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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)

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1 Structure of a binary digit

It is important how a binary digit of memory is realized in a cell, because a strange element must be steady and robust. In this section we propose a simple structure where the binary digit is constructed cleverly, and make an analysis of it. We are especially interested in correlation between the total site number and the steadiness of the binary digit. Moreover, we examine the robustness by changing several parameters in the model system.

1.1 Model Equations

The basic assumptions are the following:

1. The receptor protein converges very rapidly to equilibrium between two configulations (S and T).
2. S stands for a state which has accepted attractants and receives covalent modifiers one by one in a definite order. T stands for the opposite.
3. The equilibrium shifts towards the S form as the number of covalent modifiers is increasing. The total sites of the receptor protein is n. The total quantity of the receptor protein denotes C_{total}, and

$$C_{total} = \sum_{i=0}^{n} (S_i + T_i) . \tag{1}$$

We illustrate our model in the following:

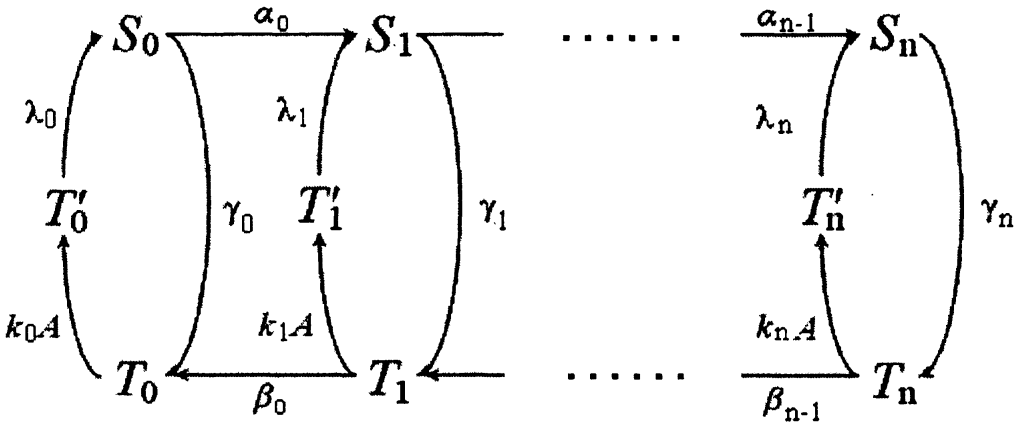

Fig. 1 The simple two-state model

The total quantity of the attractant protein is denoted A_{total}, and A represents a density of attractants and moreover, a part of the attractants is trapping in T'_i. It is therefore satisfies that

$$A_{total} = A + \sum_{i=0}^{n} T'_i . \tag{2}$$

The intermediate state (T_i') satisfies

$$\frac{dT_i'}{dt} = k_i A T_i - \lambda_i T_i'. \tag{3}$$

As it is assumed that the equilibrium state is realized very rapidly,

$$\begin{cases} k_0 A T_0 = \lambda_0 T_0', \\ k_1 A T_1 = \lambda_1 T_1', \\ k_1 A T_2 = \lambda_2 T_2', \\ \quad \vdots \\ k_n A T_n = \lambda_n T_n'. \end{cases} \tag{4}$$

When we solve (2) and (4) about A, we have

$$A = \frac{A_{total}}{1 + \sum_{i=0}^{n} \frac{k_i T_i}{\lambda_i}}. \tag{5}$$

As a result, the model equation is the following:

$$\begin{cases} \frac{dS_0}{dt} = k_0 A T_0 - (\gamma_0 + \alpha_0) S_0, \\ \frac{dS_i}{dt} = k_i A T_i + \alpha_{i-1} S_{i-1} - (\gamma_i + \alpha_i) S_i, \\ \frac{dS_n}{dt} = k_n A T_n + \alpha_{n-1} S_{n-1} - \gamma_n S_n, \\ \frac{dT_0}{dt} = -k_0 A T_0 + \gamma_0 S_0 + \beta_0 T_1, \\ \frac{dT_i}{dt} = -(k_i A + \beta_{i-1}) T_i + \gamma_i S_i + \beta_i T_{i+1}, \\ \frac{dT_n}{dt} = -(k_n A + \beta_{n-1}) T_n + \gamma_n S_n. \end{cases} \tag{6}$$

Here, $i = 1, 2, 3, \cdots, n-1$, and $\alpha_i, \beta_i, k_i, \lambda_i, \gamma_i$ are positive constants. It is easy to understand that the quantity of the C_{total} is preserved. In fact, clearly we understand that $\frac{d}{dt}\left(\sum_{i=0}^{n}(S_i + T_i)\right) = 0$ by summing up all the equations of the system of equations (6).

