Variational nonequilibrium thermodynamics of reaction-diffusion systems. II. Path integrals, large fluctuations, and rate constants

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We consider reaction-diffusion systems that can be out of equilibrium. In the preceding article a path integral formation of the Hamilton–Jacobi approximation of the Master equation of such systems. Using this path integral formulation, it is possible to calculate rate constants for the transition from one well to another well of the information potential and to give estimates of mean exit times. © *1999 American Institute of Physics.* [S0021-9606(99)51040-4]

I. INTRODUCTION

This work is the continuation of Paper I,[1] henceforth referred to as Part I. Our aim is to provide a new approach to nonequilibrium thermodynamics for reaction-diffusion systems at fixed temperature. This approach was sketched for particular systems in previously published short articles.[2] Our motivation has been explained in Part I, as well as the relation of our work to other authors'.

The general idea of nonequilibrium thermodynamics is to define various state functions generalizing the equilibrium state functions.[3–5] We shall use a state function, called the information potential, Φ, which is the negative of the logarithm of the stationary probability distribution (per unit volume).[1,5–11] This function Φ satisfies a Hamilton–Jacobi equation which is derived from the Master equation.[1,5,6] This equation is nonstandard for two reasons. First, the Hamiltonian is not quadratic in momenta (as would be the Hamiltonian for the Fokker–Planck equation). Second, the solution Φ we are looking for is a regular function, so that the traditional method to solve the Hamilton–Jacobi equation fails because this method would give singular actions. In Part I, we proved that, nevertheless, one can find Φ by a limiting procedure and that the Hamilton–Jacobi equation has a unique regular solution. Moreover, it satisfies the properties that one expects, for example, its minima are the attracting points of the deterministic vector field of the macroscopic chemical theory. This information potential makes sense in broader contexts, in general, nonequilibrium statistical mechanics[8,9] and in information theory,[10] even when no free energy is available. It has also been used to estimate the reversible work obtained in the macroscopic relaxation towards the macroscopic stationary state.[11]

This article is divided in three parts. In Sec. II, we show that in the large volume limit, the evolution is given by a standard path integral, whose weight is the exponential of minus the Lagrangian action corresponding to the Hamiltonian.[12] In Sec. III we return to the one chemical species case, already considered in Refs. 5–7. We can calculate all relevant quantities explicitly and show that there is an exponential discrepancy between the first eigenvalues of the Master equation and of the Fokker–Planck equation, as well as for the stationary state predicted by these two theories.[13] As was proved in Refs. 2 and 14, the result given by the Hamilton–Jacobi theory for the Master equation is better. We note that the Hamilton–Jacobi theory can be integrated explicitly for some multidimensional situations, although the corresponding Hamilton–Jacobi equation for the Fokker–Planck equation is not completely integrable.[14] In Sec. IV, we study the large volume limit of the first eigenvalue and the exit times, as well as the corresponding left eigenvectors of the Master equation in various situations. A similar study has been done by other authors for the Fokker–Planck dynamics.[15,16]

II. PATH INTEGRALS FOR THE MASTER AND FOKKER–PLANCK EQUATIONS

A. Notations

We recall briefly the notations introduced in Part I and refer to this work for motivations. A system with s species $i=1,...,s$ is given. We call n_i the number of particles of species i, V the volume, and $P(\{x_i\},t)$ the probability that the state is $\{x_i\}$ at time t. The system evolves by transitions $\{n_i\}\to\{n_i+r_i\}$ with probability $W_r(n)$ per unit time. The Master equation is

$$\frac{\partial P(n,t)}{\partial t}=(LP)(\{n\},t)$$

$$\equiv\sum_r\ [W_r(\{n_i-r_i\})P(\{n_i-r_i\},t)$$

$$-W_r(\{n_i\})P(\{n_i\},t)]. \tag{2.1}$$

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One can go to a large volume limit writing

$$x_i=\frac{n_i}{V},\quad dx_i=\frac{1}{V},\quad P(\{x_i\})=p(x)\prod_i dx_i,$$

$$W_r(n)=Vw_r(x),$$

and obtain the usual Fokker–Planck equation neglecting all terms of order higher than the one in $1/V$:

$$\frac{\partial p(x,t)}{\partial t}=-\sum_i \frac{\partial}{\partial x_i}(A_i p)+\frac{1}{2V}\sum_{i,j}\frac{\partial^2}{\partial x_i \partial x_j}(D_{ij}p),$$
$$A_i(x)=\sum_r r_i w_r(x),\quad D_{ij}(x)=\sum_{i,j} r_i r_j w_r(x). \tag{2.2}$$

The Hamiltonian associated to the Fokker–Planck equation is

$$H_{\mathrm{FP}}(x,\xi)=-\sum_i A_i\xi_i+\frac{1}{2V}\sum_{i,j} D_{ij}\xi_i\xi_j. \tag{2.3}$$

The corresponding Lagrangian is

$$L(x,\dot{x})=\tfrac{1}{2}(\dot{x}-A)D^{-1}(\dot{x}-A), \tag{2.4}$$

with

$$\xi=D^{-1}(\dot{x}-A)=\frac{\partial L}{\partial \dot{x}}.$$

B. The stochastic process of the Fokker–Planck equation

It is well known that there exists a stochastic process $x(t)=\{x_i(t)\}$ associated to the Fokker–Planck equation [Eq. (2.2)]. The weight of a trajectory is, up to a normalization factor:

$$\exp\left(-V\int_0^t L[x(s),\dot{x}(s)]ds\right), \tag{2.5}$$

where L is the associated Lagrangian of Eq. (2.4). In a small time interval Δt, the state x moves by Δx distributed according to the Gaussian law (depending on x):

$$\left(\frac{V}{2\pi}\right)^{d/2}(\det D)^{-1/2}$$
$$\times\exp\left[-\frac{V}{2}{}^t\left(\frac{\Delta x}{\Delta t}-A(x)\right)D^{-1}(x)\left(\frac{\Delta x}{\Delta t}-A(x)\right)\right]. \tag{2.6}$$

Consider now a dual variables ξ of Δx and compute the Laplace transform $\mathcal{L}(x,\xi,\Delta t)$ of the Gaussian distribution Eq. (2.6) with respect to Δx. This is obviously a Gaussian integral in Δx, namely,

$$\mathcal{L}=\int d(\Delta x)\left(\frac{V}{2\pi}\right)^{d/2}(\det D)^{-1/2}$$
$$\times\exp\left[-\frac{V}{2}{}^t\left(\frac{\Delta x}{\Delta t}-A(x)\right)D^{-1}(x)\left(\frac{\Delta x}{\Delta t}-A(x)\right)\right]$$
$$\times\exp(\Delta x.\xi).$$

The critical point which maximizes the exponent is $\Delta x=(1/VD\xi+A)\Delta t$ and the critical value of the exponent becomes $H_{\mathrm{FP}}(x,\xi)\Delta t$ so that

$$H_{\mathrm{FP}}(x,\xi)=\frac{1}{\Delta t}\log\mathcal{L}(x,\xi,\Delta t). \tag{2.7}$$

