

## Molecular discreteness in reaction-diffusion systems yields steady states not seen in the continuum limit

Yuichi Togashi\* and Kunihiko Kaneko

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

(Received 17 October 2003; revised manuscript received 17 February 2004; published 23 August 2004)

We investigate the effects of the spatial discreteness of molecules in reaction-diffusion systems. It is found that discreteness within the so-called Kuramoto length can lead to a localization of molecules, resulting in novel steady states that do not exist in the continuous case. These states are analyzed theoretically as the fixed points of accelerated localized reactions, an approach that was verified to be in good agreement with stochastic particle simulations. The relevance of this discreteness-induced state to biological intracellular processes is discussed.

DOI: 10.1103/PhysRevE.70.020901

PACS number(s): 82.39.-k, 05.40.-a, 82.40.Ck, 87.16.-b

Many systems in nature that involve chemical reactions can be studied with the help of reaction-diffusion equations. For certain processes, a relatively small number of suitably chosen continuous macroscopic variables yields excellent descriptive results. In biological systems, however, not only is the variety of chemicals enormous, the number of molecules of each of the chemical species can range from the relatively very large to the relatively very small. Now, if the species with small numbers of molecules were irrelevant, obviously, their existence could be ignored and one could focus on the species with large numbers of molecules that can effectively be described by a continuous variable. However, it should not really come as a surprise that it was found that, in general, species with small numbers of molecules cannot be neglected and that certain functions in cells can critically depend on very small fluctuations [1,2]. Indeed, in prior studies on reaction-diffusion systems some effects of fluctuations on pattern formation were found (see, e.g., [3,4]). Stochastic differential equations are often used to study effects of fluctuations.

Of course, on a microscopic level, chemicals are composed of molecules, and the actual reactions occur between these molecules. Therefore, in principle, reaction events must be integers and change only discretely. In an analysis with stochastic differential equations, though, the fluctuations are regarded as continuous changes. Clearly, this approximation can only be valid if applied to fluctuations that involve sufficiently large numbers of molecules and should not be applied when relevant chemical species are very rare.

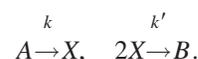
In order to address this issue, we previously studied the effects of discreteness in simple autocatalytic reaction network systems and reported discreteness-induced transitions as well as drastic effects on concentrations [5,6]. A key feature of these systems was, however, that the medium was assumed to be well stirred.

In contrast, in a system with diffusion in space, the total number of molecules may vary from point to point. By assuming that the reaction is fast and the diffusion is slow, locally, the discreteness of the molecules can become impor-

tant. In fact, this can even be the case if the total number of molecules is large but spread out over a large area as well.

Therefore, a length scale should be considered such that it can serve as a benchmark for judging whether or not a continuum approximation is applicable. To consider this problem, the ratio between the reaction and diffusion rates is important, and a candidate for the length scale is the typical distance over which a molecule diffuses during its lifetime, i.e., before it undergoes reaction as defined by Kuramoto [7,8]. For reference, let us briefly review the work.

Consider the reaction [12]



If the concentration of  $A$  is set to be constant,  $X$  is produced at a constant rate  $k$  while decaying by the reaction  $2X \rightarrow B$  at a rate  $k'$ . The average concentration of  $X$  at the steady state is  $\langle X \rangle = \sqrt{kA/2k'}$ , where, for simplicity,  $A$  is the concentration of the chemical  $A$ . Thus the average lifetime of  $X$  at the steady state is estimated to be  $\tau = 1/(2k'\langle X \rangle) = 1/\sqrt{2kk'A}$ . Suppose that  $X$  molecules diffuse with the diffusion constant  $D$ . The typical length over which an  $X$  molecule diffuses in its lifetime is then estimated to be

$$l = \sqrt{2D\tau}, \quad (1)$$

which is called the Kuramoto length [9].

The Kuramoto length  $l$  represents the relation between the reaction rate and the diffusion rate. When the system size is smaller than  $l$ , its behavior is dominated by diffusion, and local fluctuations rapidly spread throughout the system. Contrastingly, if the system size is much larger than  $l$ , fluctuations are localized only in a small part of the system, and distant regions fluctuate independently.

