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Seasonal forcing in stochastic epidemiology models

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Abstract The goal of this paper is to motivate the need and lay the foundation for the analysis of stochastic epidemiological models with seasonal forcing. We consider stochastic SIS and SIR epidemic models, where the internal noise is due to the random interactions of individuals in the population. We provide an overview of the general theoretic framework that allows one to understand noise-induced rare events, such as spontaneous disease extinction. Although there are many paths to extinction, there is one path termed the optimal path that is probabilistically most likely to occur. By extending the theory, we have identified the quasi-stationary solutions and the optimal path to extinction when seasonality in the contact rate is included in the models. Knowledge of the optimal extinction path enables one to compute the mean time to extinction, which in turn allows one to compare the effect of various control schemes, including vaccination and treatment, on the eradication of an infectious disease.

Keywords Stochastic · Epidemiology · Seasonality · Extinction · Rare events

Mathematics Subject Classification 60H30 · 92D30 · 34F05 · 70K40

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1 Introduction

Consider the research disciplines of epidemiology and mathematical modeling. Epidemiology involves the study and analysis of health-related events. One focus is the analysis of observed patterns of infectious disease in human populations, along with the implementation of programs such as mass vaccination to control the disease. Mathematical modeling aims to describe real-world physical and biological phenomena. In particular, a main goal of modeling is to predict future quantities and the dynamics of the system of interest based on current observations. Once the system is well-understood, control may be implemented to change how the system behaves so that a desired state is achieved.

These two disciplines seem to be an ideal example for research convergence [1,2], where multidisciplinary approaches and analysis provide for the emergence of novel methods to address challenging public health issues. However, many results from mathematical epidemiology, a branch of mathematical biology, are criticized by public health officials and epidemiologists. The criticism often is due to their perception that the results lack impact and cannot be implemented in the field. One reason for this disconnect may be a general misinterpretation in the goals of predicting quantitative behavior versus qualitative behavior.

When modeling large, complicated systems encountered in the real-world, such as the outbreak and spread of infectious disease, one often resorts to simplifying the system so that the associated model will be analytically and numerically tractable. The simplification process involves neglecting contributions which are believed to have a small effect on the model outcomes. A broad array of mathematical modeling approaches has been developed specifically for epidemiology [3–5], with some methods having more impact than others. Several theoretical cornerstones, including the mass-action principle for transmission rates and the threshold theory, are now widely accepted [6–9].

These modeling approaches are based on constructing deterministic compartmental models that typically consist of ordinary or partial differential equations. Analysis of the model provides the basic reproduction number, which enables one to determine if a system can support a stable endemic state, a level for which new infections are generated fast enough to replace the ones removed by recovery and/or death. Describing a complex system by a basic reproduction number is now viewed as the standard starting point for which mathematics can contribute insight to epidemiology. In addition to the reproductive number, these simplified, differential equation models allow one to derive useful qualitative observations.

However, as mentioned above, public health officials often require quantitative predictions. This desire for robust quantitative results has increased over the past decade with the advent of "big data" and enormous computational resources. In an attempt to satisfy this need, a large body of research has been generated by questioning and removing simplifying assumptions. Unfortunately, as the models capture more detail from the system at various population levels, they become far too complex to approach analytically. Instead, one must resort to numerical methods which provide a single specific solution but do not allow one to make general predictive statements.

As an alternative, one can employ stochastic modeling approaches which allow one to make quantitative, statistical predictions, while simultaneously providing qualitative descriptions of system dynamics. Moreover, another major advantage in considering stochastic models is due to the fact that classical, deterministic compartment models are often unable to capture specific disease dynamics observed in epidemiological studies. Deterministic compartment models are based on the mean behavior of individuals and do not account for demographic stochasticity [10], or the changes in population growth rates related to random events. As one example, the inclusion of stochasticity through consideration of random encounters between individuals may lead to a local disease extinction. Local extinction of disease is something that is often seen in actual disease data, but is not captured by deterministic compartment models. The inclusion of environmental stochasticity can similarly lead to observed dynamics that are not captured in the deterministic models. While the ability to generate stochastic simulations that provide quantitative statistics for the emergence of new dynamics is increasing with advances in computational power, there remains a need for new methods to analyze the underlying stochastic models.

Many researchers have investigated how noise affects physical and biological phenomena at a wide variety of levels. In biology, noise can play a role in sub-cellular processes, tissue dynamics, and large-scale population dynamics [11]. Although noise may be external or internal to the system, in this article we consider only internal noise. Internal noise is inherent in the system itself and is caused by the random interactions of individuals in a population [12,13]. The noise can induce a rare escape event from a metastable state. In the context of epidemic models, this rare event is extinction. There are many possible escape or extinction paths from the endemic state to the extinct state, but there is a path along which extinction is most likely to occur. This most likely extinction path is termed the optimal extinction path. The optimal extinction path is very useful since knowledge of the path enables one to determine the mean time to extinction from the endemic state.

Mathematically, the effect of internal noise due to the random interactions of individuals within the system is described using a master equation. The master equation is a large, or even infinite, set of differential equations. In this article, we use a WKB (Wentzel–Kramers–Brillouin), or eikonal, approximation to the master equation. The WKB method leads to the development of a Hamiltonian system, which can be solved for the optimal path [14–22]. The dimensions of the Hamiltonian are twice the dimensions of the original system due to the conjugate momenta variables, but the benefit is that the transformed system described by the Hamiltonian is deterministic, where the original problem is stochastic. The method amounts to finding a zero-energy trajectory of an effective mechanical system, and at least one of the solutions to the zero-energy Hamiltonian is the optimal extinction path. There may be other extinction paths, but the optimal path is the path that maximizes the probability of extinction.

The methodology demonstrates how these stochastic models can capture dynamics that are not observed in the classical, deterministic systems. In epidemic problems, the method has mainly been developed for simple autonomous models with few compartments. Larger, complicated systems mostly rely on numerical approximations of solutions in high-dimensional systems, but new analysis techniques can yield qualitative results [23]. In this article, we review recent work to understand noise-induced

rare events, such as the extinction of a disease. Although extinction in a time-varying environment was considered in [24], the analysis was performed only for a birth-death process with a one-dimensional mean-field equation. In this article, we incorporate seasonal forcing into realistic stochastic epidemic models, and perform the analysis to understand the effect of seasonality on epidemic extinction.

The layout for the article is as follows. Section 2 presents the master equation formalism needed to investigate demographic noise in population models and the general method to quantify rare events such as extinction. A simple population model is presented in Sect. 3. It provides an autonomous example for which a complete analytical derivation of rare events is possible. A time-dependent version of the example from Sect. 3 is considered in Sect. 4. In Sect. 5, the methods are extended to a higher dimensional model. In the last section, we summarize these results and present a brief discussion of possible extensions.