C. Path integral for the Master equation

For the Master equation [Eq. (2.1)] the stochastic process is a birth and death process, for which we cannot apply the method of Sec. II B. Nevertheless, we shall see that this method is valid in the large volume limit. First, we shall describe the birth and death process of the Master equation. At time t, the stochastic number of particles of species i is $N_i(t)$. The evolution of this number is defined as follows. During a time interval dt, the number of transitions of type $r=\{r_i\}$, $\{N_i(t)\}\to\{N_i(t)+r_i\}$, is a Poisson variable, $v[r,dt|N(t)]$ with rate $W_r(N)dt$ (see Appendix A for the details). The evolution equation is given by the stochastic integral equation:

$$N_i(t)=N_i(t_0)+\int_{t_0}^t\sum_r r_i v[r,ds|N(s)]. \tag{2.8}$$

Let us consider a time interval Δt and the Laplace transform $\mathcal{L}(\xi,N,\Delta t)$ of the increments $N_i(t+\Delta t)-N_i(t)$, with $N=\{N_i(t)\}$, namely,

$$\mathcal{L}(\xi,N,\Delta t)=\left\langle\exp\left[\sum_j \xi_j\sum_r r_j v(r,\Delta t|N)\right]\right\rangle. \tag{2.9}$$

It is proved in Appendix A that

$$\mathcal{L}(\xi,N,\Delta t)=\exp\left[V\Delta t H_M\left(\frac{N}{V},\xi\right)\right], \tag{2.10}$$

where $H_M(x,\xi)$ is the Hamiltonian associated to the Master equation:

$$H_M(x,\xi)=\sum_r w_r(x)\left[\exp\left(\sum_{i=1}^s r_i\xi_i\right)-1\right]. \tag{2.11}$$

We are now ready to invert Eq. (2.10) to obtain the probability $q(x+\Delta x,\Delta t|x)$ of a transition $x\to x+\Delta x$ in time Δt, in the large volume limit, where as usual $x_i=(N_i/V)$. The Fourier transform of this probability is

$$\int\exp(-i\xi.\Delta x)q(x+\Delta x,\Delta t|x)d(\Delta x)$$
$$=\left\langle\exp\left[-\frac{1}{V}\sum i\xi_j\sum_r r_j v(r,\Delta t|N)\right]\right\rangle$$

because $\Delta x=(\Delta N/V)$. By inversion, we have, using Eq. (2.10):

$$q(x+\Delta x,\Delta t|x)$$
$$=\int\exp(i\xi.\Delta x)\exp\left[V\Delta t H_M\left(x,-\frac{i\xi}{V}\right)\right]\frac{d\xi}{(2\pi)^s}$$
$$=\left(\frac{V}{2\pi}\right)^s\int\exp[V(i\xi,\Delta x)+\Delta t H_M(x,-i\xi)]d\xi.$$

For large V, this is estimated by the saddle point method. The main contribution corresponds to critical point in ξ of the exponent:

$$\Delta x_i = \Delta t \frac{\partial H_M(x,\xi)}{\partial \xi_i},$$

so that, up to prefactors

$$q(x+\Delta x, \Delta t|x) \sim \exp\left[-V L_M\left(x, \frac{\Delta x}{\Delta t}\right) \Delta t \right] \tag{2.12}$$

where $L_M(x,\dot{x})$ is the Lagrangian associated to H_M [and ξ is such that $\dot{x}_j = (\partial H_M / \partial \xi_j)$]. This is similar to the Feynman path integral.[12] Equation (2.12) shows that the transition probability is in the form of a standard path integral. Namely, the weight of a trajectory is the exponential

$$\exp\left(-V \int_0^t L[x(s), \dot{x}(s)] ds \right) \quad \text{up to prefactors.} \tag{2.13}$$

In Appendix B, we prove that Eq. (2.12) for the transition probability is consistent with the large volume asymptotic of the stationary state. In Part I, we have seen that the stationary state is up to prefactors:

$$p(x) \sim \exp[-V\Phi(x)], \tag{2.14}$$

where Φ is a solution of the Hamilton–Jacobi equation:

$$H_M(x, \nabla \Phi) = 0.$$

Then, up to prefactor, one has

$$\int q(x', \Delta t|x) p(x) dx \sim p(x').$$

Notice also that Eq. (2.12) is also consistent, because we proved in Part I that the Lagrangian L_M is positive.

D. Interpretation: Typical paths in the large volume limit

Equations (2.5) and (2.12) have the same structure. They say that in the large volume limit, the infinitesimal transition probability of an event $x \to x'$ in time Δt, is $\exp\{-VL[x,(x'-x/\Delta t)\Delta t]\}$ where L is the Lagrangian of the corresponding theory. This means that a typical trajectory in the state space of concentrations x, will minimize the Lagrangian action and will be the x part of a path $[x(s), \xi(s)]$ satisfying the Hamiltonian equations of the corresponding Hamiltonian:

$$\dot{x}_j = \frac{\partial H}{\partial \xi_j} \quad \dot{\xi}_j = -\frac{\partial H}{\partial x_i}.$$

This also implies, that in the large volume limit, the stochasticity is confined to the choice of the initial momenta, ξ_j, which will be the cause of the evolution of the x_j.

III. A SINGLE CHEMICAL SPECIES: EXACT AND APPROXIMATE SOLUTIONS

A. The Master equation and its adjoint for exit times

In this section, we consider the situation of a unique chemical species. Let n be the number of particles, V the volume. The system evolves by transitions $n \to n \pm 1$ with probabilities $W_\pm(n)$ (per unit time). Let $D = [aV, bV]$ be an interval of integers and $T_D(n)$ for n in D, the average of the first exit time of D, the stochastic process starting at time 0 from n. It is well known[17] that $T_D(n)$ satisfies the adjoint equation of the master equation, with second member -1, namely,

$$\begin{cases} W_+(n)[T_D(n+1) - T_D(n)] + W_-(n) \\ \quad [T_D(n-1) - T_D(n)] = -1 \\ T_D(n) = 0 \quad \text{for } n \text{ outside } D \end{cases}. \tag{3.1}$$

Let us assume that the boundary point aV is absorbing and that bV is reflecting. One can find an exact formula for the solution of Eq. (3.1)[17]

$$T_D(n) = \sum_{m=aV}^{n} \varphi(m) \sum_{p=m}^{bV} \frac{1}{W^-(p)\varphi(p)}$$
$$\varphi(p) = \prod_{\ell=p}^{bV} \frac{W^+(\ell)}{W^-(\ell)}. \tag{3.2}$$

Equation (3.2) has a large volume limit. We call $x = (n/V)$, $dx = V^{-1}$; so that for x in the interval $D = [a,b]$, $W_\pm(n) = V w_\pm(x)$ and we obtain the continuum limit:

$$T_D(x) = V \int_a^x dy \int_y^b \frac{dz}{W^-(z)} \exp\left(V \int_y^z \log \frac{w_+(x')}{w_-(x')} dx' \right). \tag{3.3}$$

B. Approximate solutions (simple domains)

We assume that $D = [a,b]$ contains a unique attracting point x_s of the vector field $A(x) = w_+(x) - w_-(x)$. In Eq. (3.3), the maximum of the argument in the exponential is obtained for $y = a$, $z = x_s$, and up to a prefactor

$$T_D(x) \sim \exp[V\Phi(a|x_s)], \tag{3.4}$$

where

$$\Phi(x|y) = \int_y^x \log \frac{w_-(x')}{w_+(x')} dx'. \tag{3.5}$$

We notice immediately that $\Phi(a|x_s) > 0$ because $w_+ > w_-$ on $[a, x_s]$ (and $w_+ < w_-$ on $[x_s, b]$.) Then, $T_D(x)$ does not depend on x in Eq. (3.4).

