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Discreteness-induced stochastic steady state in reaction diffusion systems: self-consistent analysis and stochastic simulations

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Abstract

A self-consistent equation to derive a discreteness-induced stochastic steady state is presented for reaction–diffusion systems. For this formalism, we use the so-called Kuramoto length, a typical distance over which a molecule diffuses in its lifetime, as was originally introduced to determine if local fluctuations influence globally the whole system. We show that this Kuramoto length is also relevant to determine whether the discreteness of molecules is significant or not. If the number of molecules of a certain species within the Kuramoto length is small and discrete, localization of some other chemicals is brought about, which can accelerate certain reactions. When this acceleration influences the concentration of the original molecule species, it is shown that a novel, stochastic steady state is induced that does not appear in the continuum limit. A theory to obtain and characterize this state is introduced, based on the self-consistent equation for chemical concentrations. This stochastic steady state is confirmed by numerical simulations on a certain reaction model, which agrees well with the theoretical estimation. Formation and coexistence of domains with different stochastic states are also reported, which is maintained by the discreteness. Relevance of our result to intracellular reactions is briefly discussed.

Keywords: Reaction–diffusion systems; Stochastic process; Molecular discreteness; Kuramoto length

1. Introduction

Chemical reaction dynamics are often studied with the use of rate equations for chemical concentrations. For this approach, the number of molecules is assumed to be large, which validates the continuum description. However, in a biological system such as a cell, the number of molecules within is sometimes rather small. Then the validity of continuum description by the rate equations is not evident. This problem of smallness in molecule number is not restricted in biology. Following recent advances in nanotechnology, reactions in a micro-reactor are studied

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experimentally, where the number of molecules in concern is quite small. This is also true in some surface reaction of absorbed chemicals.

Here we are interested in the effect of such smallness in molecule number. Of course, one straightforward consequence of the smallness in the number is the large fluctuations in the concentration. Indeed, the fluctuations around the continuous rate equation can be discussed by stochastic differential equation [1,2]. State change by noise has been studied as noise-induced transitions [3], noise-induced order [4], stochastic resonance [5], and so forth. The use of stochastic differential equation, as well as its consequence, has been investigated thoroughly. If the number of molecules is much smaller and can reach 0, however, another effect of "smallness" is expected, that is the discreteness in the number. Our concern in the present paper is a drastic effect induced by such discreteness in the molecule number.

Previously we have discovered a transition of a chemical state, induced by the discreteness in the molecule number, i.e., the effect of the number of molecules 0, 1, ... [6]. The transition is termed as discreteness-induced transition (DIT). This transition is not explained by the stochastic differential equation approach. Rather, discreteness, in conjunction with the stochastic effect, is essential. In particular, we studied a system with autocatalytic reaction in a well stirred container. As the volume of the container decreases and the molecule number decreases, a transition to a novel state with symmetry breaking occurs, that does not appear either in the continuous rate equation or in its Langevin version. Here the transition occurs, when the number of molecule flow from environment to the reactor is discrete, in the sense that it is less than 1 on the average, within the average reaction time. Indeed, to the discreteness-induced transition, relevant is not the molecule number itself but the discreteness in the number of some molecular process (e.g., flow of molecule into the system) within the average time scale of some other reaction process.

On the other hand, in a spatially extended system with reaction and diffusion, the total number of molecules (and molecular events) increases with the system size, and is not small. Instead, the number of molecules (or events), not in the total system but within the size of an "effective length", is relevant to determine the discreteness effect. Then, we need to answer what this effective length is. In [7], we have proposed that the so-called Kuramoto length gives an answer to it.

Kuramoto length ℓ_K is defined as the average length that a molecule diffuses within its lifetime, i.e., before it makes reaction with other molecules [1,8,9]. In the seminal papers [8,9], Kuramoto has shown that whether the total system size is larger than this length or not provides a condition to guarantee the use of the reaction–diffusion equation. When the system size (length) is smaller than ℓ_K, local fluctuations rapidly spread over the system. Contrastingly, if the system size is much larger than ℓ_K, distant regions fluctuate independently, and the system is described by local reaction process and diffusion, validating the use of reaction–diffusion equation.

For example, consider the reaction

$$A \xrightarrow{k} X, \qquad 2X \xrightarrow{k'} B.$$

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

$$\ell_K = \sqrt{2D\tau}, \tag{1}$$

which gives the Kuramoto length.

In these works, it is assumed that the average distance between molecules is much smaller than ℓ_K, and there is a large number of molecules within the region of the length ℓ_K. Thus the concentration of the chemical X can be regarded as a continuous variable. Hence the continuum description is valid. However, if the average distance between molecules is comparable to or larger than ℓ_K, local discreteness of molecules may not be negligible.

For example, consider a chemical species X_j, whose Kuramoto length is given by ℓ_j. Then we consider discreteness of molecule species X_i that produces this chemical X_j, i.e., the case that average number of X_i is less than 1 within the area of the Kuramoto length ℓ_j. With this setting, molecules X_j, produced by X_i molecules, will be localized around them, as the average distance between X_i molecules is larger than the Kuramoto length of X_j. Then, this localization of the chemical may drastically alter the total rate of the reactions, if reactions with second or higher order of X_j are involved, as will be shown later. In the present paper, following [7], we pursue the possibility that discreteness of some molecules within Kuramoto length of some other molecules may drastically change the steady state of the system, as in DIT previously studied.