In this reasoning, it is assumed that the average distance between molecules is much smaller than  $l$ . Thus the actual discreteness of the molecules can be ignored, and the concentration of the chemical  $X$  can be regarded as a continuous variable. However, if the average distance between molecules is comparable to or larger than  $l$ , local discreteness of molecules may not be negligible. Suppose a chemical  $A$ , with very low concentration, produces another chemical  $B$ . The

\*Electronic address: togashi@complex.c.u-tokyo.ac.jp

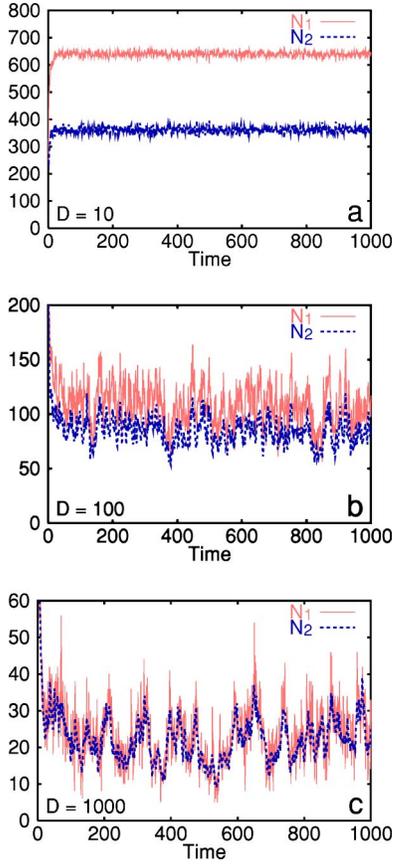
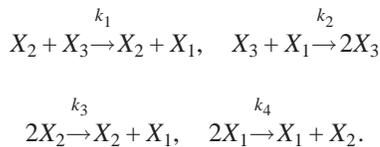


FIG. 1. (Color online) Time series of  $N_1$  and  $N_2$ .  $r=1$ ,  $a=4$ ,  $N=1000$ ,  $L_x=1000$ . (a)  $D=10$ , (b)  $D=100$ , (c)  $D=1000$ . Initially,  $(N_1, N_2, N_3) = (250, 250, 500)$ . For  $D=10$ ,  $X_3$  reaches 0, which corresponds to the unstable fixed point  $(2c/3, c/3, 0)$ .

average lifetime of  $B$  is short, such that the Kuramoto length of  $B$  is shorter than the average distance between adjacent  $A$  molecules. With this setting, chemical  $B$  molecules may be considered as localized around  $A$  molecules. This is especially so if the reactions involve second or higher orders of  $B$ . Then, the localization of chemical  $B$  may drastically alter the total rate of the reactions, and the effect of the local discreteness of the molecules may thus be rather significant.

In order to systematically investigate the effects of the local discreteness of the molecules, we consider a simple one-dimensional reaction-diffusion system with three chemicals ( $X_1$ ,  $X_2$ , and  $X_3$ ) and the following four reactions:



Here, we assume that the first two reactions are much faster than the others, i.e., the reaction constants satisfy  $k_1, k_2 \gg k_3 > k_4$ . To be specific, we take  $k_1 = k_2 = 100r$ ,  $k_3 = ar$ , and  $k_4 = r$  ( $r > 0$ ,  $1 < a \leq 100$ ).

In the continuum limit,  $c_i(t, x)$ , the concentration of chemical  $X_i$  at time  $t$  and position  $x$ , is governed by the reaction-diffusion equation for the system given by

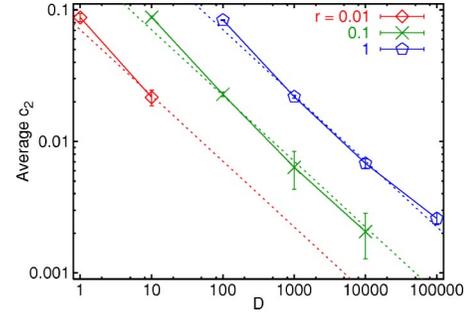


FIG. 2. (Color online) Average concentration of  $X_2$ , for different  $r$  and  $D$  ( $a=4$ ,  $N=1000$ ,  $L_x=1000$ , sampled over  $5000 < t < 10\,000$ , and ten trials. The error bars show the standard deviation between the trials). The dotted lines correspond to 0.1 molecule per the Kuramoto length  $l_1 = \sqrt{D}/50r$  for each  $r$ .