2 General theory

We consider stochastic epidemic models with internal noise that represents the random interactions of individuals in the population, and use a master equation to describe the effect of stochasticity. Let X be a state variable that represents the number of individuals in a compartment of a population.

The probability density $\rho(X, t)$ describes the probability of finding X individuals in that compartment at time t. Each possible population-changing event (birth, death, infection, etc.) is defined by a transition rate $W_r(X)$, where r is a positive or negative integer that defines an incremental change from state X to state $X+r$. Then the master equation that provides the time evolution of $\rho(X, t)$ for a single population is [12,13]

$$\frac{\partial \rho(X,t)}{\partial t} = \sum_r [W_r(X-r)\rho(X-r,t) - W_r(X)\rho(X,t)]. \tag{1}$$

In general, the solution of the master equation can be approximated using an asymptotic approach. Let X be scaled by N, the typical population size in the metastable state. Using $x = X/N$, the transition rate $W_r(X) = W_r(Nx)$ can be represented as the following expansion in N,

$$W_r(Nx) = N w_r(x) + u_r(x) + \mathcal{O}(1/N), \tag{2}$$

where x and the scaled transition rates w_r and u_r are $\mathcal{O}(1)$.

We assume that the system possesses a single, stationary solution for the probability density, $\frac{\partial \rho}{\partial t} = 0$ that corresponds to the extinct state. When the probability current at the extinct state is sufficiently small, there will exist a quasi-stationary probability distribution with a non-zero number of infected individuals that decays into the stationary solution over exponentially long times. The rate at which the extinction of infected individuals occurs may be calculated from the tail of the quasi-stationary distribution. It has been shown that a WKB approximation to the quasi-stationary distribution allows one to approximate the mean-time to extinction with high accuracy

for a population size $N \gg 1$ [25]. Therefore, we assume a probability distribution in the form of the WKB ansatz

$$\rho = e^{-N\mathcal{S}(x,t)}, \tag{3}$$

where $\mathcal{S}(x, t)$ is a quantity known as the action [15,18,20,26].

The WKB ansatz given by Eq. (3) is substituted into the scaled master equation, which is stated in terms of $w_r(x - r/N)$ and $\mathcal{S}(x - r/N, t)$, where r/N is small. A Taylor series expansion of these functions of $x - r/N$ is performed, and one arrives at a Hamilton–Jacobi equation $H(x, p; t) = -\partial\mathcal{S}(x, t)/\partial t$, where $p = \partial\mathcal{S}(x, t)/\partial x$ is called the conjugate momentum. At leading order, the Hamilton–Jacobi equation has the form $H(x, p; t) = 0$, known as the effective Hamiltonian ($\mathcal{H}(x, p)$), given as

$$\mathcal{H}(x, p) = \sum_r w_r(x)(e^{pr} - 1). \tag{4}$$

The solutions to $\mathcal{H}(x, p) = 0$ are the zero-energy curves of the system. At least one solution is the optimal extinction path where the action $\mathcal{S}$ is minimized which corresponds to the path that maximizes the probability of extinction.

Hamilton's equations,

$$\dot{x} = \partial\mathcal{H}(x, p)/\partial p, \qquad \dot{p} = -\partial\mathcal{H}(x, p)/\partial x, \tag{5}$$

describe the system's dynamics and are easily found from the Hamiltonian given by Eq. (4). The x dynamics along the $p = 0$ deterministic line are described by

$$\dot{x} = \frac{\partial\mathcal{H}(x, p)}{\partial p}|_{p=0} \tag{6}$$

which is the rescaled mean-field rate equation associated with the original deterministic problem.

We are interested in how intrinsic noise can induce a rare extinction event of long-lived stochastic populations. Extinction occurs when the population undergoes a switch from the endemic steady state (x_e) to the extinct steady state (x_0) as defined by the system of Hamilton's equations. The optimal path to extinction $p_{opt}(x)$ that connects these two steady states is a zero energy phase trajectory of the Hamiltonian. The models that we consider in this article are single-step processes so that $r = \pm 1$. For such models, the optimal path will always have the general form

$$p_{opt}(x) = \ln(w_{-1}(x)/w_1(x)). \tag{7}$$

Using the definition of the conjugate momentum $p = \partial\mathcal{S}/\partial x$, the action $\mathcal{S}_{opt}$ along the optimal path $p_{opt}(x)$ is given by

$$\mathcal{S}_{opt} = \int_{x_e}^{x_0} p_{opt}(x)dx. \tag{8}$$

Therefore, the mean time to extinction (MTE) to escape from x_e associated with the endemic state and arrive at x_0 associated with the extinct state can be approximated by

$$\tau = B \exp(N\mathcal{S}_{opt}), \tag{9}$$

where B is a prefactor that depends on the system parameters and on the population size. An accurate approximation of the MTE depends on obtaining B.

This framework can easily be extended to systems if one is interested in exploring a population, or group of populations, partitioned into homogeneous subgroups. Define $\mathbf{X}$ as a vector describing the states of n populations $X_1, X_2, \ldots, X_n$ and follow the derivation above. The complexity of exploring multi-population stochastic models becomes apparent when considering the solution to the generalized set of Hamilton's equations

$$\begin{aligned} \dot{\mathbf{x}_j} &= \frac{\partial \mathcal{H}(x_1, \ldots, x_n, p_1, \ldots, p_n)}{\partial p_j}, \\ \dot{\mathbf{p}_j} &= -\frac{\partial \mathcal{H}(x_1, \ldots, x_n, p_1, \ldots, p_n)}{\partial x_j}, \quad j = 1, \ldots, n \end{aligned} \tag{10}$$

where n is the number of distinct population groups included in a model. The dimension of the resulting Hamiltonian system is $2n$.

In the following sections, we consider two types of epidemic models, with and without seasonality, and employ the theory developed in this section to determine the optimal extinction path for each of the models.

3 The SIS model

The Susceptible-Infected-Susceptible (SIS) model describes the possible spreading dynamics of a disease, where individuals are not provided with immunity after infection but rather become re-susceptible. We use the WKB framework described in Sect. 2 on this simple model without seasonal variation as an illustrative example. We focus on results that will be useful for analyzing the time-varying case. One can find a complete, rigorous analysis of the autonomous SIS model in [14,27,28].