As a comparison, we could use the Fokker–Planck equation associated to the Master equation.[1,2] In that case we should solve

$$\left(A(x) \frac{\partial}{\partial x} + \frac{1}{2V} D(x) \frac{\partial^2}{\partial x^2} \right) T_D^{(\mathrm{FP})}(x) = -1$$
$$T_D^{(\mathrm{FP})}(a) = 0 \quad \frac{d}{dx} T_D^{(\mathrm{FP})}(b) = 0, \tag{3.6}$$

where $A = w_+ - w_-$, $D = w_+ + w_-$. We obtain

$$T_D^{(\mathrm{FP})}(x) = 2V \int_a^x dy \int_y^b \frac{dz}{D(z)} \exp\left(V \int_y^z \frac{2A}{D}(x') dx' \right),$$

which can be approximated up to prefactor by

$$T_D^{(\mathrm{FP})}(x)\sim\exp\left(V\int_a^{x_s}\frac{2A(x')}{D(x')}dx'\right). \tag{3.7}$$

If we compare the asymptotic results given by Eqs. (3.4) and (3.5), we see that

$$\frac{T_D}{T_D^{(\mathrm{FP})}}\sim\exp\left\{V\int_a^{x_s}\left[\log\left(\frac{1+A/D}{1-A/D}\right)-\frac{2A}{D}\right]dx'\right\}, \tag{3.8}$$

which is exponentially large with respect to the volume.

We can also consider the eigenvalue problems

$$L^*f_1=\lambda_1 f_1;\quad R^*f_1^{(\mathrm{FP})}=\lambda_1^{(\mathrm{FP})}f_1^{(\mathrm{FP})}$$

with L^* the adjoint operator of the master equation and R^* the adjoint operator of the Fokker–Planck equation [see Eq. (2.8)]. Because these eigenvalues are

$$\lambda_1\sim\frac{1}{T_D}$$

we see that

$$\frac{\lambda_1}{\lambda_1^{(\mathrm{FP})}}\sim\exp(-VC), \tag{3.9}$$

where C is a certain positive constant.

This means that the Fokker–Planck approximation overestimates the velocity of the rate process, here the rate for crossing a barrier, with respect to the more exact Master equation.[1,2]

C. Qualitative discussion of the typical trajectory

The typical trajectory of the stochastic process associated to the Master equation or the Fokker–Planck equation can be described as follows. Essentially, the evolution of the particle number n is submitted to the ''force'' exerted by the deterministic field $A(x)$, which is attracting towards x_s, and by a diffusion force. The main contribution to the calculation of $T_D(x)$ comes from trajectories joining point x in D to point a, in large times. By the results of Sec. II, these trajectories are close to Hamiltonian trajectories (either for the Hamiltonians H_M or H_{FP}). For finite times, by Kurtz theorem[1,18] such a trajectory is, however, close to the deterministic trajectory, and so goes from x to a small neighborhood of x_s. At that point, Kurtz's theorem is no longer valid, and we must follow the reasoning in Ref. 1. The trajectory finally returns to point a; following essentially the antideterministic trajectory (here this means the reverse of the deterministic trajectory from a to x_s). We shall see, in Sec. IV, that this gives back Eqs. (3.4) or (3.9).

For example, if $A(x)=-\alpha x(\alpha>0)$, and D is a constant, the equation of motion for $H_{\mathrm{FP}}=-\alpha xp+\frac{1}{2}Dp^2$ are:

$$\dot{x}=-\alpha x+Dp,\quad \dot{p}=\alpha p.$$

The trajectory which goes from $x(0)>0$ at $s=0$, to x at $s=t$, is

$$x(s)=x(0)e^{-\alpha s}+(x-x(0)e^{-\alpha t})\frac{sh\,\alpha s}{sh\,\alpha t}.$$

When $x(0)e^{-\alpha t}<x$, this trajectory starts at $x(0)$, goes toward 0, reaches a minimum $x_m\sim 2\sqrt{xx(0)}e^{-\alpha t/2}$ (so x_m tends to 0 when $t\to\infty$) and goes towards x. In a sense, when $t\to\infty$, the trajectory loses more and more time around 0 (see also Appendix B in Ref. 1 for a complete discussion).

D. Complex domains

We consider the more complex case where $D=[a,b]$ contains more than one zero of the vector field A (again with absorbing boundary condition at a, and reflecting at b).

Equations (3.3) and (3.6) are still valid and exact. As previously we denote

$$\Phi_M(x)=\int^x\log\frac{w^-}{w^+}dx'\quad\text{or}\quad\Phi_{\mathrm{FP}}(x)=-\int^x\frac{2A}{D}dx' \tag{3.10}$$

so that Φ is a solution of the corresponding Hamilton–Jacobi equation $H_M=0$ or $H_{\mathrm{FP}}=0$. In both cases, from Eqs. (3.3) and (3.6), and up to prefactors, we have

$$T_D(x)\sim\exp\left\{V\max_{\substack{a\leqslant y\leqslant x\\ y\leqslant z\leqslant b}}[\Phi(y)-\Phi(z)]\right\}. \tag{3.11}$$

Then it is easily seen that, according to the position of x with respect to the extrema of Φ, $T_D(x)$ has different expressions which may or not depend on x (Appendix D).

IV. EXIT TIMES AND RATE CONSTANTS

We shall now extend the previous results about exit time to the n-dimensional case.

A. Definition

We consider the situation of Sec. II A, in the large volume limit, so that we define the state space as the space of concentrations $x_i=(n_i/V)$. We shall treat together the cases of the Fokker–Planck dynamics or the Master dynamics. Let D be a certain domain in the space of concentrations and for a stochastic trajectory, starting from x in D, let t_D the first exit time of D. The distribution probability of t_D and the average exit time are

$$\tau_D(x,t)=\mathrm{prob}(t_D>t|X(0)=x) \tag{4.1}$$

$$T_D(x)=\langle t_D|X(0)=x\rangle=-\int_0^\infty t\frac{\partial}{\partial t}\tau_D(x,t)dt. \tag{4.2}$$

It is well known[17] that

$$\begin{cases}\dfrac{\partial\tau_D}{\partial t}=L^*\tau_D\\ \tau_D|_{t=0}=1,\tau_D=0\ \text{ on }\ \partial D\end{cases}, \tag{4.3}$$

where L^* is the adjoint operator (of the Fokker–Planck or of the Master operator L).