1.2 Analysis

Degree of covalent modification, P, is defined by

$$P = \sum_{i=1}^{n} i\,(S_i + T_i)\,, \tag{7}$$

which means how many covalent modifiers the receptor protein totally possesses. How does P varies as the total attractants change? We investigate P's behavior according to change of A_{total} in (5). Initial conditions of (6) are $T_0 = 1.0$, $T_i = 0.0$, and $S_j = 0.0$ ($i = 1, 2, 3, \cdots$, and $j = 0, 1, 2, \cdots, n$) at first. We increase the value of A_{total} from 0.01 to 10.0 step by step as a width of step is 0.01, and we plot the value of P after enough time goes by. Then an

each initial state is successively made the final state just in the previous simulation. Inversely, we decrease the value of A_{total} from 10.0 to 0.01 in the opposite manner, and plot it in the same figure. We repeat the same kind of numerical experiment in each possibly modifying site number. Moreover, we exactly solve the stationary problem of (6) in another way, and we make an infinitesimal stability analysis for each stationary solution. See Fig.s 2, 3, 4 and 5, and we see a bistable region existing and hysteresis occuring when the site number is bigger than two. In the figures, curves outside bistable region stand for stable branches of stationary solution, and a curve inside bistable region stands for unstable branch. The stable branches overlap completely with the final states in solving the time evolution equation, but the unstable branch goes inversely up (or down) the interior of in the bistable region, although at the end points the final states are jumping up (or down) to the nearest stable states in the same parameters. These are not overlapped with each other at all.