In Section 2, we discuss a general condition for the amplification of some reaction by such discreteness. Then by introducing a self-consistent equation for the rate of this amplification, we demonstrate the existence of stable stochastic steady state (SSS), that never appears in the continuum description. In Section 3, we numerically study a specific chemical reaction model with three components, to show the validity of this self-consistent theory for SSS. In Section 4, domain formation with this SSS is presented, as a novel possibility for pattern formation in reaction–diffusion system. Discussion is given in Section 5, with possible applications to biological problems.

2. Steady state induced by discreteness of molecule, with amplification of some reaction: self-consistent analysis

Consider a reaction system consisting of several molecule species X_m ($m = 1, \ldots, k$), with chemical reaction and diffusion. The system can involve catalytic reactions of higher order catalysis or autocatalysis. Some other molecules (e.g., resource chemicals) are supplied externally, involved in the reaction among X_m, so that the nonequilibrium condition is sustained. So far the system in concern is rather general chemical reaction system with diffusion.

Now, we take a pair of molecule species, X_i and X_j, where X_j is produced by X_i, and study how the discreteness of the molecule X_i can alter the steady state from the continuum limit case. To discuss the discreteness effect, we consider the case that the molecule X_j is localized around the molecule X_i. (Recall the molecule X_j is produced by X_i.) In order to this localization to work, the average length that the molecule X_j travels within its lifetime should be smaller than the average distance of the molecules X_i. In other words, the average number of the molecules X_i within the domain of the Kuramoto length ℓ_j is less than 1 (see Fig. 1). Here, the lifetime of the molecule X_j is determined by the collision with some other molecule species whose density is not low. Hence, the Kuramoto length of the X_j molecule, determined as in Section 1, is given independently of the concentrations of the molecules X_i and X_j.

Now, to alter drastically the steady state by discreteness, the localization of X_j molecule has to change concentrations of some other molecules, as compared with the case of homogeneous distribution of X_j. This is possible if there is a higher order reaction such as $mX_j + X_q \to X_p$, because the probability of such reaction is amplified by localization of X_j molecules in space. To compute this acceleration, we calculate the average of c_j^m, where c_j is the concentration of X_j, and compute the degree of amplification α from that for the homogeneously distributed case. In the calculation, we assume that X_j is localized around the X_i molecules, with a width of ℓ_j, the Kuramoto length of X_j (which is shorter than the average distance between X_i molecules).

Assuming that the distribution of X_j is represented by the continuous concentration $c_j(\vec{x})$, α can be expressed as

$$\alpha = \frac{\langle c_j^m \rangle}{\langle c_j \rangle^m} = \frac{V^{-1} \int c_j^m \, \mathrm{d}\vec{x}}{\left(V^{-1} \int c_j \, \mathrm{d}\vec{x}\right)^m}, \tag{2}$$

where V is the size (volume) of the system.

For simplicity, we assume that X_i is randomly distributed over d-dimensional space, and the distribution of X_j is given by a d-dimensional Gaussian distribution with a standard deviation ℓ_j around each X_i molecule, such as

$$\rho_k(\vec{x}) = \frac{1}{(\sqrt{2\pi}\ell_j)^d} \exp\left(-\frac{|\vec{x}-\vec{x_k}|^2}{2\ell_j^2}\right),$$

where $\vec{x_k}$ is the position of each X_i molecule. Now $c_j(\vec{x})$ is the sum of $\rho_k(\vec{x})$; thus, $\langle c_j\rangle = c_i$ since $\int \rho_k \,\mathrm{d}\vec{x} = 1$. For the case with $m = 2$ and sufficiently large V,

$$\langle c_j^2\rangle = \left\langle \left(\sum \rho_k\right)^2 \right\rangle = \left(\sum \langle\rho_k\rangle\right)^2 + \sum \langle\rho_k^2\rangle = \langle c_j\rangle^2 + (2\sqrt{\pi}\ell_j)^{-d}\langle c_j\rangle,$$

since X_i is randomly distributed. With Eq. (2),

$$\alpha = \frac{(\langle c_j\rangle^2 + (2\sqrt{\pi}\ell_j)^{-d}\langle c_j\rangle)}{\langle c_j\rangle^2} = 1 + (2\sqrt{\pi}\ell_j)^{-d}\langle c_j\rangle^{-1} = 1 + (2\sqrt{\pi})^{-d} c_i^{-1}\ell_j^{-d}.$$

Thus, we obtain the acceleration factor

$$\alpha = 1 + \frac{1}{(2\sqrt{\pi})^d c_i \ell_j^d}. \tag{3}$$

In the same manner, for $m = 3$,

$$\alpha = 1 + \frac{3}{(2\sqrt{\pi})^d c_i \ell_j^d} + \frac{1}{(2\sqrt{3}\pi)^d (c_i \ell_j^d)^2}, \tag{4}$$

and generally, for $c_i\ell_j^d \ll 1$,

$$\alpha \approx m^{-d/2}((2\pi)^{d/2} c_i \ell_j^d)^{1-m}. \tag{5}$$

As shown, the reaction can be drastically amplified as the number of X_i molecules within a volume of the Kuramoto length $(c_i\ell_j^d)$ is much smaller than 1.

