@bio.kyutech.ac.jp[2]

***Abstract*:** Biological memory is a ubiquitous function that can generate a sustained response to a transient inductive stimulus. To better understand this phenomenon, we must consider how the structure of different genetic networks achieves the memory. Here, we investigated two types of gene regulatory network models: regulated mutual activation network (MAN); regulated mutual repression network (MRN). The mathematical comparison was used to analyze the deterministic or stochastic memory between the proposed models at the same steady state level. The MAN model improved the memory function in both deterministic and stochastic models, compared with the MRN model. The MAN provided a robust memory window, but the MRN provided opposite gene expressions with a fragile memory. The MAN model that comprises two protein kinases p42 MAPK and Cdc2 are suggested to need robust memory. The MRN model that consists of cI and Cro proteins would require opposite gene expression rather than robust memory.

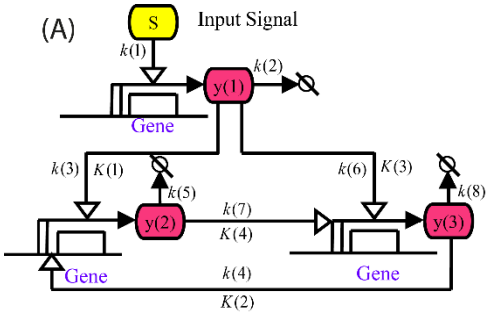
Keywords: Mutual activator loop, Mutual repressor loop, Stochasticity, Hill coefficient

1. Introduction

Systems biology and theoretical biology have revealed the mechanisms of how a biochemical network generates a variety of functions such as switching, amplification, adaptation, pulse generation, oscillation, and memory [1]. A positive feedback loop of a mutual activation network comprising p42 MAPK and Cdc2 presented a bistable memory module [2]. Coupling of mutual inhibition proteins (LacI and TetR or LacI and λcI) of prokaryotic genes with ultrasensitivity addressed the bistable gene expression memory module in E. coli [3]. To our knowledge, accurate comparison of the mutual activation and mutual repression has not been performed. It is interesting to reveal the mechanisms of how different types of mutually closed loops generate memory function. We investigated two types of gene regulatory network models: regulated mutual activation network (MAN); regulated mutual repression network (MRN). The mathematical comparison was used to analyze the deterministic or stochastic memory between the proposed models at the steady state.

2. Method and Materials

We constructed two simple models of the gene regulatory networks that consists [1, 4] of two genes encoding a transcription factor, as shown Fig. 1 [5].



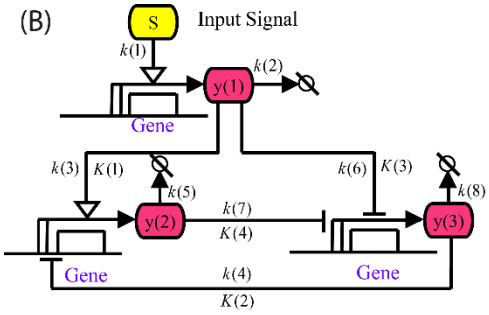


Figure 1. The Schematic models are the genetic regulated mutual networks. (A) MAN model; (B) MRN model;

The mathematical equations of MAN model

$$\frac{dy(1)}{dt} = k(1).S - k(2).y(1) \quad (1)$$

$$\frac{dy(2)}{dt} = b + k(3).\frac{y(1)}{y(1)+K(1)} + k(4).\frac{y(3)^n}{y(3)^n + K(2)^n} - k(5).y(2) \quad (2)$$

$$\frac{dy(3)}{dt} = b + k(6).\frac{y(1)}{y(1)+K(3)} + k(7).\frac{y(2)^n}{y(2)^n + K(4)^n} - k(8).y(3) \quad (3)$$

The mathematical equations of MRN model

$$\frac{dy(1)}{dt} = k(1).S - k(2).y(1) \quad (4)$$

$$\frac{dy(2)}{dt} = k(3).\frac{y(1)}{y(1)+K(1)} + k(4).\frac{K(2)^n}{y(3)^n + K(2)^n} - k(5).y(2) \quad (5)$$

$$\frac{dy(3)}{dt} = k(6).\frac{K(3)}{y(1)+K(3)} + k(7).\frac{K(4)^n}{y(2)^n + K(4)^n} - k(8).y(3) \quad (6)$$

where the employed parameters are described in Table 1.