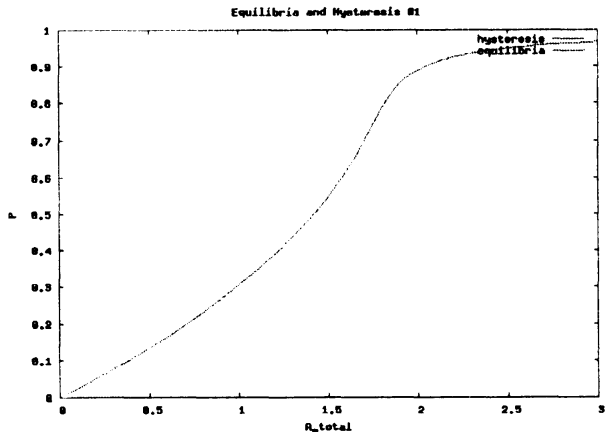

Fig. 2 1-site

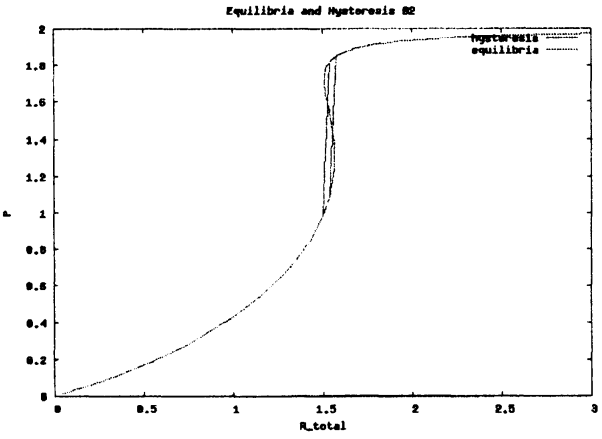

Fig. 3 2-site

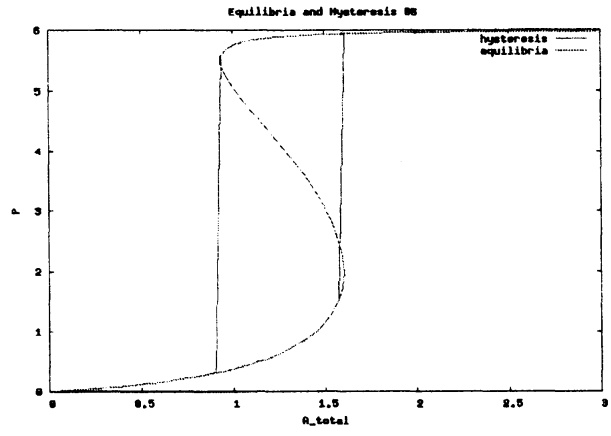

Fig. 4 6-site

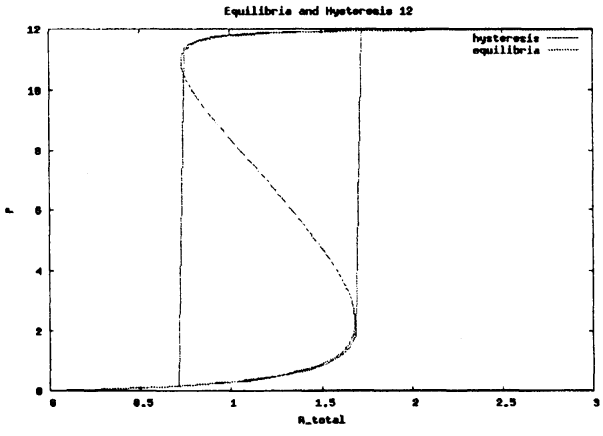

Fig. 5 12-site

2 Circadian rhythm of *cyanobacteria*

In this section we consider the mathematical model of circadian rhythm of *cyanobacteria* by use of the model of a binary digit of strage element constructed and analized in the previous section. Before presenting our model, we briefly explain the circadian rhythm of *cyanobacteria* and the recent development.

The circadian rhythm of *cyanobacteria* is discovered in 1986 by Prof.s Kondo's and Iwasaki's research group in Nagoya University. It is the most primitive life of organism obtaining circadian rhythm known so far. The clock genes (kaiA, kaiB, kaiC) and proteins (KaiA, KaiB, KaiC) have been already determined in [4]. Transcription–Translation roop had been considered as the core negative feedback roop of the circadian rhythm, but recently phosphorylation–dephosphorylation cycle of the clock protein, KaiC, continues to oscillate with 24 hours period in the constantly dark condition in [16], when all the transcription stop, although. Nowaday, at least in the case of *cyanobacteria*, the core cycle is thought of as this phosphorylation–dephosphorylation feedback roop composed of the clock proteins, KaiA, KaiB, and KaiC. Here KaiC is a receptor protein, and KaiA and KaiB are enzymes and work as attractants and as repellents, respectively. The possibly modifying number n is regarded as phosphorylation site of KaiC. Usually KaiC constructs hexamer and it has twelve phosphorylation sites. But according to T. Nishiwaki et al[13], there are approximately 7.44 sites utilized in the average, when the phosphorylation of KaiC's hexamer is maximum. In this section we let n moving from 2 to 12 to compare the qualitation properties.

2.1 Model Equations

The clock protein KaiC is the receptor protein of phosphoric acids, and as it conbined with KaiA (which is another clock protein), it is likely to promote phosphorylation. The other clock protein KaiB is known as a repellent, which operates the complex KaiA–KaiC to let the receptor protein be likely to be dephosphorylation. The correlation is illustrated in Fig.6. As we consider that the total quantities of the three proteins must be preserved, respectively, by writing these as A_{total}, B_{total}, and C_{total}, then we see

$$\begin{cases} A_{total} = A + (AB) + \sum_{i=0}^{n} T_i' = A + (AB) + \left(\sum_{i=0}^{n} \frac{k_i}{\lambda_i} T_i \right) A, \\ B_{total} = B + E + (AB), \\ C_{total} = \sum_{i=0}^{n} (S_i + T_i). \end{cases} \tag{8}$$

According to Fig.6, we present our model equations of A, (AB), and B, respectively.

$$\frac{dA}{dt} = d \left\{ \frac{1}{1 + \sum_{i=0}^{n} \frac{k_i}{\lambda_i} T_i} \left\{ m_2 A_{total} - \left(l_2 B + \sum_{i=0}^{n} \frac{k_i}{\lambda_i} \frac{dT_i}{dt} \right) A \right\} - m_2 A \right\}, \tag{9}$$

$$\frac{d(AB)}{dt} = d \{ l_2 BA - m_2 (AB) \}, \tag{10}$$

$$\frac{dB}{dt} = d \{ l_1 P (B_{total} - (AB) - B) + m_2 (AB) - (m_1 + l_2 A) B \}. \tag{11}$$