We consider the eigenvalues λ_n of L in D with absorbing conditions on ∂D, ordered by decreasing order (they are negative), and φ_n (resp. θ_n) the corresponding eigenvectors of L (resp. L^*)

$$L\varphi_n=\lambda_n\varphi_n,\quad L^*\theta_n=\lambda_n\theta_n. \tag{4.4}$$

The eigenvectors are normalized so that

$$\int_D\theta_n(x)\varphi_m(x)dx=\delta_{nm}.$$

Then,

$$\delta(x-x_0)=\sum_n \varphi_n(x)\theta_n(x_0).$$

Call $p_D(t,x|x_0)dx$ the probability that the process $x(t)$ is in dx at time t, without having left the domain D during $[0,t]$, knowing that it starts from x_0 at $t=0$

$$p_D(t,x|x_0)dx=\text{prob}[x(t)\in dx, t\leqslant t_D|x(0)=x_0],$$

so that

$$p_D(t,x|x_0)=\sum_{n\geqslant 1} e^{\lambda_n t}\varphi_n(x)\theta_n(x_0), \tag{4.5}$$

$$\tau_D(x_0,t)=\sum_{n\geqslant 1} e^{\lambda_n t}\theta_n(x_0)\int_D \varphi_n(x)dx, \tag{4.6}$$

and finally

$$T_D(x_0)=-\sum_n \frac{\theta_n(x_0)}{\lambda_n}\int_D \varphi_n(x)dx. \tag{4.7}$$

B. Estimation of τ_D, λ_1, T_D (simple domain)

We recall that the deterministic vector field $A(x)$ is defined as

$$A_i(x)=\sum_r r_i w_r(x).$$

In this section, we shall assume that D contains only one attracting point x_s of A and no other zero of A (except perhaps on the boundary of D).

In Appendix C, we shall sketch the proof that for large V,

$$T_D(x)\sim\exp\left[V\min_{y\in\partial D}\Phi(y|x_s)\right], \tag{4.8}$$

again up to a prefactor, and $\Phi(x|x_s)$ is the nonconstant regular solution of the Hamilton–Jacobi equation in the whole state space which vanishes at x_s:

$$\begin{aligned} &H_M(x,\nabla\Phi)=0\\ &\Phi(x_s|x_s)=0. \end{aligned} \tag{4.9}$$

We have proved in Ref. 1 that the function $\Phi(x|x_s)$ is unique. In particular, $T_D(x)$ is independent of x (up to a prefactor). Clearly, the prefactor is such that $T_D(x)$ should tend to zero for x near the boundary of D, but we are unable to give the form of this prefactor.

Then, from Eq. (4.7), we see that

$$\theta_1(x)\sim K, \tag{4.10}$$

where K is an absolute constant (up to prefactor).

However, because $\int_D \varphi_1(x)\theta_1(x)dx=1$ because of our normalization condition, we see from Eq. (4.7) that

$$-\lambda_1\sim\frac{1}{T_D(x)}\sim\exp\left(-V\min_{y\in\partial D}\Phi(y|x_s)\right) \tag{4.11}$$

and that

$$\tau_D(x,t)\sim\exp(\lambda_1 t). \tag{4.12}$$

The estimations of Eqs. (4.10)–(4.12) rely on the usual hypothesis that the eigenvalue λ_1 is well separated from the other eigenvalues λ_2, λ_3

The estimation of the first eigenvalue in Eq. (4.9) has been given by several authors for the case of Fokker–Planck dynamics.[15,16] We notice that the proof given in Ref. 16 is not logically consistent, although the result is correct (see Appendix C).

C. Estimation of τ_D, λ_1, T_D (complex domains)

In this section, we shall assume that the domain D may contain several critical points of Φ, besides a stable point x_s. We shall see that the mean exit time may depend on the starting point. The estimation of $T_D(x)$ is based on the following fact: the contribution to $T_D(x)$ does not necessarily come from the trajectories starting from x and leaving D, which have the highest probability, but also from the time taken by these trajectories to leave D. So a trajectory with the highest probability may leave D immediately and will not contribute to the calculation of T_D while a trajectory of exponentially small weight could take an exponentially long time to leave D and therefore have a large contribution to T_D. The balance between the probable weight of a trajectory and the time taken by that trajectory to leave D is exactly what will contribute to T_D. The explications of the results in this section are explained in the Appendix. (a) *D contains only a single stable zero and a single unstable zero of A.*

We call x_s (resp. x_u) the stable zero (resp. the unstable zero) of A which are in D. We shall assume that D is the union of two domains

$$D=D(x_s)\cup D(x_s'), \tag{4.13}$$

where $D(x_s)$ and $D(x_s')$ are the intersections of D with the basins of attraction of x_s and x_s'. Here x_s' is another stable zero of A which is not in D, so that x_s' is not in $D(x_s')$. As usual, we denote $\Phi(x|x_s)$ the smooth solution of Eq. (4.9). In Appendix D, we prove that

$$\lambda_1\sim\exp\left(-V\min_{y\in\partial D(x_s)}\Phi(y|x_s)\right) \tag{4.14}$$

and that

(i) for $x\in D(x_s)$:

$$\begin{aligned} &T_D(x)\sim T_{D(x_s)}(x_s)\sim\exp\left(V\min_{y\in\partial D(x_s)}\Phi(y|x_s)\right)\\ &\theta_1(x)\sim 0(1). \end{aligned} \tag{4.15}$$

(ii) For $x\in D(x_s')$:

$$T_D(x)\sim\exp\left(V\left[\Phi(x|x_s)-\Phi(x_u|x_s)+\min_{y\in\partial D(x_s)}\Phi(y|x_s)\right]\right) \tag{4.16}$$

$$\theta_1(x)\sim\exp\{V[\Phi(x|x_s)-\Phi(x_u|x_s)]\}. \tag{4.17}$$

(b) *D contains two stable zeroes and a single unstable zero of A.*

Again we write Eq. (4.13), but now $D(x_s')$ contains x_s' and we assume that $\Phi(x_s'|x_s)>0$. Each domain $D(x_s)$ or $D(x_s')$ has its own eigenvalue calculated as in Sec. IV B namely,

$$\lambda_1[D(x_s)] = \exp\left(-V \min_{y \in \partial D(x_s)} \Phi(y|x_s) \right), \tag{4.18}$$

$$\lambda_1[D(x_s')] = \exp\left(-V \min_{y \in \partial D(x_s')} \Phi(y|x_s) \right). \tag{4.19}$$

Moreover by the unicity of Φ one has

$$\Phi(x|x_s') = \Phi(x|x_s) + \Phi(x_s|x_s'). \tag{4.20}$$

The full discussion of the mean exit times is given in Appendix E. It depends on the position of the levels of $\Phi(x|x_s)$ and on the fact that the minima in Eqs. (4.18) and (4.19) are attained on ∂D or on the common boundary $\partial D(x_s) \cap \partial D(x_s')$.