So far we have shown that for reaction system involving the process from X_i to X_j, the discreteness can alter the concentration of some chemicals drastically, if (1) the density of X_i molecule is so low that the number is discrete within the size of the Kuramoto length of X_j molecule and (2) there is a high order (higher than linear) reaction with regards to X_j.

Next, to confirm that this acceleration of reaction alters the steady state from the continuum case, we need to check if the condition for the discreteness is sustained under the above amplification of concentration of some chemicals, as a steady state solution. Hence we study some feedback from the concentration of X_p to X_i that is generated by some reaction path(s). If X_i is produced or catalyzed by X_p, the concentration of X_i depends on that of X_p, c_p. With such feedback, the change of concentration c_i is given by some function $F(c_j, c_p)$, while the change of the concentration c_j depends on c_i, and is given by some function as $G(c_i)$. Since c_p is a function of $\alpha(c_i)$, $F(c_j, c_p)$ is rewritten as $\hat{F}(c_j, \alpha(c_i))$. Hence the concentrations of X_i and X_j molecules must satisfy

$$\frac{\mathrm{d}c_i}{\mathrm{d}t} = \hat{F}(c_j, \alpha(c_i)); \qquad \frac{\mathrm{d}c_j}{\mathrm{d}t} = G(c_i) \tag{6}$$

(F and G may have dependence on other concentrations or reaction rates, e.g., $G(c_i)$ can also depend on c_j or α). The steady state solution is obtained by setting the right hand of these equations as 0.

Note that the solution with $\alpha = 1$ corresponds to the continuum case, given by the standard rate equation. For some case, this is the only solution for the concentrations. For some other cases, however, there is some other solution(s) with $\alpha > 1$. This is a solution with the amplification by localization of molecules due to the discreteness of the X_i molecule. If the concentration of c_i obtained from this solution satisfies $c_i \ell_j^d < 1$, this discreteness-induced solution is self-consistent. Furthermore, the stability of this solution is computed by linearizing the solution around this fixed point. If this solution is linearly stable, stability of this novel steady solution is assured, which does not exist in the continuum description (or in its Langevin equation version). We call the state represented by this solution as stochastic steady state (SSS), as it is sustained stochastically through discreteness in molecule numbers. We will show an explicit example of this SSS in the next section.

2.1. Self-consistent solution involving the change of Kuramoto length

So far we have assumed that the Kuramoto length ℓ_j of the X_j molecule is constant. This is true as long as the concentration of the molecule relevant to the decomposition or transformation of the X_j molecule is constant. However, if the concentration of the chemical that is relevant to the determination of ℓ_j depends on the concentration of either X_i, X_j, or X_p, the Kuramoto length, as well as α, depends on it. Accordingly, in Eq. (6), we need to regard ℓ_j in α as a variable that depends on either c_i, c_j or α. With the inclusion of the dependence, we again obtain a self-consistent solution, to get the concentrations c_i and c_j (and accordingly α and ℓ_j). If there is a stable solution with $\alpha > 1$ and $c_i \ell_j^d < 1$, then we get a SSS as a self-consistent solution both on α and ℓ_j. We will discuss a related example in Section 4, where two solutions with $\alpha = 1$ and $\alpha > 1$ coexist in space, and form a domain structure.

2.2. Combination of several processes

So far we have discussed a simple case of discreteness-induced state. The discussion with the use of amplification factor α, however, is generalized to include temporally or spatially dependent solutions of c_i and c_j, with temporal (or spatial) dependence of α. This solution represents an average behavior longer than the time scale for stochastic collisions or longer scale than ℓ_j. With this extension, we can discuss discreteness-induced rhythm or pattern, that is stochastically sustained.

Such spatiotemporal dynamics can often appear in a reaction network of several molecules, with two or more pairs of discreteness in number. For example, consider reactions $X_{i1} \to$ (produces) $\to X_{j1}, X_{j1} \to$ (produces with high order reaction) $\to X_{p1}, X_{p1} \to$ (produces) $\to X_{i2}$; and $X_{i2} \to$ (produces) $\to X_{j2}, X_{j2} \to$ (produces with high order reaction) $\to X_{p2}, X_{p2} \to$ (produces) $\to X_{i1}$ (see Fig. 2), where we assume that the density c_{i1}, c_{i2}, of X_{i1} and X_{i2} molecules are so low that $c_{i1} \ell_{j1}^d < 1$ and $c_{i2} \ell_{j2}^d < 1$, respectively for the Kuramoto lengths of X_{j1} and X_{j2}. Then, following the scheme we discussed, we get a coupled equation for the concentrations of $c_{i1}, c_{j1}, c_{i2}, c_{j2}$ with two amplification factors α_1 and α_2. In general, there may be a time- or space-dependent solution (by including diffusion term with much longer spatial scale), that leads to a novel stochastic pattern or rhythm. Explicit examples for such case will be discussed in future.

