Extinction of an infectious disease: A large fluctuation in a nonequilibrium system

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We develop a theory of first passage processes in stochastic nonequilibrium systems of birth-death type using two closely related epidemiological models as examples. Our method employs the probability generating function technique in conjunction with the eikonal approximation. In this way the problem is reduced to finding the optimal path to extinction: a heteroclinic trajectory of an effective multidimensional classical Hamiltonian system. We compute this trajectory and mean extinction time of the disease numerically and uncover a nonmonotone, spiral path to extinction of a disease. We also obtain analytical results close to a bifurcation point, where the problem is described by a Hamiltonian previously identified in one-species population models.

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Statistics of large fluctuations in stochastic nonequilibrium systems has received much attention [1]. While the equilibrium fluctuation probability is determined by the Boltzmann distribution, there is no similar general principle away from equilibrium. The underlying reason is the absence of time reversal symmetry between the relaxation and excitation dynamics in out-of-equilibrium systems. As a consequence, the most probable fluctuation path is not determined by the relaxation trajectory of the underlying deterministic system.

An important class of stochastic nonequilibrium systems is reaction kinetics, or birth-death, systems [2]. Rather than being caused by external factors, the noise in these systems is intrinsic, as it originates from discreteness of the reacting agents and random character of their interactions. When the typical number of agents is large, the Fokker-Planck (FP) approximation to the master equation, see, e.g., Ref. [2], can accurately describe small deviations from the probability distribution maxima. It fails, however, in determining the probability of large fluctuations [3–5]. Therefore, developing adequate theoretical tools for dealing with large fluctuations is an important task.

One of the areas where the birth-death models have been very successful is mathematical epidemiology, see Ref. [6]. In this work we consider two closely related models of the spread of disease in a population. Although they have served as standard multipopulation epidemiological models, the analysis of large fluctuations in each of these models has not been satisfactory. We will use the two models as prototypical examples of multidimensional stochastic nonequilibrium systems.

Observing the dynamics of a disease in a finite population, one notices the remarkable phenomenon of extinction of the disease in a finite time. The expected time to extinction (and the possibility to affect it) is of great practical interest. Here we develop an efficient theoretical approach capable of computing, among other things, this quantity. The approach employs the probability generating function formalism in conjunction with the eikonal approximation. In this way the problem is reduced to the dynamics of an effective classical Hamiltonian system. The intrinsic-noise-induced extinction of the disease proceeds, with a high probability, along the optimal path: a special (heteroclinic) trajectory in the phase space of the classical Hamiltonian flow. An additional challenge of this type of problem is in the fact that the emerging multidimensional Hamiltonian flows are generally nonintegrable. We compute the optimal path, and the mean extinction time of the disease, numerically and also obtain analytical results close to a bifurcation point.

Model. Let us consider two stochastic epidemiological models: the endemic SI model and the endemic SIR model. In the SI model the host population is divided into two dynamic subpopulations: Susceptible (S) and Infected (I). The model is specified by the set of reactions and their rates given in Table I. We can always represent the renewal rate (an independent parameter of the model) as μN, where N scales as the total population size in a steady state. Taking $\mu_I > \mu$, one allows for an increased death rate of the infected.

The endemic SIR model deals, in addition to the S and I subpopulations, with a third subpopulation: Recovered (R), with the recovery rate γI. It is assumed that the recovered cannot become susceptible. The death rate of the recovered is $\mu_R R$. The endemic SIR model (which generalizes the original SIR model: the one without renewal and death) gives a satisfactory description to the spread of measles, mumps, and rubella [6].

Let us briefly review the deterministic, or mean-field, version of the SIR model:

$$\dot{S} = \mu N - \mu S - (\beta/N)SI, \tag{1}$$

$$\dot{I} = -\mu_I I - \gamma I + (\beta/N)SI, \tag{2}$$

TABLE I. Transition rates for the stochastic SI model.

