

Exchange of stability as a function of system size in a nonequilibrium system

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In equilibrium systems with short-ranged interactions, the relative stability of different thermodynamic states generally does not depend on system size (as long as this size is larger than the interaction range). Here, we use a large deviations approach to show that, in contrast, different states *can* exchange stability as system size is varied in a driven, bistable reaction-diffusion system. This striking effect is related to a shift from a spatially uniform to a nonuniform transition state and should generically be possible in a wide range of nonequilibrium physical and biological systems.

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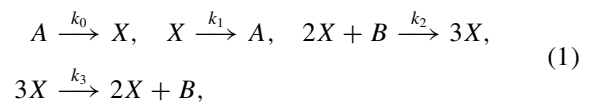
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The statistical physics of nonequilibrium systems has proven to be an enduring source of unexpected and intriguing phenomena. Historically, studies of driven systems have tended to focus on the thermodynamic limit of infinite system size. In recent years, however, experimental advances have made it possible to study everything from micromagnets and nanotubes to living cells at the mesoscopic scale, and this in turn has led to a growing theoretical interest in finite-sized stochastic systems. A major problem is to understand the relative stability of, and transition rates among, different (meta)stable states; this issue has been studied extensively for some equilibrium, detailed-balance-obeying models [1–5]. Here, we consider the same question in a simple model of a far-from-equilibrium, driven chemical system and show that far richer behavior is possible when detailed balance is violated. In particular, we find that—unlike in an equilibrium system—the system’s two stable states can exchange stability as the system size increases. This reversal is related to competition between a homogeneous and a spatially varying transition state [4,6], and we expect it generically to be possible whenever there is no underlying Boltzmann distribution to ensure that the relative stability is independent of the transition path. Similar results may thus apply to a wide range of systems of interest in condensed matter, chemical, and biological physics.

In what follows, we start by introducing the Schlögl model of a bistable chemical system and formulating its mean-field rate equations in terms of a *deterministic potential* $\mathcal{V}(c)$. The minima of this potential correspond to two locally stable states, and one might naively imagine that the state with the lower \mathcal{V} is the more stable of the two. Indeed, in a spatially extended system with diffusive transport, the mean-field equations have front solutions in which the state with lower \mathcal{V} always invades that with higher \mathcal{V} . In a well-stirred system, in contrast, only noise-induced transitions between states are possible, and the mean-field description provides no information about relative stability. Surprisingly, in this case, an analysis that accounts for the fundamentally stochastic nature of chemical reactions shows that, in certain parameter ranges, the state with *higher* \mathcal{V} is found with greater probability [7,8]. To reconcile these two seemingly contradictory predictions, we consider a model including both diffusion and fluctuations. We first show numerically that the two states exchange stability as the system’s spatial size grows. We then use a semiclassical approach to explain this dependence. By placing bounds on the action that determines the transition rate between states,

we are able to show that the relative stability must follow the deterministic potential for large enough systems, where the transition occurs through nucleation followed by deterministic front motion, while the well-stirred result applies for small enough systems.

The *bistable Schlögl model* [9] consists of the chemical reactions



where the concentrations of A and B are held constant. The corresponding mean-field rate equation for the concentration c of X in a well-stirred system is

$$\dot{c} = (k_0 + k_2c^2) - (k_3c^3 + k_1c) = -\mathcal{V}'(c), \quad (2)$$

where we have absorbed the concentrations of A and B into the rates k_0 and k_2 , respectively, and the prime denotes a derivative. This equation defines the deterministic potential $\mathcal{V}(c)$. If we move away from the well-stirred limit and let c depend on a spatial coordinate z , a diffusion term must be added, and Eq. (2) generalizes to

$$\partial_t c = -\mathcal{V}'(c) + D\partial_z^2 c. \quad (3)$$

For appropriate choices of the k_i , $\mathcal{V}(c)$ has one local maximum c_s and two local minima c_1 and c_2 , with $c_1 < c_2$, corresponding to two (meta)stable states. Equation (2) is invariant with respect to a simultaneous rescaling of concentrations and of rate constants, a fact we can exhibit explicitly by introducing a typical concentration scale c_0 of the same order as c_1 and c_2 and writing the k_i as $k_i = \lambda_i(c_0)^{1-i}$, where the λ_i have dimensions of inverse time. For fixed λ_i , the dynamics of $x = c/c_0$ is independent of c_0 .