3. Specific example of stochastic steady state

To confirm our theoretical estimation for SSS, we have adopted a simple model and carried out stochastic particle simulations. Here we consider a simple one-dimensional reaction–diffusion system with three chemicals (X_1, X_2,

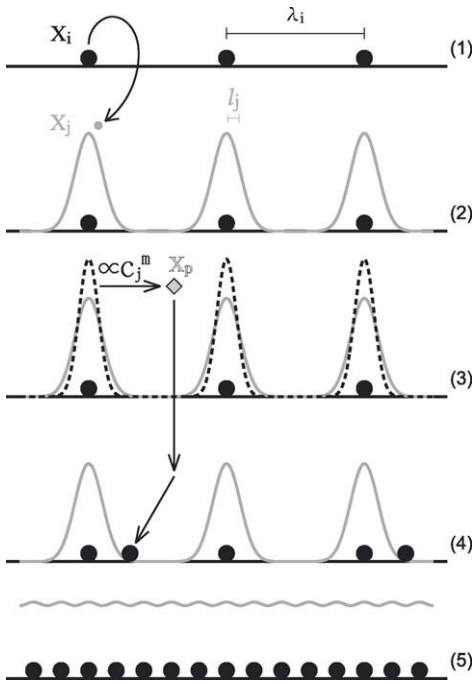

Fig. 1. Schematic representation for the mechanism to produce SSS. Assume that (1) the chemical X_j is produced by X_i, and (2) ℓ_j, the Kuramoto length of X_j, is shorter than $\lambda_i (= c_i^{-1})$, the average distance of X_i molecules (i.e., $c_i \ell_j^d < 1$). Then, X_j is localized around X_i molecules. (3) If there is mth order reaction of X_j ($m > 1$), the rate of the reaction is proportional to c_j^m; hence, the reaction is accelerated. (4) Additionally, if the reaction promotes (directly or indirectly) the production of X_i, the acceleration of the reaction may cause increase of c_i. (5) On the other hand, if c_i is high ($c_i \ell_j^d \approx 1$ or > 1), X_j is almost uniformly distributed; thus, the acceleration is weak, and the production of X_i is degraded. Hence, there is a stable steady state of c_i at an intermediate value.

and X_3) and four reactions:

$$X_2 + X_3 \xrightarrow{k_1} X_2 + X_1, \qquad X_3 + X_1 \xrightarrow{k_2} 2X_3, \qquad 2X_2 \xrightarrow{k_3} X_2 + X_1, \qquad 2X_1 \xrightarrow{k_4} X_1 + X_2.$$

Here, we assume $k_1, k_2 \gg k_3 > k_4$. We take $k_1 = k_2 = br, k_3 = ar$, and $k_4 = r$ ($r > 0, 1 < a \ll b$) for further discussion. We assume that the system is closed with regards to the molecules $X_m (m = 1, 2, 3)$. Thus, N, the total number of molecules (or c, the total concentration), is conserved.

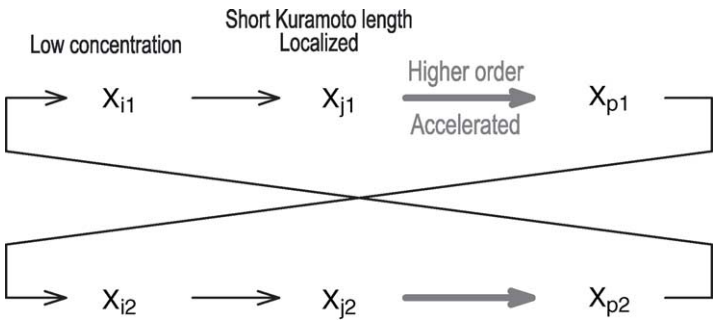

Fig. 2. Schematic diagram of an example of reaction cascade.

In the continuum limit, each $c_i(t, x)$, the concentration of X_i at time t and position x, obeys the following reaction–diffusion equation:

$$\frac{\partial c_1}{\partial t} = -br(c_1 - c_2)c_3 - r(c_1^2 - ac_2^2) + D_1\frac{\partial^2 c_1}{\partial x^2}, \tag{7}$$

$$\frac{\partial c_2}{\partial t} = r(c_1^2 - ac_2^2) + D_2\frac{\partial^2 c_2}{\partial x^2}, \tag{8}$$

$$\frac{\partial c_3}{\partial t} = br(c_1 - c_2)c_3 + D_3\frac{\partial^2 c_3}{\partial x^2}, \tag{9}$$

where D_i is the diffusion constant of X_i. For simplicity, we assume $D_i = D$ for all i. This reaction–diffusion equation has homogeneous fixed point solutions with $(c_1, c_2, c_3) = (0, 0, c), (\sqrt{a}c/(\sqrt{a}+1), c/(\sqrt{a}+1), 0)$ for all x. By linear stability analysis, it is straightforward to show that only the former is stable. Starting from any initial conditions, the partial-differential equation system simply converges to this stable fixed point.

In this system, the chemical X_1 is produced by X_2 molecules. (In the notation of Section 2, $i = 2$ and $j = 1$.) If ℓ_1, the Kuramoto length of X_1, is shorter than the average distance between X_2 molecules, X_1 is localized around the X_2 molecules, as discussed in Section 2. Then, the reaction $2X_1 \to X_1 + X_2$, which is at second order of X_1, is accelerated. Using Eq. (3) in Section 2, we obtain the acceleration factor

$$\alpha = 1 + \frac{1}{2\sqrt{\pi}c_2\ell_1}. \tag{10}$$

On the other hand, the lifetime of X_2 is so long that X_2 is not localized. Thus, the reaction $2X_2 \to X_2 + X_1$ is not accelerated.

