DIVISION OF THEORETICAL BIOLOGY

Professor (Concurrent)
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We are studying biological phenomena using mathematical models. This method gives us an integrative understanding of the behavior of complex systems in biology including gene regulatory networks.

Mathematical models are especially useful in understanding pattern formation in development. The study of the mechanisms responsible for morphological differences between species is an important research focus of current developmental biology.

I. Steepness of thermal gradient is essential to obtain a unified view of thermotaxis in *C. elegans*

One of the adaptive behaviors of animals in their environment is thermotaxis, by which they migrate toward a preferred temperature. This sensorimotor integration is accomplished by choosing one of two behaviors depending on the surrounding temperature, namely thermophilic or cryophilic movement. C. elegans exhibits thermotaxis and its migration behavior has been analyzed experimentally at both the population and individual levels. However, some experimental data are inconsistent especially for thermophilic movement, which is expected to be observed in lower than favorable temperatures. There are no experimental analyses that find thermophilic tendencies in the individual behavior of worms, despite multiple reports supporting thermophilic movement of the population. Although theoretical methods have been used to study thermotaxis of C. elegans, no mathematical model provides a consistent explanation for this discrepancy. This study was done by Dr. Nakazato in our group as a a collaboration work with Drs. Mori and Kuhara in Nagoya University.

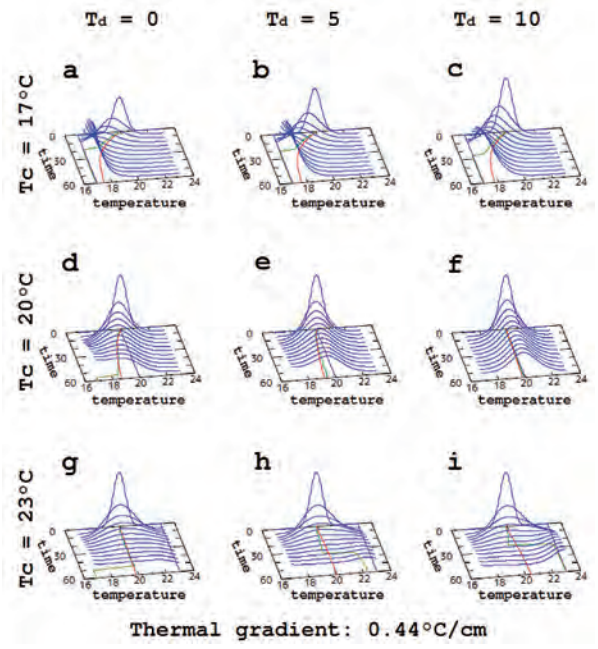

Figure 1. Thermophilic tendency in distribution behavior can be seen only if we adopt the parameter sets with a thermophilic bias. Sufficiently strong thermophilic bias is needed to observe thermophilic tendency in distribution behavior. Red, green and purple lines show the mean of population, the position of maximum peak and cultivated temperature respectively.

Here we develop a simple biased random walk model, which describes population behavior, but which is based on the results of individual assays. Our model can integrate all previous experiments without any contradiction. We regenerate all the population patterns reported in past studies and give a consistent explanation for the conflicting results. Our results suggest that thermophilic movement is observed, even in individual movements, when the thermal gradient is sufficiently slight. On the contrary, thermophilic movement disappears when the thermal gradient is too steep. The thermal gradient is thus essential for a comprehensive understanding of the experimental studies of thermotaxis in C. elegans. Our model provides insight into an integrative understanding of the neural activity and thermotactic behavior in C. elegans.

II. Mathematical modeling for gene expression of vertebrate segmentation

Segmentation in the vertebrate PSM (presomitic mesoderm) is established by a series of pattern formation through the dynamics of gene expression at different levels. Some downstream genes suppress the activity of upstream genes. The negative feedback seems to realize transient dynamics of patterning. We developed two mathematical models, where the negative-regulator genes are different. We found that the previously believed regulation model cannot explain the mutant expression patterns, but the newly proposed model can. The mathematical model gives an integrative understanding and a working hypothesis for a regulatory network system including many genes. This study was done by Dr. Saitou of our group at the RIKEN Advanced Science Institute in collaboration with Drs. Takada and Takahashi of NIBB.

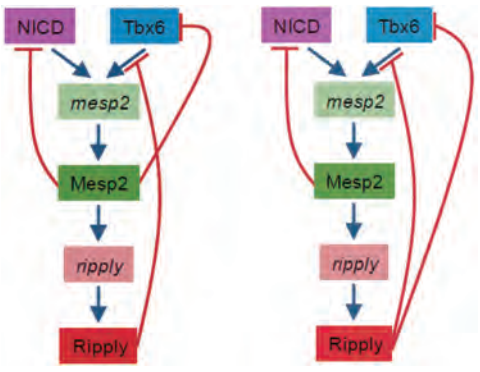

Figure 2. Two models for the regulations of segmentation genes. Left; Model A (Previously believed), Right; Model B (Our hypothesis).