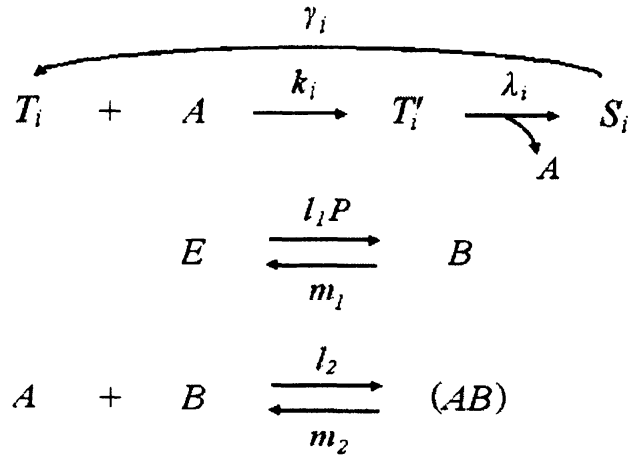

Fig. 6 relation of clock proteins

λ_i, k_i $(i = 0, 1, 2, \cdots n)$, l_j, m_j $(j = 1, 2)$, d are positive constents. We remark that (6), (7), (8), (9), (10), and (11) are a consistent system of equations, although it seems to be surplus, apparently. In fact, we can derive the conservation law of A_{total} in (8) by use of (9) and (10) easily. We remark that the right hand side of (9) has the terms dependent upon T_i or $\frac{dT_i}{dt}$, which come from the implicit change of A because of shift of chemical equilibrium according to A's and B's varying explictly. These terms need for conservation law of A_{total} of (8).

2.2 Analysis

In this subsection we solve the system (6), (7), (8), (9), (10), and (11), numerically. First of all we ensure that it has a time periodic solution shown in Fig.7 and Fig.8. These are generated by the corresponding hysteresis roop to bifurcations of hysteresis type of Fig.4 and Fig.5.