Now we study the self-consistent solution from c_1 and c_2, following the argument of Section 2. (By a path from X_1 to X_2, there is a direct feedback to i, i.e., $p = 2(= i)$ in the notation of Section 2.) Here, we consider the case where $N_1, N_2 \ll N_3$, so that $c_3 \approx c$. Then, the average lifetime of X_1 is about $1/brc_3 \approx 1/brc$; we assume that $\ell_1 = \sqrt{2D/brc}$ for further discussion. When $N_1, N_2 \ll N_3$, the two reactions $X_2 + X_3 \to X_2 + X_1$ and $X_3 + X_1 \to 2X_3$ are much faster than the other two and maintain $N_1 \approx N_2$. Then, the rates of the other reactions satisfy

$$\frac{\text{The rate of } (2X_1 \to X_1 + X_2)}{\text{The rate of } (2X_2 \to X_2 + X_1)} \approx \frac{\alpha k_4 N_1^2}{k_3 N_2^2} \approx \frac{\alpha}{a}. \tag{11}$$

When $\alpha = a$, the two reactions are balanced, which leads to a novel fixed point. Assuming $c_1, c_2 \ll c_3$ and $c_3 = c$, and following Eq. (10), we obtain the condition for the balance

$$c_1 = c_2 = \frac{1}{2\sqrt{\pi}(a-1)\ell_1}(= c_s). \tag{12}$$

Subsequently, we investigate the stability of this fixed point. For $c_1 = c_s + \delta c_1$ and $c_2 = c_s + \delta c_2$, we obtain

$$\alpha = 1 + \frac{(a-1)c_s}{c_2} = a - \frac{a-1}{c_s}\delta c_2 + o(\delta c_2) \tag{13}$$

from Eqs. (10) and (12). We take into account the acceleration factor in the reaction–diffusion equation, we obtain

$$\begin{pmatrix} \dot{c_1} \\ \dot{c_2} \end{pmatrix} = r\begin{pmatrix} -2ac_s - bc & (3a-1)c_s + bc \\ 2ac_s & -(3a-1)c_s \end{pmatrix}\begin{pmatrix} \delta c_1 \\ \delta c_2 \end{pmatrix} + o(\delta c_1, \delta c_2). \tag{14}$$

For any $a, b > 1$, this Jacobi matrix has two negative eigenvalues, implying that the fixed point is stable.[1]

[1] It is also stable against spatially inhomogeneous perturbations for any $D > 0$.

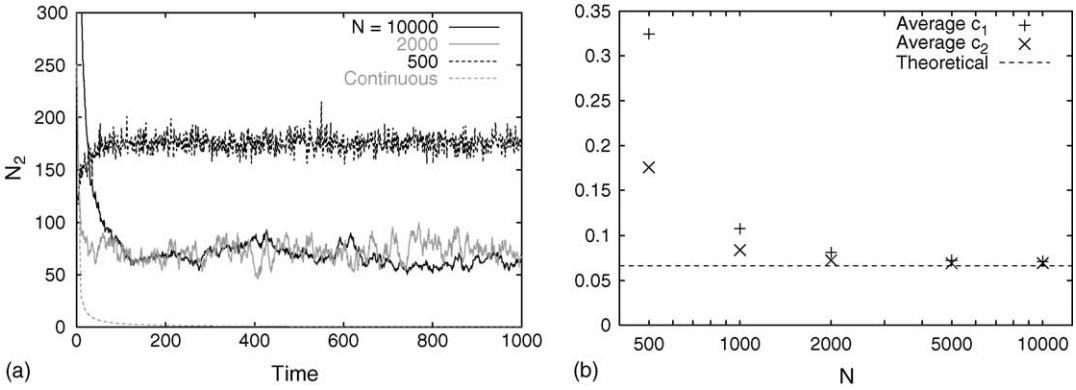

Fig. 3. (a) Time series of N_2 and (b) the average concentrations c_1 and c_2 for several values of N. $a = 4$, $b = 100$, $D = 100$, and $L_x = 1000$. We fix $rc = 1$ (i.e., $r = 1000/N$), so that $\ell_1 = \sqrt{2D/brc} = \sqrt{2}$. For $N \geq 1000$ cases, N_2 converges to the stochastic fixed point. There, c_2 should be $1/(2\sqrt{\pi}(a-1)\ell_1) = 1/6\sqrt{2\pi} \approx 0.066$ (i.e., $N_2 = c_2 L_x \approx 66$) for all cases, which agrees well with the simulation. When $N = 500$, the system reaches the unstable fixed point $(2c/3, c/3, 0)$. With the reaction–diffusion equation, c_1 and c_2 rapidly converge to 0 (the dotted line "continuous" in (a) shows c_2 for $c = 1$).