The SIS model consists of a finite population of N individuals divided into two compartments: Susceptibles S and Infectives I. We now identify the flux terms for these compartments. An individual is born susceptible, assuming a constant birth rate, μ. Then, through contact modeled by a mass action approximation, the individual may become ill and be classified as infectious. We assume the contact rate, β_0, is constant in this section. Then, assuming an average recovery rate, γ, the individual recovers and is returned to the susceptible compartment. Removal by natural death is possible from both compartments, but we assume no disease-related deaths in this model. Figure 1 shows a schematic of the model's compartments along with the transition events.

We also assume that the change in births and deaths maintain an average total number of individuals in the population, N. Therefore, the number of susceptible individuals can be approximated by the remaining population that is not in the I

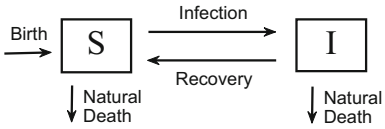

Fig. 1 A compartmental flow diagram for the transitions in the SIS model

Table 1 SIS model transitions and associated rates

Event	I transitions	Scaled rate
Infection	$W_{-1} = \beta_0(N-I)I/N$	$\beta_0(1-i)i$
Recovery	$W_{+1} = \gamma I$	γi
Death	$W_{-1} = \mu I$	μi

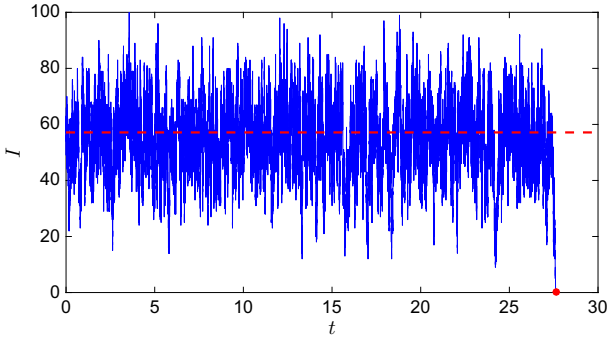

Fig. 2 A realization of the stochastic SIS model (without seasonality) with an extinction event. The parameters are $\beta_0 = 1.4$, $\gamma + \mu = 1$, and $N = 200$. The dashed red line represents the endemic steady state (color figure online)

compartment, $S = N - I$, and the dynamics can be approximated by a single infectious population. This is known as the constrained SIS model and a more detailed analysis of how this approximation varies from the full two-population SIS system can be found in [29].

A list of all possible transition events for the I population is shown in Table 1. A sample realization of this stochastic SIS model using these transitions is presented in Fig. 2. A Monte Carlo algorithm [30] is used to evolve the population in time. Figure 2 shows that the population persists for a period of time near what appears to be a stable steady state and eventually goes extinct. Spontaneous extinction is an example of a rare event, and the following analysis aims to explain, predict, and possibly control this class of dynamics.

Rescaling the population variables by the average population size N produces new variables $s = S/N$ and $i = I/N$, so that $s = 1 - i$. Using these variables, we identify the scaled transitions rates in Table 1. A master equation for the SIS example can be formulated using Eq. (1) and these scaled transitions,

$$\frac{\partial \rho(I,t)}{\partial t} = \frac{\beta_0}{N}((I-1)(N-(I-1))\rho(I-1,t) - I(N-I)\rho(I,t)) + (\gamma+\mu)((I+1)\rho(I+1,t) - I\rho(I,t)). \tag{11}$$

After employing the theory described in Sect. 2, the resulting Hamiltonian for the SIS model is found to be

$$\mathcal{H}(i, p) = \beta_0(1 - i)i(e^p - 1) + (\gamma + \mu)i(e^{-p} - 1), \tag{12}$$

where p is the conjugate momentum variable in this single population model.

As mentioned in the previous section, one can assume the WKB approximation to the probability distribution if the system is quasi-stationary, which in this case is when the probability current at the extinct state is sufficiently small. One can numerically approximate the probability distribution by solving the master equation to check this assumption. Two sample probability density functions for $N = 200$ are graphed in Fig. 3. Notice that for $R_0 = 2$, $I = 0$ is in the tail of the distribution, satisfying the assumption of quasi-stationary. Conversely, the approximation for the probability distribution associated with $R_0 = 1.1$ shows a nonzero probability at $I = 0$. In this case, extinction is not a rare event and the WKB framework does not apply. The probability density function will asymptotically drift towards $I = 0$ with time.

Hamilton's equations describe the dynamics of the augmented system and are given as

$$di/dt = \beta_0(1 - i)ie^p - (\gamma + \mu)ie^{-p}, \tag{13a}$$
$$dp/dt = \beta_0(2i - 1)(e^p - 1) - (\gamma + \mu)(e^{-p} - 1). \tag{13b}$$

The deterministic mean-field equation is then found by evaluating Hamilton's equations when $p = 0$:

$$di/dt = \beta_0(1 - i)i - (\gamma + \mu)i. \tag{14}$$

The mean field equation has two steady states: $i = 0$, called the extinct state, and $i = (1 - \frac{\mu+\gamma}{\beta_0})$, referred to as the endemic state.

The stability of the steady state solutions can be found by evaluating the eigenvalues or equivalently, finding the basic reproduction number, R_0. For this model,

$$R_0 = \beta_0/(\gamma + \mu). \tag{15}$$

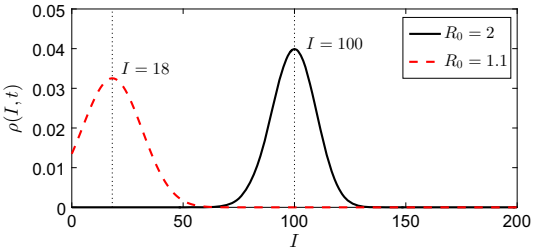

Fig. 3 Probability density functions for the stochastic SIS model (without seasonality) for two values of the reproductive number. For $R_0 = 2$, the parameters are such that the system is quasi-stationary and extinction is a rare event. The probability density function for $R_0 = 1.1$ is not quasi-stationary and will asymptotically drift towards $I = 0$ with time (color figure online)

When $R_0 > 1$, the endemic state is an attracting fixed point and the disease will persist. Otherwise, the extinct state is attracting and the disease will die out. In the problems presented in this paper, we assume parameters such that $R_0 > 1$. To illustrate the shortcomings of the mean field equation to properly capture observed dynamics, note how the stochastic realization shown in Fig. 2 fluctuates about the deterministic endemic state predicted by the mean field. Eventually, the solution escapes from this state and approaches the (unstable) extinction state. This apparent violation of the system dynamics is resolved by a careful analysis of Hamilton's equations.

