Speeding up disease extinction with a limited amount of vaccine

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We consider optimal vaccination protocol where the vaccine is in short supply. In this case, the endemic state remains dynamically stable; disease extinction happens at random and requires a large fluctuation, which can come from the intrinsic randomness of the population dynamics. We show that vaccination can exponentially increase the disease extinction rate. For a time-periodic vaccination with fixed average rate, the optimal vaccination protocol is model independent and presents a sequence of short pulses. The effect can be resonantly enhanced if the vaccination pulse period coincides with the characteristic period of the disease dynamics or its multiples. This resonant effect is illustrated using a simple epidemic model. The analysis is based on the theory of fluctuation-induced population extinction in periodically modulated systems that we develop. If the system is strongly modulated (for example, by seasonal variations) and vaccination has the same period, the vaccination pulses must be properly synchronized; a wrong vaccination phase can impede disease extinction.

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I. INTRODUCTION

Spreading of an infectious disease is a random process. An important source of randomness is the noise associated with the stochastic character of such events as infection, recovery, birth, and death. In a large population this noise is small on average, and the infection spread leads to an endemic state where a certain fraction of the population stays infected for a long time. However, if there is no influx of infected individuals from the outside, the disease will ultimately disappear due to fluctuations. Disease extinction requires a large fluctuation, as it involves an unlikely chain of elementary events where, for example, susceptible individuals happen to avoid getting infected while infected ones recover [1–3]. Such spontaneous disappearance of a disease is an example of population extinction studied in stochastic population dynamics.

Spontaneous extinction of species is important also for physical and chemical reaction systems. An underlying common feature of the phenomena involving fluctuation-induced extinction is that the extinction results from a series of short random events, such as collisions between molecules that lead to chemical reactions and interactions between individuals that lead to the disease spread. As a consequence, for different systems extinction can be described within the same general formalism. This provides a broader scope for the present paper. Moreover, the method of optimal control of extinction that we propose can be applied to systems of various types.

A conventional way of fighting epidemics is via vaccination. If there is enough vaccine, the infection can be eradicated "deterministically" by eliminating the endemic state [4]. The amount of available vaccine, however, is often insufficient. The vaccine may be expensive, or it may be dangerous to store in large amounts, as in the case of anthrax, or it may be effectively short lived due to mutations of the infection agent, as for human immunodeficiency virus [5] and influenza [6].

Even where the endemic state may not be eliminated deterministically, vaccination can dramatically affect the stochastic dynamics of the epidemics. The underlying mechanism is the change in the rate of large fluctuations leading to disease extinction. For a well-mixed population, this rate W_e is usually exponentially small for a large total population size $N \gg 1$, $W_e \propto \exp(-\mathcal{Q})$ with $\mathcal{Q} \propto N$ [3,7–16]. We call $\mathcal{Q}$ the disease extinction barrier. Vaccination changes the value of $\mathcal{Q}/N$. Even a small change in $\mathcal{Q}/N$ can lead to a significant change in $\mathcal{Q}$ and thus to an exponentially strong change in the disease extinction rate. This effect was previously discussed for vaccination applied at random [15].

The goal of this paper is to find an optimal way of administering a limited amount of vaccine which would maximally increase the disease extinction rate. We find a vaccination protocol that applies for a broad class of epidemic models. Our approach is based on the observation that, in a large fluctuation that leads to disease extinction, the population is most likely to evolve in a well-defined way. It moves along the most probable path in the space of the dynamical variables which characterize different subpopulations (cf. Refs. [15–17]). Vaccination perturbs the system as it moves along the optimal path. One can think of vaccination as "force" and its effect as "work" done on the system. This work reduces the barrier $\mathcal{Q}$. The problem then is to maximize the work for given constraints on the vaccine.

Optimization of the effect of vaccination resembles another problem of optimal control of random systems, controlling large fluctuations in noise-driven dynamical systems by applying an external field with a given average intensity [18,19]. There are, however, important differences, which come from the very nature of the control field. Indeed, vaccination only *reduces* the number of susceptible individuals. In other words, as a control field, vaccination never changes sign. Then, remarkably, if the available amount of vaccine is constrained by a given mean vaccination rate, the optimal vaccination protocol turns out to be model independent. This our finding applies also to using a limited amount of medications and other situations where the control field drives the system only in one direction.

A natural way of applying the vaccine for a given mean vaccination rate is to do this periodically in time. We show

that the corresponding optimal vaccination protocol is a sequence of δ-like pulses. The disease extinction rate can strongly depend on the period of this sequence. Furthermore, the extinction rate can display exponentially sharp peaks when the vaccination period is close to the characteristic period of oscillations of the system in the absence of fluctuations or to its multiples. We illustrate this resonant phenomenon for the susceptible-vaccinated-infected-recovered (SVIR) model. We note that strong periodic vaccination has been investigated in the framework of deterministic epidemic models, and it was found that pulsed vaccination is advantageous compared to vaccination at a constant rate [20].

Epidemics often display seasonal variations [21,22]. It is natural to apply a vaccine with period equal to the modulation period. As we show, there is a qualitative difference between the effect of a periodic vaccination in this case and in the case where seasonal modulation is absent. For a system with seasonal modulation, an improperly applied pulsed vaccination can actually reduce the disease extinction rate and therefore prolong the duration of the epidemic. The overall effect of the pulsed vaccination critically depends here on the *phase* at which the periodic pulses are applied.

The analysis of periodic vaccination, with and without seasonal variations, necessitates a general formulation of the extinction problem in a periodically varying environment, that is, for periodically modulated population dynamics. This problem was previously addressed for single-population systems [23,24]. We provide a complete extinction theory for modulated multipopulation systems in the eikonal approximation. It includes a formulation, using topological arguments, of the nontrivial boundary conditions for the optimal path of disease extinction. These conditions make the problem significantly different from the well-understood problem of switching between metastable states in periodically modulated systems with noise [25].

Section II describes the class of epidemic models we consider in this work. Section III presents a general eikonal theory of disease extinction rate in periodically modulated systems, including the theory of the boundary conditions for the optimal extinction path. Section IV formulates the optimization problem for time-periodic vaccination with a moderately small average vaccination rate. Its solution for systems that are stationary in the absence of vaccination is presented in Sec. V. The shape of the vaccination pulses is shown to be model independent. In Sec. VI the case of periodically modulated systems with periodically applied vaccine is studied. In Sec. VII we discuss the vaccination-induced reduction of the disease extinction barrier for two types of constraints on the vaccination period, a limited lifetime of the vaccine, and a limited vaccine accumulation. Section VIII illustrates, on the example of the stochastic SVIR model, the phenomenon of resonant response to vaccination. Section IX contains concluding remarks.

II. MODEL OF POPULATION DYNAMICS

We consider stochastic disease dynamics in a well-mixed population which includes infected (I) and susceptible (S) individuals and possibly other population groups such as recovered or vaccinated. The system state is described by a vector $\mathbf{X}=(S,I,\ldots)$ with integer components equal to the sizes of different population groups. Along with $\mathbf{X}$ it is convenient to consider a quasicontinuous vector $\mathbf{x}=\mathbf{X}/N$, where N is the characteristic total population size, $N\gg 1$. We assume that the population dynamics is Markovian. It is quite generally described by the master equation for the probability distribution $P(\mathbf{X},t)$,

$$\dot{P}(\mathbf{X},t)=\sum_{\mathbf{r}}\left[W(\mathbf{X}-\mathbf{r},\mathbf{r},t)P(\mathbf{X}-\mathbf{r},t)-W(\mathbf{X},\mathbf{r},t)P(\mathbf{X},t)\right]. \tag{1}$$

Here, $W(\mathbf{X},\mathbf{r},t)$ is the rate of an elementary transition $\mathbf{X}\to\mathbf{X}+\mathbf{r}$ in which the population size changes by $\mathbf{r}=(r_1,r_2,\ldots)$. Examples of such transitions are infection of a susceptible individual as a result of contacting an infected individual, recovery of an infected individual, or arrival of a susceptible individual. In population dynamics and epidemics, $|\mathbf{r}|$ is much smaller than the characteristic population size N, typically $|\mathbf{r}|\sim 1$.