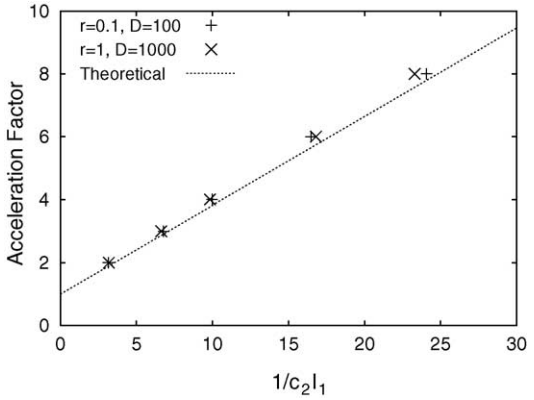

Fig. 4. The acceleration factor $\alpha = a$, plotted against $1/c_2\ell_1$. $b = 100$, $N = 1000$, $L_x = 1000$, sampled over 5000 ($r = 1$) or 50 000 ($r = 0.1$) time units. We measure the relation from average c_2 in simulations. The result agrees with the theoretical estimation $\alpha = 1 + 1/2\sqrt{\pi}c_2\ell_1$ well.

In the simulations, we have found that the system converges to the novel fixed point (Fig. 3). In fact, we have measured c_2 at the fixed point for a certain $\alpha = a$ numerically. Fig. 4 shows the relation between $1/c_2\ell_1$ and α, which agrees rather well with the theoretical estimation in Eq. (10).

In summary, we demonstrated numerically that the discreteness of molecules yields a novel stochastic steady state in a reaction–diffusion system, in agreement with the theoretical estimation.

4. Coexistence of domains with different Kuramoto lengths

In the example of the previous section, the spatial homogeneity is assumed at a coarse-grained level, and indeed, this homogeneous state was stable. However, due to fluctuations, some spatial inhomogeneity exists in SSS, and a domain that is deviated from SSS may be produced. Even if this deviated state is unstable in the continuum limit, it may be preserved over a long time, if the concentration of the molecule to destabilize it is so low that its discreteness

Table 1
Stability of each fixed point in the continuous reaction–diffusion equation and in the stochastic system taking into account discreteness in molecules

State	c_i	Continuous	Discrete
The unstable fixed point of the R–D equation	$c_3 = 0$	Unstable	Unstable
The stochastic steady state	$c_1, c_2, c_3 > 0$	Not fixed point	Stable
The stable fixed point of the R–D equation	$c_1 = c_2 = 0$	Stable	Unstable

is essential. If the average time to produce this deviated domain from SSS and the lifetime of the state is balanced, the two regions, SSS and the deviated state with different concentrations of molecules and Kuramoto lengths, may coexist. We give a simple example for it here.

Again we consider the same reactions as the preceding section. Now, we assume that the diffusion of X_3 is slower than the others, and set $(D_1, D_2, D_3) = (100D, 100D, D)$ $(D > 0)$. In this model, there are two fixed-point states: one is the stochastic steady state mentioned above (which we call state A); the other is the unstable fixed point with $c_3 = 0$ (state B), besides the stable fixed point in the continuum limit (which does not appear here; see Table 1 for the stability of the states mentioned here). In Fig. 5, we give an example of snapshot pattern of the model. In the figure, except several spots with large c_3 that corresponds to the state A, most other regions fall onto the state B that should be unstable in the continuum limit. Indeed, this pattern is not transient, and the fraction of the state B is stationary, in the long-term simulation. This suggests the possibility that the state B, unstable in the continuum limit, may be sustained over a finite period due to the discreteness in molecules, which forms a domain in space. The two states A and B coexist in space and form a domain structure.

First, we consider stability of each of the states in more detail. The state B is unstable against the inflow of X_3. If an X_3 molecule enters into a region of state B (region B), it can be amplified and form a new region (spot) of the state A (region A). From linear stability analysis, we find that the degree of instability of the region B against the flow of X_3 is proportional to $(c_1 - c_2)$. Note that in the region A, $c_1 \approx c_2$, while in the region B, $c_1 \approx \sqrt{a}c_2$, and $c_3 = 0$. Here, the concentration c_2 is almost uniform in space because of its long lifetime. Thus, the degree of the instability of the region A, that is the rate of growth of c_3, depends mainly on the distribution of X_1 (see Fig. 6).

Accordingly, the Kuramoto length of X_1 is relevant to determine if the state B is invaded or not. Here it should be noted that in the region A, c_1 is smaller than that in the region B. Hence in the vicinity of the region A

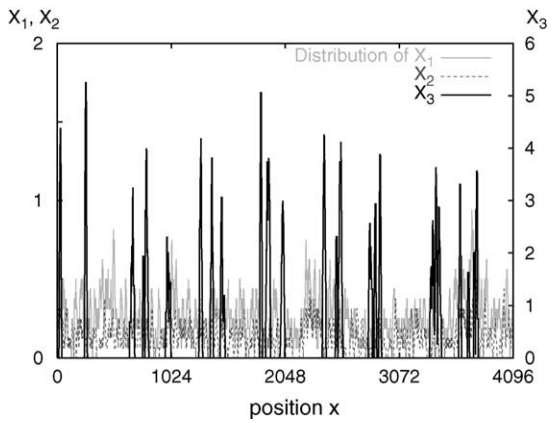

Fig. 5. The distribution of each chemical X_i (a snapshot at $t = 1000$). $r = 1.28$, $a = 4$, $b = 100$, $D = 1$, $N = 3200$, and $L_x = 4096$. (For these parameters, $\ell_{1B} \approx 17$ and $\ell_{3B} \approx 0.24$.) Plotted distribution is obtained by averaging the molecule snapshot pattern, with the bin size $\Delta x = 16$. There appear spots of X_3, in which the stochastic steady state with $\alpha > 1$ is realized. There are very few X_3 molecules between the spots, where the system stays around the unstable fixed point $(2c/3, c/3, 0)$.

