Ubiquitous "glassy" relaxation in catalytic reaction networks

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Study of reversible catalytic reaction networks is important not only as an issue for chemical thermodynamics but also for protocells. From extensive numerical simulations and theoretical analysis, slow relaxation dynamics to sustain nonequlibrium states are commonly observed. These dynamics show two types of salient behaviors that are reminiscent of glassy behavior: slow relaxation along with the logarithmic time dependence of the correlation function and the emergence of plateaus in the relaxation-time course. The former behavior is explained by the eigenvalue distribution of a Jacobian matrix around the equilibrium state that depends on the distribution of kinetic coefficients of reactions. The latter behavior is associated with kinetic constraints rather than metastable states and is due to the absence of catalysts for chemicals in excess and the negative correlation between two chemical species. Examples are given and generality is discussed with relevance to bottleneck-type dynamics in biochemical reactions as well.

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I. INTRODUCTION

Biological processes are often facilitated by catalytic chemical reactions. Most reactions do not progress within a realistic time scale without catalysts. A large number of such catalytic reactions take place in a cell. Catalysts for such reactions are not supplied externally but are synthesized as a result of reactions therein. In other words, catalysts are formed as by-products of reactions in a cell. Hence, a study of "catalytic reaction networks" is important as the first step to understand intracellular reaction dynamics, in which each catalyst (that is a protein) is a product of some reaction and works as a substrate for some other reaction [1–10].

Chemical reactions in a cell usually take place under nonequilibrium conditions. The importance of nonequilibrium conditions for the sustenance of life has been recognized by the pioneering work of Schrödinger [11]. Further, the formation of dissipative structures in an open system to maintain nonequilibrium conditions has been discussed since decades [12–14]. In a biological system, however, such nonequilibrium conditions are not imposed externally but are self-sustained. Hence, it is important to study how such sustainment is possible in order to determine the origin of life or protocells [15]. In the present paper, we will explore the possibility of the sustainment of a quasistationary state over a long time span without external inflow of chemicals.

Besides the issue of the origin of life or synthesis of protocells, the study of the long residence time for quasistationary states may provide an insight into the present intracellular dynamics. The present living systems usually work under a continuous inflow of chemicals. However, quasistationary states with long residence time if their existence is confirmed in a closed system can sustain when the flow is not too heavy and may also provide a basis for transitory dynamics over quasistationary states commonly observed in the present cell dynamics [16,17]. Furthermore, it is interesting to note that some cells can remain alive without relaxing to thermal equilibrium, even under a condition with almost no energy or chemical inflow, as observed in dormant states in bacteria, yeast, spores, and plant seeds. It goes without saying that, besides possible relevance to biology, slow relaxation to equilibrium in closed systems is an important phenomenon in chemical thermodynamics.

In the present paper, we will study the possibility of suppression of relaxation to thermal equilibrium for a system simply consisting of a set of several reaction processes. We will determine whether there is a general mechanism common to catalytic reaction networks that remain in quasistationary states far from equilibrium for a long time.

Here, as the first step to elucidate characteristic features of catalytic reaction networks, we study the relaxation dynamics in a closed system consisting of a set of several reaction processes. Such catalytic reaction networks have been often investigated for studying the origin of life [1,3,7,8], protocells [4,5,9,10], and reproducing cells [6]. These studies mostly investigated unidirectional reactions, considering that chemical reactions in cells usually take place under nonequilibrium conditions and neglecting backward reactions. In contrast, in this paper, we study "reversible" catalytic reactions with forward and backward reactions with the ratio between the two satisfying the postulated detailed balance in thermodynamics.

In a closed system, thermal equilibrium is ultimately achieve after a certain relaxation time. Relaxation to equilibrium is exponential with the time scale governed by reaction kinetic coefficients if we start from an initial state close to the equilibrium state. This exponential relaxation is independent of the initial condition when the system follows linear reaction kinetics, i.e., reactions without catalysts or catalytic reactions with a fixed concentration of catalysts. In contrast, the reaction kinetics are nonlinear if the concentration of catalysts is variable because the rate of such catalytic reactions is given by the product of the concentrations of substrates and catalysts. We determine the mechanism required to slow down the relaxation to equilibrium in such catalytic reaction networks. The determination of whether such a mechanism exists or not is trivial since catalysts facilitate

both forward and backward reactions equally, and there is no *a priori* reason why catalytic reaction networks may introduce such slow relaxation dynamics with itinerancy over quasistationary states.