Table 1. List of kinetic parameters used in the gene regulatory networks

Kinetic parameters	Definition
S	input signal
$k(1)$, $k(3)$, $k(4)$, $k(6)$, $k(7)$	protein synthesis rate constants
$k(2)$, $k(5)$, $k(8)$	degradation rate constants
$K(1)$, $K(2)$, $K(3)$, $K(4)$	dissociation constants

We used a very low rate constant of $b = 0.01$ as basal synthesis of activators to prevent the protein synthesis from being shutdown [6]. We calculated the ordinary differential equations

[1]Department of Bioscience and Bioinformatics, Kyushu Institute of Technology, Iizuka, Fukuoka, Japan

[2] Director of the Biomedical Informatics R&D Center, Kyushu Institute of Technology, Iizuka, Fukuoka, Japan

(ODEs) for deterministic simulation. The Gillespie algorithm was used to perform the stochastic simulation [7]. The MATLAB (Math works) was employed.

3. Results

To analyze the mechanism of how different architectures of gene regulatory networks alter the persistence of memory. This is very much in the spirit of the mathematically controlled comparison [8]. Therefore, we compared the memory windows, while the values of the corresponding kinetic parameters within each model and between the competitive models and the steady state levels of $y(2)$ and $y(3)$ were conserved as much as possible. Corresponding parameters within each network $k(1)=100$, $k(2)=1$, $k(3)=k(6)=18.1$, $k(5)=k(8)=0.8$, $K(1)=K(3)=9$. In MAN model, the synthesis rates $k(4)=k(7)$ gain the value at steady state analysis i.e. depends on dissociation constant and hill coefficients. But in MRN model, synthesis rates $k(4)>k(7)$ to conserve the same steady state level between the models.

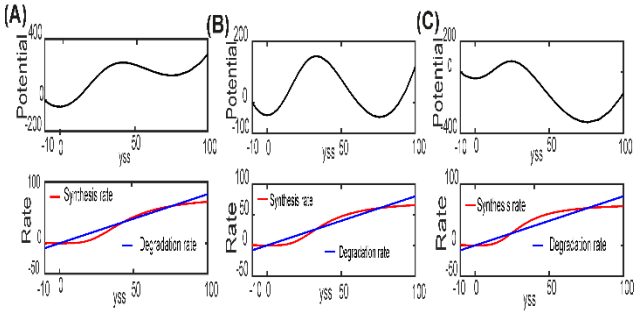


Fig 3. Double-well potentials

(A-C) The system passes through a low concentration state to high concertation state (B) The system is equally stable states.

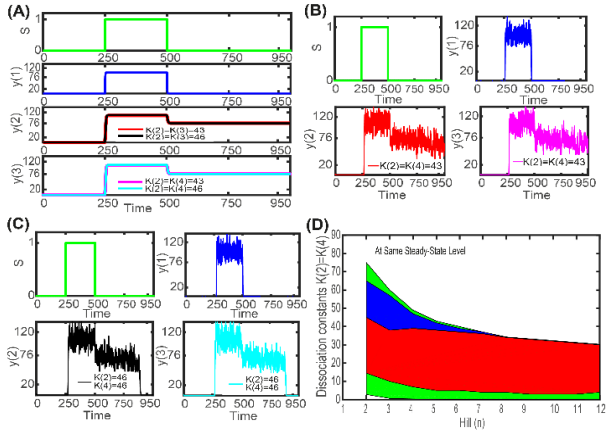


Fig 2. Deterministic and stochastic simulations of the MAN model

(A) Deterministic simulation of proteins $y(1)$, $y(2)$ and $y(3)$ at different dissociation constants. Signal S is input from time 250 to 500. The red and magenta lines indicate $y(2)$ and $y(3)$ at dissociation constant $K(2)=K(4)=43$, respectively. The black and cyan lines indicate $y(2)$ and $y(3)$ at $K(2)=K(4)=46$, respectively. The Hill coefficient is set to $n=2$. (B-C) Corresponding stochastic simulations. (D) The memory window consists of three areas: deterministic (green, blue and red), short stochastic (blue), and full stochastic (red) memories are illustrated with respect to the Hill coefficient and dissociation constants