Event	Type of transition	Rate
Infection	$S \to S-1, I \to I+1$	$(\beta/N)SI$
Renewal of susceptible	$S \to S+1$	μN
Death of susceptible	$S \to S-1$	μS
Death of infected	$I \to I-1$	$\mu_I I$

$$\dot{R} = -\mu_R R + \gamma I. \tag{3}$$

As the dynamics of S and I decouples from that of R, the SIR model is effectively two population, and we will not deal with the R dynamics. Furthermore, one immediately notices that, by setting $\mu_I+\gamma=\Gamma$, the S and I dynamics in the SIR model becomes identical to that in the SI model, up to interchange of μ_I and Γ. This also holds for the stochastic versions of the two models, and so we can treat them on equal footing, using Γ for the effective death rate constant of the infected.

For a sufficiently high infection rate, $\beta>\Gamma$, there is an attracting fixed point

$$\bar{S} = \frac{\Gamma}{\beta}N, \quad \bar{I} = \frac{\mu(\beta-\Gamma)}{\beta\Gamma}N \tag{4}$$

which describes an endemic infection level, and an unstable fixed point $\bar{S}=N$, $\bar{I}=0$ which describes an uninfected population. At $\mu<4(\beta-\Gamma)(\Gamma/\beta)^2$ the attracting fixed point is a stable focus, while in the opposite case it is a stable node. The inverse of the real part of the eigenvalues (for the focus) or the inverse of the smaller of the eigenvalues (for the node) yields the characteristic relaxation time τ_r toward the "endemic point."

The stochastic formulation of the SI and SIR models accounts for the demographic stochasticity and random character of contacts between the susceptible and infected. The master equation for the probability $P_{n,m}(t)$ of finding n susceptible and m infected individuals has the form

$$\begin{aligned}\dot{P}_{n,m} = {} & \mu[N(P_{n-1,m}-P_{n,m})+(n+1)P_{n+1,m}-nP_{n,m}] \\ & +\Gamma[(m+1)P_{n,m+1}-mP_{n,m}] \\ & +(\beta/N)[(n+1)(m-1)P_{n+1,m-1}-nmP_{n,m}],\end{aligned} \tag{5}$$

and the total population size is fluctuating in time. We will be interested in the regime where the fluctuations are relatively weak (but still very important). In this case, after the relaxation time τ_r a long-lived (quasistationary) distribution is formed that has a bivariate Gaussian peak with relative width $\sim N^{-1/2}$ around the stable state (4) of the mean-field description [7–9]. The long-time behavior of the stochastic model is quite remarkable: Owing to a rare sequence of discrete events the disease goes extinct in a finite time. Given that a major outbreak of the disease occurred, what is the mean extinction time τ of the disease? For the endemic SIR model this question was addressed previously [7,8] in the framework of the van Kampen system size expansion that brings about the approximate FP equation [2]. Our approach considerably (exponentially) improves on these earlier results. In the regime we are interested in τ is exponentially large compared with the relaxation time τ_r. The presence of the large parameter facilitates the use of the (fully controlled) eikonal approximation: either directly in the master equation, as suggested by Dykman *et al.* [10], or in the evolution equation for the probability generating function, as suggested by Elgart and Kamenev [4].

Probability generation function and eikonal approximation. We adopt the latter approach and introduce the probability generating function $G(p_S,p_I,t)=\Sigma_{n,m=0}^{\infty}p_S^n p_I^m P_{n,m}(t)$. Once $G(p_S,p_I,t)$ is found, the probabilities $P_{n,m}(t)$ are given by the coefficients of its Taylor expansion around $p_S=p_I=0$. Using the master equation (5), we obtain an evolution equation for G: $\partial_t G=\hat{H}G$ with the effective Hamiltonian operator

$$\hat{H} = \mu(p_S-1)(N-\partial_{p_S})-\Gamma(p_I-1)\partial_{p_I}-(\beta/N)(p_S-p_I)p_I\partial^2_{p_S p_I}. \tag{6}$$

In contrast to the FP equation this equation is exact [11].

