

Switching dynamics in reaction networks induced by molecular discreteness

This article has been downloaded from IOPscience. Please scroll down to see the full text article.

2007 J. Phys.: Condens. Matter 19 065150

(<http://iopscience.iop.org/0953-8984/19/6/065150>)

View [the table of contents for this issue](#), or go to the [journal homepage](#) for more

Download details:

IP Address: 129.252.86.83

The article was downloaded on 28/05/2010 at 16:04

Please note that [terms and conditions apply](#).

Switching dynamics in reaction networks induced by molecular discreteness

Yuichi Togashi¹ and Kunihiko Kaneko^{2,3}

¹ Department of Physical Chemistry, Fritz Haber Institute of the Max Planck Society, Faradayweg 4-6, 14195 Berlin, Germany

² Department of Basic Science, School of Arts and Sciences, The University of Tokyo, Komaba, Meguro, Tokyo 153-8902, Japan

³ ERATO Complex Systems Biology Project, JST, Komaba, Meguro, Tokyo 153-8902, Japan

E-mail: togashi@fhi-berlin.mpg.de

Received 29 July 2006

Published 22 January 2007

Online at stacks.iop.org/JPhysCM/19/065150

Abstract

To study the fluctuations and dynamics in chemical reaction processes, stochastic differential equations based on the rate equation involving chemical concentrations are often adopted. When the number of molecules is very small, however, the discreteness in the number of molecules cannot be neglected since the number of molecules must be an integer. This discreteness can be important in biochemical reactions, where the total number of molecules is not significantly larger than the number of chemical species. To elucidate the effects of such discreteness, we study autocatalytic reaction systems comprising several chemical species through stochastic particle simulations. The generation of novel states is observed; it is caused by the extinction of some molecular species due to the discreteness in their number. We demonstrate that the reaction dynamics are switched by a single molecule, which leads to the reconstruction of the acting network structure. We also show the strong dependence of the chemical concentrations on the system size, which is caused by transitions to discreteness-induced novel states.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

In nature, there exist various systems that involve chemical reactions. Some systems are on a geographical scale while others are on a nanoscale, for example, the biochemical reactions in a cell. To study the dynamics of reaction systems, we often adopt rate equations in order to observe the change in the chemical concentrations. In rate equations, we consider the concentrations to be continuous variables and the rate of each reaction to be a function of

the concentrations. In fact, in macroscopic systems, there are a large number of molecules; therefore, continuous representations are usually applicable.

When the concentration of a certain chemical is low, fluctuations in the reactions or flows cannot be negligible. They are usually treated by employing stochastic differential equations, in which the noise is used as a continuum description of the fluctuations [1, 2]. The employment of stochastic differential equations has led to some important discoveries such as noise-induced transitions [3], noise-induced order [4], and stochastic resonance [5].

In stochastic differential equations, the quantities of chemicals are still regarded as continuous variables. At a microscopic level, however, we need to seriously consider the fact that the number of molecules is an integer (0, 1, 2, ...) that changes in a discrete manner. Fluctuations originate from the discrete stochastic changes; thus, continuum descriptions of fluctuations are not always appropriate.

Biological cells appear to provide a good example for such discreteness in molecule numbers. The size of the cells is of the order of microns, in which nanoscale 'quantum' effects can be ignored. However, in these cells, some chemicals act at extremely low concentrations of the order of pM or nM. Assuming that the typical volume of a cell ranges from 1 to $10^3 \mu\text{m}^3$, the concentration of one molecule in the cell volume corresponds to 1.7 pM to 1.7 nM. It is possible that the molecule numbers of some chemicals in a cell are of the order of 1 or sometimes even 0.

If such chemicals play only a minor role in a cell, we can safely ignore these chemicals to study intracellular chemical processes. However, this is not always the case. In biological systems, chemical species with a small number of molecules may critically affect the behaviour of the entire system. As an extreme example, there exist only one or a few copies of genetic molecules such as DNA, which are important to characterize the behaviour of each cell. Further, some experiments show that doses of particular chemicals at concentrations of the order of pM or fM may alter cell behaviour (e.g., [6, 7]). Biological systems also include positive-feedback mechanisms such as autocatalytic reactions, which may amplify single molecular changes to a macroscopic level. It is only recently that the stochastic effect due to small molecule numbers in cells has been noticed both theoretically [8, 9] and experimentally [10].