$$\frac{\partial c_1}{\partial t} = -100r(c_1 - c_2)c_3 - r(c_1^2 - ac_2^2) + D_1 \frac{\partial^2 c_1}{\partial x^2}, \quad (2)$$

$$\frac{\partial c_2}{\partial t} = r(c_1^2 - ac_2^2) + D_2 \frac{\partial^2 c_2}{\partial x^2}, \quad (3)$$

$$\frac{\partial c_3}{\partial t} = 100r(c_1 - c_2)c_3 + D_3 \frac{\partial^2 c_3}{\partial x^2}, \quad (4)$$

where  $D_i$  is the diffusion constant of  $X_i$ . The system is closed and thus the total concentration  $c$  is conserved. For simplicity, we assume  $D_i = D$  for all  $i$ .

The reaction-diffusion equation has fixed points at  $(c_1, c_2, c_3) = (0, 0, c)$ ,  $(\sqrt{ac}/(\sqrt{a+1}), c/(\sqrt{a+1}), 0)$  for all  $x$ . By performing a straightforward linear stability analysis, it is shown that only the former is stable. Indeed, by starting from an initial condition with  $c_i > 0$ , this reaction-diffusion equation always converges to the fixed point  $(0, 0, c)$ .

Next, in order to obtain insights into the case when the continuum limit cannot be taken, we carry out direct particle simulations. Each molecule diffuses randomly (showing Brownian motion) in a one-dimensional space with periodic boundary conditions (length  $L_x$ ). When two molecules are within a distance  $d_r$ , they react with a certain probability and the total number of molecules ( $N$ ) is conserved.

First, we investigate the case with  $a=4$  and show a time series of the number of molecules  $N_i$  of chemical species  $X_i$  in Fig. 1. As can be seen,  $N_1$  and  $N_2$  do not converge to 0 but to relatively large numbers. As can be expected, the final concentrations depend on  $r$  and  $D$ , and for  $X_2$  it is depicted in Fig. 2. Approximately, the concentration turns out to be proportional to  $\sqrt{r/D}$  when  $N_1, N_2 \ll N$ .

To elucidate the origin of this proportionality, we take a closer look at the Kuramoto length, which, of course, depends on the molecule species. In the case of the  $X_1$  molecules it is given by  $l_1 = \sqrt{D/50rc_3}$ , as the average lifetime of  $X_1$  is  $1/100rc_3$ . Here we consider the situation  $N_1, N_2 \ll N$ , so that  $c_3 \approx c$ . In the discussion below, we assume that  $l_1 = \sqrt{D/50rc} = \sqrt{DL_x/50rN}$ .

Using this length  $l_1$ , the density of the remaining  $X_2$  molecules is found to be about 0.1 molecule per  $l_1$ , independent of the parameters, as shown in Fig. 2. After relaxation, this density does not depend on the initial conditions, as long as  $N_i \gg 1$  is satisfied initially. Furthermore, the density is independent of the system size  $L_x$ , if  $L_x \gg l_1$ , so that the number of remaining molecules  $N_2$  is simply proportional to  $L_x$ . Consequently, in this analysis one obtains a finite  $c_2$  regardless of the system size or initial conditions, which is clearly different from the continuum limit where  $c_2$  goes to 0.

In this system,  $X_1$  molecules are produced by  $X_2$  molecules. If  $\lambda_2$ , the average distance between  $X_2$  molecules is smaller than  $l_1$ , the distributions of  $X_1$  around neighboring  $X_2$  molecules overlap each other significantly and one can regard  $X_1$  to be uniformly distributed. In contrast, if  $\lambda_2$  is much larger than  $l_1$ , molecules  $X_1$  will localize around the  $X_2$  molecules (the size  $L_x \gg \lambda_2$ ). Then, the reaction  $2X_1 \rightarrow X_1 + X_2$  is accelerated when compared to the case that the same total number of  $X_1$  molecules is uniformly distributed.