The existence of two (meta)stable states invites the question of their relative stability. One expects that, when noise is properly taken into account, c will be found with high probability near c_1 or c_2 , and one might guess that $\mathcal{V}(c)$ determines which of the two is more probable (i.e., stable) and which is less probable. Indeed, in the limit of infinite system size, Eq. (3) admits traveling front solutions of the form $c(z, t) = f(z - vt)$ in which the state with lower \mathcal{V} expands into the one with higher \mathcal{V} [3,6,10].

Equation (3), however, is only a mean-field approximation to a more realistic model that accounts for the random nature of the molecular collisions that lead to chemical reactions. To

incorporate both these intrinsic stochastic effects and diffusion, we use a mesoscopic compartment model. In general, a d -dimensional reaction vessel is partitioned into M elementary compartments of linear size h and volume $V = h^d$, and each

molecule can jump between neighboring compartments but can react only with other molecules in the same compartment. The stationary probability $P(n^1, n^2, \dots, n^i, \dots)$ to find n^i molecules in compartment i then satisfies

$$\sum_i [W_+(n^i - 1)P(\dots, n^i - 1, \dots) - W_+(n^i)P(\dots, n^i, \dots)] + \sum_i [W_-(n^i + 1)P(\dots, n^i + 1, \dots) - W_-(n^i)P(\dots, n^i, \dots)] + D \sum_{(i,j)} [(n^i + 1)P(\dots, n^i + 1, n^j - 1, \dots) - n^i P(\dots, n^i, n^j, \dots)] = 0, \quad (4)$$

where D is the jump rate between compartments and the last sum is taken over neighboring compartments (i, j) . The reaction rates are

$$\begin{aligned} W_+(n) &= k_0 V + (k_2/V)n(n-1), \\ W_-(n) &= k_1 n + (k_3/V^2)n(n-1)(n-2). \end{aligned} \quad (5)$$

In general, this model allows for barriers that slow diffusion between compartments, but we are primarily interested in using it as an approximate description of a spatially continuous system. One can show that the average behavior of the stochastic compartment model (4) approaches that of the continuum reaction-diffusion equation (3), with $\mathcal{D} = h^2 D$, when $Dt_r = \mathcal{D}t_r/h^2 \gg 1$ and $c_0 V \gg 1$ [11,12]. Here $t_r \sim 1/\lambda_i$ is a typical time between reactions of an individual molecule. The first inequality ensures that individual compartments are well mixed; while this could be accomplished by decreasing h at fixed \mathcal{D} , the second inequality demands that this not be done at the expense of having very few molecules in each compartment.

Although there is no general analytical expression for the stationary distribution satisfying Eq. (4) [13], one can be found when $M = 1$ and the entire reaction volume is well stirred. In this case the total number of molecules n is distributed according to

$$P_{ws}(n) = K \prod_{j=1}^{n-1} \frac{W_+(j-1)}{W_-(j)}, \quad (6)$$

where K is a normalization constant. Below, we will be particularly interested in asymptotic results in the limit that the typical number of particles per compartment $\Omega \equiv c_0 V$ becomes large, and it is thus useful to rewrite P_{ws} in terms of

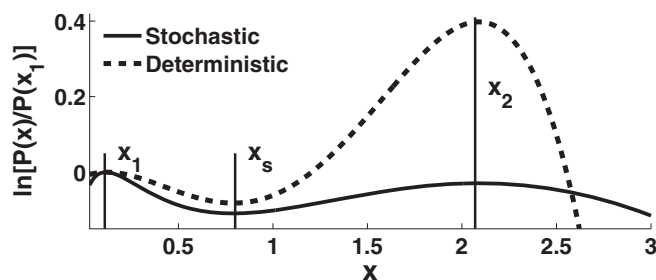


FIG. 1. Logarithms of the probability distribution $P_{ws}(x)$ in the well-stirred model and of the deterministic potential $\mathcal{V}(c_0 x)$ [15]. Both logarithms are shifted vertically by their values at x_1 and are plotted as a function of the rescaled concentration $x = c/c_0$.

