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Metastable states in a nonlinear stochastic model

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A type of metastable state is found and analyzed for a nonlinear model of self-replicating biomolecules under constraint. This state, described by the deterministic theory as one of the stable steady states, is studied stochastically by using various approximation schemes. The time-dependent behavior is derived so that the lifetime can be estimated numerically. The possible transitions induced by the fluctuation perturbations are also discussed.

I. INTRODUCTION

Many physical, chemical, and biological processes are found to be governed by similar equations which are usually nonlinear and coupled.[1,2] While most of the studies of nonlinear problems are deterministic, stochastic behaviors can be quite different from the deterministic ones.[3–7]

Our nonlinear rate equations can be expressed as[8,9]

$$\frac{dn_k}{dt}=W_k n_k-\sum_j W_j n_j n_k/\Omega,\quad k=1,2,\ldots,N\ . \tag{1}$$

These describe the time evolutions of the molecular numbers for the kth species of biological macromolecules which are self-replicating with the net increasing rate $W_k=A_k-D_k$. A_k and D_k are, respectively, the synthesis and degradation rate constants. The nonlinearity in Eqs. (1) is due to the external constraints imposed on the system consisting of N species of biomolecules to have an ultimate total population Ω. We note that Eqs. (1) resemble the Lotka-Volterra equations for interacting populations[1,3] and the equations for the multimode operation of a laser.[10] The stochastic analysis of our model system will also provide deeper insight into these other nonlinear systems.

In the present studies we assume all possible combinations of the initial molecular numbers $n_k(0)$ but consider only the special case of $W_k=W$ for all k. The deterministic Eqs. (1) predict a steady state (SS) in which all species coexist with their relative populations defined by the initial values. This SS, which will last forever with infinite lifetime, can be achieved immediately from the beginning or in a short time, depending on the initial conditions. This coexisting SS will be shown to be metastable in a stochastic sense that all the average molecular numbers $\bar{n}_k$ achieve their respective SS values, in a more or less deterministic way, while the variances diverge with time. Though the fluctuations are small and increasing very slowly, they will eventually perturb this deterministic-type coexistence and induce a stochastic transition. This metastable state is found to have a lifetime which is much larger than the time needed to develop the SS in $\bar{n}_k$. The metastability is purely stochastic in nature. This distinct state is neither the unstable SS,[7] nor the usual stochastic SS which according to Oppenhiem *et al.* are quasistationary.[12]

In Sec. II, a stochastic model will be formulated. In Sec. III, we present the existence of the metastable state in the framework of the system-size expansion approximation.[5,11] In Sec. IV, this state is studied by using the moment expansion technique[6,7] to reveal its stochastic features in a more precise way. Numerical estimations and discussions are presented in Sec. V.

II. STOCHASTIC DIFFERENTIAL EQUATIONS

A system consisting of N species of bimolecules having populations $\{n\}$ at time t can be described by the probability function $P(\{n\};t)$. By considering the synthesis and degradation processes as the one-step Markovian processes, the master equation associated with the deterministic Eqs. (1) can be expressed as[6]

$$\begin{aligned}\frac{\partial P(\{n\};t)}{\partial t}=\sum_k\{&(n_k-1)A_kP(n_1,\ldots,n_k-1,\ldots,n_N;t)\\&+(n_k+1)[D_k+E(n_1,\ldots,n_k+1,\ldots,n_N)]P(n_1,\ldots,n_k+1,\ldots,n_N;t)\\&-n_k[A_k+D_k+E(\{n\})]P(\{n\};t)\}\ ,\end{aligned}\tag{2}$$

where

$$E(\{n\})=\sum_j W_j n_j/\Omega \ . \tag{3}$$

Due to the inherent nonlinearity of the system, the master equation (2) is practically unsolvable. Approximation schemes must be employed in order to solve for $P(\{n\};t)$. The standard system-size expansion technique[5,11] can be used to obtain the multivariate Gaussian form for $P(\{n\};t)$, which peaks at points where the average populations $\bar{n}_k$ equal the deterministic values. The spread of the Gaussian form depends on the variances of n_k. In fact, the first two moments play the decisive role in the stochastic analysis with any approximation scheme. Within the framework of the system-size expansion approximation, the first moments, i.e., the average populations $\bar{n}_k$, satisfy the deterministic type of equation,

$$\frac{d\bar{n}_k}{dt}=W_k\bar{n}_k-\bar{E}\bar{n}_k \ . \tag{4}$$

The variances can be defined in terms of the first and the second moments ($\langle n_i n_j\rangle$, where we use both $\langle\ \rangle$ and the overbar for the average) as

$$\sigma_{ij}=\langle n_i n_j\rangle-\bar{n}_i\bar{n}_j \ , \tag{5}$$

and are found to satisfy the following,

$$\frac{d\sigma_{ij}}{dt}=(W_i+W_j-2\bar{E})\sigma_{ij}-\sum_k W_k(\bar{n}_i\sigma_{jk}+\bar{n}_j\sigma_{ik})/\Omega \\ +\delta_{ij}(2A_i\bar{n}_i-d\bar{n}_i/dt) \ . \tag{6}$$