The present paper is organized as follows. In Sec. II, we introduce a model of reversible catalytic reaction networks with reaction rates satisfying the detailed balance condition. The rate equations are given by a set of nonlinear differential equations with a unique stable fixed point corresponding to the equilibrium point. The study of the dynamics of relaxation to equilibrium is described in Sec. III. When the temperature is low or the energy variance among chemicals is sufficiently large, two salient features are ubiquitously observed: slow relaxation with dependence and the existence of plateaus in relaxation courses, i.e., quasistationary states. Relaxation is generally suppressed in these quasistationary states. Thus, the two features expected for intracellular reaction dynamics—the suppression of relaxation to equilibrium and the existence of quasi-stationary states—are shown. A study of a variety of randomly selected catalytic reaction networks revealed that these two features are ubiquitous. The origin of the two features are also analyzed. First, by estimating the distribution of the smallest eigenvalue of the Jacobian matrix for relaxation, the $\log(t)$ relaxation is explained. In Sec. IV, the origin of the plateaus in the relaxation time courses is elucidated. At each plateau of the relaxation time courses, local equilibrium within a group of chemicals is achieved; however, it is not possible to achieve equilibration among groups when there is a negative correlation between the abundances of substrates and the amount of catalysts that are responsible for the equilibration between intergroup chemicals. This negative correlation is explained by considering simple networks with few chemicals. Such negative correlation is generally observed in a network with a large number of chemicals. The dependence of such states on the initial condition observed in the course of relaxation is also explained. Summary and discussion are given in Sec. V, where the possible relationship between the glassy behavior and kinetic constraints as well as the relevance to intracellular dynamics is discussed.

II. MODEL OF REVERSIBLE CATALYTIC REACTION NETWORKS

We consider a network of reactions consisting of M chemical components (X_i, $i=0,\ldots,M-1$), each of which is catalyzed by one of the M components. The transformation between chemicals X_i and X_j is catalyzed by $X_c(i,j)$, i.e.,

$$X_i + X_c \underset{k_{j,i}}{\overset{k_{i,j}}{\rightleftharpoons}} X_j + X_c. \tag{1}$$

The reaction network consists of the above-mentioned reactions, with the total number of reactions $G \geq M$. We assume that all chemical species are connected to each other through these reactions. The system is closed, without the inflow of chemicals or energy from outside. Note that the number of molecules, accordingly $\Sigma_i x_i \equiv S$, is conserved because of the above-mentioned reactions, where x_i is the concentration of each chemical species i.

For relaxation to thermal equilibrium to take place, the ratio of forward reactions to backward reactions is set such that it satisfies the detailed balance condition. Let E_i denote the energy of each molecular species. The balance condition is satisfied by setting the ratio of forward reactions ($k_{i,j}$) to backward reactions ($k_{j,i}$) in Eq. (1) to $k_{i,j}/k_{j,i}=\exp[-\beta(E_j-E_i)]$, where β is the inverse temperature. As a result, the equilibrium concentration x_i^{eq} satisfies $x_i^{eq}=s\exp(-\beta E_i)$, with $s=S[\Sigma_l \exp(-\beta E_l)]^{-1}$.

Here, we consider the continuum description so that the dynamics of concentration changes can be given by the rate equation

$$\dot{x}_i = \sum_{j,c} W(i,j;c) x_c (k_{j,i} x_j - k_{i,j} x_i), \tag{2}$$

with $k_{i,j}=\min\{1,\exp[-\beta(E_j-E_i)]\}$ and $W(i,j;c)=W(j,i;c)=1$ if there is a reaction path, as in Eq. (1), and 0 otherwise. [Note that we can adopt other forms of $k_{i,j}$ satisfying the detailed balance condition, say $k_{i,j}=\exp(-\beta E_j)$. However, the overall qualitative behaviors—the $\log(t)$ relaxation and the existence of plateaus—do not change with this choice.] Note that Eq. (2) has a unique stable fixed point attractor x_i^{eq} without any metastable states. In the following examples, we assume a uniform distribution of energy E_i, given by $\frac{i}{M}\varepsilon$ (ε is a constant). Qualitatively identical behaviors are generally observed when the energy distribution has a finite variance without a long tail, say, a Gaussian distribution with the variance ε^2. (For log-normal or power-law distributions of energy, the relaxation behavior is different.)