$x = c/c_0 = n/\Omega$ as [14]

$$P_{ws}(x) = K(x; \Omega) e^{-\Omega S_{ws}(x)}, \quad (7)$$

where $K(x_1; \Omega)/K(x_2; \Omega)$ is bounded as $\Omega \rightarrow \infty$ for every $x_1, x_2 > 0$, so that $\exp[-\Omega S_{ws}(x)]$ determines the dominant large Ω contribution to any probability ratio.

The action $S_{ws}(x)$ is defined by

$$dS_{ws}(x)/dx = \ln[w_-(x)/w_+(x)], \quad (8)$$

where $w_+(x) = \lambda_0 + \lambda_2 x^2$ and $w_-(x) = \lambda_1 x + \lambda_3 x^3$. It is clear from this equation that the extrema of $S_{ws}(x)$ and of $\mathcal{V}(c_0 x)$ occur at the same values of x . The two functions, however, can otherwise be very different. Indeed, for the parameters used in Fig. 1 [15], $\mathcal{V}(c_2) - \mathcal{V}(c_1)$ and $\Delta_{ws} = S_{ws}(x_2) - S_{ws}(x_1)$ (where the extrema $x_i = c_i/c_0$) have opposite signs. Since Eq. (7) implies that it is the sign of Δ_{ws} that determines which of the two states is more probable, the deterministic potential does not reliably predict relative stability in the well-stirred case.

Semiclassical approach. In a well-stirred system, no transitions between states can occur without fluctuations. In contrast, the kinetics (3) with diffusion does allow for front-driven transitions between states even in the mean-field limit. This suggests that, unlike in the well-stirred system, there may be cases in spatially extended systems where the deterministic potential $\mathcal{V}(c)$ *does* in fact determine relative stability. Direct simulations of the fully stochastic compartment model (using a kinetic Monte Carlo algorithm with separate treatment of reaction and diffusion steps [11]) demonstrate that this intuition is correct. Indeed, Fig. 2 shows that the two states can exchange stability as M is increased; for small M , their

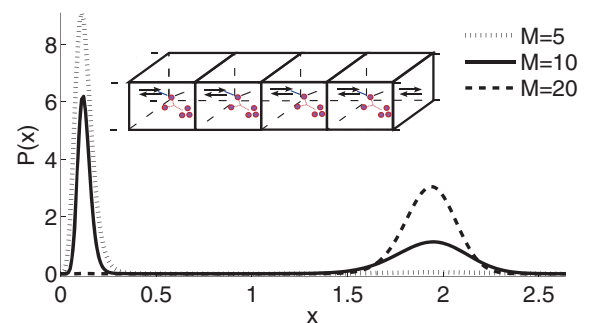


FIG. 2. (Color online) The distribution of the average scaled concentration $x = \sum n_i / (M\Omega)$ for different M and $V = 20$ [15]. Inset: Schematic of the compartment model, with molecules allowed to hop between compartments and to react within each compartment.

relative stability is the same as in the well-stirred limit, but for larger M , the state with lower \mathcal{V} regains the upper hand. As we now show, this stability inversion can be understood within a semiclassical approximation.

Just as in the well-stirred case, the stationary distribution P satisfying Eq. (4) can be written for large Ω as

$$P(x^1, \dots, x^M) = K_M(x^1, \dots, x^M; \Omega) e^{-\Omega S(x^1, \dots, x^M)}, \quad (9)$$

where $x^i = \frac{n^i}{\Omega}$, and $\Omega = c_0 V$ remains the typical number of particles per compartment [14]. For well-mixed systems, the eikonal approximation (9) is often thought of as a large volume approximation, but here the requirement that the compartment model approximate a continuous reaction-diffusion system constrains the volume of each compartment, and it is more useful to think of making Ω large by letting $c_0 \rightarrow \infty$ with the λ_i , D , and V fixed.