In this paper, we focus on the possible effects of molecular discreteness. Through stochastic simulations, we showed that the discreteness can induce transitions to novel states in autocatalytic systems [11], which may affect macroscopic chemical concentrations [12]. In the first part of this paper, we briefly review these studies and explain other aspects of such effects. See also [13–15] for recent advances in the present topic using analytic methods and numerical simulations and [16, 17] for related simulation methods.

In some cases, the discreteness in the molecule numbers may cause switches between two or more states with distinct concentrations and dynamical behaviours. Further, even though the concentration of chemicals is sufficiently high for one state, the concentration could be low in another state, in which a chemical with a very low concentration could work as a stochastic switch. In the second part of this paper, we discuss how molecular discreteness leads to switching between states with distinct dynamical behaviours in an autocatalytic chemical reaction network system. This spontaneous switching is characterized as an alteration (i.e., disconnection and reconnection) of the acting reaction paths.

2. Discreteness-induced transitions and alteration of concentrations

We have previously reported that the discrete nature of molecules may induce transitions to novel states, which are not reproduced by the continuous descriptions of the dynamics (stochastic differential equations) [11, 12]. Here, we briefly review that result by including some novel results.

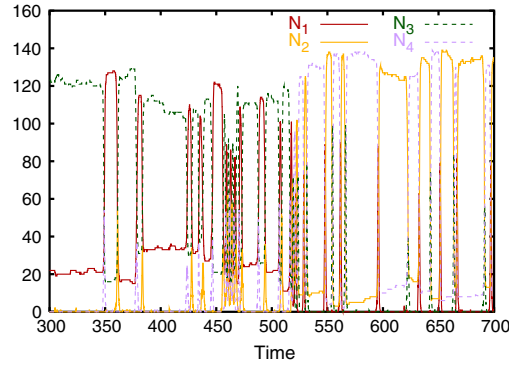


Figure 1. Time series of N_i for $V = 32$, $D_i = 1/256$, and $r_i = s_i = 1$. In this case, N_i can reach 0, and the switching states appear. In the 1–3 rich state, the system successively switches between the $N_1 > N_3$ and $N_1 < N_3$ states. The interval of switching is considerably longer than the period of continuous vibration ($\approx \pi$). At around $t = 520$, a transition occurs from the 1–3 rich state to the 2–4 rich state.

We consider a simple autocatalytic network (loop) with four chemicals X_i ($i = 1, \dots, 4$). We assume the reactions $X_i + X_{i+1} \rightarrow 2X_{i+1}$ (with $X_5 \equiv X_1$) between these chemicals. All the reactions are irreversible.

We assume that the reactor is a well-stirred container with a volume V . The set of N_i , the number of X_i molecules, determines the state of the system. The container is in contact with a chemical reservoir in which the concentration of X_i is fixed at s_i . The flow rate of X_i between the container and the reservoir is D_i , which corresponds to the probability of the flow-out of a molecule per unit time⁴.

We can consider the continuum limit as $V \rightarrow \infty$. In this limit, the change in x_i , the chemical concentration of X_i in the container, obeys the following rate equation:

$$\frac{dx_i}{dt} = r_{i-1}x_{i-1}x_i - r_i x_i x_{i+1} + D_i(s_i - x_i), \quad (1)$$

where r_i is the rate constant of the reaction $X_i + X_{i+1} \rightarrow 2X_{i+1}$, and $X_0 \equiv X_k$.

In [11], we considered a case with four equivalent chemical species, given as $r_i = r$, $D_i = D$, and $s_i = s$ for all i ($r, D, s > 0$), $k = 4$. In the continuum limit, the dynamics are represented by the rate equation, which has only one attractor: a stable fixed point $x_i = s$ for all i . Around the fixed point, x_i vibrates with the frequency $\omega_p \equiv rs/\pi$. If the number of molecules is finite but fairly large, we can estimate the dynamical behaviour of the system using the Langevin equation, which is obtained by adding a noise term to the rate equation. Each concentration x_i fluctuates and vibrates around the fixed point. An increase in the noise (corresponding to a decrease in the number of molecules) merely amplifies the fluctuation.

However, as we have shown in [11], when the number of molecules is small, novel states that do not exist in the continuum limit are observed. Two chemicals are dominant and the other two are mostly extinct ($N_i = 0$). Figure 1 shows the time series of N_i in such a case. At $t < 520$, N_1 and N_3 dominate the system and $N_2 = N_4 = 0$ for the most part (the 1–3 rich state). Once the system reaches $N_2 = N_4 = 0$, all the reactions stop. The system remains at $N_2 = N_4 = 0$ for a long time as compared with the ordinary timescale of the reactions

⁴ D_i is the diffusion rate across the surface of the container. Here, we choose a flow proportional to V in order to obtain a well-defined continuum limit.

