

## Switching rates of multistep reactions

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We consider the switching rate of a metastable reaction scheme, which includes reactions with arbitrary steps, e.g.,  $kA \leftrightarrow (k+r)A$  (both forward and reverse reaction steps are allowed to happen). Employing a WKB approximation, controlled by a large system size, we evaluate both the exponent and the preexponential factor for the rate. The results are illustrated on a number of examples.

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Since the celebrated work of Kramers [1] on reaction-rate theory, much effort has been devoted to extending and generalizing his results, see Ref. [2] for a review. Applications of this theory can be found in fields as diverse as high-energy physics, nucleation, chemical kinetics, electric transport, diffusion in solids, and population dynamics among many others. In this work we consider the switching rate in a generic reaction scheme, which admits more than one (quasi)stationary state.

The particular case of single-step reactions allows for an exact solution and is well studied in the literature [3,4]. We thus concentrate on generic multistep reactions. Although an exact solution is not known, a substantial progress may be achieved by adopting an analog of the quantum-mechanical WKB approximation [5–7], controlled by a large system size. With an exponential accuracy it gives the switching rate as an exponentiated action of an auxiliary mechanical problem. Evaluation of the preexponential factor requires a matching of the quasistationary distribution (QSD) function, found in the WKB framework, with the constant current “behind the barrier” solution [1,8]. The first consistent application of this strategy to a model reaction scheme was presented recently by Meerson and Sasorov [9]. Here we generalize their approach to an arbitrary scheme with metastable states. Let us note that the approximation of the master equation by a Fokker-Planck equation by means of a Kramers-Moyal or van Kampen system size expansion is not applicable in this case. These expansions assume that the stochasticity reduces to small Gaussian fluctuations around the mean-field state, a category to which large fluctuations do not belong [4–9].

Consider a generic multistep reaction scheme, where a state with  $n$  particles may be transformed into a state with  $n+r$  particles with the rate  $W_r(n)$ . Here  $r$  is a set of integers not necessarily equal  $\pm 1$ . The corresponding master equation for the probability distribution  $P_n(t)$  is

$$\begin{aligned} \partial_t P_n(t) &= \sum_r [W_r(n-r)P_{n-r}(t) - W_r(n)P_n(t)] \\ &= \sum_r (e^{-r\partial_n} - 1)W_r(n)P_n(t). \end{aligned} \quad (1)$$

We focus on reactions which admit a QSD centered at  $n = n_0$  and an unstable equilibrium (saddle point) at  $n = n_s$ . For

definiteness we assume that  $n_0 < n_s$ . We also assume that both  $n_0$  and  $n_s$  scale in the same way with a large parameter  $N \gg 1$ , hereafter referred to as the system size, i.e.,  $n_{0,s} \sim N$ . It is then convenient to pass to a scaling variable  $q = n/N$  and separate the leading and the first subleading orders in  $N$  in the corresponding reaction rates,

$$W_r(n) = Nw_r(q) + u_r(q) + O(1/N), \quad q = n/N. \quad (2)$$

We seek for a QSD in the form  $P_n(t) = \pi(n)e^{-E_0 t}$ , where  $E_0 = 1/\tau$  is an exponentially small eigenvalue of the master equation. In the rescaled coordinate the corresponding eigenvector may be sought in the WKB form

$$\pi(q) = \exp[-NS(q) - S_1(q)]. \quad (3)$$

Substituting this form in the master Eq. (1) and keeping terms up to the order of  $O(1)$ , one finds

$$0 = \sum_r (Nw_r + u_r) \left( e^{rS'} \left[ 1 - \frac{r^2}{2N} S'' + \frac{r}{N} S'_1 - \frac{r}{N} \frac{w'_r}{w_r} \right] - 1 \right), \quad (4)$$

where the primes denote derivatives with respect to the rescaled reaction coordinate  $q$ . We have also taken into account that the eigenvalue  $E_0$  is expected to be exponentially small in  $N$  (see below) and thus may be omitted.

At order  $N$  this equation acquires the form of the stationary Hamilton-Jacobi equation  $H(q, S') = 0$ , where the effective classical Hamiltonian takes the form [6,8]

$$H(q, p) = \sum_r w_r(q)(e^{rp} - 1), \quad (5)$$

and we have denoted  $S' = p$ . Therefore to the order  $N$  the problem is reduced to finding zero-energy trajectories  $p = p(q)$ , such that  $H(q, p(q)) = 0$ , of a corresponding “mechanical” problem.

