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Robust patterning of gene expression based on internal coordinate system of cells

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ABSTRACT

Cell-to-cell communication in multicellular organisms is established through the transmission of various kinds of chemical substances such as proteins. It is well known that gene expression triggered by a chemical substance in individuals has stable spatial patterns despite the individual differences in concentration patterns of the chemical substance. This fact reveals an important property of multicellular organisms called "robustness", which allows the organisms to generate their forms while maintaining proportion. Robustness has been conventionally accounted for by the stability of solutions of dynamical equations that represent a specific interaction network of chemical substances. However, any biological system is composed of autonomous elements. In general, an autonomous element does not merely accept information on the chemical substance from the environment; instead, it accepts the information based on its own criteria for reaction. Therefore, this phenomenon needs to be considered from the viewpoint of cells. Such a viewpoint is expected to allow the consideration of the autonomy of cells in multicellular organisms. This study aims to explain theoretically the robust patterning of gene expression from the viewpoint of cells. For this purpose, we introduced a new operator for transforming a state variable of a chemical substance from an external coordinate system to an internal coordinate system of each cell, which describes the observation of the chemical substance by cells. We then applied this operator to the simplest reaction–diffusion model of the chemical substance to investigate observation effects by cells. Our mathematical analysis of this extended model indicates that the robust patterning of gene expression against individual differences in concentration pattern of the chemical substance can be explained from the viewpoint of cells if there is a regulation field that compensates for the difference between cells seen in the observation results. This result provides a new insight into the investigation of the mechanism of robust patterning in biological systems composed of individual elements.

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1. Introduction

In the field of theoretical biology, many researchers have devoted their efforts to investigate how a biological system can generate various kinds of well-ordered patterns, even though each element has only limited information on the environment, including other elements (Goodwin and Cohen, 1969; Wolpert, 1969). To help explain this problem, physics provides an answer in which the driving mechanism is various local interactions between elements. Based on this idea, many theoretical studies have provided mathematical models of interesting biological phenomena such as the development of multicellular organisms. Specifically, cell-to-cell interactions of a biological system are modeled based on the reaction–diffusion mechanism of chemical substances intermediating cells. Reaction–diffusion models are commonly applied to the concentration of chemical substances in the environment of a biological system, and many interesting solutions have been studied in such models (Geirier and Meinhardt, 1972; Haken, 1983; Murray, 2003; Prigogine, 1981; Turing, 1952).

However, a problem still exists from a biological perspective: how does each cell of a multicellular organism receive the chemical substances that intermediate interactions with the other cells? Any biological system is composed of autonomous elements. In general, an autonomous element does not merely accept information on the chemical substance from the environment; instead, it accepts the information based on its own criteria for reaction. Therefore, investigating what chemical substances intermediating interactions look like from an autonomous element making up a biological system and how the observation of the chemical substances by the element affects the interactions are

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important to understand the autonomy of the element. In this study, our aim is to answer theoretically these questions in terms of robust patterning of gene expression in a biological system because biological robustness is essentially a cognitive feature dependent on the viewpoint of an observer.

2. Background

It is known that many patterns formed by biological systems are invariant in response to environmental fluctuation. This property is called "robustness" (Barkai and Shilo, 2009; Wolpert, 1969). A typical phenomenon can be found in anterior–posterior axis formation of *Drosophila melanogaster*. During this process, the spatial boundary of hunchback gene expression is robust for an individual (early embryo) difference in the concentration pattern of the bicoid protein. The bicoid protein is a trigger factor of the hunchback expression (Houchmandzadeh et al., 2002). Robustness is an important property for the formation and maintenance of the body proportion of a multicellular organism. In general, this property is essential for multicellular organisms to retain their identities while responding flexibly to unknown environments (Kitano, 2007). Against this background, many theoretical studies have investigated the mechanism of robust patterning of the concentration of chemical substances during the development of multicellular organisms.