($\sim 1/rs$). Conversely, at $t > 520$, N_2 and N_4 are large and usually $N_1 = N_3 = 0$ (the 2–4 rich state). In the 1–3 or 2–4 rich states, the system alternately switches between either $N_1 > N_3$ and $N_1 < N_3$ or $N_2 > N_4$ and $N_2 < N_4$. We name these states the ‘switching states’.

The appearance of discreteness-induced novel states is described as a phase transition with a decrease in the system size (or flow rate), where the histogram of $(N_1 + N_3) - (N_2 + N_4)$ exhibits a change from single-peaked to double-peaked distribution.

In this example, although the state at each instant exhibits a clear transition, the average concentrations of the chemicals are not altered since the system resides equally in the 1–3 rich and 2–4 rich states over a long time span. On the other hand, we found examples in [12], where the long-term average concentration of the molecule species is altered by the discreteness as well. A simple example is provided by considering the same reaction model as that depicted by equation (1), but by considering the case where the parameters D_i , s_i , or r_i are species dependent. Note that the rate equation (1) obtained in the continuum limit does not contain the volume V ; hence, the average concentrations should be independent of V . Here, we seek the possibility of the change in the average concentrations depending on the decrease in the system size V by taking advantage of the switching states.

Recall that for the transitions to the switching states to occur in [11], it was necessary for the interval of the inflow to be greater than the timescale of the reactions. In the present case, the inflow interval of X_i is $\sim 1/D_i s_i V$, and the timescale of the reaction $X_i + X_{i+1} \rightarrow 2X_{i+1}$ in order to consume X_i is $\sim 1/r_i x_{i+1}$. If the conditions of all the chemicals are equivalent, the discreteness of all the chemicals takes effect equally and the 1–3 and 2–4 rich states coordinately appear at $V \approx r/D$.

Now, since the parameters are species dependent, the effect of the discreteness may be different for each species. For example, by assuming that $D_1 s_1 < D_2 s_2$, the inflow interval of X_1 is greater than that of X_2 . Thus, the discreteness in the inflow of X_1 can be significant for larger V .

In the previous paper [12], we studied the case in which only the external concentrations (chemical inflows) s_i were dependent on the species. Based on the degree of $s_i V$, the discreteness-induced transition occurs successively with the decrease in V , and the average concentrations of the chemicals take distinct values from those of the continuum limit case. Similarly, we can study the effect of the discreteness when each of the chemical reaction rates r_i is species dependent. In fact, the dependence of \bar{x}_i on V in this case is different from the previous study in which only s_i was species dependent.

For example, we consider the case that $r_1 = r_3 > r_2 = r_4$ and $\forall i : s_i = 1$. Figure 2 shows the dependence of \bar{x}_i on V . Recall that the concentrations should not depend on V as long as the continuum representations hold (equation (1) does not contain V). Here, in the continuum limit or in the case of large V , $\bar{x}_2 = \bar{x}_4 > \bar{x}_1 = \bar{x}_3$, as shown in figure 2(a). In contrast, when V is small, $\bar{x}_i \approx 1$. If V is very small, so that the total number of molecules is mostly 0 or 1, the reactions rarely occur and the flow of chemicals dominates the system. Thus, $\bar{x}_i \approx s_i$.

If both the reactions and the flows are species dependent, we can simply expect the behaviour to be a combination of the above-mentioned cases. Even this simple system can exhibit a multi-step change in the concentrations along with the change in V . Furthermore, the present behaviour is not limited to the simple autocatalytic reaction loop. In fact, we observe this type of change in randomly connected reaction networks. For a large reaction network with multiple timescales of reactions and flows, the discreteness effect may bring about behaviours that are more complicated, although our discussion is generally applicable to such cases if the timescales are appropriately defined.