We define the acceleration factor  $\alpha(\lambda_2, l_1)$  as the ratio between the reaction rate with localized  $X_1$  and the reaction rate with uniformly distributed  $X_1$ . If  $\lambda_2 \gg l_1$ , it is expected that  $\alpha \gg 1$ . Assuming that the distribution of  $X_1$  is continuous and represented by the concentration  $c_1(x)$  [13], the acceleration factor can be expressed as

$$\alpha = \frac{\langle c_1^2 \rangle}{\langle c_1 \rangle^2} = \frac{L_x^{-1} \int c_1^2 dx}{(L_x^{-1} \int c_1 dx)^2}. \quad (5)$$

For simplicity, we assume that the distribution of the localized  $X_1$  molecules is Gaussian with a standard deviation  $l_1$  centered around the  $X_2$  molecules (which may overlap each other). Suppose that the  $X_2$  molecules are randomly distributed over the system with an average distance  $\lambda_2$ , we then obtain [14]

$$\alpha = 1 + \frac{1}{2\sqrt{\pi}} \cdot \frac{\lambda_2}{l_1} = 1 + \frac{1}{2\sqrt{\pi} \cdot l_1 c_2}. \quad (6)$$

On the other hand, the average lifetime of  $X_2$  molecules is much longer, so that the Kuramoto length for  $X_2$  molecules is longer than  $\lambda_2$ . Consequently, the reaction  $2X_2 \rightarrow X_2 + X_1$  is not accelerated by localization.

Provided that  $N_1, N_2 \ll N_3$ ,  $N_1 \approx N_2$  due to the fast reactions  $X_2 + X_3 \rightarrow X_2 + X_1$  and  $X_3 + X_1 \rightarrow 2X_3$ . As a result, the ratio between the two reaction rates is given by

$$\frac{\text{The rate of } (X_1 \rightarrow X_2)}{\text{The rate of } (X_2 \rightarrow X_1)} \approx \frac{\alpha k_4 N_1^2}{k_3 N_2^2} \approx \frac{\alpha}{a}. \quad (7)$$

Following Eq. (7), the two reaction rates are balanced if  $N_2$  takes a value such that  $\alpha = a$  is satisfied. Corresponding to  $\alpha = a$ , a fixed point appears at

$$c_1 = c_2 = [2(a-1)\sqrt{\pi}l_1]^{-1} (=c_s), \quad (8)$$

provided  $c_1, c_2 \ll c_3$  and  $c_3 = c$ . The stability of this fixed point is analyzed, by linearizing Eqs. (6) and (8) around the fixed point. Noting that

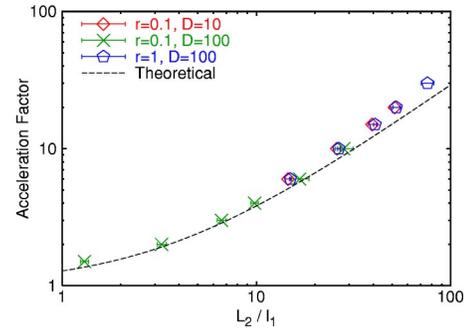


FIG. 3. (Color online) The acceleration factor  $\alpha$ , plotted against  $\lambda_2/l_1$ . We measure the relation from simulations with different  $r$ ,  $D$ , and  $a$  ( $N=1000$ ,  $L_x=1000$ , sampled over  $5000 < t < 10\,000$ , and ten trials). The error bars show the standard deviation of  $c_2$  between the trials). This is very close to the theoretical estimation  $\alpha = 1 + 1/(2\sqrt{\pi}) \cdot \lambda_2/l_1$ .

$$\alpha = 1 + \frac{(a-1)c_s}{c_2} = a - \frac{a-1}{c_s} \delta c_2 + o(\delta c_2), \quad (9)$$

with  $c_1 = c_s + \delta c_1$  and  $c_2 = c_s + \delta c_2$ , and rewriting Eqs. (2) and (3) with  $\alpha$  in Eq. (9), we obtain

$$\begin{pmatrix} \dot{c}_1 \\ \dot{c}_2 \end{pmatrix} = \begin{pmatrix} -2ac_s - 100c & (3a-1)c_s + 100c \\ 2ac_s & -(3a-1)c_s \end{pmatrix} \begin{pmatrix} \delta c_1 \\ \delta c_2 \end{pmatrix} + o(\delta c_1, \delta c_2). \quad (10)$$

The Jacobi matrix has two negative eigenvalues, and the fixed point is stable. (This is natural, since if  $\alpha < a$ ,  $N_2$  decreases, leading to the increase of  $\alpha$ , and vice versa.) This fixed point (steady state) is distinct from that of the original reaction-diffusion equation,  $(0, 0, c)$ .