A solution of n_k and σ_{ij} completes the stochastic analysis for the system since $P(\{n\};t)$ can then be described by the moments in an approximate way.

III. THE METASTABLE STATE

We define the stochastic SS as the one with time-independent averages and variances. A set of SS exists for the stochastic model of molecular self-replications, and is found to be not necessarily overlapping with the deterministic set.[7] Strictly speaking, there is no real SS in the stochastic sense. The usual stable SS can be reached in a relative short time $O(\Omega^0)$ and are all subjected to the fluctuation catastrophe[8] that the system eventually relaxes into the absorbing state with $\{\bar{n}\}=0$ after a much longer time $O(\Omega^{-1/2}e^{\Omega})$.[12] We present in the following a distinct stochastic state which is neither the unstable SS,[7] nor the quasistationary state described by Oppenheim *et al.*[12]

Consider a special case in which all molecular species have identical rate constants, $W_k=W$. From the general solutions of Eqs. (4),

$$\bar{n}_k(t)=\Omega n_k(0)\exp(W_k t)\left[\Omega-\sum_j n_j(0) \right. \\ \left. +\sum_j n_j(0)\exp(W_j t)\right]^{-1} , \tag{7}$$

we find a deterministic type of coexistence among all species, with their relative populations remaining constant in time. The SS values of the averages $(\bar{n}_k^s)$ and the relative populations (ρ_k^s) are related to the initial values by

$$\rho_k^s=\bar{n}_k^s\Big/\sum_j \bar{n}_j^s=\rho_k(0)=\rho_k(t) \ . \tag{8}$$

The behaviors of constant *relative* populations $\rho_k(t)=\rho_k(0)$ are the distinct characteristics of the degenerate case. In order to avoid confusion in discussing the metastability, it should be emphasized that these behaviors are different from those of constant *total* populations $\sum_k \bar{n}_k=\Omega$ which may happen either at the SS, or at all the time if a special initial condition $\sum_k n_k(0)=\Omega$ is assumed.

We note that this SS in $\bar{n}_k$ is purely deterministic and is thus independent of the development of $\sigma_{ij}(t)$. It can be shown from Eq. (6) that the SS solution for σ_{ij} is not allowed after $\bar{n}_k=\bar{n}_k^s$. A standard though tedious matrix method can be used to solve for σ_{ij} from the $N(N+1)/2$ linearly-coupled differential Eqs. (6). For the case of $N=2$, the leading time-dependences of σ_{ij} are found to be given by

$$|\sigma_{ij}(t)-\sigma_{ij}(t_s)| \\ \approx 2\rho_1(0)\rho_2(0)[\mu_1\rho_1(0)+\mu_2\rho_2(0)]\Omega W(t-t_s) \ , \tag{9}$$

where t_s is the time when $\bar{n}_k$ attain the SS values, and

$$\mu_k=A_k/W \tag{10}$$

is the metabolism factor which is found to be of profound importance in the stochastic properties[6] and the stability analysis[7] of the SS. This conclusion is reliable so far as the approximation scheme remains valid, i.e., the relative fluctuations

$$R_k(t)=[\sigma_{kk}(t)]^{1/2}/\bar{n}_k^s \tag{11}$$

are small over a reasonably long time. We shall elaborate this point in Sec. V.

The metastable state is also characterized by the Gaussian probability function $P(\{n\};t)$ which has its peak fixed at a point while its width is narrow but spreading with time slowly. This state will eventually shift away stochastically as $P(\{n\};t)$ spreads significantly to the absorbing state where $\{\bar{n}\}=0$, or as $\{R\}$ becomes close to the order of unity.

IV. THE MOMENT EXPANSION TREATMENT

The system-size expansion treatment has an inherent disadvantage in describing the stochastic metastable state because the averages $\bar{n}_k$ are solved only from the deterministic type of equations, independent of the variances $\sigma_{ij}(t)$. The stochastic behaviors of a system in which all the stationary $\bar{n}_k$ are coupled to the time-varying $\sigma_{ij}(t)$ can be analyzed by using another approximation scheme.

