Discreteness-induced transition in catalytic reaction networks

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Drastic change in dynamics and statistics in a chemical reaction system, induced by smallness in the molecule number, is reported. Through stochastic simulations for random catalytic reaction networks, transition to a state is observed with the decrease in the total molecule number N, characterized by (i) large fluctuations in chemical concentrations as a result of intermittent switching over several states with extinction of some molecule species and (ii) strong deviation of time averaged distribution of chemical concentrations from that expected in the continuum limit, i.e., $N\to\infty$. The origin of transition is explained by the deficiency of the molecule leading to termination of some reactions. The critical number of molecules for the transition is obtained as a function of the number of molecule species M and that of reaction paths K, while total reaction rates, scaled properly, are shown to follow a universal form as a function of NK/M.

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I. INTRODUCTION

In intracellular biochemical reaction processes, some chemical species often play an important role at extremely low concentrations, amounting to only a few molecules per cell [1–4]. In such situations, the fluctuations and discreteness in the molecule number are obviously important. On the other hand, in rate equations, generally adopted in chemical kinetics, the concentration of each chemical species is treated as a continuous variable, and the fluctuations and the discreteness of the number of molecules are neglected. However, if the molecule number is not very large, the number fluctuations as well as discreteness in the number, rather than a continuous concentration, must be considered seriously.

Of course, effects of fluctuations in concentrations are considered by using stochastic differential equations. Indeed, several nontrivial noise-induced phenomena have been reported [5–7]. However, in most of such studies, discreteness in the molecule numbers, i.e., the number being $0,1,2,\ldots$, has not been considered seriously.

Recently, Togashi and Kaneko reported a drastic change in the steady distribution of chemical concentrations as a result of discreteness in the molecule number, by studying a catalytic reaction network with a few molecule species [8,9]. Types of dissipative structure formation, induced by very low concentration molecules, have also been investigated [10–15] in a class of reaction-diffusion systems or the models of biochemical reactions in cells. The observed states in these studies are a result of fluctuations and discreteness in the molecular numbers, in particular of extinction and reemergence of some molecule species, which alternate in time.

Relevance of such discreteness in molecule number to emergence of states should not be restricted to a simple reaction network with a few molecule species, but is also expected to exist in a wide variety of chemical reaction systems with a large number of species. Here, dynamics and statistics of chemical reaction systems with a finite (small) number of molecules and a large number of molecule species must be investigated. Such study is important not only for biochemical reaction kinetics generally, but also as a problem of nonequilibrium statistical mechanics. Here, the criterion on "smallness" in the number itself should be clarified as a condition for the discreteness-induced transition for a given chemical reaction network system.

In this paper, we study the discreteness-induced transition in a reaction network where a large number of chemical species is connected by catalytic reaction paths chosen randomly. Use of random catalytic reaction network is pioneered by Kauffman [16,17] for the problem of the origin of life, while studies in a growing cell model consisting of such reaction network have unveiled universal statistical behaviors of chemical concentrations, which are confirmed in the gene expression data in the present cells [18,19]. Here, we are interested in how discreteness in the molecule numbers affect global behavior of chemical reaction dynamics in such network. For simplicity, we only consider the reaction network whose steady state is unique and stationary when the number of molecules is infinite, i.e., the corresponding rate equation has just a unique fixed point attractor. Even in such a simple system, we find the following transition to a discreteness-induced state, which appears when the total number of the molecules is below a critical value.

(a) Chemical concentrations exhibit intermittent switching among several states with distinct chemical compositions.

(b) The long time average of the chemical concentrations deviate distinctly from those expected in the continuum limit with a large number of molecules where the rate equation description is valid.

We will also obtain the critical molecule number for this discreteness-induced transition, whose dependence on the number of chemical species and path ratio of the reaction network will be derived.

In the next section, we introduce a specific reaction network model, while numerical results to show the above transition with the decrease in the molecule number are pre-

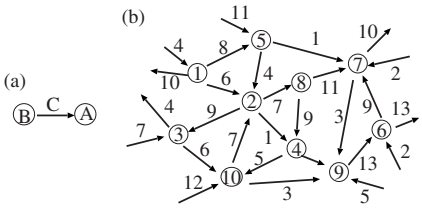

FIG. 1. (a) Illustration of catalytic reaction $B+C\rightarrow A+C$ and (b) an example of catalytic reaction networks.

sented in Sec. III. Possible mechanism for the transition is described in Sec. IV, where deficiency in some molecules is shown to introduce switching among several effective reaction networks that consist only of nonvanishing chemical species. In Sec. V, we obtain the critical number of molecules for the transition as a function of the number of molecule species and connectivity in the network. Summary and discussion will be given in Sec. VI.