From Eq. (6),  $\alpha$  becomes 4 when  $\lambda_2/l_1 = 6\sqrt{\pi} \approx 10.6$ . In our simulation with  $a=4$ , about 0.1  $X_2$  molecule per  $l_1$  remains, as shown in Fig. 2. In other words,  $\lambda_2/l_1 \approx 10$ , in good agreement with the estimate. By changing  $a$ , we numerically obtain the relation between the  $\lambda_2/l_1$  and the actual acceleration factor  $\alpha$ , again agreeing well with the above theoretical estimate  $\alpha = 1 + 1/(2\sqrt{\pi}) \cdot \lambda_2/l_1$ , as shown in Fig. 3.

In the estimate above, we consider the case where  $N_1, N_2 \ll N$ . On the other hand, if  $N$  is set to be smaller than the estimated value of  $N_2$  at the steady state,  $N_2$  increases to satisfy the balance, and finally reaches the state  $N_1 + N_2 = N$ ,  $N_3 = 0$ , which corresponds to the unstable fixed point of the reaction-diffusion equation,  $[\sqrt{ac}/(\sqrt{a+1}), c/(\sqrt{a+1}), 0]$ , as shown in Fig. 1(a).

The localization of  $X_1$  cannot be maintained without the spatial discreteness of  $X_2$  molecules. In reaction-diffusion equations, any pattern will disappear eventually when given a sufficiently long evolution time, unless it is somehow sustained. This is even the case when the initial distribution of  $X_2$  is discrete. But again, it is essential to recall that reaction-diffusion equations are an approximation and in that sense an idealization. In reality, a single molecule itself can of course not be broadened by diffusion and the spatial discreteness of

$X_2$  molecules is always maintained. By itself, a molecule is a diffusion-resistant pattern.

The alteration of the steady state due to localization is not limited to the present type of reaction network. Provided that the following conditions are satisfied, discreteness may alter the dynamics:

- (i) Chemical  $A$  generates another chemical species  $B$ .
- (ii) The lifetime of  $B$  is short or the diffusion of  $B$  is slow so that the Kuramoto length of  $B$  is much smaller than the average distance between  $A$  molecules.
- (iii) The localization of molecule  $B$  accelerates some reactions.

The last condition is easily satisfied if species  $B$  is involved in second- or higher-order reactions. Finally, if

- (iv) the acceleration alters the density of  $A$  molecules, the above acceleration mechanism may control the density of  $A$  to produce a steady state.

As for the localization effect by the discreteness of catalytic molecules, Shnerb *et al.* recently showed that it can amplify autocatalytic reaction-diffusion processes [10,11]. In their model, however, the density of the catalyst is fixed as an externally given value, and the concentration of the product, localized around the catalyst, diverges in time. In our mechanism, the density of the catalyst ( $A$ , or  $X_2$ ) changes autonomously and reaches a suitable value to produce the discreteness effect. Hence, the effect of discreteness is controlled by the discreteness itself, leading to a steady state. Indeed, theoretical estimates for the concentrations based on the self-consistent fixed point of acceleration due to the localization agree well with numerical results.

In so far as the conditions (i) and (iv) are met, our result does not depend on the details of the reactions, and should generally be valid for reaction-diffusion systems. We have carried out simulations of similar reaction-diffusion systems, and again the discreteness effect led to pattern formation that cannot be accounted for by Turing-type mechanisms (with or without noise).