To be specific, we generate $W(i,j;c)$ as follows. First, we randomly select G pairs of numbers (chemical species), i and j ($i \neq j$). For each pair of (i,j), we randomly select a number c, a catalyst for i and j, satisfying $c \neq i$ and $c \neq j$, and set $W(i,j;c)=1$ and $W(j,i;c)=1$. Otherwise, we set $W(i,j;c)$ and $W(j,i;c)$ to 0. Finally, we determine if all chemicals are involved in these G reactions. The average number of paths for each chemical is given by $K=2G/M$.

In the following, we set $S=M$. As an example of a typical relaxation course, we set the initial concentration of all chemicals assuming equal distribution, i.e., the high-temperature limit (corresponding to $\beta=0$), and study the evolution for a given β.

III. RESULTS

A. Ubiquitous slow relaxation

Figure 1 shows examples of relaxation time courses for four sets of networks ($M=24$, $S=24$, $K=8$), where the deviation from the equilibrium concentration is given by $C(t)=\{\Sigma_i[x_i(t)-x_i^{eq}][x_i(0)-x_i^{eq}]\}/\{\Sigma_i[x_i(0)-x_i^{eq}]^2\}$. The relaxation time courses exhibit two types of salient behaviors when β is sufficiently larger than $\beta_c \sim 3/\varepsilon$, which is the inverse of the average difference between energy levels. First, there exists overall $\log(t)$ relaxation, in contrast to exponential relaxation for a small β.

Second, there are several plateaus in the relaxation time courses. The logarithmic relaxation is generally observed at a large β, independent of networks or K, when the distribution

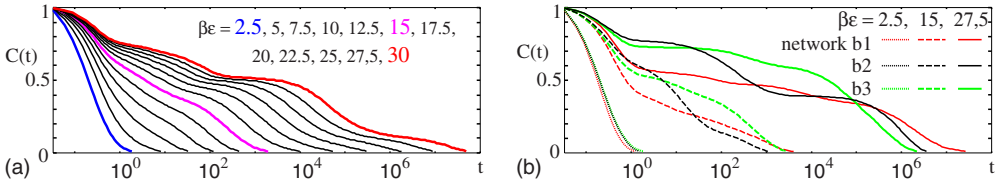

FIG. 1. (Color online) Relaxation time course for four sets of networks ($M=24$, $S=24$, $K=8$) for several β.

of energy E_i is Gaussian or homogeneous within an interval. However, if the rate constant k_i, instead of the energy E_i, follows a Gaussian distribution, the relaxation is considerably faster. The existence of plateaus is generally found to be independent of networks, while the number of plateaus depends on the network [Fig. 1(b)], generally decreasing as K increases.

The integrated relaxation time $\tau=\langle\int_0^\infty|C(t)|dt\rangle$ is plotted as a function of β for several M and K in Fig. 2, where $\langle\cdots\rangle$ indicates the average over networks for a given M and K [18]. For the small β regime in which $C(t)$ decays exponentially, τ follows $\exp(\beta/\beta_c)$. It is the inverse of the average reaction rate to increase the energy that gives the order of the relaxation time. Note that, by linearizing the relaxation dynamics to equilibrium (as discussed later) and by replacing the energy difference between chemicals by the average $\varepsilon/3$, we get $\tau\propto\exp(\beta\varepsilon/3)$ by suitable approximations. For a large β exhibiting $\log(t)$ relaxation, τ follows $\exp(R\beta\varepsilon)$ with R approaching a large constant value with an increase in β. R increases with the an increase (a decrease) in M (K).

