A binary digit of memory induced by multiple covalent modifications and its application to molecular rhythm

(多重分子修飾による記憶の誘導とその分子リズムへの応用)

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1 Introduction

Life can be considered to be a complex, but delicate, sensitive, and efficient system of organism obtaining high reproducibility and high evolvability in order to grow up, to undergo metabolic change, to react to stimulation, to control its feature, and so forth. For embodying these purposes, it is important to memorize and to communicate information on the past about themselves as precisely as possible. An organism can survive more stably, if the memorization is more correctly and more steadily, and if the communication is more rapidly. It is considered that these characters must be realized by a combination of some biochemical reactions. Especially, it is important how a strage element is constructed in a cell. In this paper we propose a kind of standard structure of mathematical model constructing a binary digit of storage element in a cell by use of covalent modifications and analyse it to elucidate its characteristic and important properties.

We consider a simple two-state (S and T) model for receptor proteins. This is based on and is modified the model a little in the classical work of Professors S. Asakura and H. Honda [1], where they have originally considered about the problem of temporary reaction and post-adaptation process in a cell. S stands for a state which has accepted attractants and is likely to take a convalent modifier, and T stands for the opposite state. S receives convalent modifiers one by one in a definite order, while T releases them in the reverse order. There are n possibly modifying sites receiving convalent modifiers in a receptor protein. Here we assume that a very rapid equilibrium of S and T is realized according to the mass-action law. We change some of important parameters' directions to get a kind of hysterecally switching structure of steady states, which is a foundation on the desirable storage element. In fact, the receptor protein constructs a binary digit in such a way that a state taking more convalent modifiers than a threshold number is regarded as "1", the inverse state as "0". In order to realize it, there must be a kind of bistability and hysterically switching mechanism of the system. In order to get this desirable nature, we adjust paramerers in the system in which the equilibrium between S and T goes to S side more, when the receptor protein has more convalent modifiers, and vice versa. This can make a state changing hysterically according to quantity of attractants, and as a result, it can make a digitally switching function robustly.

One of our important and interesting points is a correlation between the number of the possibly modifying sites and a kind of stability of the storage element. We therefore investigate how the width of hysteresis range varies, as the number of the sites tends larger. The result is that the wider the hysteresis range is, the bigger the number is. Thus it is considered that the existence of a lot of sites contributes the stability of the storage element. In order to

verify usefulness of this fact more concretely, for example, later in §**??**, we apply this model to the phosphorylation–dephosphorylation circadian rhythm of clock proteins of *cyanobacteria*. *Cyanobacteria* are among the simplest organisms that show circadian rhythm. As this model is coupled with equations of attractants and repellents adequately as in Fig.2 and as time constant moves appropriately, the system undergoes Hopf bifurcation to get a time periodic solution, and moreover, the periodic solution survives more robustly, as the number of sites is larger. In a consequence, we elucidate a piece of significant meaning of existence of a lot of sites in the receptor protein. In fact, in the case of circadian rhythm of *cyanobacteria* (See for the details in [16], and [12]), a receptor protein monomer has two sites and it usually composes a hexamer, so that there are 12 sites per a hexamer of recepter protein. It seems that there is slightly many modification sites, but this contributes a stable oscillation daily. In our study, we ensure this fact by use of both deteministic and stochastic ways of simulations here. These two ways are not conflict with each other, but rather, these work to complement to each other. In fact, generally speaking, there may be fewer genes, proteins, and molecular than we can discuss about some qualitative and quantitative properties in a cell. In the case, it seems that we can hardly apply the model of differential equations to the interesting object. But in this paper, we ensure that the system preserves the hystrecally switching structure and robustness of time-periodical behavior of solutions even in the corresponding model system of stochastic way. Moreover, we compute the average and variance of rotation number of the time-periodical solutions of the stochastic model to verify the advantage of a lot of site numbers.

After we saw a kind of structural stability of the system in noisy field of biochemical reaction by poisson process simulation, we investigate several qualitative properties corresponding to some facts of biochemical experiments, for example in [4, 5, 6, 12, 16], by use of the system of the differential equations. Qualitative research for our system has meaning because of a paper of Kitayama et. al[6] in which it is seen that more than 10000 molecules of KaiA, KaiB, and KaiC exist in a cell of *cyanobacteria*, respectively. Then, *rescaling covariance property* is very useful. In fact, our system of equations has a kind of covariance according to rescaling the system. We call this covariance *rescaling covariance property* in this paper. This property permit rigorously and clearly that change of some reaction constants is restate by change of the total mass of some target proteins. We use this property of the system to understand that the system has oscillation solutions with same period in various ratios of total mass of the clock proteins under consideration, although some reaction coefficients should be changed appropriately. But only a few parameters should be changed here. *rescaling covarience property* is convenient for discussion because in simulation we are easy to change total values of proteins with preserving the hysterecal structure, and on the other hand, in biochemical experiment, they are easy to change reaction constants by use of mutants.

Furthermore, by *rescaling covariance property*, we can discuss about the period's varying according to changing environment. For example, surely, in constant dark condition, all the transcriptions and translations cease in *cyanobacteria*, but in natural condition, the ratio of all the clock proteins changes through the day. In spite of it, the circadian rhythm of phosphorylation–dephosphorylation in *cyanobacteria* is very stable. If there is a function adjusting the reaction parameters appropriately according to altering the conditions in *cyanobacteria*, then this kind of stability can be comprehensible by applying *rescaling covariance property*. In fact, at least in *cyanobacteria*, it is said that parameters can be adaptive to environment. *rescaling covariance property* can predict how parameters should change in a simple and clear manner. Moreover, we may also understand the temperature compensation in circadian rhythm of *cyanobacteria*, if the adjusting function works well for changing temperature. Finally, we remark that we do not take the re-regulation by light into account. Light

makes the phase modulated and re-regulated in circadian rhythm by use of another principle, what is called phase syncronizing phenomena, whose effect is not considered in our system.

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