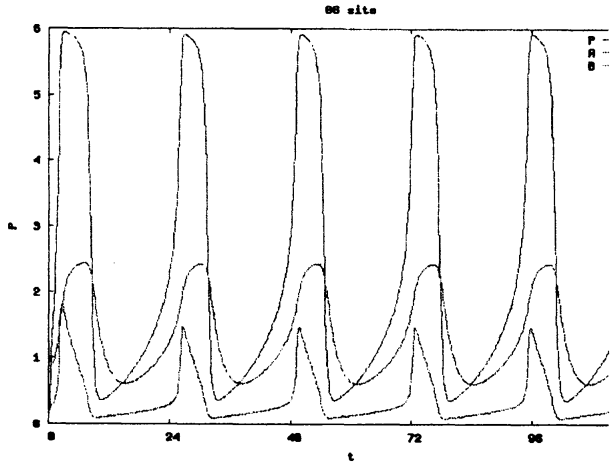

Fig. 7 6-site

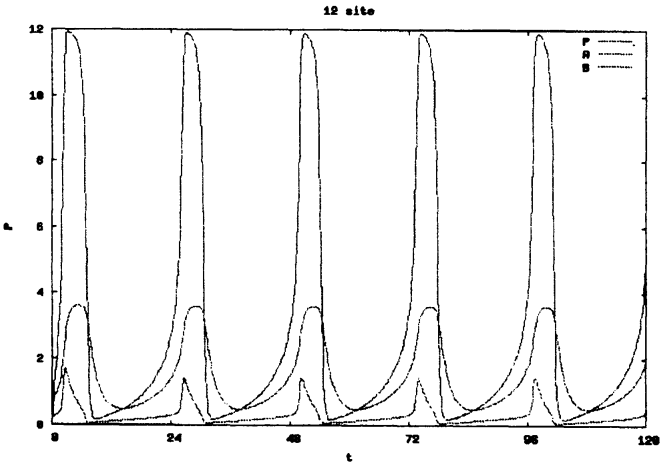

Fig. 8 12-site

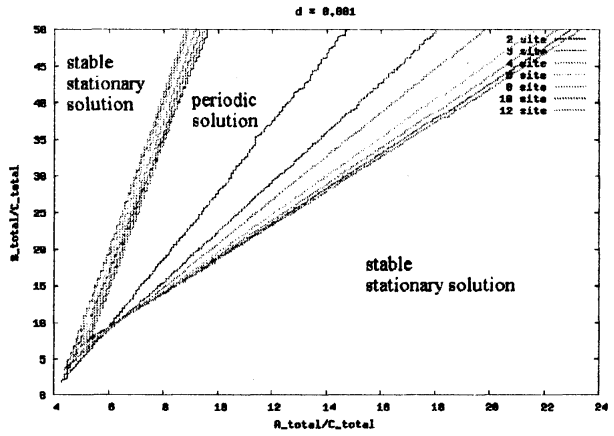

Fig. 9 oscillation range in various sites

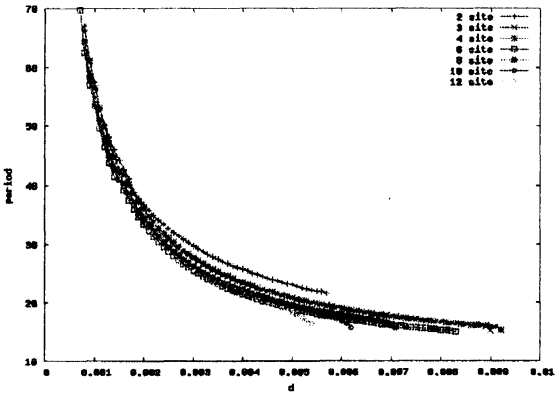

Fig. 10 period's change as d's moving

We investigate how the period changes, as some parameters move.

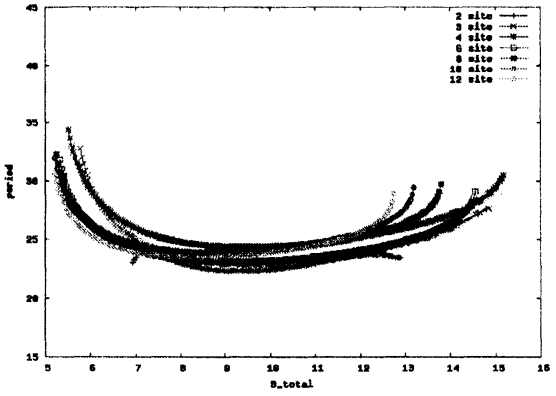

Fig. 11 period's change as B_{total}'s moving

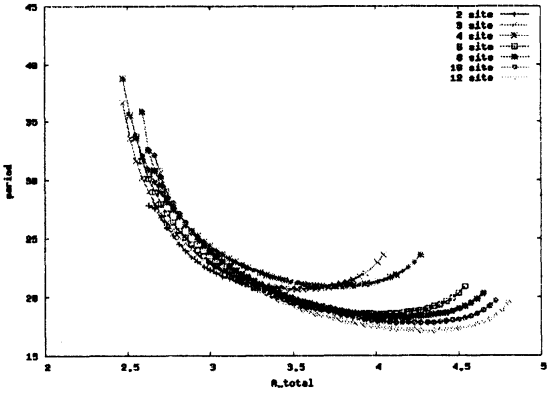

Fig. 12 period's change as A_{total}'s moving

3 Poisson process simulation

In this section we investigate the same system by use of stochastic process. In fact, this is important and useful, as each event of the chemical reactions in the system should be regarded as one following Poisson process.

But in the case of a lot of site-numbers, it seems that shakes are relatively small. To ensure the site-number's effect, we calculate the rotation number in the phase space of the system. The rotation number is defined as how many times the corresponding orbit rotates around the proper center point in the phase space. We first compare the average value of rotation number of Poisson process system with the rotation number of the system of differential equations. We moreover compute the variance of the value. By use of these value, we see a kind of stability of periodic solution of the system for this kind of shakes.

References

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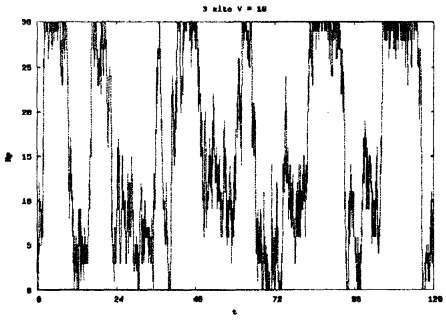