II. MODEL

Now, we introduce a simple model of a network of elementary reactions that consists of a variety of chemical species [18]. State of the system is represented by a set of numbers $(n_1,n_2,\ldots,n_M)$, where $n_i(=0,1,\ldots)$ indicates the number of molecules of the chemical species $i(1\leq i\leq M)$, with M as a total number of molecule species. Here, the total number of molecules is fixed at N, and accordingly $0\leq n_i \leq N$. For the chemical reaction dynamics, we choose a catalytic network among these chemical species, where each reaction from a chemical B to another chemical A is assumed to be catalyzed by a third chemical C; i.e., $B+C\rightarrow A+C$ (see Fig. 1). The reaction coefficients are set to be identical for all reactions for simplicity, and chosen to be 1. Then, the growth rate in n_A (or the decay rate in n_B) through this reaction is given by n_Bn_C/N^2, on the average.

The connection paths in a reaction network are chosen randomly (and then fixed), where the average number of the reaction paths from a chemical i to any other chemical species j catalyzed by a chemical l is set at a given connection number K. We do not include autocatalytic reaction in the form of $B+C\rightarrow 2C$, because such type of reaction is not usually elementary but is realized as a result of a series of (nonautocatalytic) elementary reactions. Also, inclusion of autocatalytic paths sometimes leads to nonfixed point or multiple attractors, which makes discussion on the discreteness effect complicated.

We also include a flow of chemicals into and out of the system from the reservoir. With this process, the total number of molecules is fixed so that a molecule is regarded to be replaced by some other with a certain rate. Instead of considering such flow, one can equivalently consider a combination of decomposition and synthesis of some chemicals, or noncatalytic changes between different molecule species that are chosen randomly from all chemicals with equal probability. For simplicity, we assume that this noncatalytic change occurs with equal probability ϵ for all molecules, while its rate is much smaller than that of the catalytic reaction.

Numerical simulations are carried out by iterating the following stochastic processes. First, we randomly pick up a pair of molecules and if the pair is a substrate and catalyst according to the reaction network, the substrate molecule is transformed to the product molecule according to the reaction. Second, we randomly pick up a molecule and transform it by a noncatalytic change, with a given, much lower, rate. Here, a unit time is given as the time span in which Monte Carlo steps for catalytic reactions are repeated $N/2$ times and those for noncatalytic processes are repeated N times. In each time, each molecule collides with another molecule once on average, to check if the catalytic reaction occurs, while it is transformed to some other chemical with probability ϵ by a noncatalytic process. Numerically, we apply this stochastic simulation, while in the cases with $N\gg M$ (i.e., continuous limit), the reaction dynamics are represented by the following rate equation:

$$\dot{n_i}=\sum_{j,l} C(j,i,l)\frac{n_jn_l}{N^2}-\sum_{j',l'} C(i,j',l')\frac{n_in_{l'}}{N^2}+\epsilon\left(\frac{1}{M}-\frac{n_i}{N}\right), \tag{1}$$

where $C(i,j,l)$ is 1 if there is a reaction $i+l\rightarrow j+l$, and 0 otherwise.

In the following sections, we present numerical results of the stochastic simulations and show how the steady state properties of such catalytic reaction networks depend on the number of chemical species M and of molecules N. In this paper, we consider the case with K as $K_c<K\ll M$ where K_c indicates the critical connection number of the percolation transition in random networks. It is noted that the rate equation (1) in the continuum limit has only a unique fixed point attractor that gives the concentrations at the steady state.

III. DISCRETENESS-INDUCED TRANSITION

We show the results of the stochastic simulation of catalytic reaction networks with $\epsilon=10^{-4}$. We study how dynamical aspects of the system change depending on the number of molecules N, by taking a given reaction network. Figures 2(a) and 2(b) show typical temporal evolutions of the concentrations of each chemical species n_i for a reaction network with $M=100$ and $K=12$. Two cases with (a) large ($N=800$) and (b) small ($N=12$) N are plotted, while Fig. 2(c) shows the reaction ratio (RR) of these cases, where RR is defined by (number of reacting molecules)/N at each time. If N is much larger than M (e.g., $N=800$), as seen in Figs. 2(a) and 2(c), the distribution of n_i is almost stationary and RR takes a constant value except for small fluctuations.

On the other hand, if N is much smaller than some value (that is of the order of M) (e.g., $N=12$), the distribution of n_i exhibits remarkable changes in time, and RR fluctuates intermittently between large values and 0, as seen in Figs. 2(b) and 2(c). Such nonstationary behavior is caused by the discreteness in the molecular number. When N is much smaller than some threshold of the order of M, the concentrations of some chemical species n_i go to 0 at some time instance. Then the number of reactive chemicals or of the catalysts often goes to 0, for all reaction paths. Then, the catalytic reactions