As seen above, the discreteness of molecules can alter the average concentrations. When the rates of inflow and/or the reaction are species dependent, the transitions between

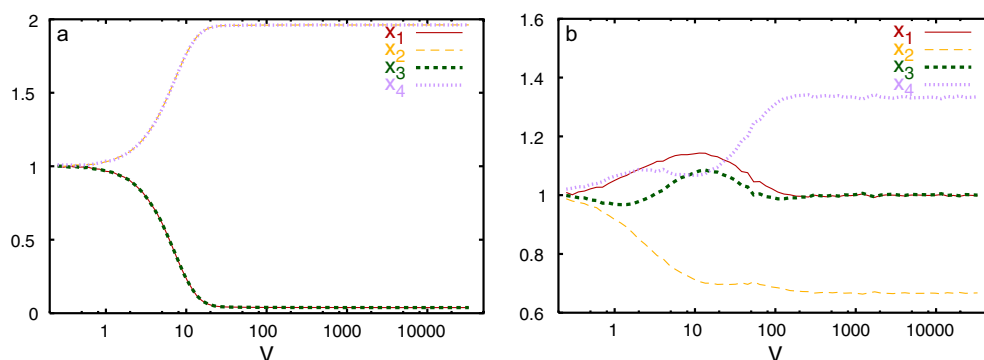


Figure 2. The average concentrations \bar{x}_i in the autocatalytic loop system for $\forall i : s_i = 1$ and $D_i = 1/128$ with nonequivalent reaction constants. For small V , the flow of molecules dominates the system. Thus, $\bar{x}_i \approx 1$, which simply reflects $s_i = 1$; this does not depend on how the continuum limit is imbalanced by the reactions. (a) $r_1 = r_3 = 1$ and $r_2 = r_4 = 0.9$. (b) $r_1 = r_2 = 2$ and $r_3 = r_4 = 1$.

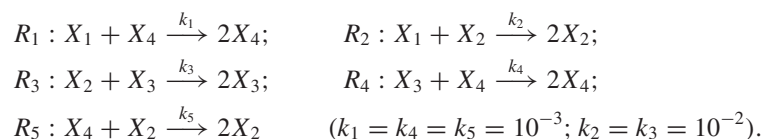
the discreteness-induced states are imbalanced. This may drastically alter the average concentrations from those of the continuum limit case.

Note that although the concentrations are altered in both cases, their dependence on V is different. If the system is extremely small ($V \sim 1$), the frequency of the reaction event, in comparison to the diffusion, is low. The reaction is limited by the inflows, and therefore, the system is dominated by diffusion. The average concentrations \bar{x}_i depend on V , but the dependence is quite different from the case with uniform reaction rates (r_i) and imbalanced inflows (s_i), which were previously reported by us.

3. Discreteness-induced switching of catalytic reaction networks

Molecular discreteness may not only affect the chemical concentrations but also the network of reactions. As seen above, if the number of molecules required for a certain reaction is 0, the reaction cannot take place at all. If such a situation continues for a long time, when compared to the timescales of other reactions, the system behaves as if the reaction never existed, i.e., the reaction is virtually eliminated from the network. Furthermore, the existence of even one or a few molecules could cause the resumption of the reaction and the recovery of the network. In contrast to the continuum limit, where decay or recovery of the chemical is gradual, such changes in the network structure are discrete and therefore quick.

Here, we show an example in which the discreteness alters the actual network and switches the dynamical behaviour. We adopt a simple model with four chemicals and five reactions among them (see figure 3) such that



Again, we assume a well-mixed reactor of volume V in contact with a chemical reservoir, where the concentration of X_i is maintained at s_i (D_i is the flow rate of X_i). In the continuum limit, the system is governed by the following rate equations:

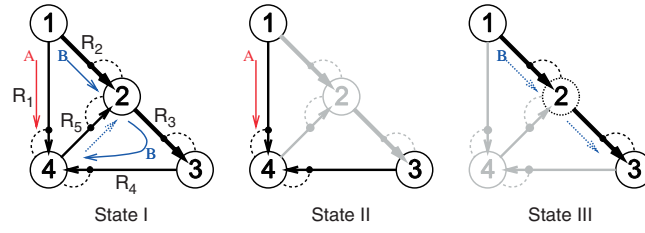


Figure 3. Model catalytic network. There are two reaction paths—indicated by arrows A and B—from the chemical X_1 (substrate). (I) If all the chemical species exist, all the reactions may occur. The system exhibits damped oscillations. (II), (III) If the system lacks one or more chemicals, some of the reactions cannot proceed. The portion of the reaction path beyond the stalled reaction is disconnected; consequently, the actual topology of the network may change.

$$\begin{aligned} \dot{x}_1 &= -k_1x_1x_4 - k_2x_1x_2 + D_1(s_1 - x_1) \\ \dot{x}_2 &= k_2x_1x_2 - k_3x_2x_3 + k_5x_4x_2 + D_2(s_2 - x_2) \\ \dot{x}_3 &= k_3x_2x_3 - k_4x_3x_4 + D_3(s_3 - x_3) \\ \dot{x}_4 &= k_1x_1x_4 + k_4x_3x_4 - k_5x_4x_2 + D_4(s_4 - x_4) \end{aligned}$$

where x_i is the concentration of the chemical X_i .