As it is often done in the models of epidemics [1–3], we assume that there is no influx of infected individuals into the population. Therefore, no transitions occur from states where there are no infected to states where infected are present,

$$W(\mathbf{X},\mathbf{r},t)=0 \quad \text{for } X_E=0, \quad r_E\neq 0, \tag{2}$$

where the subscript E is used for the component of $\mathbf{X}$ which enumerates infected, $X_E\equiv I$. This condition plays an important role in the analysis.

In the neglect of fluctuations the population dynamics can be described by the deterministic (mean-field) equation for the reduced mean population size $\bar{\mathbf{x}}$,

$$\dot{\bar{\mathbf{x}}}=\sum_{\mathbf{r}}\mathbf{r}w(\bar{\mathbf{x}},\mathbf{r},t), \tag{3}$$

$$\mathbf{x}=\mathbf{X}/N, \quad w(\mathbf{x},\mathbf{r},t)=W(\mathbf{X},\mathbf{r},t)/N.$$

It immediately follows from Eq. (1) if the width of the probability distribution $P(\mathbf{X},t)$ is set equal to zero.

A. Static environment

We start with the case of static environment where the transition rates $W(\mathbf{X},\mathbf{r},t)$ are independent of time, $W(\mathbf{X},\mathbf{r},t)=W(\mathbf{X},\mathbf{r})$. We refer to this case in a standard way as the case of stationary systems. We assume that the system has an endemic state. This state is characterized by a finite fraction of infected and corresponds to an attracting fixed point $\mathbf{x}_A$ of the mean-field dynamics [Eqs. (3)]. We will assume throughout this work that there is only one such point, typical of many epidemics models [1–3]. We will also assume that Eqs. (3) have one fixed point $\mathbf{x}_S$ in the hyperplane $x_E=0$. The state $\mathbf{x}_S$ is stable with respect to all variables except x_E. We call it the disease extinction state. If $x_E>0$ (there is a nonzero number of infected), the deterministic trajectory leaves the vicinity of $\mathbf{x}_S$ and approaches the endemic state $\mathbf{x}_A$.

Due to fluctuations the endemic state is actually *metastable*. The fluctuations ultimately drive the population into a disease-free state. The rate W_e of fluctuation-induced disease extinction is given by the probability current to the extinction plane, reminiscent of the problem of escape from a metastable state where the escape rate is determined by the probability current away from the basin of attraction [26]. For time-independent $W(\mathbf{X},\mathbf{r})$ this current is quasistationary for times $t_r \ll t \ll W_e^{-1}$, where t_r is the characteristic relaxation time for the noise-free motion described by Eqs. (3).

The exponent $\mathcal{Q}$ in the rate W_e is determined by the most probable fluctuation leading to extinction; this fluctuation brings the system to the fixed point $\mathbf{x}_S$ [15,16]. Even though the state $\mathbf{x}_S$ is a saddle point in the mean-field approximation, it differs from the saddle-point states encountered in the problem of switching between metastable states of reaction systems. In the case of interstate switching, the rates of elementary transitions $W(\mathbf{X},\mathbf{r})$ in the unstable direction are nonzero, and ultimately fluctuations drive the system away from the saddle point. In contrast, the extinction hyperplane is absorbing. Fluctuations around $\mathbf{x}_S$ occur only in this hyperplane; the probability of exiting is zero, as a consequence of Eq. (2).

B. Periodically varying environment

The above picture can be extended to the case where the transition rates are periodic functions of time, $W(\mathbf{X},\mathbf{r},t+T)=W(\mathbf{X},\mathbf{r},t)$. Time periodicity of the rates is a natural way of modeling seasonal variations of epidemics [21,22]. Periodicity may be also imposed by vaccination. In physics terms, the system is periodically modulated in time. We use the term "modulation" in what follows to account for all types of periodic variations of the system parameters.

In a modulated system, the attracting solution of Eqs. (3), which describes the endemic state, is no longer stationary. We will assume that this solution, $\mathbf{x}_A(t)$, is periodic in time with the modulation period T, $\mathbf{x}_A(t+T)=\mathbf{x}_A(t)$. The asymptotic disease extinction state $\mathbf{x}_S(t)$ is also periodic in time; it lies in the hyperplane $x_E=0$.

An important characteristic of a modulated system is the period-averaged disease extinction rate W_e. It can be introduced if the modulation period $T \ll W_e^{-1}$ and, in addition, $t_r \ll W_e^{-1}$. In this case, for time t such that $t_r, T \ll t \ll W_e^{-1}$, a quasistationary time-periodic probability distribution is formed, centered at $\mathbf{x}_A(t)$. The probability current from $\mathbf{x}_A(t)$ into the extinction plane is also periodic in time, and the period-averaged value of this current gives W_e [24], in a direct analogy with the problem of switching between metastable states in noise-driven dynamical systems [27–29].

III. EIKONAL APPROXIMATION

A. Equations of motion

We will be interested in evaluating the disease extinction barrier $\mathcal{Q}$ which gives the exponent in the disease extinction rate, $W_e \propto \exp(-\mathcal{Q})$, at $N \gg 1$. This barrier is entropic in nature, as it results from an unlikely sequence of elementary transitions. The entropic barrier and the extinction rate can be found by solving the mean first passage time problem for reaching $\mathbf{x}_S(t)$ [7–9], or by calculating the lowest positive eigenvalue of the evolution operator of master equation (1) [13], or from the tail of the quasistationary probability distribution $P(\mathbf{X},t)$ for $\mathbf{x}$ close to $\mathbf{x}_S(t)$ [11,14–16,30]. Here, we choose the latter strategy and determine, to the leading order in N, the logarithm of the distribution tail.

We seek the solution of Eq. (1) in the eikonal form, $P(\mathbf{X},t)=\exp[-Ns(\mathbf{x},t)]$ [31–33]. In the limit of large N, from Eq. (1) we obtain the following equation for $s(\mathbf{x},t)$:

$$\partial_t s = -H(\mathbf{x},\partial_{\mathbf{x}} s,t), \tag{4}$$

$$H(\mathbf{x},\mathbf{p},t)=\sum_{\mathbf{r}} w(\mathbf{x},\mathbf{r},t)[\exp(\mathbf{pr})-1].$$

Here, we have taken into account that, as mentioned above, $|\mathbf{r}| \ll N$, and that typically $W(\mathbf{X},\mathbf{r},t)$ depends on $\mathbf{X}$ polynomially, whereas P is exponential in $\mathbf{X}$. Therefore, we expanded $P(\mathbf{X}+\mathbf{r},t) \approx P(\mathbf{X},t)\exp(-\mathbf{r}\partial_{\mathbf{x}} S)$ and replaced, to the leading order in $1/N$, $w(\mathbf{x}-N^{-1}\mathbf{r},\mathbf{r},t)$ with $w(\mathbf{x},\mathbf{r},t)$.

Equation (4) has the form of the Hamilton-Jacobi equation for an auxiliary Hamiltonian system with Hamiltonian $H(\mathbf{x},\mathbf{p},t)$; $s(\mathbf{x},t)$ is the action of this system. The Hamilton equations of motion are

$$\dot{\mathbf{x}}=\sum_{\mathbf{r}} \mathbf{r} w(\mathbf{x},\mathbf{r},t)e^{\mathbf{pr}},$$

$$\dot{\mathbf{p}}=-\sum_{\mathbf{r}} \partial_{\mathbf{x}} w(\mathbf{x},\mathbf{r},t)(e^{\mathbf{pr}}-1). \tag{5}$$

These trajectories determine, in turn, the most probable or optimal trajectories that the system follows in a fluctuation to a given state $\mathbf{x}$ at time t. We will calculate the action $s(\mathbf{x},t)$ using these trajectories.

