Mathematical analysis of dynamical robustness in biological networks

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Biological systems are highly tolerant to some types of perturbations to which the systems are usually exposed. It is thought that this robustness has been acquired through an adaptation to the environment in the evolutionary process. However, they can be extremely fragile to other types of perturbations which rarely happen. Although this ‘robust but fragile’ property is an essential feature of biological systems, a mathematical theory to understand this property is yet to be fully established. A potent mathematical approach to examine structural robustness of biological networks has been developed in complex network theory. It has been revealed that heterogeneously connected networks (e.g. scale-free networks) are highly robust against random removal of nodes but extremely vulnerable to targeted removal of hubs. However, dynamics is not considered in this framework. Here we focus on another framework to deal with the robustness of dynamic activity in biological networks consisting of elements having intrinsic dynamics. When some elements are inactivated, the level of dynamic activity of the whole network is lowered. There is a critical ratio of inactivated elements, at which the network dynamics vanishes. By analyzing this phase transition, we show that heterogeneously connected networks are highly fragile to targeted inactivation of low-degree elements. This is in strong contrast to the property of structural robustness. Our result implies that the interplay between dynamics and structure plays an important role in network robustness.

1SC-05 自律的酵素量制御による時間スケール調節：ホメオスタシスと記憶

Homeostasis and memory by autonomous regulation of timescales through enzyme abundances

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Biological systems generally consist of a variety of time scales. These timescales also change in time depending on their internal state, according to the change in abundances of enzyme that governs the reaction speed. Here we discuss that homoeostatic response and memory emerge as autonomous regulation of enzyme concentrations. First it is shown that slow relaxation process with some plateaus generally emerge in dynamics of catalytic reaction networks, where the negative correlation between the enzyme and substrate abundances is a key factor for such ‘glassy’ dynamics [1]. Second, we demonstrate that the enzyme-limited competition leads to a homeostasis in the system. To be specific, we study temperature compensation in period of circadian rhythm [2]: By considering a simple system consisting just of Kai proteins, the period of the rhythm is found to be kept constant against temperature change. The origin of this temperature compensation is attributed to enzyme-limited competition, where negative correlation between abundances of substrates and enzymes again plays an important role. Finally, another consequence of long-term dynamics by autonomous regulation of enzyme abundances is generation of cellular, epigenetic memory. After discussing this possibility, I will also illustrate relevance of epigenetic memory to adaptation [3] and differentiation, if I have time.


1SD-02 The mechanism of nuclear protein searching on DNA: Coarse-Grained simulation study

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Various nuclear proteins search their specific binding sites on DNA and function at proper time and location. This process is important for gene expression regulation. Previous theoretical studies have revealed that combination of one-dimensional diffusion along the DNA chain and three-dimensional diffusion in the bulk solution makes it possible for these proteins to search their cognate binding site efficiently. Although this theory is based on an assumption that these proteins can quickly diffuse on DNA, the mechanism of the quick diffusion at molecular level has been elusive. In addition, it has been controversial whether the same mechanism is valid in nucleosomal environment in which histone proteins bind to DNA and possibly hinder the one-dimensional diffusion. In order to approach such problems, we have developed coarse-grained model for protein-DNA complex where most of the parameters are derived from atomic structural information or atomic simulation results. Using this model, we conducted molecular dynamics simulations of several proteins (e.g. TF IIIA, p53, and PCNA) with DNA and got insights into the mechanism of one-dimensional diffusion on DNA. We also performed simulations of the proteins with DNA to which histone proteins bind. Then, we will discuss the validity of this mechanism in nucleosomal environment.

1SD-03 Differences in dissociation free-energy profiles between cognate and non-cognate protein-DNA complexes

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DNA-binding proteins recognize cognate and non-cognate DNA sequences with two different binding modes, in which proteins loosely bind to non-cognate DNA sequences, but to cognate sequences they tightly bind. Experimental structures of such complexes provides us an atomic view of the binding modes, however, it is not so simple to dissect which is cognate or non-cognate complexes by seeing the structures. In this study, free-energy profiles for dissociation of a cognate and a non-cognate Lac repressor-DNA complexes were calculated to obtain energetic views by performing atomic-level molecular dynamics simulations. We implemented an algorithm of adaptive biasing force (ABF) [E. Darve, A. Pohorille, J. Chem. Phys. 128, 144120 (2008)] into the AMBER software to calculate free energy changes in dissociation along a dissociation path. The results showed that the free energy profiles were clearly distinct between the cognate and non-cognate complexes. We found that this difference can be interpreted in terms of changes in the protein-DNA contacts and the number of interfacial hydration water. The calculated dissociation process here agrees with that suggested from an H/D exchange experiment. In the talk, we will discuss how gene regulatory proteins find their target sites on the DNA and what are determinants for distinguishing cognate and non-cognate targets.

1SD-04 竜虫発生期における染色体ダイナミクスの定量的解析

Quantitative analyses of chromosome dynamics in C. elegans early embryos

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During development and differentiation, it has been suggested that chromatin remodeling occurs and contributes to cell fate determination. However, there are few studies for chromatin dynamics during the course of development. We visualized and tracked chromatin loci in C. elegans early embryos. Based on the experimental data, we statistically analyzed dynamics of the chromatin locus, and then revealed quantitative features of chromatin dynamics for several developmental stages. We found several quantitative features that depend on