This reaction network mainly comprises constant flows of chemicals (R_1 and R_2) and an autocatalytic loop (R_3 , R_4 , and R_5). Here, we set $D_i = D = 0.02$ (for all i), $s_1 = 10^3$, $s_3 = 10$, and $s_2 = s_4 = 1$. With these settings, generally, X_1 molecules flow into the container and serve as substrates. They are then converted into other chemicals, following which they flow out; this maintains the nonequilibrium condition. In the continuum limit, the concentrations x_i vibrate and converge to the fixed point.

To elucidate the behaviour at a condition distant from the continuum limit, we have investigated the dynamical behaviour in such a condition by stochastic simulation. Figure 4 shows the time series of N_i , the number of X_i molecules. When V is large, generally, N_i remains large. This behaviour is similar to the rate equation with the addition of noise. However, when V is small, N_i may reach 0. In our model, if the system lacks a substrate or a catalyst for a certain reaction, the reaction ceases completely. Consequently, the dynamics of the system with such a small V are qualitatively different.

We define the state of the system based on the combination of the reactions that cease. A system has the following three distinct states (see figure 3):

State I. $N_i > 0$ for all i , and all the reactions occur.

This state is determined by the fixed point concentrations obtained by the continuum limit, and the system converges to the fixed point, while the vibration around it is sustained when the number of molecules is finite.

State II. For the majority of the time, $N_2 = 0$, and reactions R_2 , R_3 , and R_5 cease.

The reaction loop cannot proceed, while reaction R_1 continuously converts X_1 into X_4 .

State III. For the majority of the time, $N_4 = 0$, and reaction R_1 ceases.

In the absence of any reactions, the X_1 molecules accumulate. An X_2 molecule flowing in may trigger reactions R_2 and R_3 and convert X_1 into X_3 .

In the continuum limit, the concentrations cannot reach 0 due to the constant inflows, and the system remains at state I when V is sufficiently large, as shown in figure 4(a), even though the concentrations fluctuate and vibrate around the fixed point.

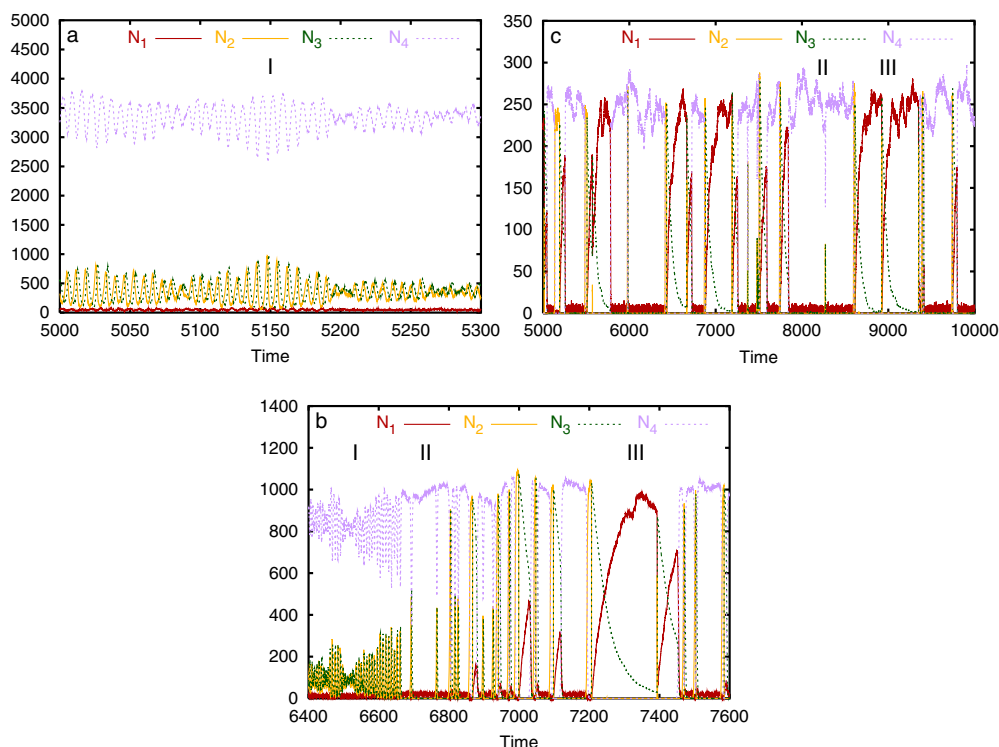


Figure 4. Time series of N_i , the number of molecules. (a) $V = 4$, (b) $V = 1$, and (c) $V = 0.25$.