The $\log(t)$ relaxation along with plateaus is often observed in glass theory and experiments [23,31]. In the present case, these relaxation characteristics are partially explained by roughly estimating the eigenvalue distribution by linear stability analysis. Let the deviation from the equilibrium concentration be given by $x_i(t)=x_i^{eq}+\delta x_i(t)$, where the equilibrium concentration $x_i^{eq}=s\exp(-\beta E_i)$ is the fixed point solution of Eq. (2). By linearizing Eq. (2) with respect to $\delta x_i(t)$ $(i=1,\ldots,M)$, we get

$$\delta\dot{\mathbf{x}}(\mathbf{t})=\mathbf{J}\delta\mathbf{x}(\mathbf{t}), \tag{3}$$

with the Jacobian matrix $\mathbf{J}$ directly computed. For a large β, $J_{i,j}$ for $i>j$, given by $W(i,j;c')x_{c'}^{eq}e^{-\beta(E_i-E_j)}$, is considerably smaller than that for $i<j$, $W(i,j;c'')x_{c''}^{eq}$. If the former terms are neglected, $\mathbf{J}$ is a triangular matrix such that the eigenvalues λ_i of $\mathbf{J}$ are given by the diagonal elements

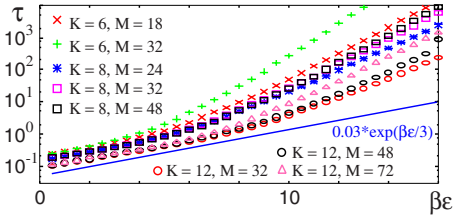

FIG. 2. (Color online) Relaxation time as a function of β for the sample reaction networks shown in Fig. 1.

$$J_{i,i}=-\sum_{i>j}W(i,j;c')x_{c'}^{eq}-\sum_{i<j}W(i,j;c'')x_{c''}^{eq}e^{\beta(E_i-E_j)}. \tag{4}$$

Here, $J_{i,i}$ is found to approach $-\max_j\{W(i,j;c')e^{-\beta E_{c'}}\}$ as $\beta\to\infty$. If K is not considerably larger than M, the maximum value of $W(i,j;c')\exp(-\beta E_{c'})$ for each i is different. Then, the distribution of $J_{i,i}$ for a large β is expected to follow $\exp(-\beta\frac{k}{M}\varepsilon)$ for $k=0,\ldots,M-1$, which the distribution of λ_i for a large β (apart from the null eigenvalue $\lambda_0=0$ corresponding to the equilibrium distribution). In fact, the numerical diagonalization of the Jacobian matrix supports this estimate of the eigenvalue distribution. By using this linear approximation and the correspondence of the eigenvalue with $\exp(-\beta E)$, $C(t)$ is approximated by

$$C(t)\sim\int_0^\varepsilon D(E)a(E)\exp(-e^{-\beta E}t)dE, \tag{5}$$

where the distribution of energy is denoted by $D(E)$, which is roughly homogeneous, and the fractions of the eigenmodes $a(E)$ are considered under the initial condition, which are almost equal. Hence, $D(E)$ and $a(E)$ are roughly constant. [When there is no singular dependence of $D(E)$ and $a(E)$ on E (such as the power-law dependence), the estimate given below is valid.] By setting $u=\exp(-\beta E)t$, the integral is calculated as

$$\begin{aligned}C(t)&\sim\frac{1}{\beta}\int_{te^{-\beta\varepsilon}}^{t}\frac{1}{u}e^{-u}du\\&=\left(\varepsilon-\frac{1}{\beta}\log t\right)e^{-te^{-\beta\varepsilon}}+\frac{e^{-t}}{\beta}g(t)+\frac{e^{-\beta\varepsilon}}{\beta}h(t,\beta).\end{aligned} \tag{6}$$

Here, the divergence of $g(t)$ and $h(t,\beta)$ as $t\to\infty$ and $\beta\varepsilon\to\infty$ is considerably slower than the exponential. By considering a large β such that $e^{-\beta\varepsilon}\to0$,

$$C(t)\sim\varepsilon-\frac{1}{\beta}\log t+\frac{e^{-t}}{\beta}g(t) \tag{7}$$

is obtained, and $\log t$ dependence is obtained asymptotically for a large t.

Although this estimate is originally asymptotic for a large t, here we have used it for the time interval where many eigenvalues contribute to the relaxation time. A linear analysis also explains the existence of plateaus in the relaxation courses. If the ratio of two successive eigenvalues is high, there appears a plateau in the relaxation course. If there is a gap $\Delta\lambda$ between two neighboring eigenvalues, a plateau in the relaxation course is expected in the time interval $\frac{1}{\Delta\lambda}$. For a large β, the gaps between eigenvalues increase such that

the number of plateaus increases to (number of individual eigenvalues−1) as obtained from the linear analysis.