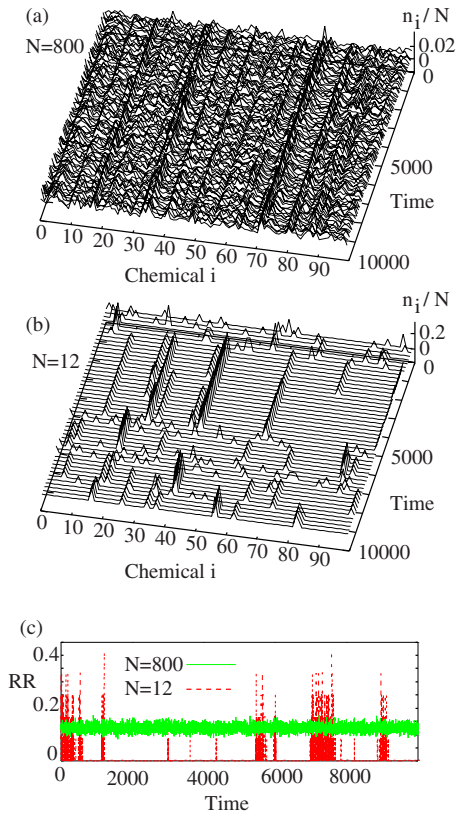

FIG. 2. (Color online) Examples of temporal evolutions of n_i for a given reaction network for the case $M=100$ and $K=12$ with (a) $N=800$ and (b) $N=12$. (c) Temporal evolutions of RR for $N=800$ [(green) solid curve] and $N=12$ [(red) dashed curve]. The network is chosen randomly, but the behavior here is typical, and observed over most networks generated randomly.

of the system freeze, while the system can escape from such freezing state as a result of noncatalytic changes (flow of molecules). Thus, RR changes intermittently with time.

Next, we focus on typical statistical aspects of the system by changing N. Long time average of the distributions of the chemical concentrations $\langle n_i/N\rangle$ for a typical reaction network with $M=100$ and $K=12$ is plotted in Fig. 3(a) (for large N, $N=800$) and Fig. 3(b) (for a small N, $N=12$). As seen in

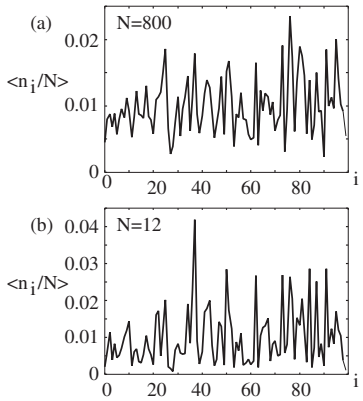

FIG. 3. (a) and (b) $\langle n_i/N\rangle$ of the same system as shown in Fig. 2 with (a) $N=800$ and (b) $N=12$.

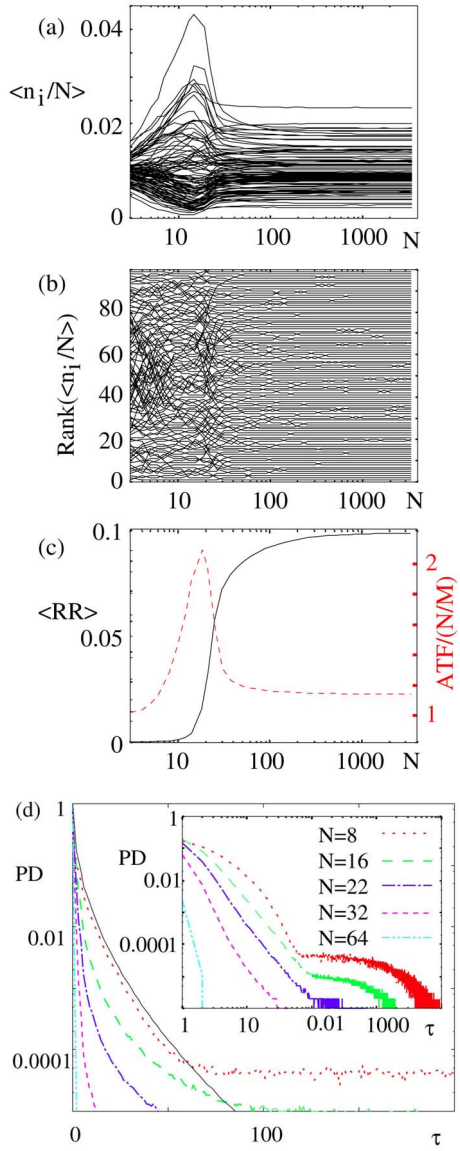

FIG. 4. (Color online) (a), (b), (c) N dependency of (a) $\langle n_i/N\rangle$, (b) the rank of each chemical concentration, and (c) $\langle$RR$\rangle$ (solid curve) and ATF/(N/M) [(red) dashed curve] of the same system as shown in Fig. 3. (d) Probability distribution of residence time τ at a freezing state for the same system with $N=8$, 16, 22, 32, and 64. Semilog plot and the log-log plot (inset). (Black solid curve $e^{-1.25\tau^{-0.5}}$ for reference.)

these figures, the profiles of the average distribution are quite different between the two. In Figs. 4(a) and 4(b), we show $\langle n_i/N\rangle$ and the rank of abundances of each chemical concentration, which is labeled in the order of magnitude of $\langle n_i/N\rangle$. These are plotted as a function of N for a given reaction network, where each successive curve indicates the change in $\langle n_i/N\rangle$ and the rank of each chemical concentration.