With a small V , however, the other states appear. For example, the time series of N_i with $V = 1$ is shown in figure 4(b). At around $t = 6500$, the system is in state I, and it switches to state II at around $t = 6700$. It then alternates between states II and III. The system spontaneously switches between these states. If V is considerably smaller, state I is rarely observed, as shown in figure 4(c).

The distribution of x_i is shown in figure 5. A transition is observed with a decrease in V . For a large V , the distribution shows a peak at around $x_1 = 12$ and $x_4 = 8 \times 10^2$, corresponding to the fixed point of the rate equation. For a small V , the distribution of x_4 shows peaks at around $x_4 = 1.0 \times 10^3$ and $x_4 = 0$, corresponding to state II ($x_1 \approx 20$, $x_4 \approx 1.0 \times 10^3$) and state III (mostly $x_4 = 0$), respectively.

As mentioned above, these states are classified based on the reactions that cease; in other words, the states are classified based on the part of the network that actually functions. In state I, all the reactions in the network function; in state II, the autocatalytic loop does not function; and in state III, the conversion of X_1 into X_4 ceases. The transitions to states II or III can be viewed as the disconnection of some parts in the reaction network. Such transitions are possible only if N_i reaches 0, and therefore, molecular discreteness is essential. The extinction of the X_2 and X_4 molecules makes the system switch to states II and III, respectively.

The question that arises here is as follows: In general, which chemicals can switch states in a network? In our model, molecule X_1 cannot serve as a switch, even though N_1 sometimes reaches 0 in the case of $V = 1$. First, for a molecule species to function as a key for switching, N_i should be maintained at 0 for a longer time than that for other reactions. For X_1 , there is considerable inflow, and the inflow rate is not affected if N_1 reaches 0. Thus, N_1 cannot remain

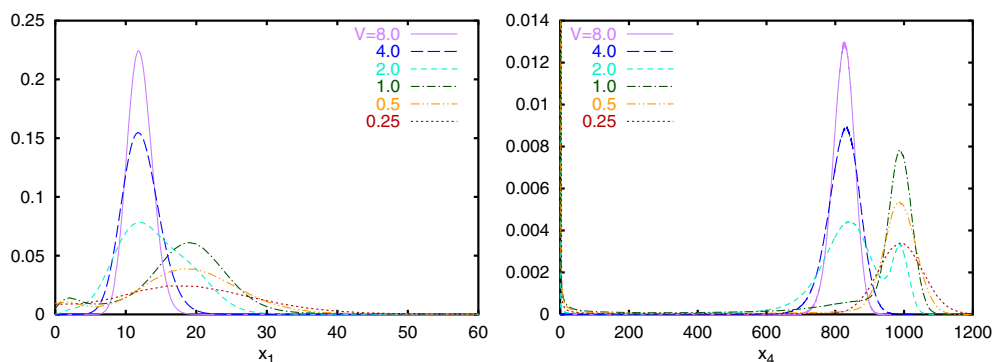


Figure 5. Distribution of the concentration x_1 and x_4 with different V . Transition is observed between the $V \leq 1.0$ and $V \geq 4.0$ cases.

at 0 for a long time, and X_1 cannot switch the dynamics. Second, a key chemical for a switch should be located within the reaction paths and the extinction of the molecule disconnects some reaction paths.

Stochasticity in gene expression is widely studied with regard to the problem of a small number of molecules in a biological system. It is often assumed that two states—on and off—are switched by a single regulatory site. The controlling chemicals and controlled chemicals can be clearly separated.

In contrast, our result shows that chemical species, which are usually abundant, may sometimes work as a stochastic switch. In this sense, molecules that are common or ions such as Ca^{2+} (see [15, 18]) may cause stochastic effects. The role of a chemical may change with time.