Fig. 13 3-site $V = 10$

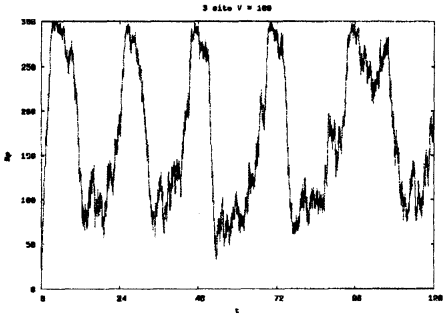

Fig. 14 3-site $V = 100$

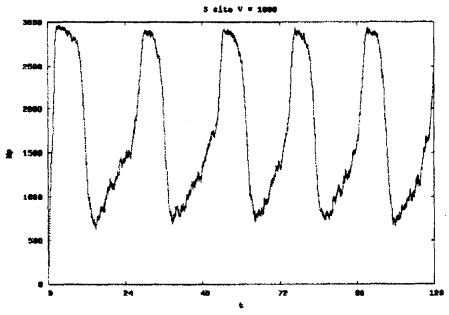

Fig. 15 3-site $V = 1000$

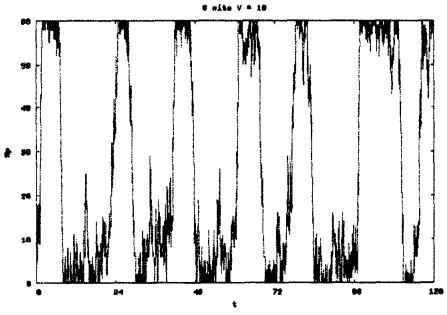

Fig. 16 6-site $V = 10$

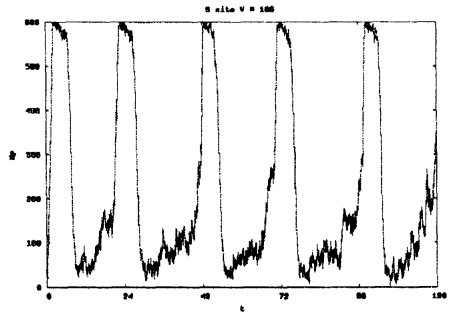

Fig. 17 6-site $V = 100$

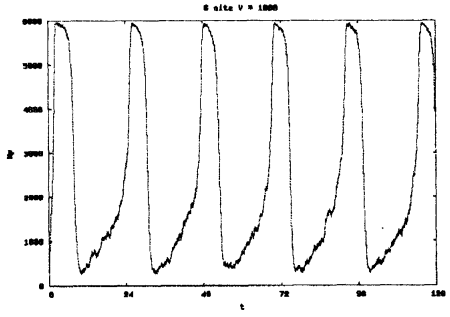

Fig. 18 6-site $V = 1000$

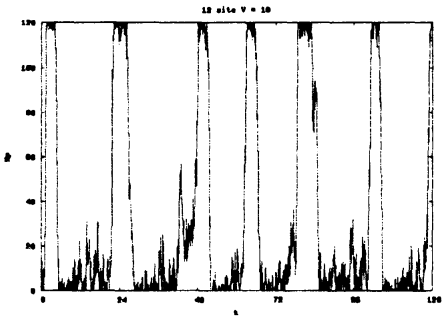

Fig. 19 12-site $V = 10$

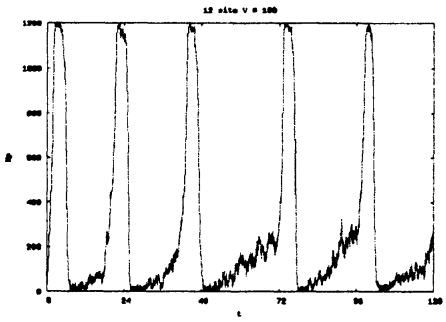

Fig. 20 12-site $V = 100$

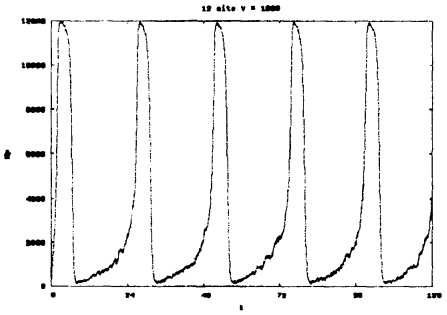

Fig. 21 12-site $V = 1000$

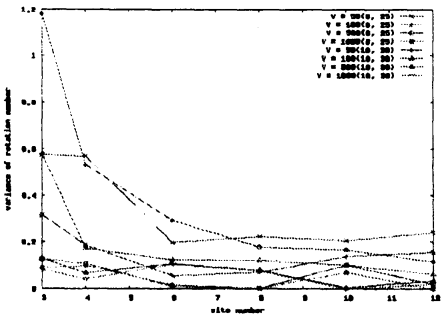

Fig. 22 variance

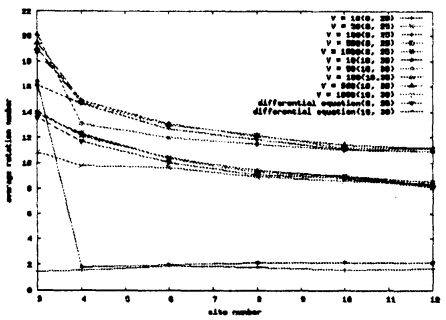

Fig. 23 average