B. Boundary conditions for the optimal extinction trajectory

To find the boundary conditions for Hamiltonian trajectories (5), we note that the quasistationary (or quasiperiodic, for a periodically modulated system) distribution $P(\mathbf{X},t)$ has a Gaussian maximum at $\mathbf{X}_A(t)$. This means that, close to attractor $\mathbf{x}_A(t)$, the action $s(\mathbf{x},t)$ is quadratic in $\mathbf{x}-\mathbf{x}_A$ for stationary systems, whereas for periodically modulated systems $s(\mathbf{x},t)=s(\mathbf{x},t+T)$ is quadratic in the distance from $\mathbf{x}_A(t)$ [34]. On the Hamiltonian trajectories that give such an action, the momentum $\mathbf{p} \equiv \partial_{\mathbf{x}} s \to 0$ for $\mathbf{x} \to \mathbf{x}_A(t)$, and since $\mathbf{x}=\mathbf{x}_A(t)$, $\mathbf{p}=0$ is a fixed point (a periodic trajectory) of the Hamiltonian dynamics, the trajectories of interest start at $t \to -\infty$,

$$s(\mathbf{x},t)=\int_{-\infty}^{t} dt L(\dot{\mathbf{x}},\mathbf{x},t),$$

$$L(\dot{\mathbf{x}},\mathbf{x},t)=\sum_{\mathbf{r}} w(\mathbf{x},\mathbf{r},t)[(\mathbf{pr}-1)e^{\mathbf{pr}}+1]. \tag{6}$$

In the Lagrangian L [Eqs. (6)], $\mathbf{p}$ should be expressed in terms of $\dot{\mathbf{x}},\mathbf{x}$ using Eqs. (5). Since $w \geq 0$, we have $L \geq 0$.

The extinction barrier $\mathcal{Q}$ is determined by $Ns(\mathbf{x},t)$ for $\mathbf{x}$ in the extinction hyperplane, $x_E=0$. In the spirit of the eikonal

approximation, we have to find the point $(\mathbf{x},t)$ in this hyperplane where that $s(\mathbf{x},t)$ is minimal. The minimum determines the boundary conditions for the optimal Hamiltonian trajectory of extinction, $(\mathbf{x}_{\rm opt}(t),\mathbf{p}_{\rm opt}(t))$. The condition that $s(\mathbf{x},t)$ is minimal with respect to $x_{i\neq E}$ on the extinction hyperplane means that, for $i\neq E$, $p_i=\partial_{x_i}s$ goes to zero as the trajectory $(\mathbf{x}_{\rm opt}(t),\mathbf{p}_{\rm opt}(t))$ approaches the hyperplane. The minimum of $s(\mathbf{x},t)$ with respect to t within the period of modulation is reached if $H(\mathbf{x},\mathbf{p},t)\to 0$ as the trajectory approaches the hyperplane.

A consequence of the conditions $H(\mathbf{x},\mathbf{p},t)\to 0$ and $p_{i\neq E}\to 0$ is that the momentum component p_E remains bounded on trajectory $(\mathbf{x}_{\rm opt}(t),\mathbf{p}_{\rm opt}(t))$. Indeed, near the extinction hyperplane, $x_E\ll 1$, we have

$$\dot{x}_E=\sum_{\mathbf{r}} r_E w(\mathbf{x},\mathbf{r},t)e^{\mathbf{pr}}\approx x_E\sum_{\mathbf{r}} r_E[\partial w(\mathbf{x},\mathbf{r},t)/\partial x_E]_{x_E=0}e^{p_E r_E}. \tag{7}$$

Here, we assumed that $w(\mathbf{x},\mathbf{r},t)$ is nonsingular at $x_E\to 0$ and, since $w=0$ for $x_E=0$ and $r_E\neq 0$ [cf. Eq. (2)], we expanded w in x_E to the lowest order. Since $w(\mathbf{x},\mathbf{r},t)\geq 0$, we have $\partial w(\mathbf{x},\mathbf{r},t)/\partial x_E\geq 0$ for $x_E=0$.

Let us assume now that $|p_E|\to\infty$ for $x_E\to 0$; it is also clear that p_E should be negative; otherwise, the trajectory would not approach $x_E=0$ [unless all r_E's in Eq. (7) are negative, which is incompatible with the assumption that $\mathbf{x}_S$ is an unstable state in the mean- field approximation]. Then only the term with maximal $-r_E\equiv -r_{Em}$ should be kept in the sum over r_E in Eq. (7). From the Hamilton equation for p_E and Eq. (7) it follows that $dp_E/dx_E\approx -1/x_E r_{Em}$. Using this relation, along with the explicit form of the Hamiltonian H, one can show that, if p_E were diverging for $x_E\to 0$, the Hamiltonian would not become equal to zero but would remain $\approx$const$\times\partial w/\partial x_E$ with the derivative calculated for $x_E=0$ and $r_E=r_{Em}$. This contradiction shows that the assumption $|p_E|\to\infty$ is wrong; p_E remains bounded for $x_E\to 0$.

If $|p_E|$ remains bounded, it follows from Eq. (7) that x_E goes to zero exponentially as $t\to\infty$. As x_E approaches zero, variables $x_{i\neq E}$ are approaching the equilibrium position in the hyperplane $x_E=0$. This happens because $p_{i\neq E}\to 0$ and the dynamics of $x_{i\neq E}$ in the hyperplane is described by the mean-field equations [Eqs. (3)]. Therefore,

$$\mathcal{Q}=Ns_{\rm ext},\quad s_{\rm ext}=\int_{-\infty}^{\infty}dtL(\dot{\mathbf{x}},\mathbf{x},t), \tag{8}$$

$$\mathbf{x}(t)\to\mathbf{x}_S(t),\quad \mathbf{p}(t)\to\mathbf{p}_S(t)\quad \text{for } t\to\infty.$$

The function $\mathbf{p}_S(t)$ is periodic in time, with $p_{i\neq E}=0$ and with hitherto unknown component $p_E(t)$, which is discussed below.

The heteroclinic Hamiltonian trajectory $(\mathbf{x}_{\rm opt}(t),\mathbf{p}_{\rm opt}(t))$ that is given by Eqs. (5) and goes from periodic orbit $(\mathbf{x}_A(t),\mathbf{p}=\mathbf{0})$ to periodic orbit $(\mathbf{x}_S(t),\mathbf{p}_S)$ plays a special role. First of all, it determines the action for extinction $s_{\rm ext}$. In addition, the trajectory $\mathbf{x}_{\rm opt}(t)$ is the optimal path to disease extinction: it describes the most probable sequence of elementary transitions leading to extinction. We note that, in periodically modulated systems, there is one optimal path per period, whereas in stationary systems trajectories $(\mathbf{x}_{\rm opt}(t),\mathbf{p}_{\rm opt}(t))$ are time-translation invariant.

C. $t\to\infty$ value of the momentum on the optimal Hamilton trajectory

The momentum component $(\mathbf{p}_S)_E$ is generically nonzero. This property is a consequence of the topology of the pattern of optimal paths in the extinction problem [15,35]. It was found for both single- and multiple-population stationary systems [9,16,36].

For periodically modulated systems, one can show that $(\mathbf{p}_S)_E\neq 0$ by extending the arguments presented in Refs. [15,35]. This amounts to showing that the stable manifold of the periodic orbit $(\mathbf{x}_S(t),\mathbf{p}=\mathbf{0})$ lies entirely in the invariant hyperplane $x_E=0$, $p_{i\neq E}=0$ and, as a consequence, does not intersect the unstable manifold of the periodic orbit $(\mathbf{x}_A(t),\mathbf{p}=\mathbf{0})$. Such an intersection is necessary in order to have a heteroclinic trajectory that would go from $(\mathbf{x}_A(t),\mathbf{p}=\mathbf{0})$ to $(\mathbf{x}_S(t),\mathbf{p}=\mathbf{0})$.

The hyperplane $x_E=0$, $p_{i\neq E}=0$ is formed by trajectories

$$\dot{x}_{i\neq E}=\sum_{\mathbf{r}}[w(\mathbf{x},\mathbf{r},t)]_{x_E=0}r_i,$$

$$\dot{p}_E=-\sum_{\mathbf{r}}[\partial_{x_E}w(\mathbf{x},\mathbf{r},t)]_{x_E=0}(e^{p_E r_E}-1). \tag{9}$$

The invariance of this hyperplane is a consequence of Eq. (2), which leads to $\dot{p}_{i\neq E}=0$ and $\dot{x}_E=0$ for $p_{i\neq E}=0$ and $x_E=0$.

To prove that the stable manifold of $(\mathbf{x}_S(t),\mathbf{p}=\mathbf{0})$ lies entirely in the invariant hyperplane $x_E=0$, $p_{i\neq E}=0$, we first show that the trajectories, which are described by Eqs. (9) and which start close to the state $(\mathbf{x}_S(t),\mathbf{p}=\mathbf{0})$, approach this state for $t\to\infty$. Then, since the dimension of the hyperplane $x_E=0$, $p_{i\neq E}=0$ is equal to the dimension of the stable manifold of $(\mathbf{x}_S(t),\mathbf{p}=\mathbf{0})$, we conclude that the stable manifold indeed lies in the hyperplane.