The results in Figs. 4(a) and 4(b) suggest the existence of a critical value of N, denoted by N_c. For N smaller than N_c, the chemical abundances of each species or their rank changes sensitively with N. The variance of $\langle n_i/N\rangle$ over time takes a maximum at some N slightly smaller than this critical value N_c. On the other hand, for N larger than N_c, $\langle n_i/N\rangle$ are

almost constant except for the small fluctuations, and indeed the profile of $\langle n_i/N\rangle$ for such larger N agrees with that obtained by the rate equation (1), i.e., the system is well described by the continuum limit $N\to\infty$.

Now, we focus on the transition of reaction dynamics at N_c. For N larger than N_c, the temporal evolution of the distribution of n_i is almost stationary except for small fluctuations as in Fig. 2(a). On the other hand, for $N<N_c$, there appears intermittent switching between different distributions of n_i as shown in Fig. 2(b). In this case, the total reaction ratio is much smaller and the temporal fluctuation of each chemical concentration is much larger than the case with $N>N_c$. We have computed N dependence of the average reaction ratio $\langle \mathrm{RR}\rangle$ and the average temporal fluctuation (ATF) of all chemical concentrations. Here, $\langle \mathrm{RR}\rangle$ is defined as the long time average of RR, and ATF is defined as the long time average of $\frac{1}{N}\Sigma_i(n_i-\langle n_i\rangle)^2$.

Figure 4(c) shows $\langle \mathrm{RR}\rangle$ and ATF/(N/M), plotted as a function of N for the same reaction network. In this figure, $\langle \mathrm{RR}\rangle$ starts to decrease drastically with the decrease in N, at the above-mentioned critical value. This figure also shows that ATF is proportional to N for $N>N_c$, while ATF/(N/M) increases sharply with the decrease in N for $N<N_c$. This increase in the fluctuation is consistent with the fact that the switching behavior becomes dominant for $N<N_c$.

To study statistics of temporal switching, we computed residence time distribution at each freezing state. In Fig. 4(d), we have plotted the probability distribution of time interval τ during which RR remains at 0, for a given network with $N=8$, 16, 22, 32, and 64. For small N ($N=8,16$), the distribution has two regions; faster decay at small τ, which is still slower than the exponential, and much slower decay for large τ with a tail much slower than the exponential but faster than power law. The long-time tail part in the distribution is consistent with the existence of quasistable states and intermittent switching over the states. The decay slower than exponential suggests some positive feedback process to enhance a residence at such state once reached.

On the other hand, for large N, the distribution decays rather fast with τ, and for $N>64$, the probability for residence at $\tau>0$ vanishes. When N is close to the value that gives the peak of ATF ($N=16,22,32$), there is only the first part in the distribution, indicating the absence of long-term residence at a quasistable state. Still, the distribution seems to follow a power law with an exponent larger than 2, and the exponent seems to approach 2 at the transition point. Appearance of the long-term part in the freezing time distribution for $N<N_c$ and the power-law distribution at $N\sim N_c$ is reminiscent of statistical behaviors in thermodynamic phase transitions, even though the number of molecules is quite small here.

As shown in Fig. 2 and Fig. 4(d), switching over several states with different effective network occurs for small N, as will be also discussed in the next section. As N is decreased further below N_c, the reaction occurs rarely, and thus the frequency of such switching decreases, while for large N, the dynamics exhibit only small fluctuations around a stationary state. Thus, the fluctuation is expected to have a peak around $N=N_c$ where the switching occurs most frequently.

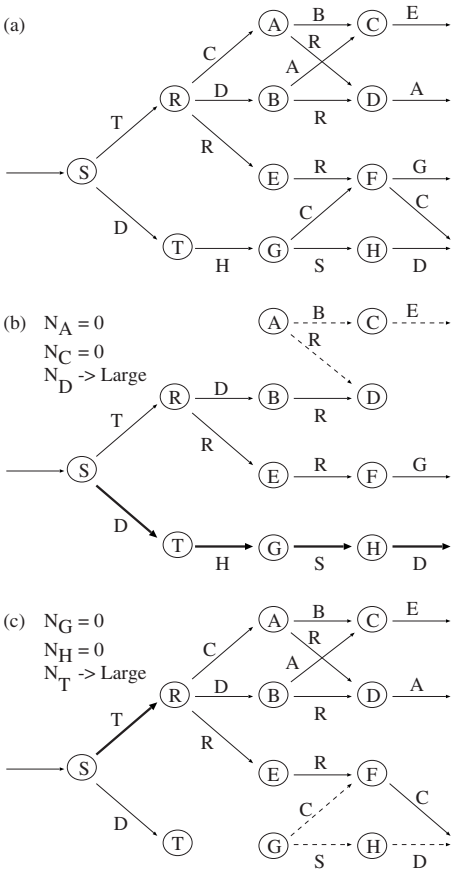

FIG. 5. Simple example of catalytic reaction network (a), and effective reaction network consisting only of nonvanishing chemicals for the state I (b) and state II (c) described in the text. Thick and dashed arrows indicate the paths with a high reaction rate and those from the extinct chemical species at the moment, respectively.