Comparing the solutions of the mean field equation to Hamilton's equations, we find the corresponding solutions on the $p = 0$ deterministic line: $(i, p) = (0, 0)$ and $(i, p) = (1 - 1/R_0, 0)$. In addition, a third solution $(i, p) = (0, -\ln(R_0))$, called the fluctuational extinction state, represents a new disease-free solution with non-zero momentum, distinguishing it from the deterministic extinct state $(0, 0)$. Note that these solutions are saddles in the (i, p) plane, rather than attractors or repellers. This allows for metastability in the system and escape from one state to another.

To find the manifolds that connect these solutions, we find the analytical zero energy solutions for the Hamiltonian. The solution $i = 0$ represents extinction; a second solution is $p = 0$, which corresponds to the deterministic dynamics. The third solution refers to the optimal path and is given by

$$p = -\ln\left(R_0(1 - i)\right). \tag{16}$$

The optimal path and steady states are graphed in the right panel of Fig. 4.

The time-dependent solutions on the optimal path can be found by using Eq. (16) in Hamilton's equations to reduce the dimension of the problem. In addition, by scaling time by $(\gamma + \mu)$, one obtains

$$di/dt = (i - R_0(1 - i)i)/(\gamma + \mu), \tag{17a}$$
$$dp/dt = (R_0(e^p - 1) + (e^{-p} - 1))/(\gamma + \mu). \tag{17b}$$

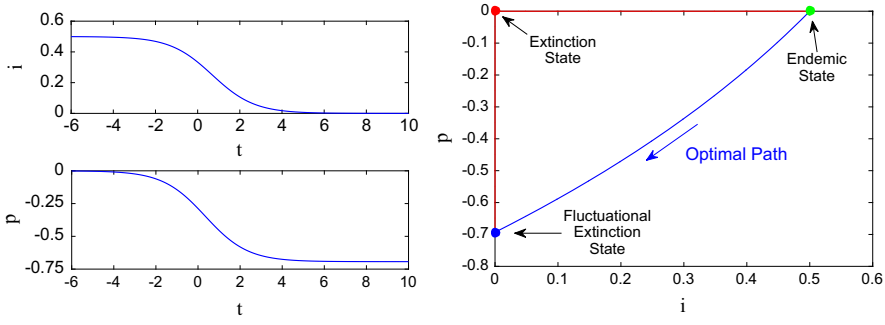

Fig. 4 The optimal path for the stochastic SIS model without seasonality. The left panels display the time dependence in Eqs. (17d) and (17d). The right panel shows the location of the steady states and zero energy curves of the Hamiltonian, including the optimal path identified by Eq. (16). The parameters in all panels are $\beta_0 = 2$ and $\gamma + \mu = 1$

One can solve Eq. (17a) and substitute it into Eq. (16) to find the following explicit solutions for the optimal path:

$$i(t-t_0) = \frac{1}{\left(\frac{R_0}{R_0-1}\right) - e^{(R_0-1)(t-t_0)/(\gamma+\mu)}}, \tag{17c}$$

$$p(t-t_0) = -\ln\left(R_0\left(1-i_0\left(t-t_0\right)\right)\right), \tag{17d}$$

with t_0 as an arbitrary initial time. These solutions are graphed in the left panels of Fig. 4 and correspond to the time dependence of the optimal path from the endemic steady state to the fluctuational extinction state in the right panel of Fig. 4. It should be noted that in all numerical examples, we assume $(\gamma + \mu) = 1$.

4 The time-dependent SIS model

Using the observation of periodic and aperiodic recurrence in diseases such as measles, mumps, and chickenpox in pre-vaccine US data [31] and England and Wales data [3], modelers identified that the contact rates, as well as other parameters, may vary in time. Mathematical models with periodic forcing developed to capture seasonal variation were found to capture yearly and biennial outbreaks [32]. With the addition of random perturbations, these models are also observed to exhibit switching between attractors [33–35]. We consider the SIS model with seasonal forcing incorporated into the contact rate, and use the master equation formalism and WKB theory to provide additional insight into the system's dynamics.

The time-dependent SIS model follows the formulation in Sect. 3, but assumes the contact rate varies throughout the year in a periodic fashion, approximated by the function, $\beta(t) = \beta_0(1 + \delta\cos(2\pi t))$, where δ is a small parameter. The Hamiltonian system is defined as

$$\mathcal{H}(i, p, t) = \beta(t)(1-i)i(e^p - 1) + (\gamma+\mu)i(e^{-p} - 1), \tag{18}$$

with the corresponding Hamilton's equations given by

$$di/dt = \beta(t)(1-i)ie^p - (\gamma+\mu)ie^{-p}, \tag{19a}$$

$$dp/dt = \beta(t)(2i-1)(e^p - 1) - (\gamma+\mu)(e^{-p} - 1). \tag{19b}$$

A realization of this stochastic time-dependent SIS model is presented in Fig. 5. As in the autonomous case, eventually the noise causes the population to go extinct.

The main goal of this paper is to motivate the need and lay the foundation to extend the WKB framework for analyzing rare events in time-dependent versions of epidemiological models. Previous work on activated escape from a metastable state of a system driven by a time-periodic force include Dykman et al. [36] and Maier and Stein [37]. We follow the rigorous treatment of a time modulated birth-death system presented by Assaf et al. [24]. Following this work, we assume the amplitude of the

oscillation in $\beta(t)$ is small, $0 < \delta \ll 1$, and rewrite the time-dependent Hamiltonian using a linear expansion in δ,

$$\mathcal{H}(i, p, t) = H_0(i, p) + \delta H_1(i, p, t). \tag{20}$$

The unperturbed Hamiltonian,

$$H_0(i, p) = \beta_0(1 - i)i(e^p - 1) + (\gamma + \mu)i(e^{-p} - 1), \tag{21}$$

was analyzed in the previous section, and the new time-dependent part is

$$H_1(i, p, t) = \beta_0(1 - i)i(e^p - 1)\cos(2\pi t). \tag{22}$$

We can consider the dynamics using the associated Poincaré map, which is the projection of the time dependent trajectories of the nonautonomous system in the (i, p, t) space on the (i, p) plane in unit time interval slices. In the perturbed system, the steady states are also perturbed. For generic Hamiltonians, the existence of the perturbed hyperbolic points is guaranteed by the Poincaré–Birkhoff fixed point theorem. While the extinction state remains unchanged, the others can be determined by

$$(i(t), p(t)) = \left(1 - \tfrac{\gamma+\mu}{\beta(t)}, 0\right) \quad \text{endemic,} \tag{23}$$

$$(i(t), p(t)) = \left(0, \ln\left(\tfrac{\gamma+\mu}{\beta(t)}\right)\right) \quad \text{fluctuational extinction.} \tag{24}$$

Figure 5 shows a single stochastic realization of the time-dependent system. One can see that the population oscillates periodically, following the endemic limit cycle given by Eq. (23).