V. CONCLUSION

In this article, we have given a path integral formulation of the Hamilton–Jacobi theory of the Master equation, for a general nonequilibrium reaction-diffusion system. The Hamilton–Jacobi theory is obtained as a large volume approximation of the exact Master equation. Moreover, we have given exact asymptotic results for a system with one chemical species and we have shown that the Fokker–Planck approximation of the Master equation leads to errors for the rate constants which are exponential with respect to the volume. This should not come as a surprise, because it is clear that the Fokker–Planck approximation of the Master equation does not treat correctly the evolution which occurs far from the stable macroscopic stationary state.[1] Finally, we have given formulas for the eigenvalue and the mean exit times, up to prefactor, in the general n-dimensional case. In this situation, the topology of the deterministic vector field and of the information potential Φ plays a significant role, as in shown in Sec. IV.

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APPENDIX A: BIRTH AND DEATH PROCESSES AS POISSON PROCESSES

Let E be a set of possible events (in our situation it is the set of all possible transitions $r=\{r_i\}$) and $S=E\times R^+$. If m is a positive measure on S, we define a Poisson measure v on S as the data $v(A)$ of a random variable, for each subset A of S with the following properties:

(i) if $A_1,\ldots,A_\not$ are disjoints subsets, $v(A_1),\ldots,v(A_\not)$ are independent random variables; (ii) the assignment $A \to v(A)$ is a measure on the subsets of S; (iii) $v(A)$ is a Poisson variable with distribution probability:

$$\text{prob}[v(A)=n) = \exp(-m(A)]\frac{m(A)^n}{n!},$$

so that $\langle v(A)\rangle = m(A)$.

The interpretation is that $v(X\times[t_0,t_1])$ for $X\subset E$, is the number of events of type X occurring in the time interval $[t_0,t_1]$. It is easy to see that the joint Laplace transform of $v(A_1),\ldots,v(A_n)$ for $A_1,\ldots,A_n$ disjoint subsets of S is

$$\left\langle \exp\left(\sum_{r=1}^{n} \alpha_r v(A_r) \right) \right\rangle = \prod_{r=1}^{n} \exp[m(A_r)(e^{\alpha_r}-1)]. \tag{A1}$$

In our case, if $\{r_i\}$ is a possible transition and Δt is a small time interval, we define $v(\{r_i\},\Delta t|N)$ where N is the state of the chemical system, as the total number of transitions of type r occurring in the time interval Δt when the system is in state N. This stochastic number of transitions of type r is a Poisson variable such that its average is

$$\langle v(r,\Delta t|N)\rangle = m(r,\Delta t|N) \equiv W_r(N)\Delta t. \tag{A2}$$

It is then clear that the evolution of the state $N(t)$ is given by Eq. (2.8). Notice that this is a stochastic integral equation, because $N(s)$ appears on the right-hand side of the equation.

It is now easy to verify Eq. (2.10), using Eq. (A1). We define $A_r=\{r\}\times\Delta t$ as a subset of $S=E\times R^+$ and $\alpha_r = \Sigma_i r_i \xi_i$, so that

$$\mathcal{L} = \exp\left(\sum_r W_r(N)\Delta t[\exp(\alpha_r)-1] \right),$$

which is Eq. (2.10), up to changes of notations.

APPENDIX B: PROOF OF EQ. (2.14)

Using Eqs. (2.12) and (2.13), the integral to be calculated is

$$\int \exp\left\{ -V\left[\Phi(x) + L_M\left(x, \frac{x'-x}{\Delta t} \right)\Delta t \right] \right\} dx. \tag{B1}$$

For large V, the main contribution is obtained from points x_c such that

$$\frac{\partial}{\partial x_i}\Phi(x_c) = -\Delta t \frac{\partial L}{\partial x_i}\left(x_c, \frac{x'-x_c}{\Delta t} \right) + \frac{\partial L}{\partial \dot{x}_i}\left(x_c, \frac{x'-x_c}{\Delta t} \right). \tag{B2}$$

Obviously, x' being fixed, $x_c - x'$ must be of order

$$x' - x_c \sim \dot{x}_i \Delta t \tag{B3}$$

for a certain finite $\dot{x}_c$, so that the last term in Eq. (B2) stays finite, then the first term is negligible and

$$\frac{\partial \Phi}{\partial x_i}(x_c) \sim \frac{\partial L}{\partial \dot{x}_i}(x_c, \dot{x}_c). \tag{B4}$$

This equation defines $\nabla\Phi$ as the conjugate momentum of x_c at velocity $\dot{x}_c$, but we know that $H_M[x_c, \nabla\Phi(x_c)] = 0$ which means, using the definition of H_M in term L and Eq. (B4), that

$$\dot{x}_c \nabla\Phi(x_c) = L(x_c, \dot{x}_c). \tag{B5}$$

Now we compute the value at x_c of the exponent in the integral Eq. (B1). Using Eqs. (B3)–(B5), we get

$$\begin{aligned}\Phi(x_c) + L(x_c + \dot{x}_c)\Delta t &= \Phi(x_c) + [\dot{x}_c \nabla\Phi(x_c)]\Delta t \\ &= \Phi(x_c) + (x' - x_c)\nabla\Phi(x_c) \sim \Phi(x')\end{aligned}$$

so that the integral Eq. (B1) is $\exp[-V\Phi(x')]$.

APPENDIX C: MEAN EXIT TIME FROM A SIMPLE DOMAIN

In this Appendix C, we sketch a proof of Eq. (4.8). A detailed argument will be provided in a future publication. Obviously, we cannot use the method given in Sec. III, which relied on the fact that the adjoint of the Master equation could be solved exactly. In particular, the exact formula of Eq. (3.3) looks formally as a path integral, except that there is only one path.

(i) Notations:

We use the notations of Sec. II. The state of the system is given by points $x=\{x_i\}$, $i=1,...,s$ where $x_i=(n_i/V)$. The transition $x\to x+r/V$ (where $r=\{r_i\}$) has a certain rate

$$W_r(x)=Vw_r(x),$$

and m is possible as r.

In the state space, we have a certain domain D. We call the boundary D, and denote ∂D, the set of points x which are not in D, as there is an r with $x-r/V\in D$ and $W_r(x)\neq 0$. The boundary of D is formed from the points not in D and a single step transition leads back to D. We call

$$W(x)=\sum_r W_r(x), \quad \theta(x)=\frac{1}{W(x)}, \qquad q_r(x)=\frac{W_r(x)}{W(x)} \tag{C1}$$

When the stochastic process $X(t)$ reaches the state x, it remains at x during a stochastic time T such that

$$\text{prob}(T>t)=\exp[-W(x)t],$$

and then it jumps at $x+(r/V)$ with probability $q_r(x)$, $\theta(x)$ the mean waiting time at x.