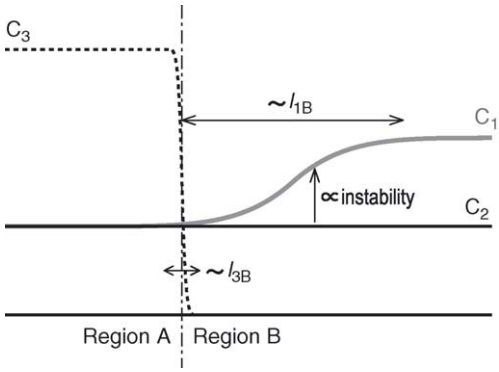

Fig. 6. Schematic diagram of the border between the regions A and B.

within the domain of the state B, c_1 is still small, as long as it is within the Kuramoto length of X_1 of the region A. Thus the instability is weak there, which prevents a novel region A (X_3 spot) growing in the vicinity of the existing region A. Hence, the interval between two neighboring regions A should be longer than the Kuramoto length of X_1. Assuming that $N_3 \ll N_1, N_2$ and $(c_1, c_2, c_3) = (\sqrt{a}c/\sqrt{a}+1, c/\sqrt{a}+1, 0)$ (i.e., the unstable fixed point of the reaction–diffusion equation) in the region B, we obtain the Kuramoto length of X_1 in the region B as

$$\ell_{1B} = \sqrt{2D_1(k_4 c_1)^{-1}} = \sqrt{\frac{200D(\sqrt{a}+1)}{r\sqrt{a}c}}.$$

Since X_3 can be amplified by using X_1 in the region B, penetration of X_3 molecules into the region B must be rare in order to maintain the region B. The penetration length is given by the Kuramoto length of X_3, that is computed as

$$\ell_{3B} = \sqrt{2D_3(k_1 c_2)^{-1}} = \sqrt{\frac{2D(\sqrt{a}+1)}{brc}}$$

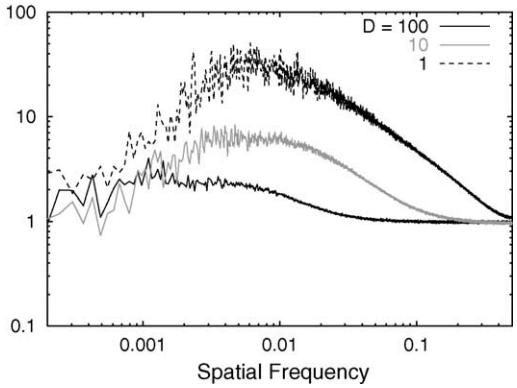

Fig. 7. Power spectra of the distribution of X_3. $r = 1$, $a = 4$, $b = 100$, $N = 16\,384$, and $L_x = 16\,384$. For small D, there appears a broad peak at the wave length around the order of 10^2, which corresponds to the interval of the spots. For large D, X_3 spreads over the space, and the peak disappears.

for the region B. For $1 < a \ll (100b)^2$, $\ell_{3B} \ll \ell_{1B}$, which implies that X_3 molecules seldom reach the area where X_3 is strongly amplified. Thus, the border of regions A and B is maintained for long time.[2]

On the other hand, due to the fluctuation inherent in SSS, the molecule X_3 may be extinct within some area of the region A, with some probability. Hence, the regions A and B coexist in space, as shown in Fig. 5. As shown, the region A is localized only as spots, and other parts are covered by the region B.

Note that in the corresponding reaction–diffusion equations, the state A, the stochastic steady state, cannot be realized, while the state B is unstable. Indeed, the reaction–diffusion equation system is quickly homogenized and converges to the stable fixed point with $c_1 = c_2 = 0$. Hence both the regions A and B, as well as a domain structure from the two, can exist only as a result of the discreteness of molecules, and are immediately destroyed in the continuum limit.

Note that in the present model, SSS does not have so-called the Turing instability,[3] and there is no characteristic wavelength. Still the spatial structure here has some characteristic length, as given by the minimal size of the region B, estimated by the Kuramoto length ℓ_{1B}. In Fig. 7, we have plotted the spatial power spectrum of the concentrations of X_3. Although there is no clear peak, there is a very broad increase around the wavenumber of 0.01, that corresponds to average domain size of the region B.

In general, the discreteness of molecules can induce novel states not seen in the continuum limit. For example, in a randomly connected catalytic reaction network, there often exist several fixed points with some chemicals going extinct, when the number of molecules is small, while there is only one attractor in the continuum limit. These discreteness-induced states may coexist in space in a similar way as discussed above. Kuramoto length will be a useful index to determine the behavior around the border of the regions.