4. Discussion

In this study, we have demonstrated that molecular discreteness may induce transitions to novel states in autocatalytic reaction systems, which may result in an alteration of macroscopic properties such as the average chemical concentrations.

In biochemical pathways, it is not uncommon to find that the number of molecules of a chemical is of the order of 10^2 or less in a cell. There are thousands of protein species, and the total number of protein molecules in a cell is not very large. For example, in signal transduction pathways, some chemicals work at concentrations of less than 100 molecules per cell. There exist only one or a few copies of genetic molecules such as DNA; furthermore, mRNAs are not present in large numbers. Thus, regulation mechanisms involving genes are quite stochastic. Naturally, molecular discreteness involves such rare chemicals.

In the second part of this paper, we have shown that the molecular discreteness may change the dynamical behaviour of reaction networks. The reaction network is virtually disconnected by the extinction of certain chemicals, which is not possible in the continuum limit. Although the network studied here is a small model, similar phenomena can exist in a complex reaction network with a large number of chemicals and reactions. We have also investigated random networks of catalytic reactions $X_i + X_j \rightarrow X_i + X_k$ ($j \neq k$). In such systems, the dynamics of chemical concentrations also depend on the system size V . In a small system, many of the chemical species become extinct ($N_i = 0$), and the actual reaction network is disconnected into fragments, which may be occasionally reconnected by inflow or generation of a molecule.

The onset of change in the concentrations due to disconnection or reconnection is stochastic and sudden. In the continuum limit, in contrast, the concentrations gradually converge to a fixed point in most cases (or to a limit cycle or other attractors). The simple model in this paper can be viewed as a switching element of such a network; however, the exact conditions that determine whether a chemical works as a stochastic switch or not should be addressed in future.

We observed the transitions in the distribution of the concentrations x_i with respect to the change in the system size V . Multiple transitions can also occur, especially if there are many chemical species for which the number of molecules is sometimes (but not necessarily always) small.

In this paper, we have considered reactions in a well-stirred medium, where only the number of molecules is taken into account for determining the system behaviour. However, if the system is not mixed well, we need to take into account the diffusion of molecules in space. From a biological viewpoint, the diffusion in space is also important because the diffusion in cells is not always fast when compared with the timescales of the reactions. If the reactions are faster than the mixing, we should consider the system as a reaction–diffusion system, with discrete molecules diffusing in space. The relation between these timescales will be important, as indicated by Mikhailov and Hess [19, 20]. With regards to these timescales, we recently found that the spatial discreteness of molecules within the so-called Kuramoto length [2, 21], over which a molecule diffuses in its lifetime (lapses before it undergoes reaction), can yield novel steady states that are not observed in the reaction–diffusion equations [22, 23]. Spatial domain structures due to molecular discreteness are also observed [23]. See also [24, 25] for relevance of the discreteness in a replicating molecule system.

The discreteness-induced effect present here does not depend on the characteristics of the reactions. Furthermore, it may be applicable to systems beyond reactions, such as ecosystems or economic systems. The inflow of chemicals in a reaction system can be seen as a model of intrusion or evolution in an ecosystem: for both systems, discrete agents (molecules or individuals) may become extinct. In this regard, our result is relevant to the studies of ecosystems, e.g., extinction dynamics with a replicator model by Tokita and Yasutomi [26, 27]; strong dependence of the survival probability of new species in evolving networks on the population size was reported by Ebeling *et al* [28]. The discreteness of agents or operations might also be relevant to some economic models, e.g., artificial markets.

Most mathematical methods that are applied to reaction systems cannot appropriately describe the discreteness effect. Although the use of simulations has become easier with the progress in computer technology, it is also important that a theoretical formulation applicable to discrete reaction systems is developed. Also, in recent years, major advances have been made in the detection of a small number of molecules and the fabrication of small reactors, which raises the possibility of experimentally demonstrating the discreteness effect predicted here.

We believe that molecular discreteness has latent but actual importance with respect to biological mechanisms such as pattern formation, regulation of biochemical pathways, or evolution, which will be pursued in the future.

Acknowledgments

This research is supported by a grant-in-aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (11CE2006, 15-11161) and research fellowships from the Japan Society for the Promotion of Science (15-11161, abroad H17).