To demonstrate that the system satisfies quasi-stationarity, we numerically approximate the probability distribution by solving the master equation for $N = 200$. The solution for the range $t = [0, 5]$ is graphed in the left panel of Fig. 6. The solution at

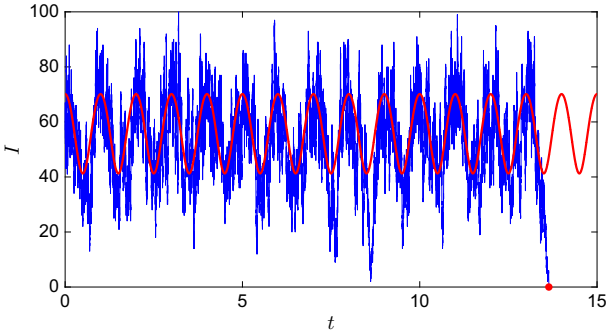

Fig. 5 A realization of the stochastic SIS model with seasonality exhibiting an extinction event is shown in blue. The parameters are $\beta_0 = 1.4$, $\gamma + \mu = 1$, $\delta = 0.1$, and $N = 200$. Note how the realization follows the red curve representing the endemic limit cycle given by $I(t) = Ni(t)$, using Eq. (23) (color figure online)

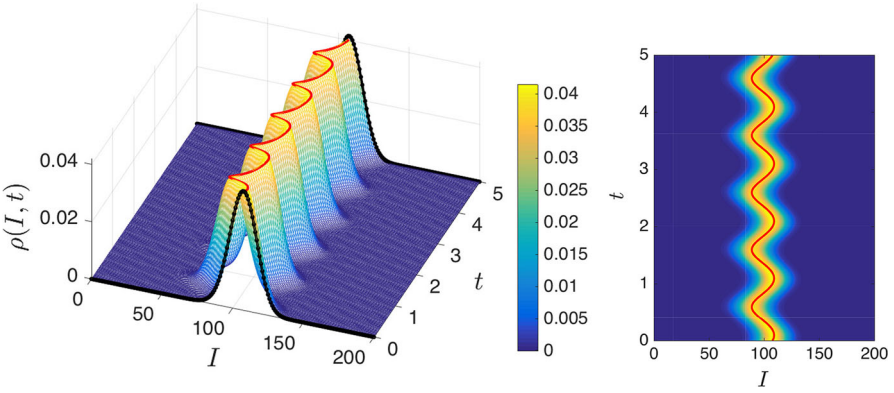

Fig. 6 The left panel is a graph of the probability density function of the stochastic SIS model with seasonality numerically approximated by the master equation. A contour plot of the same probability distribution is in the right panel. The endemic limit cycle $I(t) = Ni(t)$, using Eq. (23), is overlaid in both panels as a red curve. The parameters are $\beta_0 = 2$, $\gamma + \mu = 1$, $\delta = 0.1$, and $N = 200$ (color figure online)

$t = 0$ is overlaid in black and again repeated at $t = 5$, showing periodicity. Notice that this is similar to the probability distribution graphed in Fig. 3. The right panel of Fig. 6 shows a contour plot of the probability distribution. The endemic limit cycle given by $I(t) = Ni(t)$, using Eq. (23), is overlaid in both panels in red.

The existence of the perturbed hyperbolic fixed points is a necessary but not sufficient condition for the existence of a heteroclinic trajectory connecting the unstable manifold of the endemic state to the stable manifold of the fluctuational extinction state. Using a linear theory approach for small δ, we assume that there exists a perturbed optimal path of $H(i, p, t)$ described by the pair of equations $i(t, t_0)$, $p(t, t_0)$ and that the action can be calculated along that path using

$$\mathcal{S} = \int_{-\infty}^{\infty} \left(p(t, t_0) \frac{di(t, t_0)}{dt} - H_0(i(t, t_0), p(t, t_0)) - \delta H_1(i(t, t_0), p(t, t_0), t) \right) dt. \tag{25}$$

Note that the unperturbed Hamiltonian, H_0, is invariant with respect to the specific choice of t_0.

We can quantify the change in the action due to the perturbation as $\mathcal{S} = \mathcal{S}_0 + \Delta\mathcal{S}$, noting the action for the unperturbed SIS model is

$$\mathcal{S}_0 = \int_{1-\frac{1}{R_0}}^{0} -\ln(R_0(1-i))di = \ln(R_0) - 1 + \tfrac{1}{R_0}. \tag{26}$$

Using the linear expansion in δ, the perturbed optimal path can be expressed as

$$\begin{aligned} i(t, t_0) &= i_0(t - t_0) + \delta i_1(t, t_0), \\ p(t, t_0) &= p_0(t - t_0) + \delta p_1(t, t_0), \end{aligned} \tag{27}$$

noting that the solutions for the unperturbed solutions for i_0 and p_0 are given in Eqs. (17c) and (17d). As derived in Assaf et al. [24], the linear expansion of the integrand of Eq. (25) results in the following approximation of $\Delta\mathcal{S}(t_0)$ to first order,

$$\Delta\mathcal{S}(t_0) = -\delta \int_{-\infty}^{\infty} H_1\left(i_0(t-t_0), p_0(t-t_0), t\right) dt. \tag{28}$$

In addition, the validity of the linearization approach to approximating the action requires the change in action due to the perturbation to satisfy $\Delta\mathcal{S} \ll \mathcal{S}_0$.

To find the optimal correction to the action, we must minimize $\mathcal{S}(t_0)$ with respect to t_0. Consider the zeros of its derivative,

$$\frac{d\mathcal{S}(t_0)}{dt_0} = -\delta \int_{-\infty}^{\infty} \{H_0, H_1\}_0 \, dt = 0, \tag{29}$$

where $\{H_0, H_1\}_0$ is the Poisson bracket evaluated on the unperturbed optimal path. The quantity $\int_{-\infty}^{\infty}\{H_0, H_1\}_0 \, dt$ is the Melnikov function of the perturbed problem, which is proportional to the distance between the unstable and stable manifolds of perturbed fixed points. A sufficient condition for the existence of the perturbed optimal path is for the Melnikov function to have simple zeros. These zeros are the critical points of the action, which yields the minimal action along the optimal path of the perturbed problem.