The eikonal ansatz is $G(p_S,p_I,t)=\exp[-\mathcal{S}(p_S,p_I,t)]$, where $\mathcal{S}\gg 1$. Neglecting the second derivatives of $\mathcal{S}$ with respect to p_S and p_I, we arrive at a Hamilton-Jacobi equation $\partial_t\mathcal{S}+H=0$ in the p space with the classical Hamiltonian $H(S,I,p_S,p_I)$,

$$H = \mu(p_S-1)(N-S)-\Gamma(p_I-1)I-(\beta/N)(p_S-p_I)p_I SI, \tag{7}$$

where $S=-\partial_{p_S}\mathcal{S}$ and $I=-\partial_{p_I}\mathcal{S}$. The structure of four-dimensional (4D) phase space, defined by the Hamiltonian (7), provides a fascinating and instructive insight into the disease extinction dynamics. As H does not depend explicitly on time, it is an integral of motion, $H(S,I,p_S,p_I)=E=\text{const}$. All the mean-field trajectories, described by Eqs. (1) and (2), lie in the zero energy, $E=0$, two-dimensional plane $p_S=p_I=1$. The attracting fixed point (4) of the mean-field theory becomes a hyperbolic point $A=[\bar{S},\bar{I},1,1]$ in the 4D phase space with two stable and two unstable eigenvalues (the sum of which is zero) and respective eigenvectors. There are two more zero-energy fixed points in the system: the point $C=[N,0,1,1]$ which is present in the mean-field description and the non-mean-field point $B=[N,0,1,\Gamma/\beta]$ which we call fluctuational. Both of them are hyperbolic and describe extinction of the disease. The presence of a fluctuational fixed point, related to extinction, is characteristic of a class of stochastic birth-death systems [4,7,12,13].

The most probable sequence of discrete events, bringing the system from the endemic state to extinction of the disease, is given by the optimal path that minimizes the action $\mathcal{S}$ [10,14]. The optimal path must be a zero-energy heteroclinic trajectory. This trajectory exits, at $t=-\infty$, the "endemic" point A along its two-dimensional unstable manifold and enters, at $t=\infty$, the fluctuational disease extinction point B, along its two-dimensional stable manifold. As in one-dimensional birth-death systems [4,12], one can show that there is no trajectory going directly from A to C. Therefore, the fluctuational extinction point B, not present in the mean-field dynamics, plays a crucial role in the disease extinction.

Up to a pre-exponent, the mean extinction time of the disease is $\tau\propto\tau_r\exp(\mathcal{S}_0)$ [15], where

$$\mathcal{S}_0 = \int_{-\infty}^{\infty}(p_S\dot{S}+p_I\dot{I})dt, \tag{8}$$

and the integration is performed along the (zero-energy) optimal path. As in any generic multidimensional Hamiltonian system, the optimal path can be computed only numerically. In the following we present two typical examples of such

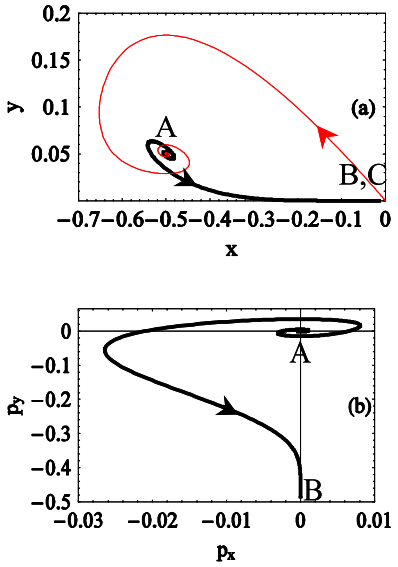

FIG. 1. (Color online) (a) Projection of the optimal path on the (x,y) plane (thick black line) and the mean-field trajectory ($p_x=p_y=0$) describing an epidemic outbreak (thin red line). (b) Projection of the optimal path on the (p_x,p_y) plane. $x=S/N-1$, $y=I/N$; $K=20$ and $\delta=0.5$.