Equations (9) for $x_{i\neq E}$ are the mean-field equations in the extinction hyperplane $x_E=0$ [cf. Eqs. (3)] and therefore $x_i\to[\mathbf{x}_S(t)]_i$ for $t\to\infty$. Linearization of the second of Eqs. (9) for p_E about $(\mathbf{x}_S(t),\mathbf{p}=\mathbf{0})$ gives

$$\dot{p}_E=-\sum_{\mathbf{r}}[\partial_{x_E}w(\mathbf{x},\mathbf{r},t)]_{\mathbf{x}_S(t)}p_E r_E. \tag{10}$$

We compare this equation with the mean-field equation for x_E near $\mathbf{x}_S(t)$. The latter has the form $\dot{x}_E=x_E\Sigma_{\mathbf{r}}r_E[\partial_{x_E}w(\mathbf{x},\mathbf{r},t)]_{\mathbf{x}_S(t)}$. Since the state $\mathbf{x}_S(t)$ is unstable in x_E direction in the mean-field approximation, from Eq. (10), $\dot{p}_E/p_E<0$. Therefore, all trajectories on the hyperplane $x_E=0$, $p_{i\neq E}=0$ close to the state $(\mathbf{x}_S(t),\mathbf{p}=\mathbf{0})$ approach this state asymptotically as $t\to\infty$, and thus the stable manifold of $(\mathbf{x}_S(t),\mathbf{p}=\mathbf{0})$ lies in this hyperplane.

From the above analysis one concludes that there are no Hamiltonian trajectories that would go from $(\mathbf{x}_A(t),\mathbf{p}=\mathbf{0})$ to $(\mathbf{x}_S(t),\mathbf{p}=\mathbf{0})$. Therefore, the optimal trajectory leading to extinction should go to a periodic state $(\mathbf{x}_S(t),\mathbf{p}_S(t))$ with $[\mathbf{p}_S(t)]_E\neq 0$. This completes the eikonal formulation of the problem of extinction rate in monostable periodically modulated systems.

D. Systems with several steady states

The above analysis should be modified if the system has, in the mean-field approximation, more than one steady state away from the extinction hyperplane. Here, extinction goes in steps, from the endemic state to another steady state and, ultimately, to the extinction hyperplane. Of interest is the situation where the state $\mathbf{x}_S$ is an attractor for the mean-field dynamics, whereas the only additional steady state is a saddle point at the boundary between the basins of attraction of $\mathbf{x}_A$ and $\mathbf{x}_S$. Here, the problem of extinction is reduced to the problem of escape over this saddle point [30,36], which was discussed for reaction systems earlier [33]. The extension to periodically varying environments is straightforward.

IV. OPTIMAL VACCINATION: THE VARIATIONAL PROBLEM

Vaccination increases the number of individuals who are at least temporarily immune to the disease. It thus reduces the pool of susceptible individuals and ultimately leads to a reduction in the number of infected. When the available amount of vaccine is small, so that the disease extinction still requires a large fluctuation, the goal of vaccination is to reduce the disease extinction barrier $\mathcal{Q}$.

An outcome of vaccination is often modeled as the creation of a subpopulation of vaccinated individuals out of susceptibles. The corresponding elementary transition rate is

$$W(\mathbf{X},\mathbf{r},t) = \xi_0(t)X_S \quad \text{for } r_S = -1, \quad r_V = 1, \quad r_{i\neq S,V} = 0,$$

where subscripts V and S refer to vaccinated and susceptible individuals, respectively, and $\xi_0(t)$ is the control field that characterizes the vaccination (subscript S should not be confused with subscript $\mathcal{S}$ used to indicate the extinction state). Another broadly used model is vaccination of newly arrived susceptibles, which leads to an effective reduction of the arrival rate μN. In this model, the elementary transition rate for the arrival is

$$W(\mathbf{X},\mathbf{r},t) = N[\mu - \xi_0(t)] \quad \text{for } r_S = 1, \quad r_{i\neq S} = 0,$$

with $\xi_0(t)N$ being the change in the arrival rate due to vaccination.

We will consider a general model where vaccination modifies the rate of an elementary transition of a certain type or creates a new transition; the change in the population in the vaccination-related transition is $\mathbf{r}_\xi$. The field $\xi_0(t)$ that characterizes the vaccination is assumed to be weak. The affected rate has the form $W(\mathbf{X},\mathbf{r}_\xi,t) = W^{(0)}(\mathbf{X},\mathbf{r}_\xi,t) + \xi_0(t)W^{(1)}(\mathbf{X},\mathbf{r}_\xi)$, with $W^{(0)}$ being the rate without vaccination. The vaccination either increases or decreases the rate, as for transitions from susceptibles to vaccinated or for vaccination of newly arrived susceptibles, respectively. Therefore, we will assume without loss of generality that $\xi_0(t) \geq 0$ and that $W^{(1)}(\mathbf{X},\mathbf{r}_\xi)$ is either positive or negative. We consider models in which the number of susceptibles changes by 1 in an elementary transition associated with vaccination, $S \to S-1$. We note that the analysis can be immediately extended to describe other processes, such as modification of the infection rates [3] or recovery acceleration by administrating medicine.

It should be noted that the vaccination model adopted in this work is probabilistic by nature. An alternative is where vaccination is done in a predetermined fashion, when individuals are vaccinated at a certain rate at a given time. The analysis of such deterministic vaccination lies beyond the scope of this paper.

We will assume that the vaccination rate is periodic, with $\xi_0(t) = \xi_0(t+T)$, and that the amount of vaccine available per period T is limited. We model this limitation as a constraint on the ensemble-averaged number of individuals vaccinated per period T. The constraint can be written as

$$T^{-1}\int_0^T dt\,\xi_0(t)\sum_{\mathbf{X}} |W^{(1)}(\mathbf{X},\mathbf{r}_\xi)|P(\mathbf{X},t) = N\Xi. \tag{11}$$

Here, Ξ is the average vaccination rate rescaled by the characteristic population size N. The constraint is well defined for $t_r \ll t \ll W_e^{-1}$, where $P(\mathbf{X},t+T) \approx P(\mathbf{X},t)$. Since for $N \gg 1$ the population distribution sharply peaks at the endemic state $\mathbf{X}_A(t)$, the sum over $\mathbf{X}$ in Eq. (11) can be replaced with $|W^{(1)}(\mathbf{X}_A(t),\mathbf{r}_\xi)|$ to the leading order in $1/N$.

In the presence of vaccination, one can still seek a solution of the master equation in the eikonal form. The exponent $\mathcal{Q}$ in the extinction rate is again given by the action of an auxiliary Hamiltonian system [Eqs. (8)]. The Hamiltonian now has the form

$$H(\mathbf{x},\mathbf{p},t) = H^{(0)}(\mathbf{x},\mathbf{p},t) + \xi_0(t)H^{(1)}(\mathbf{x},\mathbf{p}),$$

$$H^{(0)}(\mathbf{x},\mathbf{p},t) = \sum_{\mathbf{r}} w^{(0)}(\mathbf{x},\mathbf{r},t)(e^{\mathbf{pr}} - 1),$$

$$H^{(1)}(\mathbf{x},\mathbf{p}) = w^{(1)}(\mathbf{x},\mathbf{r}_\xi)(e^{\mathbf{pr}_\xi} - 1). \tag{12}$$

Our goal is to find the optimal form of $\xi_0(t)$ which would minimize the disease extinction barrier $\mathcal{Q}$ subject to constraint (11). Since $w^{(1)}(\mathbf{x}_A(t),\mathbf{r}_\xi)$ is a known periodic function of time, we can equivalently search for the optimal *vaccination rate* $\xi(t) \equiv \xi_0(t)|w^{(1)}(\mathbf{x}_A(t),\mathbf{r}_\xi,t)|$. It minimizes the functional

$$\tilde{s}_{\text{ext}}[\xi(t)] = s_{\text{ext}}[\xi(t)] + \lambda T^{-1}\int_0^T [\xi(t) - \Xi]dt,$$

$$\xi(t) = \xi(t+T) = \xi_0(t)|w^{(1)}(\mathbf{x}_A(t),\mathbf{r}_\xi)| \geq 0, \tag{13}$$

where λ is the Lagrange multiplier. The functional $s_{\text{ext}}[\xi]$ is given by Eqs. (8), where the Lagrangian corresponds to the Hamiltonian (12) and depends on the vaccination rate $\xi(t)$.