Experimental verification of our results should be possible by suitably designing a reaction system, with the use of, say, microreactors or vesicles. Also, in biological cells, many chemicals work at low concentrations on the order of 1 nM or less. Furthermore, diffusion is sometimes restricted, e.g., due to surrounding macromolecules, and may be slow. In such an environment, it is probable that the average distance between the molecules of a given chemical species is much larger than the Kuramoto lengths of some of the other chemical species. Indeed, biochemical systems contain various higher-order reactions and positive feedback mechanisms that might naturally support the conditions (iii) and (iv) above.

#### ACKNOWLEDGMENTS

This research was supported by grants in aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (11CE2006, 15-11161). One of the authors (Y.T.) is supported by a research fellowship from the Japan Society for the Promotion of Science.

- 
- [1] B. Hess and A. S. Mikhailov, *Science* **264**, 223 (1994).
  - [2] L. A. Blumenfeld and A. N. Tikhonov, *Biophysical Thermodynamics of Intracellular Processes: Molecular Machines of the Living Cell* (Springer, New York, 1994).
  - [3] D. A. Kessler and H. Levine, *Nature (London)* **394**, 556 (1998).
  - [4] M. Howard and A. D. Rutenberg, *Phys. Rev. Lett.* **90**, 128102 (2003).
  - [5] Y. Togashi and K. Kaneko, *Phys. Rev. Lett.* **86**, 2459 (2001).
  - [6] Y. Togashi and K. Kaneko, *J. Phys. Soc. Jpn.* **72**, 62 (2003).
  - [7] Y. Kuramoto, *Prog. Theor. Phys.* **49**, 1782 (1973).
  - [8] Y. Kuramoto, *Prog. Theor. Phys.* **52**, 711 (1974).
  - [9] N. G. van Kampen, *Stochastic Processes in Physics and Chemistry*, revised edition (North-Holland, Amsterdam, 1992), where, to be precise, the length is defined as the half of  $l$ , but the difference does not affect the discussion here.
  - [10] N. M. Shnerb, Y. Louzoun, E. Bettelheim, and S. Solomon, *Proc. Natl. Acad. Sci. U.S.A.* **97**, 10322 (2000).
  - [11] Y. Louzoun, S. Solomon, H. Atlan, and I. R. Cohen, *Bull. Math. Biol.* **65**, 375 (2003).
  - [12] In [7,8], this is expressed as  $A+M \rightarrow X+M$ ,  $2X \rightarrow E+D$ , where, the concentrations of  $A$ ,  $M$ ,  $E$ , and  $D$  are taken to be constant in order to make an analysis of the equations possible.
  - [13] Here, only the  $X_1$  species is relevant to this reaction, so that it is not necessary to consider detailed structures smaller than the typical distance between  $X_1$  molecules and the total rate of the reaction can therefore be described by a smoothed distribution.
  - [14] The acceleration factor  $\alpha$  is estimated as follows. We assume that the distribution of localized  $X_1$  molecules is Gaussian with a standard deviation  $l_1$  around the  $X_2$  molecules. That is,  $\rho_i(x) = (\sqrt{2\pi}l_1)^{-1} \exp[-(x-x_i)^2/2l_1^2]$ , where  $x_i$  is the position of each  $X_2$  molecule. The total distribution (concentration) of  $X_1$  is  $c_1(x) = \sum_i \rho_i(x)$ , and  $\langle c_1 \rangle = \int \rho_i(x) dx / \lambda_2 = 1/\lambda_2$ . Since the molecules  $X_2$  are randomly distributed,  $\langle c_1^2 \rangle = \langle (\sum \rho_i)^2 \rangle = (\sum \langle \rho_i \rangle)^2 + \sum \langle \rho_i^2 \rangle = \langle c_1 \rangle^2 + (2\sqrt{\pi}l_1)^{-1} \langle c_1 \rangle (L_x \gg l_1, \lambda_2)$ . Thus,  $\alpha = \langle c_1^2 \rangle / \langle c_1 \rangle^2 = 1 + (2\sqrt{\pi}l_1)^{-1} \langle c_1 \rangle^{-1} = 1 + \lambda_2 / (2\sqrt{\pi}l_1)$ . Consequently, we obtain  $\alpha = 1 + 1/(2\sqrt{\pi}) \cdot \lambda_2 / l_1$ .