computation, and also consider an important limit when the computation can be performed analytically, by exploiting time-scale separation. First we introduce new coordinates $x=S/N-1$ and $y=I/N$, time $\tilde{t}=\mu t$, momenta $p_{x,y}=p_{S,I}-1$, and bifurcation parameter $\delta=1-\Gamma/\beta$, $0<\delta<1$. The action (8) can now be rewritten as $\mathcal{S}_0=N\sigma$, where $\sigma(K,\delta)$ is the action along the optimal path, generated by the Hamiltonian

$$\tilde{H}=-p_x x-K[(1-\delta)p_y+(p_x-p_y)(p_y+1)(x+1)]y \quad (9)$$

and $K=\beta/\mu>1$. The fixed points A, B, and C become

$$\left[-\delta,\frac{\delta}{K(1-\delta)},0,0\right], \quad [0,0,0,-\delta], \quad \text{and} \quad [0,0,0,0],$$

respectively.

Optimal path and action: Numerical examples. We computed the optimal path numerically for different parameters.

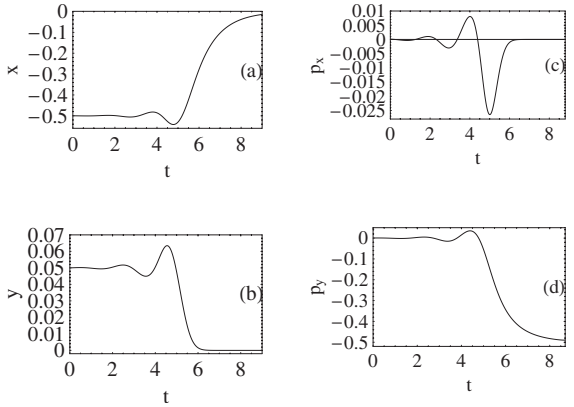

FIG. 2. Optimal path for $K=20$ and $\delta=0.5$. Shown are $x=S/N-1$ (a), $y=I/N$ (b), $p_x=p_S-1$ (c), and $p_y=p_I-1$ (d) vs rescaled time.

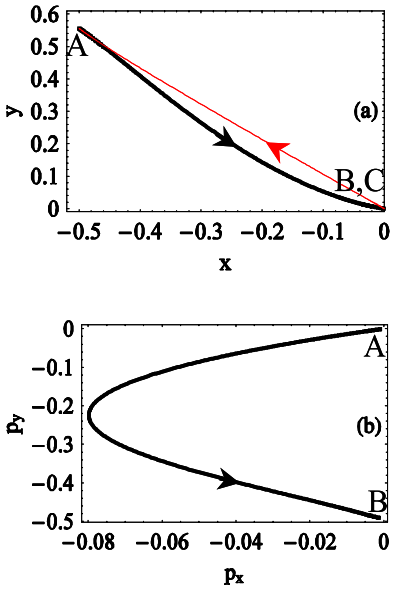

FIG. 3. (Color online) Same as in Fig. 1 but for $K=1.8$.

To find the optimal path one needs to adjust a single shooting parameter: the angle between two unstable eigendirections of the endemic fixed point A. Two typical examples of numerically computed optimal paths are shown in Figs. 1 and 2 [where $4K\delta(1-\delta)^2>1$, and the endemic point is a focus] and in Figs. 3 and 4 [where $4K\delta(1-\delta)^2<1$, and the endemic point is a node]. Figures 1(a) and 3(a) show projections of the optimal paths on the (x,y) plane. For comparison, they also show the mean-field trajectories ($p_x=p_y=0$) originating in the vicinity of the no-disease point $x=y=0$, describing an epidemic outbreak and approaching the endemic point. In contrast to equilibrium systems, the optimal path of a large fluctuation is different from the corresponding relaxation path. Notice that, although for $K=20$ the extinction proceeds along a spiral, the difference between the two spirals is striking. Figures 1(b) and 3(b) show projections of the optimal paths on the (p_x,p_y) plane. The optimal paths are presented in more detail in Figs. 2 and 4, where the time dependences of x, y, p_x, and p_y are shown. The rescaled action along the optimal path in this example is $\sigma\simeq 6.12\times 10^{-3}$ for $K=20$ and $\sigma\simeq 0.145$ for $K=1.8$, providing sharp estimates to the loga-