For the SIS model, we evaluate the Poisson bracket to find

$$\begin{aligned}\{H_0, H_1\}_0 = (\mu+\gamma)^2 R_0 \cos(2\pi(t-t_0))\, i_0(t-t_0)\Big(2 - 3i_0(t-t_0) \\ +(i_0(t-t_0)-1)e^{p_0(t-t_0)} + (2i_0(t-t_0)-1)e^{-p_0(t-t_0)}\Big).\end{aligned} \tag{30}$$

Therefore, the Melnikov function has simple zeros and the perturbed optimal path exists. We can then numerically evaluate Eq. (29) to identify a periodic set of zeros, which identify the phase for the optimal correction. For example, the parameters $\beta_0 = 2$ and $\gamma + \mu = 1$ yield the phase $t_0 = 0.3068528194 + n$, $(n = 0, \pm 1, \pm 2, ...)$.

To numerically explore the dynamics of an extinction event, we use Hamilton's equations to approximate the optimal path connecting the endemic state and the fluctuational extinction state. The system of equations that describes the time evolution for each variable are

$$di/dt = i(\gamma+\mu) - \beta(t) i(1-i), \tag{31a}$$

$$dp/dt = \beta(t)(e^p - 1) + (\gamma+\mu)(e^{-p} - 1). \tag{31b}$$

Because of the time dependence, these equations cannot be explicitly solved. Therefore, we must numerically approximate the solutions using the appropriate phase defined by the initial time t_0.

The left panels of Fig. 7 show the numerical solutions of $i(t)$ and $p(t)$ found using the implicit Matlab solver ode15i. In order to validate the numerical solution, we compared the results with those found using the Iterative Minimizing Action Method

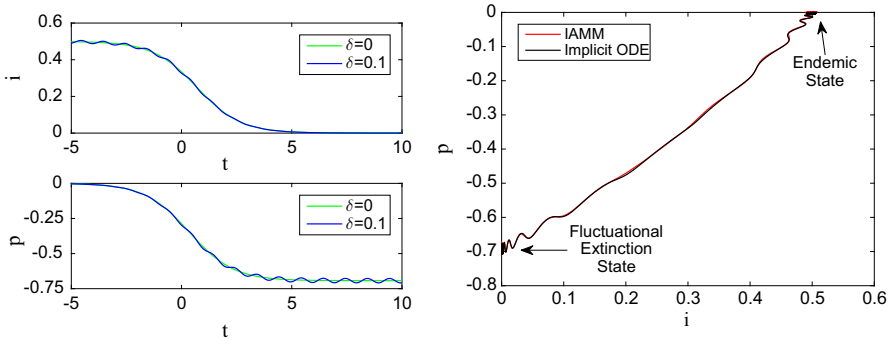

Fig. 7 The numerical approximation of the optimal path for the stochastic SIS model with seasonality. The parameters are $\beta_0 = 2$, $\gamma + \mu = 1$, and $\delta = 0.1$, unless otherwise noted. The numerical approximations of the separate time dependent solutions for the implicit ODEs given by Eqs. (31a) and (31b) are shown in the left panel. The $\delta = 0$ case is also plotted in green as a reference. The implicit ODE solutions are plotted together as $(i(t), p(t))$ in the right panel in black. The approximation of the optimal path found by using the IAMM numerical scheme is also graphed in the right panel in red. The agreement is excellent (color figure online)

(IAMM), a completely different type of numerical scheme [38]. The IAMM is a minimum action method [39,40] based on Newton's method that computes optimal transition pathways in systems of stochastic differential equations, and details can be found in "Appendix A". The IAMM, like any scheme involving Newton's method, is sensitive to the initial condition. A poor initial guess may lead to erroneous results including convergence to a curve that is not the optimal path or even no convergence. One can use a variety of methods to obtain a good initial condition [41]. For the time-dependent SIS model, the solution for the $\delta = 0$ case was found by using a line of 1600 points connecting the beginning and end points, and then a continuation algorithm was used to to find corresponding solutions as δ was increased to 0.1. The right panel of Fig. 7 shows excellent agreement for the time-dependent optimal paths found by using the two different numerical methods.

5 The SIR model

The Susceptible-Infected-Recovered (SIR) model describes a disease that confers immunity after recovery from infection. This type of model is the foundation for which the analysis of outbreaks in diseases such as chicken pox, mumps, pertussis, and measles are based. A refinement by London and Yorke [31] introduced latency, or a delay in the time from exposure to infectiousness. This aspect extended the SIR model to the SEIR model. Their work inferred seasonality in the contact rates from existing US data. Additionally, Fine and Clarkson [42] verified the correlation of measles outbreaks in England and Wales data to the opening and closing of school terms. Despite the fact that measles dynamics was considered to be extremely well explained by seasonally driven deterministic models at that time, the approach did not sufficiently capture the dynamics for the observed data of other diseases. Rohani et al. [43] demonstrated that stochasticity still plays a significant role in these models.

Therefore, we revisit the stochastic, seasonally forced SIR model using the WKB framework.

In the SIR model, the population is composed of three compartments: Susceptibles S, Infectives I, and Recovered R. The flow between compartments is similar to the SIS model, but after the individual has recovered, the individual moves to the recovered (and immune) compartment, rather than becoming re-susceptible. Removal by natural death is possible from all three compartments, and we assume no disease-related deaths in this model. Figure 8 shows a schematic of the model's compartments along with the transition events.

Because the system is overdetermined, we can assume $R = N - S - I$ and use the state variable $\mathbf{X} = (S, I)$ to represent this model. A list of all possible transition events for the S and I populations is shown in Table 2. A realization of this stochastic SIR model (without seasonality) using these transitions is presented in Fig. 9. It shows a solution where the population persists for a period of time, oscillating about what appears to be a steady state, before going extinct.

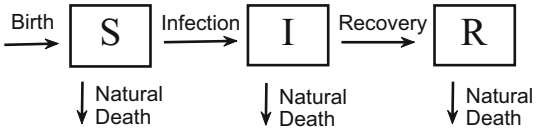

Fig. 8 A compartmental flow diagram for the transitions in the SIR model

Table 2 SIR model transitions and associated rates

Event	S transitions	I transitions	Scaled rate
Birth	$W_{+1} = \mu N$		μ
Infection	$W_{-1} = \beta(t)SI/N$	$W_{+1} = \beta(t)SI/N$	$\beta(t)si$
Recovery		$W_{-1} = \gamma I$	γi
Death	$W_{-1} = \mu S$	$W_{-1} = \mu I$	$\mu s, \mu i$