IV. EFFECTS OF MOLECULAR DEFICIENCY IN A SMALL REACTION NETWORK

The behavior observed in the preceding section is rather common over a variety of catalytic reaction networks. The dynamics and the time-averaged distributions of n_i/N for a case with $N\ll N_c$ differ distinctly from those with $N\to\infty$, because of the discreteness in the number of molecules. Here, we discuss the mechanism of this discreteness-induced transition, by taking a simple example of the catalytic reaction network with a small number of chemical species. This example system is a little specific but can illustrate the changes in the steady distribution and the effective network structure consisting only of nonvanishing chemical components (see [20] for a discreteness-induced switching over states in an autocatalytic network).

We consider a network of catalytic reactions displayed in Fig. 5(a). Here, we assume that $n_S>0$ always holds. By straightforward calculation, the rate equation for the chemical concentrations has a unique fixed-point attractor, which satisfies the relations, $2\langle n_A\rangle=2\langle n_B\rangle=\langle n_C\rangle=\langle n_D\rangle=2\langle n_E\rangle=2\langle n_R\rangle$.

On the other hand, for small N, some of n_i often happens to be 0. In such cases, the above relationship on the fixed

concentrations no longer holds, where the distribution of the chemical concentrations changes temporally among some characteristic distributions with different relations among $\langle n_A\rangle$, $\langle n_B\rangle$, $\langle n_C\rangle$, $\langle n_D\rangle$, $\langle n_E\rangle$, and $\langle n_R\rangle$.

(I) State with $n_A=0$ and $n_C=0$: When n_A happens to be 0, n_C also goes to 0, if the decrease in n_C by the reaction $C+E\rightarrow$ progresses before the reaction $R+C\rightarrow A+C$ takes place. This state is also reached when n_C happens to be 0 and if n_A goes to 0 by the reaction $A+R\rightarrow D+R$ or by the noncatalytic process. Once both n_A and n_C vanish, this state with extinction of both chemical species is preserved over a long time, because neither A nor B is synthesized by catalytic reactions, and only slow noncatalytic changes can produce such chemicals.

At this state, none of the reactions catalyzed by A or C take place. Then, as long as $n_i>0$ for $i\neq A$, C, the effective structure of the reaction network is reduced to that shown in Fig. 5(b). Only molecules within this subnetwork exist. [In Fig. 5(b), the arrows indicating the reactions catalyzed by A or C are removed.] In this case, n_D increases, because the reaction to decrease n_D catalyzed by A does not take place. Accordingly, the reaction $S+D\rightarrow T+D$ takes place frequently so that the reaction through the series $S\rightarrow T\rightarrow G\rightarrow H\rightarrow$ progresses with a high rate.

(II) The state with $n_G=0$ and $n_H=0$: When n_G happens to be 0, n_H also goes to 0, if n_H decreases by the reaction $H+D\rightarrow$. It also appears when n_H happens to be 0 and n_G decreases to 0 by the reaction $G+C\rightarrow F+C$. Once both n_G and n_H vanish, this state is preserved over a long time.

Here, when $n_i>0$ for $i\neq G$, H, the effective structure of the reaction network is given in Fig. 5(c). Similarly with the case I, chemicals are localized within this subnetwork. In this effective network the reaction progresses through the series $S\rightarrow R\rightarrow A\rightarrow$, $S\rightarrow R\rightarrow B\rightarrow$, and $S\rightarrow R\rightarrow E\rightarrow$ with a high rate.

(III) For $i\neq A$, C, G, and H, n_i is soon recovered even if it happens to be 0. For example, even if n_B happens to be 0, as long as n_D does not reach 0, n_B is soon recovered by the reaction $R+D\rightarrow B+D$. Other chemical species also behave in a similar manner. Then, disconnection of the reaction paths does not occur.

Each of these three states has a long lifetime when the number of molecules N is much smaller than the number of the chemical species. Stochastic switching over such states is commonly observed for a reaction network system with small N, as given in Fig. 2(b). Due to these switchings, the temporal fluctuation of each chemical concentration is enhanced, as given in Fig. 4(c). Thus, the behavior for small N is distinct from that obtained in the case with $N\rightarrow\infty$.

Here the relations between $\langle n_A\rangle$, $\langle n_B\rangle$, $\langle n_C\rangle$ and $\langle n_D\rangle$ differ distinctly from that in the continuum limit. For example, $\langle n_A\rangle<\langle n_B\rangle$ and $\langle n_C\rangle<\langle n_D\rangle$ are obtained here. This deviation from the continuum limit is understood easily by considering the number distribution at the states I and II.

In general, we expect that situations similar to this simple example should appear in some part of the reaction networks for a system with a large number of the chemical species, as discussed in the preceding section. This leads to the transition at $N<N_c$, with drastic difference in the number distribution from the continuum limit, as given in Figs. 3(a), 3(b), and 4(a).