(ii) A formula for $T_D(x)$:

We call $T_D(x)$ the mean first exit time from D of the stochastic process starting from a point $x\in D$. It satisfies the adjoint equation

$$L^*T(x)\equiv\sum_r W_r(x)\left[T\left(x+\frac{r}{V}\right)-T(x)\right]=-1 \qquad T(x)=0 \quad \text{for } x\notin D. \tag{C2}$$

We skip the index D for simplicity. Equation (C2) can be rewritten using the notations [Eqs. (C1)] for $x\in D$ as:

$$T(x)=\theta(x)+\sum_r q_r(x)T\left(x+\frac{r}{V}\right). \tag{C3}$$

Actually, Eq. (C2) is derived from Eq. (C3).

If we redefine θ and q_r outside D by

$$\theta(x)=0 \quad q_r(x)=0 \quad x\notin D, \tag{C4}$$

Eq. (C3) will be valid for any x. Then Eq. (C3) can be iterated: we choose a sequence of transition $r^{(1)},...r^{(k)}$ and define a corresponding trajectory $\{x^{(1)},...,x^{(k)}\}$:

$$x^{(j)}=x+\frac{r^{(1)}}{V}+...+\frac{r^{(j)}}{V}.$$

Then, we have

$$T(x)=\theta(x)+\sum_{r^{(1)}} q_{r^{(1)}}(x)\,\theta(x^{(1)})+...+\sum_{r^{(1)},...,r^{(k)}} q_{r^{(1)}}(x) \times q_{r^{(2)}}(x^{(1)})...q_{r^{(k)}}(x^{(k-1)})\,\theta(x^{(k)})+... .$$

Obviously, the trajectory $\{x^{(1)},...,x^{(k)}\}$ is to be confined in D, due to the convention Eq. (C4). We rewrite the previous equation as

$$T(x)=\theta(x)+\sum_{x'\in D}\theta(x')\sum_{k\geqslant 1}\sum_{\substack{r^{(1)},...,r^{(k)}\\ x^{(k)}=x'}} q_{r^{(1)}}(x) \times q_{r^{(2)}}(x^{(1)})...q_{r^{(k)}}(x^{(k-1)}). \tag{C5}$$

The product

$$q_{r^{(1)}}(x)q_{r^{(2)}}(x^{(1)})...q_{r^{(k)}}(x^{(k-1)})\equiv P_D(x^{(1)},...,x^{(k)}|x), \tag{C6}$$

is the probability that the stochastic process $X(t)$ starting from x, follows the path $\{x^{(1)},...,x^{(k)}\}$ in D for the first k transitions. In Eq. (C5), we must sum the quantities $P_D(x^{(1)},...,x^{(k)}|x)$ for fixed $x^{(k)}=x'$ in D, over $x^{(1)},...,x^{(k-1)}$. We proceed as follows: A certain trajectory $\{x^{(1)},...,x^{(k-1)},x^{(k)}=x'\}$ hits x' at $x^{(k)}$, but may hit x' at one of the intermediary points $\{x^{(1)},...,x^{(k-1)}\}$. We call $m\geqslant 0$ the number of ℓ with $1\leqslant\ell\leqslant k-1$, such that $x^{(\ell)}=x'$. We can sum over $\{x^{(1)},...,x^{(k-1)}\}$, first by fixing m, and then

$$\sum_{x^{(1)},...,x^{(k-1)}} P_D(x^{(1)},...,x^{(k-1)},x^{(k)}=x'|x) = \sum_{m\geqslant 0}\sum_{\substack{x^{(1)}...x^{(k-1)}\\ m x^{(\ell)}\text{ are }x'}} P_D(x^{(1)},...,x^{(k-1)},x'|x) = \sum_{m\geqslant 0} P_D(x'|x)[P_D(x'|x')]^m = P_D(x'|x)[1-P_D(x'|x')]^{-1}. \tag{C7}$$

Here, $P_D(x'|x)$ is the total probability of all trajectories starting from x, namely $\{x^{(1)},...,x^{k-1},x^{(k)}=x'\}$ which remain in D and are such that $x^{(1)},...,x^{(k-1)}$ are all different from x'. In other words, $P_D(x'|x)$ is the probability starting from x, and the process $X(t)$ hits x' before hitting ∂D. Then $1-P_D(x'|x')\equiv P_D(\partial D|x')$ is the probability that the trajectory starting from x', hits ∂D before x'. From Eqs. (C5)–(C7), we deduce the formula

$$T(x)=\sum_{x'\in D}\frac{\theta(x')P_D(x'|x)}{P_D(\partial D|x')}. \tag{C8}$$

This formula is general and it explains why probabilities occur in the denominator, so that $T(x)$ can become exponentially large.

(iii) Estimation of the formula [Eq. (C8)]:

In Eq. (C8), θ and $P_D(x'|x)$ are bounded, so, we need to find an estimation of $P_D(\partial D|x')$, which is the probability starting from x' that the process hits ∂D before x'.

We shall now assume that D contains only one stable point x_s of the deterministic vector field, which is also a minimum of Φ (see, Part I) and that D is contained within

the basin of attraction of x_s. From the results of Sec. II, the typical trajectory starting from $x' \in D$ goes to x_s in a finite time following the deterministic trajectory of the vector field A. Along that part of the typical trajectory, the Lagrangian L is 0, so the weight of that part of the trajectory is 0(1) and we deduce that $P_D(\partial D|x')$ is essentially independent of x'. We can assume that $x'=x_s$, then the typical trajectory which starts from x_s and leaves D without reaching back to x_s, is a trajectory which minimizes the Lagrangian action in

$$\exp\left(-V\int_0^t L[x(s),\dot{x}(s)]ds\right)$$

for the path joining x_s to the boundary of D, Such a trajectory has been studied in Part I, Sec. IV B and is, as stated, an antideterministic trajectory. We have seen that along such an antideterministic trajectory $\overline{x}(s)$:

$$\frac{d\Phi}{ds}=L[\overline{x}(s),\dot{\overline{x}}(s)],$$

so that the weight of such a trajectory is $\exp\{-V[\Phi(y)-\Phi(x_s)]\}$ where y is the end point on ∂D of the trajectory. Then, we see that

$$P_D(\partial D|x')\sim\exp\left(-V\min_{y\in\partial D}\Phi(y|x_s)\right). \tag{C9}$$

Here we show that the usual method to prove the equation is not consistent.[16] The idea is to start from

$$L\varphi_1=\lambda_1\varphi_1 \tag{C5}$$

and integrate on D. The integral of $L\varphi_1$ reduces to an integral of φ_1 and its first derivatives on ∂D and

$$\lambda_1\sim\frac{\int_{\partial D}(\varphi_1+\text{first derivatives of }\varphi_1)d\sigma}{\int_D\varphi_1 dx}.$$

Then, one uses as a test function $\varphi_1=\exp[-V\Phi(x)]$ and we obviously achieve the result of Eq. (4–9) (because Φ must be a smooth solution of the Hamilton–Jacobi equation). This choice of φ_1 is now inconsistent with Eq. (C5) and the estimation given by Eq. (4.9), because the calculation of $\exp[V\Phi(x)]L\{\exp[-V\Phi(x)]\}$, gives *a priori* a term of $0(V)$ which is identically 0 because Φ satisfies Hamilton–Jacobi equation, so it is of order 0(1) with respect to V. So,

$$L\exp[-V\Phi(x)]=\exp[-V\Phi(x)]\times 0(1),$$

but in any case this cannot be of the type $\lambda_1\exp[-V\Phi(x)]$ where λ_1 satisfies Eq. (4.9).