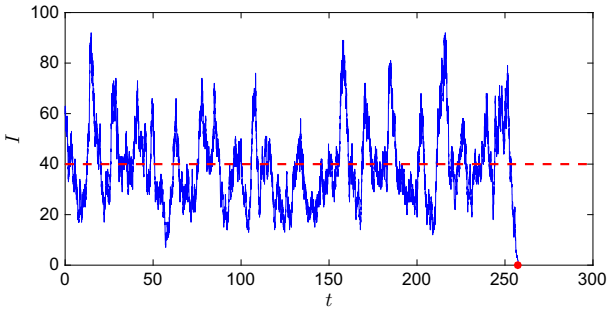

Fig. 9 A realization of the stochastic SIR model (without seasonality) with an extinction event. The parameters are $\beta_0 = 2$, γ=1, $\mu = 0.1$, $\delta = 0$, and $N = 600$. The dashed red line represents the endemic solution, $I = Ni(t)$ given by Eq. (37b) (color figure online)

A master equation for the SIR example can be formulated using Eq. (1) and the scaled transitions in Table 2. The resulting Hamiltonian is

$$\begin{aligned}\mathcal{H}(s, i, p_s, p_i) = \mu(e^{p_s} - 1) + \beta(t)si(e^{-p_s+p_i} - 1) + \gamma i(e^{-p_i} - 1) \\ + \mu s(e^{-p_s} - 1) + \mu i(e^{-p_i} - 1),\end{aligned} \tag{32}$$

where p_s and p_i are the conjugate momentum variables associated with the scaled s and i variables, respectively.

The analytical zero energy solutions for the Hamiltonian again help identify the locations and paths between the metastable states. The solution $i = 0$ represents extinction, and a second solution, $p_s = p_i = 0$, corresponds to the deterministic dynamics. In this case, we cannot analytically determine the third solution that corresponds to the optimal extinction path.

Hamilton's equations are found by evaluating the partial derivatives,

$$ds/dt = \partial\mathcal{H}(s, i, p_s, p_i)/\partial p_s, \qquad di/dt = \partial\mathcal{H}(s, i, p_s, p_i)/\partial p_i \tag{33}$$

$$dp_s/dt = -\partial\mathcal{H}(s, i, p_s, p_i)/\partial s, \qquad dp_i/dt = -\partial\mathcal{H}(s, i, p_s, p_i)/\partial i, \tag{34}$$

which results in the four-dimensional system

$$ds/dt = \mu e^{p_s} - \beta(t)sie^{-p_s+p_i} - \mu se^{-p_s}, \tag{35a}$$

$$di/dt = \beta(t)sie^{-p_s+p_i} - \gamma ie^{-p_i} - \mu ie^{-p_i}, \tag{35b}$$

$$dp_s/dt = -\beta(t)i(e^{-p_s+p_i} - 1) - \mu(e^{-p_s} - 1), \tag{35c}$$

$$dp_i/dt = -\beta(t)s(e^{-p_s+p_i} - 1) - (\gamma + \mu)(e^{-p_i} - 1). \tag{35d}$$

The mean field equations, determined by evaluating Hamilton's equations when $p_s = 0$ and $p_i = 0$, are

$$ds/dt = \mu - \beta(t)si - \mu s, \tag{36a}$$

$$di/dt = \beta(t)si - \gamma i - \mu i. \tag{36b}$$

This system exhibits two steady state solutions when there is no forcing, $\delta = 0$ and $\beta(t) = \beta_0$. There is an extinct state and an endemic state, with their stabilities depending on the basic reproduction number, $R_0 = \beta_0/(\gamma + \mu)$. The extinct state, $(s(t), i(t)) = (1, 0)$, is stable when $R_0 < 1$ and the endemic state is stable when $R_0 > 1$. Except for a very small parameter region close to $R_0 = 1$, the steady state can be classified as a spiral sink with complex eigenvalues. In the deterministic setting, solutions will asymptotically oscillate towards the steady state in a spiral fashion. When simulating the associated stochastic model, this underlying oscillatory structure impacts the dynamics. Note that in Fig. 9, the time series exhibits oscillations for the SIR model *without* seasonal forcing.

The endemic steady state is perturbed by the forcing to become a limit cycle described by, $(s(t), i(t)) = (\frac{\gamma+\mu}{\beta(t)}, \frac{\mu}{\beta(t)}(\frac{\beta(t)}{\gamma+\mu} - 1))$. At higher amplitude forcing, the

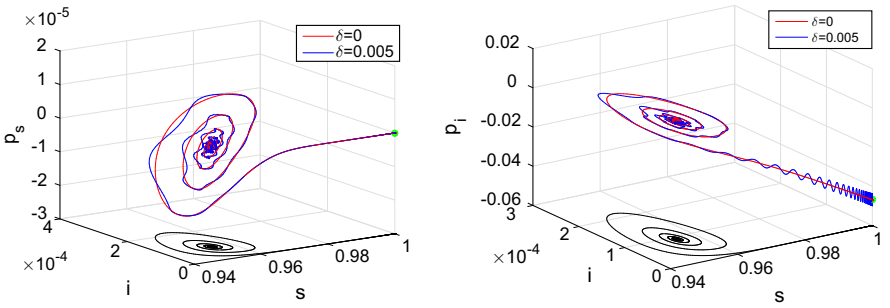

Fig. 10 The numerical approximation of the optimal path for the stochastic SIR model found using the IAMM method. The blue curve is the solution for system with seasonal forcing ($\delta = 0.005$), with the left panel displaying (s, i, p_s) and the right panel displaying (s, i, p_i). As a reference, the solution for the system without seasonality ($\delta = 0$) is graphed in red, with a projection of just the (s, i) variables below in black. The parameters are $\beta_0 = 105$, $\gamma = 100$, and $\mu = 0.2$ (color figure online)

limit cycle will double in period. A careful treatment of the derivation of the stability of the steady states of the periodically forced SIS model can be found in Glendinning and Perry [44]. This work derives the conditions for which the system undergoes a Takens–Bogdanov bifurcation, after a sequence of subharmonic bifurcations, and results in chaotic dynamics.

