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<td>Author(s)</td>
<td>Ohnishi, Isamu; Ebisu, Kazumi; Shibata, Tatsuo</td>
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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)

Isamu Ohnishi (大西 勇)
(Collaborated by Kazumi Ebisu (胡子 和実) and Tatsuo Shibata (柴田 達夫))

Department of Mathematical and Life Sciences
Graduate School of Science
Hiroshima University
(広島大学大学院理学研究科数理分子生命理学専攻)

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 storage 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 covalent modifier, and $T$ stands for the opposite state. $S$ receives covalent modifiers one by one in a definite order, while $T$ releases them in the reverse order. There are $n$ possibly modifying sites receiving covalent 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 hystereically 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 covalent 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 hystereically 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 covalent 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 receptor 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 deterministic 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 hystecally 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
covariance 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 ra-
tio 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 func-
tion adjusting the reaction parameters appropriately according to altering the conditions in
cyanobacteria, then this kind of stability can be comprehensible by applying rescaling covari-
ance 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 tem-
perature. 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 synchronizing phenomena, whose effect is not considered in our system.

References