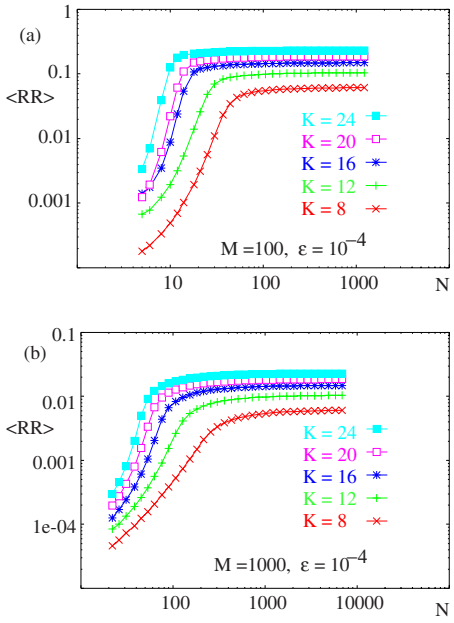

FIG. 6. (Color online) Typical examples of $\langle RR\rangle$ plotted as a function of N for several K and (a) $M=100$ with $\epsilon=10^{-4}$ and (b) $M=1000$ with $\epsilon=10^{-4}$.

V. CRITICAL VALUE OF MOLECULAR NUMBER

In Sec. III, we suggested the existence of the critical total number of molecules N_c, at which the behaviors of random catalytic networks change drastically. For $N>N_c$, the behavior is well represented by continuum description, while for $N<N_c$, deficiency in some molecule species suppresses the ongoing reaction. In this section, we study dependence of this critical number N_c on K and M quantitatively, by computing the reaction rate RR.

Figure 6 shows examples of dependence of $\langle RR\rangle$ on N for several values of K, $K=8$, 12, 16, 20, and 24, and M, (a) $M=100$ with $\epsilon=10^{-4}$, (b) $M=1000$ with $\epsilon=10^{-4}$. As N is decreased, there is a drastic drop in $\langle RR\rangle$ at some value of N. When N is sufficiently larger than this value, $\langle RR\rangle$ is almost constant, approaching a value at the continuum limit $\sim O(\langle RR\rangle_{N\rightarrow\infty})$ where chemical concentrations are almost stationary except for small fluctuations. On the other hand, for N smaller than this critical value, the chemical concentrations exhibit intermittent switching among several states.

Now, we consider $\langle RR\rangle$ for a specific case with $N\rightarrow\infty$; for all chemical species, the number of the reaction path from other chemical species and those to other chemical species are given a unique value K. In such cases, the distribution of the chemical concentrations goes to uniform. In each time step, each molecule collides one molecule on average, and the probability that the molecule catalyzes the reaction from the collided molecule is K/M. Then, $\langle RR\rangle$ is given by K/M.

If the fluctuation of the number of the reaction paths for each chemical specie increases, the reaction from the chemi-

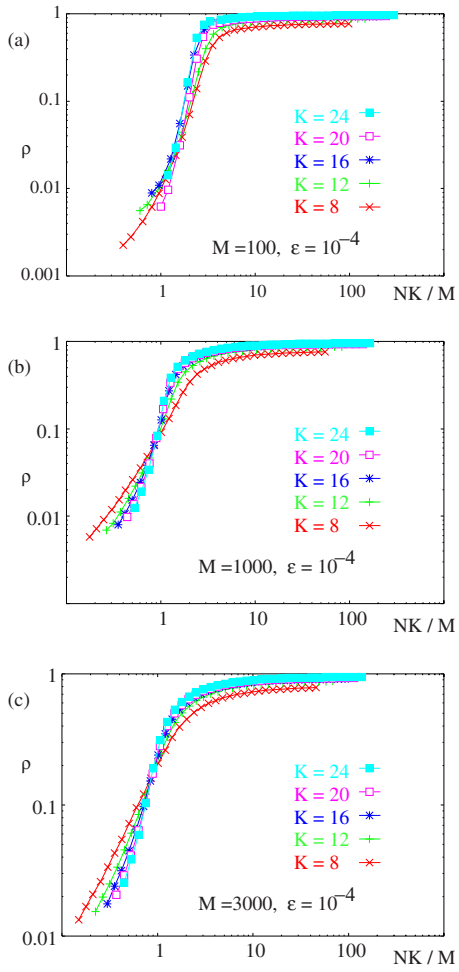

FIG. 7. (Color online) Scaled reaction rate ρ as a function of NK/M for several values of K and (a) $M=100$, (b) $M=1000$, and (c) $M=3000$ with $\epsilon=10^{-4}$.

cal species which have small number of reaction paths limit the reaction rate. Then, $\langle \mathrm{RR} \rangle$ is smaller than K/M in general.

Now, to study dependence of $\langle \mathrm{RR} \rangle$ on K, M, and N, we introduce the following scaling functions; $\rho=\langle \mathrm{RR} \rangle / \left(\frac{K}{M}\right)$ as a normalized reaction rate and NK/M. Note that N/M is nothing but the average molecular number of each chemical, which gives the average probability that each reaction path is catalyzed. Thus, NK/M gives the average number of the effective reaction paths in the network. Based on these considerations, we plot this normalized reaction rate as a function of NK/M, to see N,K,M dependence.