V. VACCINATION PROTOCOL FOR A STATIC ENVIRONMENT

In this section we consider optimal vaccination for systems that are stationary in the absence of vaccination. Respectively, the rates $W^{(0)}$ and the states $\mathbf{x}_A, \mathbf{x}_S$ are independent of time.

A. Double optimization problem

For a low average vaccination rate Ξ it suffices to keep in the action $s_{\text{ext}}[\xi(t)]$ only the leading-order term in $\xi(t)$. Since

Hamiltonian (12) is linear in ξ, this term is linear in ξ, too. In the spirit of the standard perturbation theory for Hamiltonian systems [37], the change in the action, caused by the small perturbation, can be calculated along the unperturbed trajectory $(\mathbf{x}_{\rm opt}^{(0)}(t), \mathbf{p}_{\rm opt}^{(0)}(t))$ of the Hamiltonian $H^{(0)}$, which describes the optimal path of disease extinction in the absence of vaccination.

For systems that are stationary in the absence of vaccination,

$$s_{\rm ext}[\xi(t)] = s_{\rm ext}^{(0)} + s_{\rm ext}^{(1)}[\xi(t)],$$

$$s_{\rm ext}^{(1)}[\xi(t)] = \min_{t_0} \int_{-\infty}^{\infty} dt \chi(t - t_0)\xi(t),$$

$$\chi(t) = -H^{(1)}(\mathbf{x}_{\rm opt}^{(0)}(t), \mathbf{p}_{\rm opt}^{(0)}(t))|w^{(1)}(\mathbf{x}_A, \mathbf{r}_\xi)|^{-1}. \quad (14)$$

The quantity $\chi(t)$ is called logarithmic susceptibility [15,24,38]; it gives the change in the logarithm of the extinction rate, which is linear in the vaccination rate for moderately low vaccination rate.

The minimization over t_0 in Eqs. (14) accounts for lifting the time-translational invariance of the optimal extinction paths mentioned earlier. For $\xi(t) \equiv 0$, extinction can occur at any time $(t_r \ll t \ll W^{-1})$ with rate W_e. Periodic vaccination synchronizes extinction events; it periodically modulates the extinction rate, and the modulation is exponentially strong for $\exp(N|s_{\rm ext}^{(1)}|) \gg 1$ (see below). Formally, in a modulated system there is only one optimal extinction path per period, as explained in Sec. III, which is reflected here in the minimization over t_0. This optimal path minimizes the disease extinction barrier $\mathcal{Q} = N s_{\rm ext}$ [15,23,24,27,38]. Equations (14) are closely related to the Mel'nikov theorem for dynamical systems [39].

The constraint for minimizing the action over $\xi(t)$ in Eqs. (13) has a form of an integral over the vaccination period T. It is therefore convenient to write action $s_{\rm ext}^{(1)}$ also in the form of such an integral,

$$s_{\rm ext}^{(1)}[\xi(t)] = \min_{t_0} \int_0^T dt \xi(t) \chi_T(t - t_0),$$

$$\chi_T(t) = \sum_{n=-\infty}^{\infty} \chi(t + nT). \quad (15)$$

The function $\chi_T(t)$ is obtained by superimposing the parts of $\chi(t)$ which differ by T. By construction, $\chi_T(t)$ is periodic in time t.

Synchronization of extinction events, which underlies the approximation (14), occurs if the temporal width of the tube of fluctuational paths leading to extinction is smaller than T; this tube is centered at the optimal extinction path $\mathbf{x}_{\rm opt}(t - t_0)$. From the analogy with the problem of escape of modulated systems [25,27] we expect that this tube is Gaussian, with a characteristic width determined by the change in $s_{\rm ext}^{(1)}$ when t_0 is changed from its optimal value, that is, this width is $\sim T|N s_{\rm ext}^{(1)}|^{-1/2}$. The actual condition of synchronization is that the corresponding Gaussian distribution has a sharp peak, which requires $\exp(N|s_{\rm ext}^{(1)}|) \gg 1$. In the case where T is small compared to the relaxation time t_r and with the characteristic oscillation period of the path $\mathbf{x}_{\rm opt}(t)$ (if this path is oscillating), the synchronization may be lost for not too large $|N s_{\rm ext}^{(1)}|$; the value of $s_{\rm ext}^{(1)}$ is then determined by the time-average component of the modulation, but the modulation still leads to the strong effect for $\exp|N s_{\rm ext}^{(1)}| \gg 1$. We note that we have not considered the prefactor in the disease extinction rate. The corrections to the prefactor due to the vaccination are small compared to the factor $\exp|N s_{\rm ext}^{(1)}|$.

B. Temporal shape of optimal vaccination

To find the optimal shape of vaccination rate $\xi(t)$ we first minimize the time integral in the variational problem (13)–(15) with respect to $\xi(t)$ for a given t_0. Since $\xi(t) \geq 0$, it is convenient to perform the minimization with respect to $\xi^{1/2}(t)$ rather than $\xi(t)$. The minimization shows that $\xi^{1/2}(t) \neq 0$ only for $t = t_\lambda$, where t_λ is given by the equation $\chi_T(t_\lambda - t_0) = -\lambda/T$. From the constraint on the period-averaged $\xi(t)$ we then have

$$\xi(t) = \Xi T \sum_n \delta(t - t_\lambda + nT). \quad (16)$$

Substituting this expression into the functional $\tilde{s}_{\rm ext}$ and minimizing with respect to t_0, we obtain the action in a simple explicit form

$$s_{\rm ext} = \min \tilde{s}_{\rm ext} = s_{\rm ext}^{(0)} + s_{\rm ext}^{(1)},$$

$$s_{\rm ext}^{(1)} = \Xi T \min_{0 \leq t < T} \chi_T(t). \quad (17)$$

Alternatively, this expression can be rewritten in terms of the Fourier transform of the logarithmic susceptibility,

$$s_{\rm ext}^{(1)} = \Xi \min_t \sum_n \tilde{\chi}(n\Omega)\exp[in\Omega t],$$

$$\tilde{\chi}(\omega) = \int_{-\infty}^{\infty} dt \chi(t)\exp(i\omega t), \quad (18)$$

where $\Omega = 2\pi/T$ is the cyclic frequency of vaccination.

We are interested in the solution for which $s_{\rm ext}^{(1)}$ is negative, which requires $\min \chi_T(t) < 0$. Only in this case will vaccination reduce the barrier for disease extinction and increase the disease extinction rate. The barrier reduction due to vaccination, $\mathcal{Q}^{(1)} = N s_{\rm ext}^{(1)} \propto N\Xi$, becomes large for $N \gg 1$ even if the average vaccination rate Ξ is small. The effect of vaccination on the disease extinction rate is exponentially strong for $\exp|\mathcal{Q}^{(1)}| \gg 1$.

The expression for the action change $s_{\rm ext}^{(1)}$ [Eqs. (17)] can be also obtained in a more intuitive way. Indeed, since $\xi(t)$ is non-negative, it follows from Eqs. (15) that

$$s_{\rm ext}^{(1)}[\xi(t)] \geq \min_t \chi_T(t) \int_0^T dt \xi(t) = \Xi T \min_t \chi_T(t). \quad (19)$$

The minimum is provided by $\xi(t) = \Xi T \Sigma_n \delta(t - t_{min} + nT)$. Formally, t_{min} is the instance of time where $\chi_T(t)$ is minimal. In fact, it is the optimal path that adjusts to the vaccination

pulses so as to increase the probability of disease extinction. This provides the mechanism of synchronization by vaccination. Equation (19) immediately leads to Eqs. (16) and (17) with t_λ replaced with t_{min}.