Of course, the linear analysis is not sufficient to understand the complete relaxation process. In fact, simulation results for many sample networks show the following characteristics. (i) The number of plateaus observed during the transient process is considerably smaller than the number of eigenvalues. (ii) The number of plateaus and the corresponding time strongly depend on the reaction network structure even though they have asymptotically identical eigenvalues for $\beta \to \infty$. These network-structure-dependent relaxation characteristics and the number of plateaus are not directly obtained from the linear analysis. Here, we present a heuristic argument for the origin of plateaus.

B. Origin of plateaus: Negative correlation between substrate and its catalyst

To examine the nature of each plateau, we have computed $x_i^{dev}(t)=x_i(t)/x_i^{eq}$ for all chemicals. At each plateau, there are several "cluster(s)" of elements. A cluster here is defined as elements in which $x_i^{dev}(t)$ takes almost the same value without directly depending on their proximity in the network. (Recall that the spatial inhomogeneity of concentrations is not considered in our study, and the cluster here does not include any spatial information.) Within each cluster, chemicals are in local equilibrium through mutual reactions, whereas no equilibrium is achieved among the elements outside the clusters. This suppression of equilibration occurs when the concentrations of catalytic components responsible for reactions for such equilibration are low.

Consider a chemical with x_i^{dev} larger than that in other clusters. If the concentration of the catalyst(s) necessary to equilibrate the abundant chemical i is small, the equilibration process is suppressed. The negative correlation in the abundances between the excess chemical and its catalyst, thus, suppresses relaxation to equilibrium.

We confirm this mechanism by considering a network with few chemicals, as shown in Figs. 3 and 4, in which besides $C(t)$, the time course of $x_i^{dev}(t)=x_i(t)/x_i^{eq}$ is also plotted. In networks I and II, shown in Fig. 3(b), consisting of five chemicals ($S=5$), the component X_0 (with the lowest E) is transformed to all other components. For a large β, because E_0 is minimum, chemicals $i \geq 1$ flow into X_0 under the initial condition with $\beta=0$, having $x_i^{dev}(0)>1$ for $i \geq 1$ for a large β. For both the networks, the asymptotic eigenvalues of $\mathbf{J}$ are $\exp(-\beta E_1)$, $\exp(-\beta E_2)$, $\exp(-\beta E_4)$, and 0 ($E_i=\frac{i}{4}\varepsilon$) as β increases. As shown in Fig. 3(a), however, the number of plateaus appearing in the relaxation courses are different for the two networks.

In network I, the first plateau consists of a local-equilibrium cluster of X_0, X_2, and X_4; X_3 joins the cluster at the second plateau, as shown in Fig. 3(c). The suppression of the equilibration of X_1 is explained as follows. The relaxation (i.e., decrease) of X_1 (X_4) is catalyzed by X_4 (X_1). If the amount of one of the species X_1 or X_4 decreases rapidly, the relaxation of the other is suppressed. Because x_1^{eq} is greater than x_4^{eq}, X_4 relaxes rapidly such that the relaxation of X_1 is suppressed. The negative correlation between the abundances of X_1 and its catalyst X_4 hinders the relaxation of X_1. Since the relaxation of X_2 and X_4 is catalyzed by X_1, they equilibrate with X_0. Thus, a local-equilibrium cluster consisting of X_0, X_2, and X_4 is formed, as shown by the agreement between x_i^{dev} for $i=0,2,4$ at $t \sim 10^2$ in Fig. 3(c). Later, at $t \sim 10^4$, X_3, which is catalyzed by X_2, joins the cluster and is more abundant than X_4, the catalyst of X_1.