It is known [14,16] that the function $S(x)$ can be expressed as the minimal action

$$S(x) - S(x_i) = \min_{x(t)} \max_{p(t)} \left\{ \int_{x_i}^x dt [\mathbf{p}\dot{\mathbf{x}} - H(\mathbf{p}, \mathbf{x})] \right\},$$

$$H(\mathbf{p}, \mathbf{x}) = \sum_i (e^{p^i} - 1) [w_+(x^i) - w_-(x^i) e^{-p^i} + D\Delta_i(x e^{-p})], \quad (10)$$

where x_i is a stable stationary point of the deterministic kinetics, \mathbf{x} a point in its basin of attraction, and Δ_i the appropriate discrete Laplacian centered on compartment i . The extrema of $S(x)$ correspond to the fixed points of the dynamical system

$$\dot{x}^i = w_+(x^i) - w_-(x^i) + D\Delta_i(x) \quad (11)$$

and have the same stability [14].

In the continuum limit $h \rightarrow 0$, Eq. (11) becomes a rescaled version of Eq. (3), whose stationary states are well characterized [4,17–19]. It is reasonable to expect that the stationary states of the discretized version have similar properties for small enough h [20]. Then, with reflecting or periodic boundary conditions, only the uniform states $\mathbf{x}_1 = (x_1, \dots, x_1)$ and $\mathbf{x}_2 = (x_2, \dots, x_2)$ are stable, and there is a unique (up to symmetries) fixed point \mathbf{x}_s of (11) with only one unstable direction. This saddle is used to define the function $S(x)$ everywhere, i.e., to fix the value of $S(x_i)$ and thus of the stability index Δ through a matching procedure [14,16]:

$$\Delta = S(\mathbf{x}_2) - S(\mathbf{x}_1) = \Delta S_{1,s} - \Delta S_{2,s},$$

$$\Delta S_{1,s} = \min_{x(t)} \max_{p(t)} \int_{x_1}^{x_s} dt [\mathbf{p}\dot{\mathbf{x}} - H(\mathbf{p}, \mathbf{x})], \quad (12)$$

$$\Delta S_{2,s} = \min_{x(t)} \max_{p(t)} \int_{x_2}^{x_s} dt [\mathbf{p}\dot{\mathbf{x}} - H(\mathbf{p}, \mathbf{x})].$$

Both $\Delta S_{i,s}$ are non-negative [14]. Their exponentials are known to determine, respectively, the transition rates from \mathbf{x}_1 to \mathbf{x}_2 and vice versa [14,16]; $\exp(-\Omega\Delta)$, which gives the relative stability of the two states for large Ω , can thus be thought of as essentially the ratio of forwards to backwards transition rates.

We now focus on the regime where (as in Fig. 1) $\mathcal{V}(c_2) - \mathcal{V}(c_1) < 0$, but $\Delta_{ws} > 0$, and study the sign of Δ , and through it the relative stability of the two uniform states. This sign

strongly depends on the saddle \mathbf{x}_s , which, in the continuum limit $h \rightarrow 0$, is spatially uniform for a small enough system but becomes nonuniform at a critical linear system size [3,4,6]. In the limit of large system size, the saddle profile is close to x_1 everywhere except in a localized region whose size remains constant as the system size grows. This form reflects the fact that the deterministic traveling waves favor the state x_2 , so that only a small nucleus is required to initiate a transition from uniform x_1 to uniform x_2 . Similarly, for our compartment model, the stationary states and optimal trajectories in Eq. (12) are uniform for M less than some M_c , and one can show that $\Delta = M\Delta_{ws}$. The stability is then that of a well-stirred system, independent of D . For $M > M_c$, solving the double optimization problem (12) is extremely difficult. One can, however, verify numerically [20] that \mathbf{x}_s has the same shape as in the continuum limit, and thus deviates appreciably from x_1 only in a small region. Using this fact, one can derive bounds on Δ .

In particular, it is not hard to see that $\Delta S_{1,s}$, which describes the difficulty of reaching \mathbf{x}_s from \mathbf{x}_1 , remains smaller than a fixed constant, independent of M . This bound is simply given by a particular trajectory solving the first maximization problem in Eqs. (12). As \mathbf{x}_s , and thus the trajectory, differ from \mathbf{x}_1 only in a small region, the total action is finite, even for infinite M [20].