C. Effect of the constraint on the maximal vaccination rate

In addition to the constraint on the average vaccination rate, there may be an upper limit on the instantaneous vaccination rate, which is imposed by the condition $w(\mathbf{x},\mathbf{r})=w^{(0)}(\mathbf{x},\mathbf{r}_\xi)+\xi(t)w^{(1)}(\mathbf{x},\mathbf{r}_\xi)\geq 0$. In the case where $w^{(1)}(\mathbf{x},\mathbf{r}_\xi)<0$, as for vaccination of newly arrived susceptibles, this condition is met provided $\xi_0(t)\leq\xi_{0m}\equiv\min\{w^{(0)}(\mathbf{x},\mathbf{r}_\xi)/|w^{(1)}(\mathbf{x},\mathbf{r}_\xi)|\}$. In this case the optimal vaccination protocol changes.

The new protocol can be found from the variational problem (13) by changing from $\xi(t)\equiv\xi_0(t)|w^{(1)}(\mathbf{x}_A,\mathbf{r}_\xi)|$ to an auxiliary function $\eta(t)$ such that $\xi_0(t)=\xi_{0m}[1+\eta^2(t)]^{-1}$, and then finding the minimum of $\tilde{s}_{\rm ext}$ with respect to $\eta(t)$. This choice satisfies the constraints $0\leq\xi_0(t)\leq\xi_{0m}$. Variation with respect to $\eta(t)$ shows that $\tilde{s}_{\rm ext}$ has an extremum for $\eta(t)=0$ or $\eta(t)=\infty$ for $t\neq t_\lambda$, where t_λ is given by the equation $\chi_T(t_\lambda-t_0)=-\lambda/T$. The value of $\eta(t)$ at the isolated instances $t=t_\lambda$ is arbitrary. Only regions where $\eta(t)=0$, so that $\xi_0(t)=\xi_{0m}$, contribute to $\tilde{s}_{\rm ext}$. Obviously, $\tilde{s}_{\rm ext}$ is minimal when $\xi_0(t)=\xi_{0m}$ for $|t-t_{min}|\leq\Delta t/2$, where t_{min} is the time when $\chi_T(t)$ is minimal and Δt is determined by the average vaccination rate Ξ. In other words, the vaccination rate $\xi(t)$ has the form of periodic rectangular pulses of width Δt, centered at $t_{min}+nT$, with $n=0,\pm1,\pm2,\ldots$. The pulse width is

$$\Delta t=\frac{\Xi T}{\xi_{0m}|w^{(1)}(\mathbf{x}_A,\mathbf{r}_\xi)|}. \tag{20}$$

Since the vaccination rate is limited by the rate of elementary transitions without vaccine, we have $\xi_{0m}|w^{(1)}(\mathbf{x}_A,\mathbf{r})|\lesssim t_r^{-1}$. Then for weak vaccination, $\Xi T\ll 1$, from Eq. (20), $\Delta t\ll t_r$. Therefore, $\chi_T(t)=\chi_T(t_{min})$ during the pulse of $\xi(t)$ to the leading order in ΞT [we note that $\chi_T(t)$ may vary on a time scale shorter than t_r (see below); however, this time scale is always long compared to Δt for sufficiently weak vaccination]. The resulting change in the action is again given by Eqs. (17).

VI. VACCINATION PROTOCOL FOR A PERIODICALLY VARYING ENVIRONMENT

Optimal vaccination requires a separate consideration if the environment is periodically varying in time, and thus the system is strongly periodically modulated even without vaccination. Here, there is only one optimal extinction path per modulation period T. The optimal paths are periodically repeated (cf. Ref. [25]). If the added vaccination has a low average rate Ξ and the same period T, it will only weakly perturb the paths. It is important, however, that the vaccination will only slightly shift each optimal path in time. This is a consequence of the lack of the continuous time-translation symmetry in a modulated system. Qualitatively, this means that vaccination does not synchronize extinction events; they are already synchronized by the modulation.

Formally, to first order in Ξ, the linear in ξ term in the action still has the form of Eqs. (15), but without minimization over t_0, which corresponds to shifting optimal paths in time. Since $\xi(t)\geq 0$, the minimum of the action is still achieved for $\xi(t)=\Xi T\Sigma_n\delta(t-t_{min}+nT)$, but now t_{min} is uniquely determined by the variations in the environment. This means that the phase of the optimal vaccination pulses is uniquely determined. The resulting expression for $s_{\rm ext}^{(1)}$ for the optimal vaccination protocol has the form of Eqs. (17).

If the vaccination pulses are applied at a wrong time, that is, the phase difference between the vaccination and the modulation differs from the optimal one, the vaccination will not be as efficient. Quite counterintuitively, vaccination may even be harmful: it may prolong the lifetime of the endemic state by *increasing* the disease extinction barrier $\mathcal{Q}$.

The possibility of a harmful effect of vaccination can be understood by noting that the logarithmic susceptibility $\chi(t)$ may change sign and become oscillating [40]. An example of such a behavior is given in Sec. VIII. In particular, it happens where, in the absence of fluctuations, the system does not simply monotonically approach the endemic state $\mathbf{x}_A(t)$ but performs decaying oscillations about it. Formally, it means that the characteristic exponent of $\mathbf{x}_A(t)$ (the Floquet exponent) is complex. In this case, on the optimal extinction path different population groups also oscillate in time, at least not too far from $\mathbf{x}_A(t)$. As the amplitude of these oscillations increases the system moves away from $\mathbf{x}_A(t)$ toward the extinction plane.

If the vaccine pulses are applied in such a way as to amplify the oscillations along the optimal extinction path, the vaccination will accelerate disease extinction. In the opposite case, even though the vaccination pulses decrease the number of susceptibles, they will decrease the oscillation amplitude and drive the system back toward $\mathbf{x}_A(t)$, making the disease extinction less likely. Alternatively, and more formally, one can notice that a δ-shaped vaccination pulse shifts the system along the optimal path. This shift has a certain sign since the vaccination is sign definite. If the shift is in the positive direction, the extinction probability increases. However, if the optimal path is oscillating, the shift can be also in the negative direction, leading to the increase in the extinction barrier.

VII. DISEASE EXTINCTION BARRIER AS A FUNCTION OF VACCINATION PERIOD

The vaccination-induced reduction of the disease extinction barrier $\mathcal{Q}^{(1)}=Ns_{\rm ext}^{(1)}$, as given by Eqs. (17), depends on the interrelation between the vaccination period T and the characteristic time scales of the logarithmic susceptibility $\chi(t)$. The function $\chi(t)$ may or may not oscillate in time, but generally $\chi(t)$ is relatively large within a time interval of the order of the relaxation time of the system t_r [24,38,40]. To reveal some qualitative features of the effect of vaccination and, in particular, its dependence on the vaccination period, we will consider $s_{\rm ext}^{(1)}$ for two types of constraint on this period.

A. Limited lifetime of the vaccine

The vaccination period T is naturally limited by the effective lifetime τ_v of the vaccine. This lifetime is usually deter-

mined by the maximum storage time of the vaccine and/or by the mutation rates of the infectious agent. If τ_v is long, $\tau_v \gg t_r$, vaccination can be made most efficient by increasing the vaccination period up to $\sim \tau_v$. It follows from Eqs. (17) that $s_{ext}^{(1)} \propto T$ in this case. Indeed, it can be seen from Eqs. (5), (12), and (14) that, as the system moves along the optimal path to extinction, $\chi(t)$ is significant when the system is far from the stationary states $\mathbf{x}_A$ and $\mathbf{x}_S$. The characteristic time scale of this motion is $\sim t_r$. For $T \gg t_r$ we have $\min_{0\le t\le T} \chi_T(t) \approx \min_t \chi(t)$ and

$$s_{ext}^{(1)} = \Xi T \min_t \chi(t), \quad \tau_v \gtrsim T \gg t_r. \tag{21}$$

We note that the decrease in $\Omega = 2\pi/T$ causes a decrease in the effect of the vaccination on the disease extinction rate W_e, just because a smaller number of vaccination pulses are applied per unit time. However, the sharp increase in the exponential factor $\exp(-N s_{ext}^{(1)})$ in W_e is far more important (we remind that $W_e T \ll 1$).

In the opposite limit of $\tau_v \ll t_r$, and thus $T \ll t_r$, we have from Eqs. (18)

$$s_{ext}^{(1)} = \Xi \tilde{\chi}(0), \quad t_r \gg \tau_v \gtrsim T. \tag{22}$$

In this case the vaccination-induced reduction of the extinction barrier is independent of the vaccination period and is determined by the zero-frequency component of the logarithmic susceptibility.