Figure 7 shows ρ as a function of NK/M for several values of K, $K=8$, 12, 16, 20, and 24, and M, (a) $M=100$, (b) $M=1000$, and (c) $M=3000$ with $\epsilon=10^{-4}$. As K is increased, this scaled function approaches a form independent of K. Here we note that there is a specific value of $NK/M=\kappa_c$ at which all the curves of ρ for different values of K crosses. Below this value κ_c, the normalized reaction rate decreases with the increase in K, suggesting that the deficiency in molecule number per reaction path further suppresses the ongoing reaction. On the other hand, beyond κ_c, the normalized reaction rate slightly decreases with the decrease in K, due to

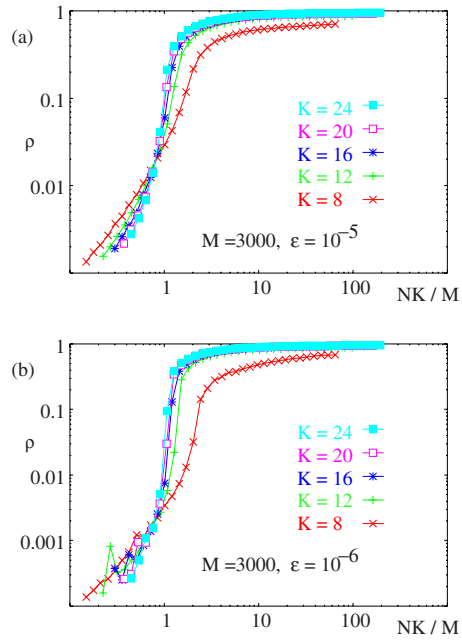

FIG. 8. (Color online) Scaled reaction rate ρ as a function of NK/M for several values of K with (a) $M=3000$ and $\epsilon=10^{-5}$ and (b) $M=3000$ and $\epsilon=10^{-6}$.

the increase in the reaction path number fluctuation per path. As the reaction is suppressed due to deficiency in molecule number for $NK/M<\kappa_c$, this value of κ_c gives a criterion for the discreteness-induced transition.

Dependence of the reaction rate on ϵ is shown in Fig. 8. Here, the value of κ_c seems to be independent of M and ϵ for larger M ($M=1000$, $M=3000$ or larger M) and smaller ϵ (as is also compared with that in Fig. 7), where $\kappa_c \sim 0.8$ holds. On the other hand, the value of ρ at $NK/M=\kappa_c$ decreases as $\epsilon \to 0$, as shown in Fig. 7(c) and Fig. 8. Then, for $NK/M<\kappa_c$, the reaction rate ρ approaches 0, while ρ at $NK/M>\kappa_c$ is almost unchanged. In other words, as ϵ goes to zero, the normalized reaction rate seems to approach a step function with 0 for $NK/M<\kappa_c$. This means that the catalytic reactions often freeze. Some reaction paths are terminated frequently if $NK/M<\kappa_c$, and only noncatalytic changes give dominant contributions to the reaction dynamics. On the other hand, for $NK/M>\kappa_c$, all chemicals can react along the connected paths in the catalytic reaction network for most of time, so that the behavior at the continuum limit is valid, i.e., $\langle \mathrm{RR} \rangle \sim O(\langle \mathrm{RR} \rangle^K_{N\to\infty})$. To sum up the value κ_c gives a criterion for the discreteness-induced transition, i.e., $N_c \sim \kappa_c \times M/K$ for large M.

VI. SUMMARY AND DISCUSSIONS

In this paper, we have reported a discreteness-induced transition (DIT) in catalytic reaction networks with random connections. When the total number of the molecules is smaller than a critical value, transition to a dynamical state is observed with a distinct behavior from that expected in the continuum limit, i.e., the molecular number $\to\infty$. The behavior is characterized by switching over quasistationary states

where some reaction paths are terminated effectively due to deficiency in molecule numbers. Each quasistationary state is characterized by a smaller set of effective reaction networks.

The critical molecule number for this transition is shown to be proportional to the number of chemical species M divided by the average number of reaction path per species K, with a proportion coefficient, estimated to be $\kappa_c \sim 0.8$ in a limit with large M. Whether the number of molecules is large enough to be approximated by the continuous rate equation or not is thus determined by $N \gtrsim 0.8M/K$. The transition is well characterized by a unique scaling function, for the variable $NK/M\kappa_c$. Even though the DIT itself may be expected, the existence of such universal scaling relationship, as well as the enhancement of fluctuation of reaction rate and the power-law distribution of freezing time, is discovery here. Even though these behaviors on scaling, fluctuation, and time distributions are rather common in phase transitions, they generally appear in a system with a large number of elements (ideally in the thermodynamic limit). In the DIT we studied here, the number of molecules is typically small, and indeed as the transition occurs the number is decreased. Hence, the appearance of behaviors similar to thermodynamic phase transition is not trivial at all.

So far we have not succeeded in estimating this value of κ_c analytically. It could possibly be related with the percolation threshold of a random network, although the relationship is not so straightforward. The percolation transition point k_c in general random networks is known to increase logarithmically with the increase in the number of nodes of the network [21] while κ_c decreases to converge to a constant value, with the increase in the number of nodes (chemical species). In fact, the disconnection of a reaction path here is not structural, but dynamical, as a result of the temporal process leading to the extinction of some molecules. How long this extinction is preserved is a result of dynamics, which involves the nonlinear (and sometimes positive-feedback) process. Extinction of some molecules species at one time influences all paths related with the species that vanish. These distinguish the DIT from standard percolation. Thus, the relation between k_c and κ_c is still unclear, and analytic estimate of κ_c is still an open question.