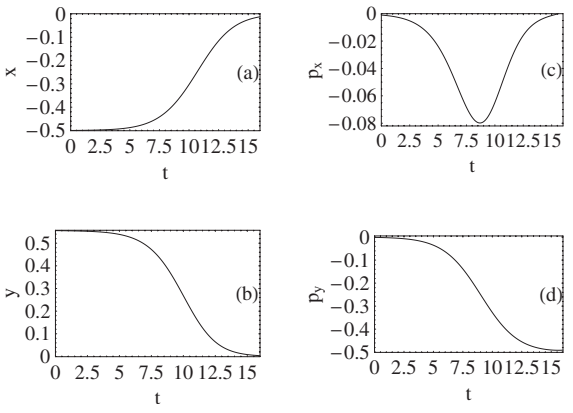

FIG. 4. Same as in Fig. 2 but for $K=1.8$.

rithm of the corresponding mean extinction times of the disease.

Optimal path and action: Asymptotic theory in the vicinity of the bifurcation point. For $K\delta \ll 1$ we can compute the optimal path and the rescaled action $\sigma(K,\delta)$ analytically, by exploiting time-scale separation. Let us introduce rescaled variables, $q_1=x/\delta$, $q_2=yK/\delta$, $p_1=p_x/\delta^2$, and $p_2=p_y/\delta$. This rescaling is motivated by the values of the coordinates of the fixed points, and reflects the important feature that, at $\delta \ll 1$, the fluctuations in the number of susceptible are much weaker than the fluctuations in the number of infected. Neglecting higher-order terms in δ, we arrive at the following approximate equations of motion:

$$\dot{q}_1 = -q_1 - q_2, \quad \dot{q}_2 = K\delta q_2(1+q_1+2p_2),$$

$$\dot{p}_1 = p_1 - q_2 p_2, \quad \dot{p}_2 = K\delta(p_1 - p_2 - p_2^2 - q_1 p_2). \tag{10}$$

The fixed points become $A=[-1,1,0,0]$, $B=[0,0,0,-1]$, and $C=[0,0,0,0]$. For $K\delta \ll 1$ the subsystem (q_1,p_1) is fast, whereas (q_2,p_2) is slow. On the fast time scale (that is, the time scale μ^{-1} in the original, dimensional variables) the fast subsystem approaches the state $q_1 \simeq -q_2$ and $p_1 \simeq q_2 p_2$ which then slowly evolves according to the equations

$$\dot{q}_2 \simeq K\delta q_2(1-q_2+2p_2), \quad \dot{p}_2 \simeq K\delta p_2(2q_2-1-p_2) \tag{11}$$

that are Hamiltonian, as they follow from the reduced Hamiltonian $H_r(q_2,p_2)=K\delta q_2 p_2(1-q_2+p_2)$. This Hamiltonian appears in the theory of a class of *single*-species models in the vicinity of a bifurcation point [12]. As $H_r(q_2,p_2)$ is independent of time, it is an integral of motion. The optimal extinction path goes along the zero-energy trajectory $1-q_2+p_2=0$ [16]. Evaluating the action (8) along this line, we find in the leading order $\mathcal{S}_0 \simeq [N\delta^3/(K\delta)]\int_1^0 p_2 dq_2 = N\delta^2/(2K)$. For the mean extinction time of the disease we obtain

$$\ln(\tau)/N \simeq \delta^2/(2K) = [\mu/(2\beta)](1-\Gamma/\beta)^2; \tag{12}$$

this asymptote is valid when $\mathcal{S}_0 \gg 1$.