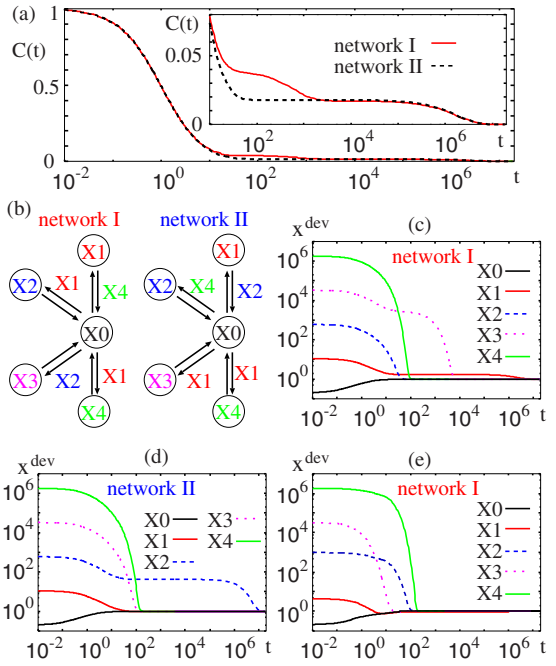

FIG. 3. (Color online) (a) Time course of $C(t)$ for two sample networks, I and II, given in (b), with $S=5$ and $\beta=16/\varepsilon$. In (b), the chemicals attached to the arrows showing reactions indicate the catalysts. Time courses of $x_i^{dev}(t)$ of (c) network I and (d) network II corresponding to (a). In (a), (c), and (d), all chemicals have equal number initially (i.e., $\beta=0$). (e) Time courses of $x_i^{dev}(t)$ of network I from the initial condition $x_i=1$ for $i=0,2,3$, $x_1=0.4$, and $x_4=1.6$.

In network II, on the other hand, the relaxation of X_1 is not suppressed since its catalyst X_2 relaxes slowly because its catalyst X_4 relaxes faster as it is catalyzed by a large amount oft X_1. A negative correlation does not exist between X_1 and its catalyst but exists between X_2 and its catalyst X_4. Thus, the local equilibrium among X_0, X_1, X_3, and X_4 is realized to produce only one plateau at $t \sim 10^2$. The negative correlation between X_2 and X_4 suppresses the relaxation of X_2 since X_4 is less abundant than X_2. Recall that the eigenvalues of the Jacobian matrix are asymptotically identical for networks I and II. Hence, the existence of plateaus depends on the detailed network structure besides the eigenvalues.

As expected from the above-mentioned argument, the types of plateaus that appear in the relaxation courses may also depend on the initial condition because the reactions that are suppressed depend on the catalysts that are used up first. Figure 3(e) shows the relaxation process of network I from the initial condition with $x_4=4x_1$. In this case, due to the abundance of X_4, the relaxation of X_1 is no longer suppressed, in contrast to the case of Fig. 3(c). Instead, the negative correlation between X_4 and X_1 leads to the suppression of the relaxation of X_4, which, however, is not so significant