It is noted that the random network does not give a good approximation of the real biological network. However, the results obtained in such simplest reaction network should give a base to characterize the behaviors in several types of networks. The present study gives a starting point for the statistical physics of several catalytic reaction networks.

On the other hand, even by random catalytic reaction networks, some universal features such as Zipf's law in the gene expressions and log-normal distributions of the fluctuations of chemical concentration in cells are reproduced [18,19]. We may expect that our results will provide some insight to biological phenomena.

In the presented model, below the critical number of molecules (or beyond the critical number of molecule species), there appears intermittent transitions over several states, which leads to the change in the structure of the effective reaction network. Such dynamics may give a hint to uncover possible mechanisms of switching behavior in the signaling pathways [22].

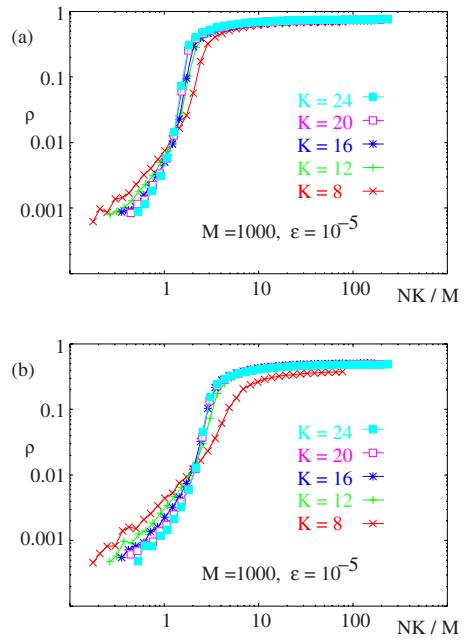

FIG. 9. (Color online) Scaled reaction rate ρ as a function of NK/M for several values of K for reaction networks with the power-law distribution $P(k)=k^{-\beta}$ for outgoing path connectivity k (i.e., the so-called scale-free network), with $M=1000$ and $\epsilon=10^{-5}$. The exponent β is (a) 3 and (b) 2.33.

Also, dominantly acting paths in the metabolic reaction network of E. coli change in accordance with the concentration of the nutrient, as observed by the flux analysis [23]. In the nutrient poor environment, some chemical species may be deficient in a cell. The DIT studied here may be relevant to such switch in the effective network.

Recently, large phenotype fluctuations in isogenetic cells are reported in several organisms [19,24–26]. In such cells, abundances of some molecule species are not so large (10–100 molecules) while there exist more than 1000 chemical species [27]. The intermittent switching induced by molecular deficiency may underlie such large fluctuations.

To apply the DIT to biological problems, the use of a preset random network may not be appropriate, as biological networks are quite heterogeneous with regards to connection degrees and reaction coefficients. Last, we briefly discuss dependences of the transition on the network topology or a connecting distribution. We have confirmed that the value of κ_c as well as the peak (or dip) in $\langle n_i/N \rangle$ and ATF are almost unchanged, even if the reaction coefficients are distributed uniformly between 0 and 1, or take two distinct values, say 0.1 and 0.9 randomly. The results are not changed either, even if there are some chemical species that catalyze many reaction paths and those catalyzing only a few paths.

However, the value of κ_c can be shifted if the autocatalytic productions are dominant. If the reaction to a chemical species is catalyzed by itself, its concentration can increase rapidly, which may decrease the number of the species at the upstream in the reaction towards zero. The probability that some molecule species become extinct is increased, as has been recently reported for a simple reaction network of a few species [8,9].

Moreover, κ_c depends strongly on the topology of the network of the reaction paths. Here, as examples, we studied the reaction dynamics for the network with a scale-free network [28–30], in which the outdegree in the network follows a power-law distribution, i.e., the probability of having k outgoing paths from each molecule species follows $P(k) \sim k^{-\beta}$. Figure 9 shows the $\rho - NK/M$ relations for such reaction network with exponent β=(a) 3 and (b) 2.33 (M =1000, K=8, 12, 16, 20, and 24). Again, we have found a scaling relationship of reaction rate, while the threshold value κ_c characterizing the DIT depends on the connectivity distribution. As the exponent β is decreased toward 2, κ_c increases as shown in Fig. 9. This means that the DIT occurs for larger value of N. Indeed, with this power-law distribution in connectivity, variation in the (average) number of each molecule species is increased. In the present case, there is negative correlation between the number and connectivity, so that species with a higher connection is prone to extinction, which stops many reaction paths. This, we expect, is the reason why κ_c is increased in the scale-free network. This increase in κ_c may be relevant to the application of the DIT to cell-biological problems.

Dependence of the DIT on the network topology is an important future issue both for chemical reaction network dynamics in general and also for the understanding of intracellular chemical reactions.

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