An interesting situation may occur in the intermediate range $\tau_v \sim t_r$ if, in the mean-field description, the system approaches the endemic state in an oscillatory manner. In this case the function $\chi(t)$ is also expected to oscillate. The oscillations are well pronounced if their typical frequency is $\omega_0 \gg t_r^{-1}$. It is clear from Eqs. (18) that a strong effect on disease extinction can be achieved by tuning the vaccination frequency $\Omega = 2\pi/T$ or its overtones in resonance with ω_0. An example of such a resonance will be discussed in Sec. VIII.

B. Limited vaccine accumulation

A different situation occurs if the total amount of vaccine that can be accumulated is limited. This limitation implies that $\Xi T \le M$; note that M constrains the *ensemble-averaged* amount of the accumulated vaccine. A limitation on vaccine accumulation is typical for live vaccines, as it may be dangerous to store too much vaccine in this case. The actual average vaccination rate can be now T dependent. We use the notation Ξ_a for this rate, with

$$\Xi_a = \min(\Xi, M/T). \tag{23}$$

This is Ξ_a that should be used in Eqs. (21) and (22) for $s_{ext}^{(1)}$ in the limits $T \gg t_r$ and $T \ll t_r$, respectively.

The behavior of $s_{ext}^{(1)}$ with varying vaccination period T depends on the form of the logarithmic susceptibility $\chi(t)$. Let us first consider the case where $\chi(t)$ has a single local minimum (at $t=t_*$), $\chi(t_*) < 0$, and $|\chi(t)|$ monotonically decays to zero with increasing $|t-t_*|$. Here, once the vaccine accumulation has reached saturation with increasing T (which happens for $\Xi T = M$), the action $|s_{ext}^{(1)}| = M|\min \chi_T(t)|$

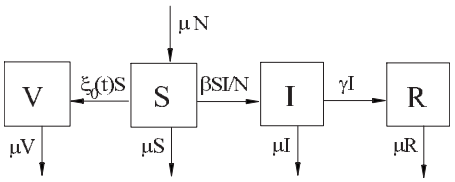

FIG. 1. The SVIR epidemic model with susceptible, vaccinated, infected, and recovered subpopulations. The arrows indicate processes leading to changes in subpopulation sizes. The corresponding rates are indicated next to the arrows.

monotonically decreases with further increase in T. To show this we introduce a parameter a_* that defines the minimum of $\chi_T(t)$ over t and is given by the equation $\partial \chi_T(t_* - a_* T)/\partial a_* = 0$; we choose $0 < a_* < 1$. In terms of this parameter,

$$\frac{d}{dT} \min_{0<t<T} \chi_T(t) = \frac{\partial}{\partial T} \sum_n \chi(t_* - a_* T + nT)$$
$$= \sum_n \left(\frac{d\chi(t - a_* T + nT)}{dt} \right)_{t=t_*} (n - a_*) > 0. \tag{24}$$

We have used here that, if $\chi(t)$ is minimal for $t=t_*$, then $d\chi/dt > 0$ for $t > t_*$ and $d\chi/dt < 0$ for $t < t_*$. It follows from Eq. (24) that, once the vaccine accumulation has reached saturation, an increase in T will only reduce the effect of the vaccine. This result is understandable because, if T increases beyond M/Ξ, the actual average vaccination rate Ξ_a decreases.

A counterintuitive situation may occur if $\chi(t)$ is oscillating. Here, the inequality (24) may be violated. As a result, the dependence of the effect of the vaccine on T and, consequently, on the actual vaccination rate Ξ_a [Eq. (23)] may be nonmonotonic. An example of this behavior is discussed in the next section.

VIII. RESONANCES IN THE STOCHASTIC SVIR MODEL

A. Logarithmic susceptibility

We now apply some of our results to a widely used stochastic epidemic model, the susceptible-vaccinated-infected-recovered (SVIR) model. The model is sketched in Fig. 1. In the absence of vaccination, $\xi_0(t) = 0$, the SVIR model reduces to the susceptible-infected-recovered (SIR) model with population turnover, which was originally introduced to describe the spread of diseases that confer long-lasting immunity, such as measles, mumps, and rubella (see [1,3]). In the SIR model, susceptible individuals are brought in, individuals in all population groups leave (for example, die), a susceptible individual can become infected upon contacting an infected individual, and an infected individual can recover. If we set $X_1 = S$, $X_2 = I$, and $X_3 = R$, the rates of the corresponding processes are (i) influx of the susceptibles, $W(\mathbf{X}, \mathbf{r}) = \mu N$ for $r_1 = 1, r_{i\ne 1} = 0$; (ii) leaving, with the same rate for all populations, $W(\mathbf{X}, \mathbf{r}) = \mu X_i$ for $r_i = -1, r_{j\ne i} = 0$; (iii) infection, $W(\mathbf{X}, \mathbf{r}) = \beta X_1 X_2 / N$ for $r_1 = -1$, $r_2 = 1$, $r_{i\ne 1,2} = 0$; and (iv) recovery of the infected, $W(\mathbf{X}, \mathbf{r}) = \gamma X_2$ for $r_2 = -1, r_3 = 1, r_{i\ne 2,3} = 0$ (Fig. 1).

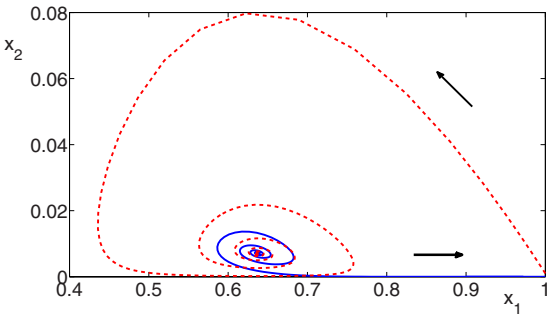

FIG. 2. (Color online) The most probable trajectories in the stochastic SIR model on the plane of the scaled numbers of susceptibles and infected, $x_1=X_1/N$ and $x_2=X_2/N$, respectively. The dashed line shows a mean-field trajectory toward the endemic state, and the solid line shows the most probable trajectory followed during the fluctuation-induced disease extinction [16]. The plot refers to $\beta/\mu=80$ and $\gamma/\mu=50$.

In the SIR model the recovered keep their immunity; they do not become susceptible again. The pool of recovered is a "sink;" there is no influx to other groups and the transition rates are independent of R. Therefore, the model is described by two dynamical variables: S and I. For $\beta>\Gamma\equiv\gamma+\mu$ the SIR model possesses a single endemic state. This state corresponds, in the mean-field theory, to an attracting fixed point $\mathbf{x}_A$ on the two-dimensional phase plane of susceptibles and infected. For $\mu<4(\beta-\Gamma)(\Gamma/\beta)^2$ this attracting point is a focus.

In the mean-field approximation, the populations of susceptibles and infected exhibit decaying oscillations in time as the system approaches the endemic state. This is a generic behavior for a two-variable dynamical system. It was found in Ref. [16] that, in the same parameter range, the populations oscillate also on the optimal disease extinction path. These oscillations are illustrated in Fig. 2.

We will now incorporate vaccination and introduce a subpopulation of vaccinated $X_4=V$. The vaccination is described by the transition rate $W(\mathbf{X},\mathbf{r})=\xi_0(t)x_1$ for $r_1=-1$, $r_4=1$, $r_{i\neq1,4}=0$. The corresponding term in the Hamiltonian (12) has the form $\xi_0(t)H^{(1)}$ with

$$H^{(1)}(\mathbf{x},\mathbf{p})=x_1(e^{p_4-p_1}-1). \tag{25}$$

Vaccinated individuals leave at the same rate μ as individuals in other populations. For simplicity, we assume that the immunity from the vaccination is never lost. In this case fluctuations of the vaccinated population do not affect fluctuations of other populations, and $p_4\equiv0$ along the optimal extinction path. Then from Eqs. (14), the logarithmic susceptibility is $\chi(t)=x_{1\mathrm{opt}}^{(0)}(t)x_{1A}^{-1}\{1-\exp[-p_{1\mathrm{opt}}^{(0)}(t)]\}$, where $x_{1\mathrm{opt}}^{(0)}(t)$, $p_{1\mathrm{opt}}^{(0)}(t)$, and x_{1A} are calculated for the SIR model.