APPENDIX D: ASYMPTOTIC OF τ_D, λ_1, T_D FOR COMPLEX DOMAIN (ONE STABLE AND ONE UNSTABLE ZERO OF A)

1. One degree of function

In one dimension, the formula for the exact time is given by Eqs. (3.3) or (3.8) which can be an analyzed exactly and leads to Eq. (3.13). The detailed discussion is as follows. We consider two cases.

Case 1: $[a,b]$ contains only one stable point x_s and one unstable point x_u of A, with $a<x_u<x_s<b$ and we assume $\Phi(a)>\Phi(x_s)$.

Then, one has:

(i) if $x_u<x<x_s$, $T_D(x)\sim\exp\{V[\Phi(x_u)-\Phi(x_s)]\}$,

(ii) if $a<x<x_u$, $T_D(x)\sim\exp\{V[\Phi(x)-\Phi(x_s)]\}$.

Case 2: $[a,b]$ contains two stable points x_s, x_s' and one unstable point x_u and we assume $\Phi(x_u)>\Phi(a)>\Phi(x_s')>\Phi(x_s)$:

(i) $x_u<x<x_s$, $T_D(x)\sim\exp\{V[\Phi(x_u)-\Phi(x_s)]\}$.

(ii) $a<x<x_u$. We call x_1 the value of x in $[x_s',x_u]$ such that $\Phi(x_1)=\Phi(a)$, then

$T_D(x)\sim\exp\{V[\Phi(x)-\Phi(x_s)]\}$ $x_1<x<x_u$,

$T_D(x)\sim\exp\{V[\Phi(a)-\Phi(x_s)]\}$ $a<x<x_1$.

We see that the asymptotic formulas for the exit time may depend on the exact position of x in $[a,b]$. The reason is the following one. The asymptotic behavior of $T_D(x)$ is given by the contributions of trajectories starting from x and by definition leaving D through a. However, there are two factors in such a contribution. First, the weight of a certain trajectory which must be ''maximal'' in a sense, but always less than one, because it is a probability, and second, the total time spent in D by that trajectory before leaving D through a. In case 1, when $a<x<x_u$ the most probable trajectory starts from x and leaves D by a, following the deterministic trajectory towards x_s', but the total time of that trajectory is 0(1). On the other hand, there is another trajectory starting from a and coming back in the well of x_s, which has a very small weight $\exp -V[\Phi(x_u)-\Phi(x)]$. This trajectory, once at x_u, rolls down to x_s in time 0(1) but needs to return to a, and so takes time $\exp V[\Phi(x_u)-\Phi(s_s)]$ to return to x_u. All other times are smaller. The contribution of this trajectory to T_D is thus:

$$\exp\{-V[\Phi(x_u)-\Phi(x)]\}\times\exp\{V[\Phi(x_u)-\Phi(x_s)]\}$$
$$=\exp\{-V[\Phi(x_s)-\Phi(x)]\}$$

which is case 1 (ii) above.

2. Several degrees of freedom

The same method can be applied to several degrees of freedom. In this case, we do not have a formula such as Eqs. (3.3) or (3.8). The total time $T_D(x_0)$ is obtained as a contribution of trajectories taking a long time before leaving D (now at any point on the boundary of D) but which are the most probable (or more exactly the most probable among improbable). Still, we must discuss the case of a simple domain (Sec. IV B and Appendix C).

We analyze a typical trajectory which starts from x_0 and leaves D after a very large time t:

(i) For $x_0\in D(x_s)$.

The typical trajectory starting from x_0 must first leave $D(x_s)$. So, using the results of Appendix C applied to the domain $D(x_s)$, we find: The trajectory starts following the deterministic path starting from x_0, to a neighborhood of x_s; then goes out from $D(x_s)$ using the antideterministic path, at a point a which realizes $\min\Phi(y|x_s)$ on $\partial D(x_s)$. At that time, either the trajectory is out of D, or it is in $D(x_s')$, where it

follows the deterministic path towards x_s' and leaves D out in a finite amount of time. As a consequence for large t:

$$\tau_D(x,t) \sim \tau_{D(x_s)}(x_s,t), \tag{D1}$$

and the λ_1 of D is $D(x_s)$. Moreover, Eq. (4.15) holds [due to Eqs. (D1), (4.2), and (4.7)].

(ii) For $x_0 \in D(x_s')$:

A trajectory starting from a point $x_0 \in D(x_s')$ cannot spend a long time in $D(x_s')$ because it can leave D using the deterministic path starting from x_0. Therefore, if we want a trajectory which stays for a long time in D, it must go back in $D(x_s)$, then lose time around x_s, and leave $D(x_s)$ as previously described. So, for $\tau_D(x_s,t)$ should be proportional to the probability to return to $D(x_s)$, which is exponentially small and depends on x_0. Now, using Eq. (4.6) we see that $\theta_1(x_0)$ should depend on $x_0 \in D(x_s')$. From Eq. (4.7), $T_D(x_0)$ should also depend on x_0, but $T_D(x_0)$ satisfies:

$$L^* T_D = -1, \tag{D2}$$

so that $T_D = \exp(V\Phi)$ where Φ satisfies the Hamilton–Jacobi equation (or is a constant). So finally, if T_D is not a constant, we can write in $D(x_s')$:

$$\theta_1(x) \sim \exp\{V[\Phi(x|x_s)+K]\}, \tag{D3}$$

where K is a constant which can be obtained by saying that θ_1 is as close as possible to its value in $D(x_s)$ which is 0(1); at least at the point x_u of maximal probability to leave $D(x_s')$ through $D(x_s)$, and therefore through x_u, this becomes Eq. (4.17). Using Eq. (4.7), we get

$$T_D(x) \sim \lambda_1^{-1} \theta_1(x),$$

and using Eq. (4.13), we recover Eq. (4.16).