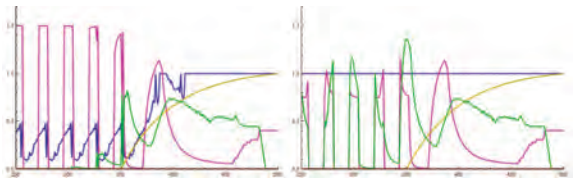

Figure 3. Dynamics of gene expressions for wild type are almost equivalent between the two models. Left; Model A (Previously believed), Right; Model B (Our hypothesis).

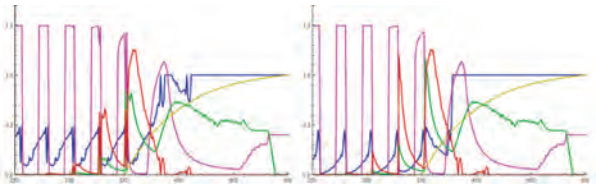

Figure 4. Dynamics of gene expressions for *Ripply* null-mutant are completely different between the two models. Left; Model A (Previously believed), Right; Model B (Our hypothesis). Only model B can explain the experimental results.

III. Structure of regulatory networks and diversity of gene expression patterns

The complexity of gene regulatory networks is considered responsible for the diversity of cells. Different types of cells, characterized by the expression patterns of genes, are produced in early development through the dynamics of gene activities based on the regulatory network. However, very little is known about the relationship between the structure of regulatory networks and the dynamics of gene activities.

In this study I introduce the new idea of "steady state compatibility," by which the diversity of possible gene activities can be determined from the topological structure of gene regulatory networks. The basic premise is very simple: the activity of a gene should be a function of the controlling genes. Thus a gene should always show unique expression activity if the activities of the controlling genes are unique. Based on this, the maximum possible diversity of steady states is determined using only information regarding regulatory linkages and without knowing the regulatory functions of genes.

Using the concept of "steady state compatibility," three general properties of the relationship between the topology of regulatory networks and the maximum number of steady states can be derived (Figure 2). (A) Cascade structures in regulatory networks do not increase the number of possible steady states (Fig. 2a). (B) Loop structures in networks are necessary to generate multiple steady states. The number of separated loops increases the maximum diversity of steady states (Fig. 2b). (C) Multiple loops that are connected by sharing the same genes do not increase the maximum diversity of steady states (Fig. 2c).

The method was applied to a gene regulatory network responsible for early development in a sea urchin species. A set of important genes responsible for generating diversities of gene activities was derived based on the concept of compatibility of steady states.

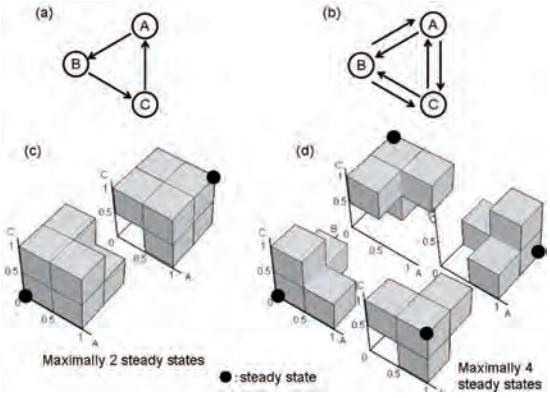

Figure 5. An intuitive explanation of "steady state compatibility". (a) An example of the regulatory links of a mono-directional loop with three genes. (b) Another example of the regulatory links of a bi-directional loop with three genes. (c) The shaded domains show the region where other steady states should not appear except for the original point (0,0,0) and (1,1,1) based on the network in (a). The network (a) has two steady states at maximum. (d) The network (b) determines the different shapes of the domains of no-steady-state except for the points (0,0,0), (0,1,1), (1,0,1) and (1,1,0). This network allows four steady states at maximum.

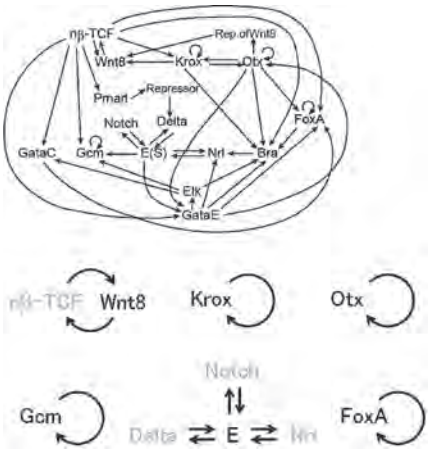

Figure 6. Analysis of an actual gene network responsible for the early development of a sea urchin species. (a) The network is simplified from the one of Fig. 3 in Davidson *et al*. (2002). The maximum diversity generated from this network is determined by the analysis as 64. (b) All of the "reduced observation point" ROP genes are derived. At least one of the ROPs should change its activities in the alternative steady states.

Publication List

〔Original paper〕

● Nakazato, K., and Mochizuki, A. (2009). Steepness of thermal gradient is essential to obtain a unified view of thermotaxis in C. elegans. J. theor. Biol. *260*, 56-65.