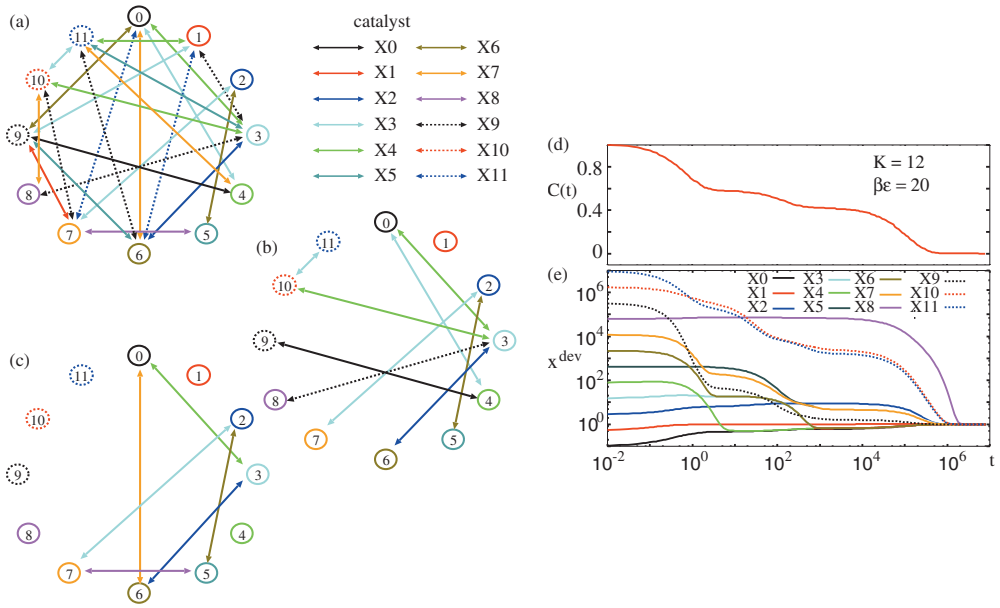

FIG. 4. (Color) (a) Reaction network with $M=12$ and $K=4$ ($S=12$), where the color of each arrow indicates the catalyst for the reaction, (b) "major relaxation" for each chemical (see text), (c) "major relaxation" path for $\{X_3,X_6\}$ and $\{X_5,X_7\}$ clusters (see text), (d) time course of $C(t)$ for network, and (e) time courses of $x_i^{dev}(t)$ for $\beta=20/\varepsilon$.

since the equilibrium concentration of X_1 is considerably larger than that of X_4. Hence, the relaxation time of X_4 is the longest among the chemicals, but it is considerably shorter than the equilibration time shown in Fig. 3(c).

In general, the number of plateaus and components of each cluster depend not only on the network structure but also on the initial condition. From the abovementioned argument, we can predict the formation of a cluster with local equilibrium by detecting a negative correlation between substrates and catalysts on the basis of the network structure and the initial abundance of each chemical.

For complex catalytic reaction networks, the argument is not so simple, but the existence of local equilibrium and the suppression of relaxation by the negative correlation mechanism generally underlie the formation of plateaus. Figure 4(a) shows a catalytic reaction network with $M=12$ and $K=4$ ($S=12$), Figs. 4(b) and 4(c) show "major" relaxation processes, mentioned below, and Figs. 4(d) and 4(e) show the time courses of $C(t)$ and $x_i^{dev}(t)$ for $\beta=20/\varepsilon$. As shown in Fig. 4(d), this network exhibits three plateaus in the relaxation process. At each plateau, chemicals $i=1,\ldots,M$ are clustered into few groups within which x_i^{dev} is almost constant [Fig. 4(e)]. The clusters $\{X_0,X_4\}$, $\{X_3,X_6\}$, and $\{X_{10},X_{11}\}$ are formed successively at the first plateau; $\{X_0,X_3,X_4,X_6\}$, $\{X_5,X_7\}$, and $\{X_{10},X_{11}\}$, at the second plateau; and $\{X_0,X_1,\ldots,X_7,X_9\}$ and $\{X_{10},X_{11}\}$ at the third plateau.

Each of these plateaus can be explained by determining if the catalyst for the major relaxation process for each X_i is dominant or not. This major reaction for each i is that catalyzed by X_k with the smallest k among the reactions $X_i+X_k \leftrightarrow X_j+X_k$ with $j<i$ (recall that the smaller the index, the smaller is the energy). At the first plateau, X_3 and X_4 have a negative correlation since the major relaxation of X_3 is the reaction catalyzed by X_4 and the reaction of X_4 catalyzed by X_3 [Fig. 4(b)], such that the formation of the cluster $\{X_0,X_4\}$ suppresses the equilibration between X_0 and X_3.

At the second plateau, the $\{X_3,X_6\}$ and $\{X_5,X_7\}$ clusters have a negative correlation. For the $\{X_5,X_7\}$ clusters, the reactions $X_5+X_6 \rightarrow X_2+X_6$ and $X_7+X_3 \rightarrow X_2+X_3$ give the major relaxations [see in Fig. 4(c)]. On the other hand, the reactions $X_6+X_7 \rightarrow X_0+X_7$ and $X_3+X_4 \rightarrow X_0+X_4$ cause the major relaxation processes for the $\{X_3,X_6\}$ cluster [Fig. 4(c)], but the reaction $X_3+X_4 \rightarrow X_0+X_4$ is suppressed since the amount of its catalyst X_4 has already decreased. In this case, the $\{X_5,X_7\}$ cluster does not join X_2, but the $\{X_3,X_6\}$ and $\{X_0,X_4\}$ clusters aggregate.

In general, among a variety of chemical components, there exists a negative correlation between the chemicals in excess and the catalysts such that it leads them to equilibrium. Then, the equilibration of chemicals is suppressed, leading to the formation of plateaus in the relaxation course. Then, the entire relaxation process can be described as the successive aggregation of clusters to achieve equilibrium.