The Fourier spectrum of the logarithmic susceptibility $\tilde{\chi}(\omega)$ is plotted in Fig. 3(a). It corresponds to the optimal extinction path shown in Fig. 2. As one can see, the spectrum has a peak at the characteristic frequency of oscillations of the system in the absence of vaccination ω_0. For the chosen parameter values $\omega_0\approx5.2\mu$ and the vibration decrement near $\mathbf{x}_A$ is $\beta\mu/2\Gamma\approx0.8\mu$. The height of the peak of $\tilde{\chi}(\omega)$ increases and the width decreases with the decreasing decrement.

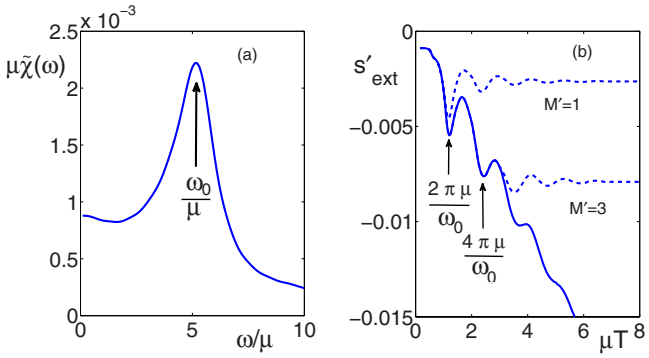

FIG. 3. (Color online) (a) The Fourier transform of the logarithmic susceptibility in the SIR model. The parameters are the same as in Fig. 2. The susceptibility spectrum displays a sharp peak at the characteristic vibration frequency ω_0. (b) The change in the scaled extinction barrier $s'_{\mathrm{ext}}=\mu s_{\mathrm{ext}}^{(1)}/\Xi$ with vaccination period T. The solid line shows s'_{ext} where there is no limit on vaccine accumulation, whereas the dashed lines refer to the case of a limited amount of accumulated vaccine. The accumulation limit M is scaled by the small-T average vaccination rate Ξ, $M'=\mu M/\Xi$. The locations of resonances of $s_{\mathrm{ext}}^{(1)}$ are independent of M.

As mentioned above, the occurrence of a spectral peak in the logarithmic susceptibility for noise-driven dynamical systems was discussed earlier [40]. Soskin *et al.* [41] noticed that, if in the absence of noise a dynamical system (a particle in a double-well potential) has an extremely weak damping, a periodic driving can lead to a stochastic layer near the separatrix, which also reduces the barrier for noise-induced switching. The problem discussed in this paper is very different. Even though the mean-field trajectories can be tight spirals, there are no two stable states and no separatrix (the extinction hyperplane is not a separatrix), and therefore the mechanism of Ref. [41] is irrelevant. We consider the case where vaccination only weakly perturbs the mean-field dynamics.

B. Resonant vaccination

We now consider the features of the optimal vaccination protocol related to the occurrence of a resonant peak in $\tilde{\chi}(\omega)$. The dependence of the scaled change in the disease extinction barrier $s_{\mathrm{ext}}^{(1)}=\mathcal{Q}^{(1)}/N$ on vaccination period T is shown in Fig. 3(b). The solid line in Fig. 3(b) shows the behavior of $s_{\mathrm{ext}}^{(1)}$ where there is no limit on vaccine accumulation or, equivalently, for such periods where the limitation does not come into play and the actual vaccination rate Ξ_a [Eq. (23)] is independent of T. The function $|s_{\mathrm{ext}}^{(1)}|\equiv-s_{\mathrm{ext}}^{(1)}$ is seen to be strongly nonmonotonic; it displays pronounced maxima (which correspond to the minima of $s_{\mathrm{ext}}^{(1)}$). They occur where the vaccination period T coincides with the multiples of the characteristic period of the system motion without vaccination $2\pi/\omega_0$.

For limited vaccine accumulation M, the actual average vaccination rate Ξ_a depends on the vaccination period [see Eq. (23)]. Beyond a certain value of T, the increase in T is

accompanied by the decrease in Ξ_a. This leads to a change in the dependence of $s_{\rm ext}^{(1)}$ on T. Remarkably, $|s_{\rm ext}^{(1)}|$ still displays resonant peaks at $2\pi n/\omega_0$ with integer n. Their amplitude decreases with increasing n.

The occurrence of the peaks of $|s_{\rm ext}^{(1)}|$ shows that, by tuning the vaccination period, the effect of the vaccination can be resonantly enhanced. The quantity that displays the resonant behavior in this case is in the exponent of the disease extinction rate, and therefore the resonance is extremely strong. Counterintuitively, since the actual average vaccination rate Ξ_a decreases with increasing T, a strong enhancement of the effect of vaccination can be achieved by increasing T and thus decreasing the rate Ξ_a. For example, in Fig. 3(b) the maxima of $|s_{\rm ext}^{(1)}|$ for $\mu M/\Xi=1$ and $\mu M/\Xi=3$ are achieved for such T that $\Xi_a<\Xi$. This means that using less vaccine on average gives a better effect provided the vaccination is resonant.

IX. CONCLUSIONS

We have developed a theory of optimal periodic vaccination against an endemic disease for low average vaccination rate, where this rate is insufficient for eliminating the endemic state and thus exterminating the disease by "brute force." Such a situation occurs where the vaccine is in short supply, or short lived, or cannot be stored in the sufficient amount. We find that, nevertheless, vaccination can exponentially strongly change the rate of spontaneous disease extinction, which occurs as a result of a large and comparatively rare fluctuation. This happens because the vaccine changes the effective entropic barrier that needs to be overcome for the disease to become extinct.

Our analysis refers to fluctuations caused by the randomness of the individual events of infection, recovery, etc. These fluctuations are similar to those coming from the randomness of elementary reactions in reaction systems of various types. Our results can be immediately applied to such systems, with vaccination being understood as inhibition of certain reactions, for example.

The approach is based on the master equation for the stochastic population dynamics. We solve it in the eikonal approximation and reduce the problems of the tail of the distribution and of the disease extinction rate to Hamiltonian dynamics of an auxiliary system. A general formulation of the corresponding Hamiltonian problem is obtained for population dynamics in a periodically varying environment, i.e., for periodically modulated population systems. This formulation is used to find the optimal vaccination protocol for a limited average vaccination rate. The feature of the problem that makes it different from other problems of optimal control of rare events is that the control field, which is the vaccination rate, cannot be negative. The analysis can be extended to other problems of optimal control of fluctuation-driven extinction with similar constraints.

We show that, for a fixed average vaccination rate, vaccination should be performed as a periodic sequence of δ-like pulses. This protocol is essentially independent of the epidemics model; it only requires that the population be spatially uniform. In a static environment (stationary systems in the absence of vaccination), the phase of the vaccination pulses is not important. In contrast, in a periodically varying environment, like in the case of seasonally varying infection, it is necessary to appropriately synchronize vaccination pulses with the environment variations. Moreover, if the pulse phase is wrong, vaccination may hamper disease extinction.

We find that the disease extinction rate as a function of vaccination period T can display exponentially strong resonances. Such vaccination resonances occur if T coincides with the period of decaying oscillations of the population, which characterize the approach to the endemic state in the mean-field (fluctuation-free) approximation. The resonances occur also where T coincides with a multiple of the dynamical period, although they may be less pronounced in this case. The onset of the vaccination resonances is illustrated using the well-known SVIR model of population dynamics.

For a fixed average vaccination rate, the effect of vaccination in stationary systems increases with the increasing vaccination period. However, this increase is generally nonmonotonic where there are vaccination resonances. On the other hand, the results change if there are constraints on the vaccination period. We have obtained explicit results for two types of such constraints: a limited lifetime of the vaccine and a limited maximal amount of the vaccine.

It turns out that, counterintuitively, the effect of vaccination can be sometimes enhanced by reducing the average vaccination rate. This happens where the system displays vaccination resonances and there is a constraint on the amount of vaccine that can be stored. In this case lowering the average vaccination rate can allow one to tune the vaccination period to a resonant value.

To summarize, vaccination at even a comparatively small mean rate can exponentially increase the rate of spontaneous disease extinction. The optimal vaccination strategy for periodic vaccination is to apply the vaccine in the form of δ-like pulses. Tuning these pulses in resonance with the system dynamics leads to a further exponential enhancement of the effect of the vaccination.

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