Returning to Hamilton's equations to study the stochastic SIR model with seasonal forcing, we identify three solutions on the zero-energy curves:

$$(s(t), i(t), p_s(t), p_i(t)) = (1, 0, 0, 0) \qquad \text{extinction,} \tag{37a}$$

$$(s(t), i(t), p_s(t), p_i(t)) = \left(\frac{\gamma+\mu}{\beta(t)}, \frac{\mu}{\beta(t)}\left(\frac{\beta(t)}{\gamma+\mu} - 1\right), 0, 0\right) \qquad \text{endemic,} \tag{37b}$$

$$(s(t), i(t), p_s(t), p_i(t)) = \left(1, 0, 0, \ln\left(\frac{\gamma+\mu}{\beta(t)}\right)\right) \qquad \text{fluctuational extinction.} \tag{37c}$$

The IAMM method is used to compute the optimal extinction path from the endemic solution to the fluctuational extinction state. The solution for the $\delta = 0$ case was found by using a line of 1600 points connecting the beginning and end points, and then a continuation algorithm was used to to find corresponding solutions as δ was increased to 0.005. The results for both $\delta = 0$ and $\delta = 0.005$ are shown in Fig. 10. The parameters follow the optimal path results in [22]. Note the fluctuations in the p_i component, but not the p_s component, as the solution approaches extinction ($(s, i) = (1, 0)$), which agrees with the fluctuational extinction solution identified in Eq. (37c). Rigorous analytical results similar to the approach presented for the SIS model will be the subject of future work.

6 Conclusions

In this article we have motivated the analysis of a variety of stochastic epidemic models and outlined a general methodology that allows one to compute rare events such

as the optimal path to extinction. As we have described in the introduction and in Sect. 2, we transform the original stochastic problem into a new deterministic system described by a Hamiltonian that has twice the dimensions as that of the original system. For simpler systems, such as the SIS model without seasonality described in Sect. 3, one can analytically find the optimal path to extinction. For more complicated time-dependent systems, like the ones described in Sects. 4 and 5, we use analytic perturbation expansions along with numerical computations to find the perturbed optimal path to extinction.

Knowledge of the optimal path is extremely useful since it enables one to find the mean time to extinction from the endemic state, which can be verified by stochastic realizations. For the SIS model without seasonality (Sect. 3), the mean time to extinction can be analytically determined by evaluating the action along the optimal extinction path. Using the expression in Eq. (9), we find

$$\tau = B \exp\left(N \int_{1-\frac{1}{R_0}}^{0} \ln\left(\frac{\gamma+\mu}{\beta_0(1-i)} \right) di \right) \tag{38a}$$

$$= \frac{R_0}{(R_0-1)^2} \sqrt{\frac{2\pi}{N}} \exp\left(N(\ln(R_0) - 1 + \tfrac{1}{R_0}) \right). \tag{38b}$$

For the other models presented in this paper, the integral given by Eq. (8) that quantifies the action can be computed numerically in a straightforward manner by using the data provided by the IAMM method.

Once the mean time to extinction is determined, it is possible to quantify the effect of various control schemes on an infectious disease. For example, Khasin et al. [45] identified the resonant effect of vaccination pulses in an SIR model and derived an optimal vaccination protocol that can speed up extinction when the vaccine is in short supply. Billings et al. [29] considered the effect of treatment for the SIS model, and showed an exponential improvement in extinction times. In the future, we plan to study how control, including vaccine and treatment, affects the mean time to extinction for epidemic models that include seasonal forcing.

Appendix A: Iterative Action Minimizing Method (IAMM)

To analyze the dynamics of spontaneous escape from an endemic state, we numerically compute the optimal path, which is a zero-energy curve for the Hamiltonian that connects two steady state saddle points. We use the Iterative Action Minimizing Method (IAMM) [38], a numerical scheme based on Newton's method. The IAMM is useful in the general situation where a path connecting steady states C_a and C_b starts at C_a at $t = -\infty$ and ends at C_b at $t = +\infty$. A time parameter t exists such that $-\infty < t < \infty$. For this method, we require a numerical approximation of the time needed to leave the region of C_a and arrive in the region of C_b. Therefore, we define a time T_ϵ such that $-\infty < -T_\epsilon < t < T_\epsilon < \infty$. Additionally, $C(-T_\epsilon) \approx C_a$ and $C(T_\epsilon) \approx C_b$. In other words, the solution stays very near the equilibrium C_a for $-\infty < t \leq -T_\epsilon$, has a transition region from $-T_\epsilon < t < T_\epsilon$, and then stays near C_b

for $T_\epsilon < t < +\infty$. The interval $[-T_\epsilon, T_\epsilon]$ is discretized into n segments using a uniform step size $h = (2T_\epsilon)/n$ or a suitable non-uniform step size h_k. The corresponding time series is $t_{k+1} = t_k + h_k$.

The derivative of the function value $\mathbf{q}_k$ is approximated using central finite differences by the operator δ_h given as

$$\frac{d}{dt}\mathbf{q}_k \approx \delta_h \mathbf{q}_k \equiv \frac{h_{k-1}^2 \mathbf{q}_{k+1} + (h_k^2 - h_{k-1}^2)\mathbf{q}_k - h_k^2 \mathbf{q}_{k-1}}{h_{k-1}h_k^2 + h_k h_{k-1}^2}, \quad k = 0, \ldots, n. \tag{39}$$

Clearly, if a uniform step size is chosen then Eq. (39) simplifies to the familiar form given as

$$\frac{d}{dt}\mathbf{q}_k \approx \delta_h \mathbf{q}_k \equiv \frac{\mathbf{q}_{k+1} - \mathbf{q}_{k-1}}{2h}, \quad k = 0, \ldots, n. \tag{40}$$

Thus, one can develop the system of nonlinear algebraic equations

$$\delta_h \mathbf{x}_k - \frac{\partial H(\mathbf{x}_k, \mathbf{p}_k)}{\partial \mathbf{p}} = 0, \quad \delta_h \mathbf{p}_k + \frac{\partial H(\mathbf{x}_k, \mathbf{p}_k)}{\partial \mathbf{x}} = 0, \quad k = 0, \ldots, n, \tag{41}$$

which is solved using a general Newton's method. We let

$$\mathbf{q}_j(\mathbf{x}, \mathbf{p}) = \{\mathbf{x}_{1,j} \ldots \mathbf{x}_{n,j}, \mathbf{p}_{1,j} \ldots \mathbf{p}_{n,j}\}^T \tag{42}$$

be an extended vector of $2nN$ components that contains the jth Newton iterate, where N is the number of populations. When $j = 0$, $\mathbf{q}_0(\mathbf{x}, \mathbf{p})$ provides the initial "guess" as to the location of the path that connects C_a and C_b. Given the jth Newton iterate $\mathbf{q}_j$, the new $\mathbf{q}_{j+1}$ iterate is found by solving the linear system

$$\mathbf{q}_{j+1} = \mathbf{q}_j - \frac{\mathbf{F}(\mathbf{q}_j)}{\mathbf{J}(\mathbf{q}_j)}, \tag{43}$$

where $\mathbf{F}$ is the function defined by Eq. (41) acting on $\mathbf{q}_j$, and $\mathbf{J}$ is the Jacobian. Equation (43) is solved using LU decomposition with partial pivoting.

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