APPENDIX E: ASYMPTOTIC OF τ_D, λ_1, T_D FOR COMPLEX DOMAINS (TWO STABLE ZEROES AND ONE UNSTABLE ZERO)

The notations in Sec. IV C case b.

a. Both minima in Eqs. (4.18) and (4.19) are attained on ∂D

We call a (resp. a') the points of $\partial D \cap \partial D(x_s)$ [resp. $\partial D \cap \partial D(x_s')$], where the minima are attained,

(i) $x \in D(x_s)$;

The trajectories contributing to $T_D(x)$ start from x, which live a long time, are of two kinds.

Trajectories which run towards x_s (probability ~ 1) and leave D through a, on a time scale $\lambda_1[D(x_s)]^{-1}$. These are contributed as $\exp[V\Phi(a|x_S)]$. Trajectories which climb up to x_u (these have probability $\sim \exp\{-V[\Phi(x_u|x_s)-\Phi(x|x_s)]\}$ and leave D through a' on a time scale $\lambda_1[D(x_s')]^{-1}$. These are contributed as $\exp\{-V[\Phi(x_u|x_s)-\Phi(x|x_s)]\}\exp[V\Phi(a'|x_s')]$.

The largest of these two contributions gives $T_D(x)$. Therefore, we get

$$\text{if } \Phi(a'|x_s') < \Phi(a|x_s), \quad T_D(x) \sim \exp[V\Phi(a|x_s)] \tag{E1}$$

$$\text{if } \Phi(a'|x_s') > \Phi(a|x_s), \tag{E2}$$

one defines

$$\begin{aligned} D_1 &= [x \in D(x_s)/\Phi(x|x_s) - \Phi(x_u|x_s) \\ &\quad + \Phi(a'|x_s') > \Phi(a|x_s)], \\ &\text{for } x \text{ in } D_1, \ T_D(x) \sim \exp\{V[\Phi(a'|x_s') \\ &\qquad + \Phi(x|x_s) - \Phi(x_u|x_s)]\}, \\ &\text{for } x \text{ in } D(x_s)\backslash D_1, \ T_D(x) \sim \exp[V\Phi(a|x_s)]. \end{aligned} \tag{E3}$$

(ii) $x \in D(x_s')$.

The discussion is entirely parallel:

$$\text{if } \Phi(a'|x_s') > \Phi(a|x_s), \quad T_D(x) \sim \exp[V\Phi(a'|x_s')], \tag{E4}$$

$$\text{if } \Phi(a'|x_s') < \Phi(a|x_s), \tag{E5}$$

we define

$$\begin{aligned} D_1' &= [x \in D(x_s')/\Phi(x|x_s) - \Phi(x_u|x_s) + \Phi(a|x_s) \\ &\quad > \Phi(a'|x_s')], \\ &\text{for } x \text{ in } D_1', \ T_D(x) \sim \exp\{V[\Phi(a|x_s) \\ &\qquad + \Phi(x|x_s) - \Phi(x_u|x_s)]\} \\ &\text{for } x \text{ in } D(x_s')\backslash D_1', \ T_D(x) \sim \exp[V\Phi(a'|D_1')]. \end{aligned} \tag{E6}$$

b. Min $\Phi(x|x_s)$ in $\partial D(x_s)$ is attained at a and min $\Phi(x'|x_s')$ on $\partial D(x_s')$ is attained at x_u

(i) $x \in D(x_s)$:

The two contributions originate from trajectories leaving $D(x_s)$ through a [contribution $\exp V\Phi(a|x_s)$], from trajectories leaving $D(x_s)$ through x_u (probability $\exp\{-V[\Phi(x_u|x_s) - \Phi(x|x_s)]\}$) and then leaving $D(x_s')$ through x_u in a time $\exp[V\Phi(x_s|x_s')]$ and finally leaving $D(x_s)$ through a in a time $\exp[V\Phi(a|x_S)]$. The contribution is:

$$\exp\{-V[\Phi(x_u|x_s) - \Phi(x|x_s)]\} \times \{\exp[V\Phi(x_u|x_s')] + \exp[V\Phi(a|x_s)]\}$$

if

$$\Phi(x_u|x_s') < \Phi(a|x_s), \ T_D(x) \sim \exp[V\Phi(a|x_s)], \tag{E7}$$

if

$$\Phi(x_u|x_s') > \Phi(a|x_s), \tag{E8}$$

we define

$$\begin{aligned} D_1 &= [x \in D(x_s)/\Phi(x|x_s) + \Phi(x_u|x_s') \\ &\quad - \Phi(x_u|x_s) > \Phi(a|x_s)] \\ &\text{if} \\ &x \in D_1, \ T_D(x) \sim \exp\{V[\Phi(x|x_s) - \Phi(x_s'|x_s)]\} \\ &\text{if} \\ &x \in D(x_s)\backslash D_1, \ T_D(x) \sim \exp[V\Phi(a|x_s)]. \end{aligned} \tag{E9}$$

(ii) $x \in D(x_s')$:

The typical trajectory leaves $D(x_s')$ through x_u and $D(x_s)$ through a

$$T_D(x)\sim\exp(V\Phi(x_u|x_s'))+\exp[V\Phi(a|x_s)]. \tag{E10}$$

Note that $T_D(x)$ is made as smooth as possible in the entire domain D, i.e., with a continuous transition at x_u.

c. $\min\Phi(x|x_s)$ on $\partial D(x_s)$ is attained at x_u and $\min\Phi(x|x_s')$ on $\partial D(x_s')$ is attained at a'

$$\begin{aligned}&\text{(i)}\quad x\in D(x_s):\\ &T_D(x)\sim\exp[V\Phi(x_u|x_s)],\\ &[\text{because}\quad \Phi(a'|x_s')<\Phi(x_u|x_s)].\end{aligned} \tag{E11}$$

(ii) $x\in D(x_s')$:

Call

$$D_1'=[x\in D(x_s')/\Phi(x|x_s')-\Phi(x_u|x_s')+\Phi(x_u|x_s)>\Phi(a'|x_s')].$$

If

$$x\in D_1'\quad T_D(x)\sim\exp\{-V[\Phi(x_u|x_s')-\Phi(x|x_s')-\Phi(x_u|x_s)]\} \tag{E12}$$

$$x\in D(x_s')\backslash D_1,\quad T_D(x)\sim\exp[V\Phi(a'|x_s')]. \tag{E13}$$

d. Both minima in Eqs. (4.18) and (4.19) are attained at x_u

Call b the minimum of $\Phi(x|x_s)$ on ∂D and suppose that b is $\partial D(x_s)$. Then as in Appendix C, we have

$$\begin{aligned}&|\lambda_1|\sim\exp[-V\Phi(a|x_s)],\\ &T_D(x)\sim\exp[-V\Phi(a|x_s)].\end{aligned} \tag{E14}$$

The reason for this is that the trajectory wanders between the two basins of attraction through x_u and the first eigenstates are then $\varphi_1\sim\exp[-V\Phi(x|x_s)]$ [if $\Phi(x_s'|x_s)\geqslant 0$] so that one can apply the method of Appendix C.

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