References

- [1] Nicolis G and Prigogine I 1977 *Self-Organization in Nonequilibrium Systems* (New York: Wiley)
- [2] van Kampen N G 1992 *Stochastic Processes in Physics and Chemistry* (New York: North-Holland) rev. edn
- [3] Horsthemke W and Lefever R 1984 *Noise-Induced Transitions* ed H Haken (Berlin: Springer)
- [4] Matsumoto K and Tsuda I 1983 Noise-induced order *J. Stat. Phys.* **31** 87
- [5] Wiesenfeld K and Moss F 1995 Stochastic resonance and the benefits of noise: from ice ages to crayfish and SQUIDS *Nature* **373** 33
- [6] Olsson N, Piek E, ten Dijke P and Nilsson G 2000 Human mast cell migration in response to members of the transforming growth factor- β family *J. Leukocyte Biol.* **67** 350
- [7] Wang X, Feuerstein G Z, Gu J, Lysko P G and Yue T 1995 Interleukin-1 β induces expression of adhesion molecules in human vascular smooth muscle cells and enhances adhesion of leukocytes to smooth muscle cells *Atherosclerosis* **115** 89
- [8] McAdams H H and Arkin A 1999 It's a noisy business! Genetic regulation at the nanomolar scale *Trends Genet.* **15** 65
- [9] Rao C V, Wolf D M and Arkin A P 2002 Control, exploitation and tolerance of intracellular noise *Nature* **420** 231
- [10] Elowitz M B, Levine A J, Siggia E D and Swain P S 2002 Stochastic gene expression in a single cell *Science* **297** 1183
- [11] Togashi Y and Kaneko K 2001 Transitions induced by the discreteness of molecules in a small autocatalytic system *Phys. Rev. Lett.* **86** 2459
- [12] Togashi Y and Kaneko K 2003 Alteration of chemical concentrations through discreteness-induced transitions in small autocatalytic systems *J. Phys. Soc. Japan* **72** 62
- [13] Bettelheim E, Agam O and Shnerb N M 2001 Quantum phase transitions in classical nonequilibrium processes *Physica E* **9** 600
- [14] Marion G, Mao X, Renshaw E and Liu J 2002 Spatial heterogeneity and the stability of reaction states in autocatalysis *Phys. Rev. E* **66** 051915
- [15] Zhdanov V P 2002 Cellular oscillator with a small number of particles *Eur. Phys. J. B* **29** 485
- [16] Gibson M A and Bruck J 2000 Efficient exact stochastic simulation of chemical systems with many species and many channels *J. Phys. Chem. A* **104** 1876
- [17] van Zon J S and ten Wolde P R 2005 Green's-function reaction dynamics: a particle-based approach for simulating biochemical networks in time and space *J. Chem. Phys.* **123** 234910
- [18] Thul R and Falcke M 2004 Release currents of IP₃ receptor channel clusters and concentration profiles *Biophys. J.* **86** 2660
- [19] Hess B and Mikhailov A 1994 Self-organization in living cells *Science* **264** 223
- [20] Mikhailov A S and Hess B 2002 Self-organization in living cells: networks of protein machines and nonequilibrium soft matter *J. Biol. Phys.* **28** 655
- [21] Kuramoto Y 1973 Fluctuations around steady states in chemical kinetics *Prog. Theor. Phys.* **49** 1782
- [22] Togashi Y and Kaneko K 2004 Molecular discreteness in reaction-diffusion systems yields steady states not seen in the continuum limit *Phys. Rev. E* **70** 020901
- [23] Togashi Y and Kaneko K 2005 Discreteness-induced stochastic steady state in reaction diffusion systems: self-consistent analysis and stochastic simulations *Physica D* **205** 87
- [24] Shnerb N M, Louzoun Y, Bettelheim E and Solomon S 2000 The importance of being discrete: life always wins on the surface *Proc. Natl Acad. Sci.* **97** 10322
- [25] Shnerb N M, Bettelheim E, Louzoun Y, Agam O and Solomon S 2001 Adaptation of autocatalytic fluctuations to diffusive noise *Phys. Rev. E* **63** 021103
- [26] Tokita K and Yasutomi A 1999 Mass extinction in a dynamical system of evolution with variable dimension *Phys. Rev. E* **60** 842
- [27] Tokita K and Yasutomi A 2003 Emergence of a complex and stable network in a model ecosystem with extinction and mutation *Theor. Popul. Biol.* **63** 131
- [28] Ebeling W, Feistel R, Hartmann-Sonntag I, Schimansky-Geier L and Scharnhorst A 2006 New species in evolving networks—stochastic theory of sensitive networks and applications on the metaphorical level *BioSystems* **85** 65