Similar reasoning indicates that $\Delta S_{2,s}$ should grow linearly with M . Indeed, in the limit $M \rightarrow \infty$, the region where \mathbf{x}_s differs from \mathbf{x}_1 becomes negligible, and one can focus on an optimal trajectory that must take the system from x_2 to x_1 on an essentially infinite domain. Physically, one expects that such an optimal trajectory should correspond to a front solution of the variational equations traveling with constant speed. Each successive compartment then makes the same contribution to the action, and one has $\Delta S_{2,s}(M) \simeq M\Delta_0$ for some Δ_0 . (See also the Supplemental Material [20].) Moreover, it is clear that for any integers M and l , $\Delta S_{2,s}(M) \geq \Delta S_{2,s}(Ml)/l$, because an optimal trajectory for a system of size M can be mirrored l times to create a suboptimal trajectory for a system of size Ml . Thus, the asymptotic large M behavior $\Delta S_{2,s}(M) \simeq M\Delta_0$ implies that $\Delta S_{2,s}(M) \geq M\Delta_0$ even for finite M . Since $\Delta S_{1,s}$ remains finite as M increases while $\Delta S_{2,s}$ grows without bound, $\Delta = \Delta S_{1,s} - \Delta S_{2,s}$ must change sign at some $M > M_c$, and the two states exchange stability as the system size increases (Fig. 3).

Discussion. The large deviations approach that we have used to show that an exchange of stability must occur is formally valid in the limit that $\Omega \rightarrow \infty$ at fixed compartment volume V and number of compartments M . This order of limits is important. In particular, because the prefactor K_M in Eq. (9) depends on M , it can overwhelm the exponential factor if M tends toward infinity at fixed Ω ; thus, our calculations describe transitions between (meta)stable states in a finite-sized, mesoscopic system but cannot be used to study the phase transition in the Schlögl model defined in the limit of infinite system size [21]. Similarly, our results hold in the limit of a large number of reacting particles and thus describe a distinct phenomenon from the exchange in the most probable state observed in a well-stirred system with a finite (small) particle number [22] or the recently described noise-induced reversal of front propagation direction [10]. Our calculations also go

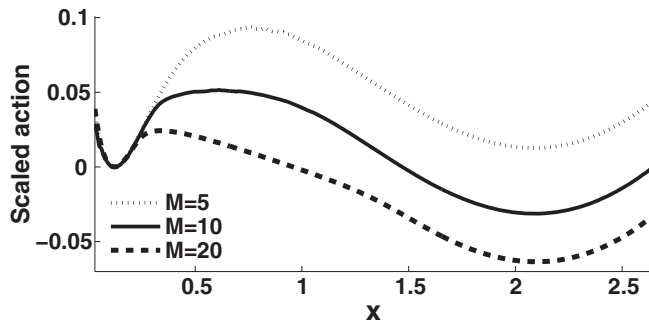


FIG. 3. The scaled action $-S/M$ for different numbers of compartments. The plotted values represent the logarithm of the probability of an average concentration $x = \sum_i x^i / M$ in Monte Carlo simulations [11], extrapolated to $\Omega = \infty$. Curves are shifted such that $S(x_1) = 0$ in order to clearly indicate the stability exchange. Note that the peaks in the curves move towards x_1 as M grows, reflecting the fact that most of the saddle profile is near x_1 for large M .

considerably beyond a previous study that examined transition rates very near a bifurcation in the Schlögl model but did not consider relative stability [6]. Finally, although the exchange of stability discussed here could not happen if the transition state did not become nonuniform at $M = M_c$ (leading to a

nonanalyticity in Δ) [4,5], the actual exchange occurs at some $M > M_c$ and need not coincide with any further bifurcations of the transition state.

Although we have presented our results for a specific model of a bistable chemical system, the system-size-dependent relative stability that we describe is far more general and should in principle be possible in models describing everything from pattern formation [23] to ecological population dynamics [6] or the complex reaction networks present in living cells [24]. All that is absolutely required is multistability and violation of detailed balance. In some cases, more complex stability diagrams are likely to be possible. For example, if we no longer insist that the compartment model studied here be a good approximation to a continuum system and thus allow ourselves to vary D arbitrarily, we expect a reentrant exchange of stability: As $D \rightarrow \infty$, the entire system should be well mixed, while each individual compartment behaves as a separate well-mixed vessel as $D \rightarrow 0$ [25]. In either limit, the relative probability of the two states should depend on Δ_{ws} , while for intermediate values of D the sign of Δ may differ from that of Δ_{ws} . These and similar effects should be accessible within the same formalism employed here.

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