Directly from the master equation (2), the first moments are found to satisfy the following equations,

$$\frac{d\bar{n}_k}{dt}=W_n\bar{n}_k-\bar{E}\bar{n}_k-\sum_j W_j\sigma_{kj}/\Omega \ , \tag{12}$$

in which the relevant variances are coupled to $\bar{n}_k$ explicitly. Similarly, the second moments are coupled to the third ones by

$$\frac{d\langle n_i n_j\rangle}{dt}=(W_i+W_j)\langle n_i n_j\rangle-2\langle E n_i n_j\rangle+\delta_{ij}\left[2A_i n_i-\frac{d\bar{n}_i}{dt}\right] . \tag{13}$$

The moment expansion treatment[6] can be used to approximate the average of a triplet product by the first two moments. We finally find that all σ_{ij} satisfy exactly the same mathematical form of Eqs. (6) provided that the term involving $d\bar{n}_k/dt$ is now given by the new equation (12).

For the present approximation scheme, just because σ_{ij} are coupled to $\bar{n}_k$, we can combine the two sets of Eqs. (6) and (12) into a simple one,

$$\frac{d}{dt}(\sigma_{ij}-\bar{n}_i\bar{n}_j+\bar{n}_i\delta_{ij})=2W\left[1-\sum_k \bar{n}_k/\Omega\right](\sigma_{ij}-\bar{n}_i\bar{n}_j)+2A_i\bar{n}_i\delta_{ij} . \tag{14}$$

Though this set of equations allows SS solutions for σ_{ij} as well as $\bar{n}_k$, it can be shown that the solutions are unphysical since all $\sigma_{kk}^s<0$. The expected metastability can be solved from Eqs. (6) and (14). We find that after $\bar{n}_k=\bar{n}_k^s$,

$$\sum_j \sigma_{ij}(t)=\bar{n}_i^s\left[\Omega-\sum_j \bar{n}_j^s\right],\quad t\geq t_s \tag{15}$$

and

$$\sigma_{ij}(t)=S_{ij}+[\sigma_{ij}(t_s)-S_{ij}]\times\exp\left[2\left[1-\sum_k \bar{n}_k^s/\Omega\right]W(t-t_s)\right] , \tag{16}$$

where

$$S_{ij}=\bar{n}_i^s\left[\bar{n}_j^s-\delta_{ij}\mu\Omega\Big/\left[\Omega-\sum_k \bar{n}_k^s\right]\right] . \tag{17}$$

It is not easy to visualize the metastability through these equations unless we proceed with the following analysis. We can show that, for $W_k=W$ and $A_k=A$, the two sums

$$\bar{n}=\sum_k \bar{n}_k,\quad \sigma=\sum_i\sum_j \sigma_{ij} \tag{18}$$

satisfy exactly the stochastic equations (6) and (12) for a one-species case. The SS solution for this special case is found to be[6]

$$\bar{n}^s=\Omega[3+(1-8\mu/\Omega)^{1/2}]/4 , \tag{19}$$

and

$$\sigma^s=\bar{n}^s[\bar{n}^s-\mu\Omega/(\Omega-\bar{n}^s)]=\bar{n}^s(\Omega-\bar{n}^s) . \tag{20}$$

With the help of Eq. (19), the two expressions of σ^2 can be shown to be identical.

Within the framework of moment expansion approximation the metastability that $\dot{\bar{n}}_k=0$ even though $\sigma_{ij}(t)$ is varying, can be described in a more precise way through Eqs. (15)–(20). From Eq. (16) if $\mu/\Omega\ll 1$ is assumed (as is always satisfied), we have

$$\sigma_{ij}(t)\approx S_{ij}+[\sigma_{ij}(t_s)-S_{ij}]\exp[2W(t-t_s)\mu/\Omega] . \tag{21}$$

The time-dependence of σ_{ij} is therefore extremely weak and there is practically no difference between this exponential dependence and the linear dependence given by Eq. (9).

While Eqs. (18) are valid all the time, we have the less restricted relationships after $t\geq t_s$,

$$\bar{n}_k^s=\rho_k(0)\bar{n}^s,\quad \sum_j \sigma_{ij}(t)=\rho_i(0)\sigma^s . \tag{22}$$

All these results are supported by numerical results, some of which are discussed in Sec. V.

