論 文 の 内 容 の 要 旨

論文題目　A Mathematical Study on Ligand Discrimination
by Chemical Reaction Networks
(化学反応ネットワークによるリガンド識別に関する数理的研究)

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In this thesis, we investigate the mechanism of ligand discrimination system, which is a type of cellular information processing system. Cells sense environmental information through a presence or concentration of particular molecules, which enables cells to survive or adapt to the environment. This sensing process is realized by the interaction between the "ligand" molecules in the environment and the receptor molecules on the cell surface, which have high affinity to the ligand.

For the accurate sensing of the environmental information, cells need to "discriminate" ligands because cells are surrounded by various molecules. Some of them might have similar structures and affinities to the receptors. If the incorrect interaction between the "non-target ligand" and the receptor sends a signal as if the receptors interact with "target ligand," it will decrease the accuracy of information processing. Therefore, cells need to discriminate the target ligand from the non-target ligands.

In this thesis, we firstly review the experimental and theoretical research on the ligand discrimination by cellular systems. We show that the ligand discrimination systems have several characteristics, which are "specificity," which is a selective response to the affinity of ligands, "sensitivity" to the small numbers of the target ligand, "speedy response" to the target ligands, and "insensitivity" to large numbers of non-target ligands. Although some mechanisms for specificity have been proposed, little is known about the mechanism that can balance all of the four characteristics. In addition, recently, bio-imaging techniques have revealed that the microscopic structures, receptor clustering, are formed when cells discriminate ligands. The effects of receptor clustering on the ligand discrimination are also not well understood.

Next, we have investigated the underlying mechanism of the ligand discrimination from the different approaches: deterministic modeling approach and stochastic modeling approach.

In the deterministic modeling approach, we model the ligand discrimination system as a deterministic model, which assume that the system is noiseless and well-mixed. We propose that the zero-order specificity, which has a non-linear response to the affinity of the ligands implemented by enzyme limited reaction networks, as a possible mechanism of the three characteristics: specificity, sensitivity, and speedy response. We also propose that, without losing the three characteristics, the insensitivity to a large number of non-target ligands can appear from the concentration compensation mechanism, which is naturally derived from the zero-order specificity mechanism.

In the stochastic modeling approach, we model the ligand discrimination system as the stochastic process of receptor clustering and deal with the problem that can not be solved by the deterministic model. By using the stochastic model, we find that the stochasticity in the clustering process can induce qualitatively different behavior compared to the deterministic system. We also find that the noise-induced transition helps to reduce the discrimination error.

Our contributions are expected to be a significant step towards the theoretical understanding of the ligand discrimination system. Also, we believe that our works contribute to the further understanding of the cellular decision-making system.