Dykman *et al.* [13] have recently shown that reduced Hamiltonian dynamics of the same type as Eqs. (11) holds, close to the bifurcation point, in the endemic SIS model: still another two-population stochastic epidemic model where the infected individuals again become susceptible upon recovery.

In summary, we have developed the eikonal theory for stochastic multipopulation birth-death systems. The theory is especially suitable for analysis of large fluctuations, such as disease extinction. For the SI and SIR models we have found the optimal path to extinction of the disease and the mean extinction time. The optimal path to extinction, including its remarkable oscillatory behavior, is not model specific. It should be observable in stochastic simulations of a broad class of models, and in real data on fade out, of infectious diseases in small communities.

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[1] *Noise in Nonlinear Dynamical Systems*, edited by F. Moss and P. V. E. McClintock (Cambridge University Press, Cambridge, 1989); *Fluctuations and Order: The New Synthesis*, edited by M. Milonas (Springer, New York, 1996).

[2] C. W. Gardiner, *Handbook of Stochastic Methods* (Springer, Berlin, 2004); N. G. van Kampen, *Stochastic Processes in Physics and Chemistry* (North-Holland, Amsterdam, 2001).

[3] B. Gaveau, M. Moreau, and J. Toth, Lett. Math. Phys. **37**, 285 (1996); C. R. Doering, K. V. Sargsyan, and L. M. Sander, Multiscale Model. Simul. **3**, 283 (2005).

[4] V. Elgart and A. Kamenev, Phys. Rev. E **70**, 041106 (2004).

[5] M. Assaf and B. Meerson, Phys. Rev. Lett. **97**, 200602 (2006); Phys. Rev. E **75**, 031122 (2007).

[6] M. S. Bartlett, *Stochastic Population Models in Ecology and Epidemiology* (Wiley, New York, 1961); H. Andersson and T. Britton, *Stochastic Epidemic Models and Their Statistical Analysis*, Lect. Notes Stat., Vol. 151 (Springer, New York, 2000); O. Diekmann and J. A. P. Heesterbeek, *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation* (Wiley, Chichester, 2000); D. J. Daley and J. Gani, *Epidemic Modelling: An Introduction*, Cambridge Studies in Mathematical Biology (Cambridge University Press, Cambridge,2001).

[7] O. A. van Herwaarden and J. Grasman, J. Math. Biol. **33**, 581 (1995).

[8] I. Nåsell, J. R. Stat. Soc. Ser. B. (Stat. Methodol.) **61**, 309 (1999).

[9] When the fixed point (4) is a stable focus, the quasistationary state, as described by the stochastic model, will exhibit sustained noisy oscillations, in analogy with other two-species systems [J. P. Aparicio and H. G. Solari, Math. Biosci. **169**, 15 (2001); A. J. McKane and T. J. Newman, Phys. Rev. Lett. **94**, 218102 (2005)].

[10] M. I. Dykman, E. Mori, J. Ross, and P. M. Hunt, J. Chem. Phys. **100**, 5735 (1994).

[11] For a single species the equation $\partial_t G = \hat{H} G$ can be analyzed by the spectral theory [5]. This theory, however, has not been extended to multiple species.

[12] V. Elgart and A. Kamenev, Phys. Rev. E **74**, 041101 (2006).

[13] M. Dykman, I. B. Schwartz, and A. S. Landsman, e-print arXiv:0801.4902.

[14] M. I. Freidlin and A. D. Wentzell, *Random Perturbations of Dynamical Systems* (Springer-Verlag, New York, 1984); also see the first reference in [1].

[15] B. J. Matkowsky, Z. Schuss, C. Knessl, C. Tier, and M. Mangel, Phys. Rev. A **29**, 3359 (1984).

[16] One can easily compute $q_2(t)=(e^{K\delta(t-t_0)}+1)^{-1}$ and $p_2(t)=-(e^{-K\delta(t-t_0)}+1)^{-1}$, where $t_0=$const.