V. NUMERICAL RESULTS AND DISCUSSIONS

For a system of N species of macromolecules, the complete time-dependences of $\bar{n}_k$ and σ_{ij} can be solved numerically from a set of totally $N(N+3)/2$ differential equations which are nonlinear and coupled. Figure 1 shows the results for a two-species case. Both approximation schemes give almost the same results; the differences are so small that they cannot be demonstrated on the figure. The averages $\bar{n}_k$ and their SS values are essentially deterministic and thus are independent of the metabolism factor μ. However, the relative fluctuations $R_k(t)$ depend sensitively on this stochastically important factor. For $\mu=1$ we have $A=W$ and $D=0$, i.e., the molecules are self-replicating without degradation. For $\mu=10$, we have $D=0.9A$; a process with such a high metabolism rate is

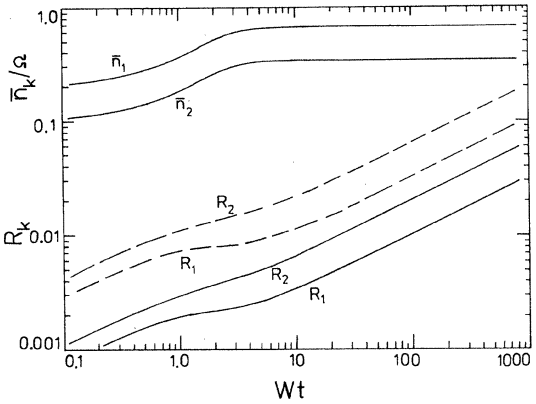

FIG. 1. Two species of macromolecules with identical replication rate constants coexist in a system having carrying capacity $\Omega=10^6$. Starting with initial numbers of molecules $n_1(0)=0.2\Omega$ and $n_2(0)=0.1\Omega$, both the averages $\bar{n}_k$ approach the deterministic type SS values in a short time while the relative fluctuations R_k remain small and increase with time steadily. Two values of the metabolism factor are used: $\mu=1$ (solid curves) and $\mu=10$ (dashed curves).

unlikely. The first set of data ($\mu = 1$) in Fig. 1 is closer to the practical cases in which $\mu \gtrsim 1$. Both sets of results in Fig. 1 show clearly the metastability.

The metastable behavior is purely stochastic in nature. The deterministic theory predicts that all species with identical rate constants will end up in a SS coexistence and that this SS is a stable one. In our stochastic analysis, the SS coexistence is only a metastable one because the fluctuations will eventually destroy it. Care must be taken in interpreting the results since both approximations are valid so far as R_k are small. Our results cannot describe the detail manner of the fluctuation catastrophe; instead, they predict this tendency.

The destination of the metastable state after the stochastic transition is believed to be either the absorbing state with all $\bar{n}_k = 0$, or the one-species SS in which all but one species vanish. The last conjecture is more likely and is well justified since we have shown in Sec. IV that the whole degenerate system behaves like a one-species system. The constrained one-species self-replication is, in fact, equivalent to the familiar process of logistic growth in the population dynamics.[1,3] This one-species surviving SS is both stochastically and deterministically stable.[7]

The stochastic selection process is possible as is evident from Fig. 1 that the species with larger initial population is subjected to smaller relative fluctuations and so will have better chance to survive the fluctuation catastrophe. For the case with all the species having the same rates and the same $n_k(0)$, the selection will probably be carried out by chance only. A special case with $\sum_k n_k(0) = \Omega$ is indeed trivial in the deterministic analysis but not so in the metastable behaviors. The predicted metastability is the same for various combinations of $n_k(0)$. The time t_s needed for the system to attain the SS values of $\bar{n}_k$ depends on the initial conditions. Since t_s itself is small, usually $Wt_s \lesssim 15$, its variations are unimportant as compared with the lifetime of the metastable state. The lifetime of the metastable state may be defined as $\tau = W\Delta t$, where Δt is the time duration starting from t_s to the time when $R = 0.5$. We find that both schemes give similar results which can be put down approximately as, for $n_1(0) = n_2(0)$,

$$\tau \sim 0.1\Omega/\mu \ .$$

For example, for $\mu = 1$ and $\Omega = 10^6$ as are used in Fig. 1, we have $\tau \sim 10^5$, which is much larger than Wt_s.

The metastability solution exists only for $W_k = W$. As the W_k are gradually changed away from equality, the coexistence in $\bar{n}_k$ breaks down and the species start to compete for the finite resource.[6] Both deterministic and stochastic theory predict that the competition will end up at a stable SS[7] in which the species having the maximum W is selected to survive at the one-species SS with the expense of all others. Therefore, by adjusting the parameters W_k away from equality, the stochastic metastable state is shifted to a stable SS, while the deterministic stable SS is shifted to another one with different distributions in n_k^s.

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