IV. SUMMARY AND DISCUSSION

In the present paper, we have provided an explanation for slow relaxation to equilibrium that is generally observed in catalytic reaction networks and determined the relaxation mechanism. When the temperature of a system is sufficiently lower than $\varepsilon/3$, the average difference between energy levels, overall $\log(t)$ relaxation is observed. Several plateaus appear successively through the relaxation course. We have studied a large number of reaction networks and confirmed that these two characteristics are ubiquitously observed when the number of species is not too small. The number and type of plateaus depend on the network and initial condition; generally, several plateaus are observed. These characteristics are ubiquitously observed when the temperature is low or the

energy variance among chemicals is sufficiently large.

We have found a general mechanism for the emergence of plateaus. The plateaus are not metastable states. Rather, they are the result of kinetic constraints and the reaction bottleneck, originating from the formation of local-equilibrium clusters and the suppression of equilibration because of the negative correlation between an excess chemical and its catalyst. The presence of such negative correlation between components depends both on the initial concentration of chemicals and the network structure. Even in randomly selected networks, several sets of chemicals have been found to show a negative correlation when the number of species is not small (say larger than 5). Plateaus can be predicted by detecting such negative correlation. However, a systematic procedure has to be developed in future to predict plateaus.

Possible configurations for local-equilibrium clusters are limited, and thus, the number and ordering of plateaus are restricted. Still, in general, there can be redundancy in such number and ordering, depending on the initial condition, because they are influenced by the catalysts that are used up first. Further, the relaxation is often nonmonotonic; the deviation from equilibrium may increase during the relaxation course. Similar relaxation has also been observed in a Hamiltonian system [19].

In the case of biological catalytic reactions, the number of molecules is sometimes not so large and the number of fluctuations has to be considered. We have confirmed the existence of long-term relaxation along with plateaus by carrying out stochastic reaction simulations. In addition, we have also found that the discreteness in the molecule number results in anomalous reaction dynamics with long-time correlations [9,10] and further suppresses the relaxation in catalytic reaction networks [20].

Glass is well known to show resistance to relaxation to equilibrium. In fact, the behaviors reported here are reminiscent of the relaxation in glass. In a class of glass studies, a certain complex free energy landscape structure has been elucidated [21–24]. However, such a landscape is not expected in this case, since the catalysts just facilitate reactions, and frustration due to positive and negative interactions as in spin glass [25] does not exist. In fact, the dynamics have a unique stable fixed point without any metastable states. However, studies have revealed an alternative to such landscape pictures: kinetic mechanisms to suppress relaxation [26–33]. In the theory of glass, kinetically constrained models have attracted considerable attention [31–33], in which relaxation to equilibrium is slowed down due to a kinetic bottleneck because of the limited spatial configuration of molecules.

Kinetic constraints can be included in our model since the absence of certain catalysts restricts the relaxation process. However, we are not concerned with the spatial inhomogeneity of concentrations, and kinetic constraints depend on the network structure. We have shown that in a system with a catalytic reaction network, kinetic constraints generally exist, which lead to slow relaxation to thermal equilibrium. Extension of theoretical frameworks for different types of glasses is necessary in order to incorporate kinetic constraints that depend on the network structure rather than on the spatial configuration.

Here, because of the difference between real space and networks, the present "glassy" behavior does not necessarily require the limit $M \to \infty$. Even if the number of components M is small, slow relaxation along with plateaus is observed. The number of plateaus increases and $\log(t)$ relaxation becomes clearer as M increases.

Note that the long residence time for quasistationary states, proved here, can be observed even in an open system when the flow of chemicals is not too heavy. Indeed, intracellular reaction dynamics show transitions over several quasistationary states [16]. During a cell cycle, switching can be observed over a few states, separated by "checkpoints" [17,34]. In addition, when cells are exposed to novel conditions, they often remain in their original state before switching to a novel state that is adapted to the novel environment [35]. The ubiquity of long residence time for several quasistationary states may help in understanding intracellular reaction dynamics.

Recall that the variance of reaction rates in biochemical reactions is quite large and often reaches several orders of magnitude [16,36]. Accordingly, even though the temperature is not low, the condition $\varepsilon \gg 1/\beta$ is often satisfied such that slow relaxation with quasistationary states is possible.

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