There are two approaches to investigating the mechanism. The first focuses on the autonomy of a biological system from the outside of the system; the second focuses on the autonomy of each element from the inside of the system. System biology is a typical example of the first approach. In system theory, a biological system is regarded as a network composed of elements and their interactions (Alon, 2006). From the viewpoint of system biology, many models have been proposed to explain the robust patterning of hunchback expression (Aegerter-Wilmsen et al., 2005; Howard and ten Wolde, 2005; McHale et al., 2006). Specifically, a phenomenological model based on the cross-regulation mechanism of gap genes has been proposed and is thought of as being highly consistent with experimental insights (Manu et al., 2009a, b). According to this model, four gap genes (*Hb*, *Kni*, *Kr*, *Gt*) mutually regulate the activation and inhibition of other gap genes, thereby reducing the effect of individual differences in the concentration pattern of the bicoid protein on hunchback expression. This property can be mathematically understood from the stability of solutions of the model equation. This represents the situation where the concentration pattern is robust for fluctuation of an initial state of a system. This approach to understanding the behaviors of a biological system from the outside of the system is useful in grasping a whole picture of the system.

The second approach includes relational biology as an important research field to understand the behaviors of biological systems by focusing on their functions (Rosen, 1991). Relational biology emphasizes functional closure as the basis of biological autonomy. This insight relates to the concept of autopoiesis, which puts weight on the autonomy of elements and in particular observation by the elements (Varela, 1979). According to autopoiesis, biological systems consist entirely of communications between autonomous elements through their observations of each other. The interaction of elements from an external viewpoint of the system is equivalent to an interobservation (communication) between the elements from an internal viewpoint of the system. Therefore, from the perspective of autopoiesis, robustness in multicellular organisms can be understood as invariance for observation by elements. From this standpoint, a mathematical model has been proposed such that each cell of a biological system observes the concentration of the bicoid protein at each position to transform the concentration value to a positional value (Ogawa and Miyake, 2011). This model explains the robust patterning of hunchback gene expression as the robustness of spatial pattern of the positional value. This hypothetical model provides a new insight for considering the autonomy of elements in multicellular organisms. This insight is useful for understanding biological systems from the inside of those systems, and for grasping the behaviors of their elements.

The two approaches are mutually complementary, and a combination of these approaches is thus crucial to develop a deeper understanding of biological systems. However, there is an important problem to be considered: how can we deal with the individuality of autonomous elements in the second approach? The term "individuality" is defined here as the difference between the autonomous elements belonging to the same species. During the development of multicellular organisms, cell-to-cell communication is frequently realized via transmission of chemical substances. A typical example of such chemical substances is various kinds of proteins connecting with cell membrane receptors. When a cell receives a kind of protein, a second messenger is transmitted to the cell nucleus, thereby generating gene expression. Seen in that light, receptors serve as an observer that connects the inside with the outside of a cell. Conventional models of such cell-to-cell communication through a kind of protein have assumed that the receptors on the cells of the same species have a common threshold for protein concentration and gene expression is generated by comparison of the threshold with the concentration at the position at which each cell is placed (Wolpert, 1969). Therefore, under this assumption, many studies have focused on how to form the concentration patterns of various kinds of proteins in the extracellular environment.

However, actual receptors on the cells of the same species have individual differences in shape (three-dimensional (3D) conformation), and much the same is true for many kinds of proteins (Wolpert et al., 2007). Such a difference in the cells or proteins of the same species has been conventionally handled with random fluctuation from an external viewpoint of the system (the first approach). However, the difference has to be captured as individuality from an internal viewpoint of the system (the second approach). In fact, the cells of the same species have a different response to the same concentration depending on the history and position (Alberts et al., 1994). Similarly, regarding the proteins of the same species, a slight difference in 3D configuration makes a change in function (James and Tawfik, 2003; Wang et al., 2004). Thus, robustness in the second approach can be regarded as invariance for the individuality of cells. Therefore, it is important for the second approach to investigate the communication between individual cells belonging to the same species through individual proteins belonging to the same species. Additionally, because genes in the cell nucleus have 3D configurations, much the same is true for the relationship between genes and proteins.

In this study, we assume a biological system composed of individual cells, and consider the dynamics of a chemical substance intermediating cell-to-cell communication from the perspective of individual cells. Specifically, this study aims to answer mathematically the following two questions about such a biological system.

(Q1) What are the conditions for the dynamics of the chemical substance to realize the consistent behavior of the biological system as a whole, even if each cell receives the chemical substance individually?

(Q2) What are the conditions for the robust patterning of gene expression in this biological system?

This study proposes a new perspective on the mechanisms of robust patterning in distributed autonomous systems composed of individual elements, such as biological systems.

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