5. Summary and discussion

In the present paper, we have reported a novel steady state in a system with reaction and diffusion, induced by discreteness in molecules. This state cannot be represented by a continuum description, i.e., partial differential equation (reaction–diffusion equation), but is sustained by amplification of some reaction due to localization of some molecule X_j. This localization is possible if the molecule species that produce X_j is "discrete", in the sense that its average number within the Kuramoto length of the X_j molecule is less than 1. We have formulated a theory to obtain a self-consistent solution for the concentrations of X_i and X_j, in relationship with the amplification rate of the reaction involved with X_j. For some reaction system, there is a solution with amplification rate larger than 1, that leads to the existence of stochastic steady state due to the discreteness in molecule number. The stability of this solution is also computed within this theoretical formulation.

We have also numerically studied a simple reaction–diffusion system to demonstrate the validity of the theory. Indeed, a novel stochastic steady state is observed, as predicted theoretically. We have also extended our theory to include the self-consistent determination of the Kuramoto length. Following this extension, we have provided a numerical example, to show formation of domains with different Kuramoto lengths.

The alteration of the steady state by the localization, as well as our formulation for it is quite general. Provided that the conditions

(i) Chemical X_i generates another chemical species X_j.
(ii) The lifetime of X_j is short or the diffusion of X_j is slow so that the Kuramoto length of X_j is much smaller than the distance between X_i molecules.

[2] For this reason, we set D_3 relatively small. If D_3 is larger, the border is blurred and the two regions are mixed.
[3] It is also possible that the acceleration of reactions by the discreteness induces or enhances the Turing instability in certain systems.

(iii) The localization of the molecule X_j accelerates some reactions.

Then, the discreteness can alter the dynamics, from that by the continuum description. The last condition is satisfied if the second or higher order reaction is involved in the species X_j. Finally, if

(iv) the acceleration of the reaction in (iii) alters the density of X_i molecules, through some reaction(s),

the density of X_i is determined self-consistently with the acceleration factor, resulting in a novel steady state.

Note that the localization effect by the discreteness of catalytic molecules itself is also noted by Shnerb et al. [10]. In their study, however, the density of the catalyst is fixed as an externally given value. Thus the concentration of the product, localized around the catalyst, diverges in time. In our theory, the density of the catalyst (X_i) changes autonomously and reaches a suitable value by following the discreteness effect.

The self-consistent solution scheme to obtain this discreteness-induced stochastic state can be extended to a case with several components $i_1, i_2, \ldots, i_k$, and the corresponding set of chemicals $j_1, j_2, \ldots, j_k$ satisfying the conditions (i)–(iii). In such case, the feedback process in (iv) is not necessarily direct from j_m to i_m. If there is a feedback from the set of chemicals $j_1, j_2, \ldots, j_k$ to the set $i_1, i_2, \ldots, i_k$ (condition (iv)′), the above scheme for the self-consistent dynamics we presented here works. With this extension, there is a variety of possibilities, that can lead to stochastic rhythm or pattern formation induced by discreteness of molecules, which is not seen in the continuum limit. For example, in a catalytic reaction network with many components and a limited number of total molecules, there always exist several species that are minority in number, and the conditions (i)–(ii) are naturally satisfied, while with higher order catalytic reaction the condition (iii) is often satisfied. In this case, minority molecules become a key factor to determine a macroscopic state with rhythm or pattern. (Note in this case, other molecules can be abundant in number, or indeed it is better to have such abundant species, so that the stochastic state is stabilized.) In fact, biochemical reaction networks involve a huge number of species, while the total number of molecules is not necessarily so large. In a cell, lots of chemicals work at low concentration in the order of 1 nM or less. The diffusion is sometimes restricted, surrounded by macro-molecules, 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 other chemical species. Some chemicals are localized around some other molecules. Furthermore, biochemical systems contain various higher order reactions (for example, catalyzed by enzyme complexes). In conjunction with the localization, such reactions can be accelerated. Hence the conditions (i)–(iii) are ubiquitously satisfied in intra-cellular biochemical reaction networks. In addition, since the biochemical reactions involve complex feedback process through mutual catalytic networks, the condition (iv) or (iv)′ is naturally satisfied.

Accordingly, it will be important to study the amplification of some reaction and its maintenance through feedback will be relevant to biochemical reactions. Indeed, some molecules that are minority in number sometimes play a key role in biological function. Relevance of minority molecules is also discussed from the viewpoint on a control mechanism of a cell, in relationship with the kinetic origin of information [11,12].

The importance of our theory is not restricted to biological problems. Verification of our result will be possible by suitably designing a reaction system, with the use of, say, microreactors or vesicles. The acceleration and maintenance of some reactions by localization of molecules will be important to design some function in such micro-reactor systems.

Acknowledgement

The present paper is dedicated to Professor Yoshiki Kuramoto on the occasion of his retirement from Kyoto University. With the papers [8,9] that introduced Kuramoto length a novel research field was opened; the study of chemical wave and turbulence with the use of *continuous, deterministic* reaction–diffusion equation. It is our pleasure to use his length in the opposite context here, for the description of novel steady states in *discrete, stochastic*

reaction–diffusion systems. The present work is supported by grant-in-aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (15-11161), and the Japan Society for the Promotion of Science.

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