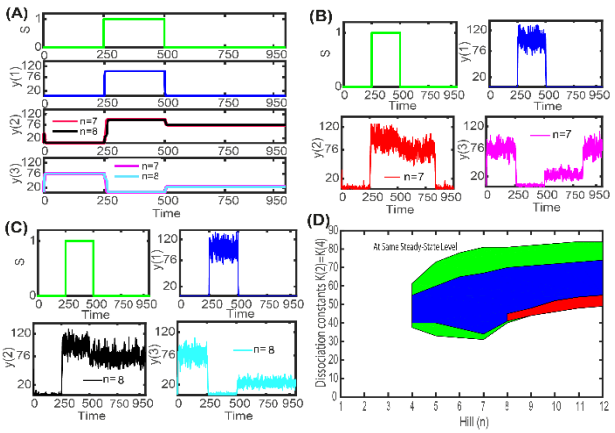


Fig 3. Deterministic and stochastic simulations of the MRN model

(A) Deterministic simulation of proteins $y(1)$, $y(2)$ and $y(3)$ at different Hill coefficients. Signal S is input from time 250 to 500. Dissociation constants are set to $K(2)=K(4)=46$ and other corresponding parameter values are set as the same as the MAN model. The red and magenta lines indicate $y(2)$ and $y(3)$ at n=7, respectively. The black and cyan lines indicate $y(2)$ and $y(3)$ at n=8, respectively. (B-C) Corresponding stochastic simulations. (D) The memory window consists of three areas: deterministic (green, blue and red), short stochastic (blue), and full stochastic (red) memories are illustrated with respect to the Hill coefficient and dissociation constants

4. Discussions

We showed that persistent memory is obtained in deterministic or in stochastic approaches of MAN for hill coefficient $n=2$. On the other hand, the MRN model neither obtained persistent memory in the deterministic nor in stochastic approaches for hill coefficients $n=2$ and $n=3$. The full stochastic memory requires a high hill coefficient $n=8$. If a robust memory is required, a mutual activation network should be selected. If the opposite state of protein synthesis is necessary, a mutual repression network must be selected although the memory effect is fragile [9]. The fragility may be caused by the fact that suppression cascades amplify noise compared with activation cascade [10]. A mutual activation network that comprises two protein kinases p42 MAPK and Cdc2 are suggested to need robust memory [2, 11]. On the other hand, a mutual repression that consists of cI and Cro proteins would require opposite gene expression rather than robust memory [12]. A Notch-Delta mutual repression network is an intelligible example to communicate between neighboring cells [13].

1.1 Conclusions

The MAN model is more convenient compared to the MRN model in order to realize more reliable memories in noisy genetic environments with conserve the steady-state level between the two models and changed in kinetic parameters. The mathematical comparison of the theoretical networks improved an understanding of the potential applications of engineered memory networks in medicine and industrial biotechnology.

Reference

[1] Kurata H, Maeda K, Onaka T, Takata T (2014) BioFNet: biological functional network database for analysis and synthesis of biological systems. Brief Bioinform 15: 699-709.
[2]Xiong W, Ferrell JE, Jr. (2003) A positive-feedback-based bistable 'memory module' that governs a cell fate decision. Nature 426: 460-465.
[3]Gardner TS, Cantor CR, Collins JJ (2000) Construction of a genetic toggle switch in Escherichia coli. Nature 403: 339-342.
[4]Alon U: An introduction to systems biology: Design principles of biological circuits. London: Chapman & Hall/CRC Mathematical & Computational Biology; 2006 .pp. 100-101.
[5]Kurata H, Matoba N, Shimizu N (2003) CADLIVE for constructing a large-scale biochemical network based on a simulation-directed notation and its application to yeast cell cycle. Nucleic Acids Res 31: 4071-4084.
[6]Cheng Z, Liu F, Zhang XP, Wang W (2008) Robustness analysis of cellular memory in an autoactivating positive feedback system. FEBS Lett 582: 3776-3782.
[7]Gillespie DT (1977) Exact Stochastic Simulation of Coupled Chemical-Reactions. Journal of Physical Chemistry 81: 2340-2361.
[8]Alves R, Savageau MA (2000) Extending the method of mathematically controlled comparison to include numerical comparisons. Bioinformatics 16: 786-798.
[9]Gardner TS, Cantor CR, Collins JJ (2000) Construction of a genetic toggle switch in Escherichia coli. Nature 403: 339-342.
[10]Acar M, Becskei A, van Oudenaarden A (2005) Enhancement of cellular memory by reducing stochastic transitions. Nature 435: 228-232.
[11]Huang CY, Ferrell JE, Jr. (1996) Ultrasensitivity in the mitogen-activated protein kinase cascade. Proc Natl Acad Sci U S A 93: 10078-10083.
[12]Casadesus J, D'Ari R (2002) Memory in bacteria and phage. Bioessays 24: 512-518.
[13]Matsuda M, Koga M, Woltjen K, Nishida E, Ebisuya M (2015) Synthetic lateral inhibition governs cell-type bifurcation with robust ratios. Nat Commun 6: 6195.

Acknowledgments

We are grateful to Dr. Kazuhiro Maeda for his helpful technical support to improve the spread of the stochastic simulation and useful discussions.