The phase portrait of a typical bistable reaction is plotted in Fig. 1. There are at least two appropriate zero-energy trajectories: the *relaxation* trajectory  $p=0$  and the *activation* trajectory  $p=p_a(q)$ , see Fig. 1. The classical equation of motion along the relaxation path  $\dot{q} = H_p(q, 0) = \sum_r r w_r(q)$  is nothing but the mean-field rate equation for our reaction scheme. According to our assumptions it admits stationary states  $q_{0,s} = n_{0,s}/N$ , where  $H_p(q_{0,s}, 0) = 0$  (other stationary states are possible, e.g.,  $q'_0$ , see Fig. 1). Those are the points where the

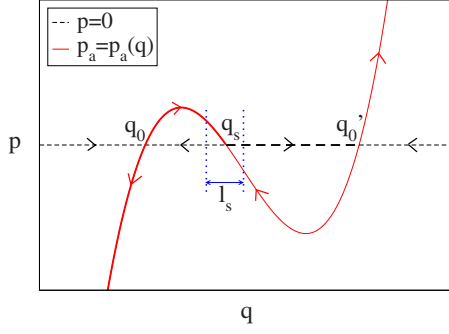


FIG. 1. (Color online) Phase portrait of a typical bistable reaction. The dashed line is the relaxation trajectory  $p=0$ ; the solid line is the activation trajectory  $p_a=p_a(q)$ . These zero-energy curves intersect at the metastable points  $q_0$ ,  $q'_0$ , and the saddle point  $q_s$ . The arrows show the direction of motion according to Hamilton equations. The matching of activation and relaxation solutions takes place in a narrow region of width  $l_s \sim N^{-1/2}$  around the saddle point.

activation trajectory  $p_a(q)$  crosses the relaxation one  $p=0$  and thus  $p_a(q_{0,s})=0$ .

To escape from a metastable state centered around  $q_0$  the system must evolve along the activation trajectory, Fig. 1. The QSD is given by Eq. (3), where  $S(q)$  and  $S_1(q)$  are determined by the order  $N$  and order 1 terms in Eq. (4) correspondingly. They lead to

$$S(q) = \int^q dq p_a(q), \quad (6)$$

$$S_1(q) = \int^q dq \frac{p'_a H_{pp} + 2H_{pq} - 2 \sum_r u_r (e^{rp_a} - 1)}{2H_p}, \quad (7)$$

where the derivatives of the Hamiltonian are evaluated along the activation path, e.g.,  $H_{pq} = \sum_r r e^{rp_a(q)} w'_r(q)$ , etc., and  $p'_a = S''$ . Equations (3), (6), and (7) determine the QSD up to a multiplicative constant. To find the latter, one needs to match the QSD with the constant current solution on the other side of the saddle point  $q_s$  [1,8,9].

At  $q > q_s$  the system evolves along the relaxation trajectory  $p=0$ , Fig. 1, and therefore  $S \equiv 0$ . Solving Eq. (4) for  $S_1$ , one finds

$$\pi(q) = J/H_p(q,0), \quad (8)$$

where  $J$  is an integration constant given by the current out of the QSD. Indeed, the master Eq. (1), having the structure of the continuity relation, in a vicinity of the relaxation trajectory  $p=0$  acquires the form

$$\partial_t P(q,t) = -\partial_q [H_p(q,0)P(q,t) + O(1/N)]. \quad (9)$$

Therefore the relaxation limit (8) of QSD  $P(q,t) = \pi(q)e^{-E_0 t}$  is nothing but a constant current,  $J$ , solution of the master equation (where we have again neglected the exponentially small eigenvalue  $E_0$  on the left-hand side). On the other hand, integrating the continuity relation (9) throughout the region of support of the QSD and assuming that the escape takes place *only* through the saddle point  $q_s$  [10], one finds

$$E_0 \int \pi(q) dq = J. \quad (10)$$

Finally to establish relation between the activation solution, Eqs. (3), (6), and (7), at  $q < q_s$  and the relaxation one, Eq. (8), at  $q > q_s$ , one needs to consider the master equation in an immediate vicinity of the saddle  $q_s$  [9]. Expanding the right-hand side of Eq. (1) to the second derivative, one finds for the current

$$[H_{pq}(q_s,0)](q - q_s)\pi(q) - \frac{H_{pp}(q_s,0)}{2N} \partial_q \pi(q) = J, \quad (11)$$

where we have used the fact that at the saddle point  $H_p(q_s,0) = \sum_r r w_r(q_s) = 0$ . Solution of Eq. (11) with the proper asymptotic behavior has the following form  $\pi(q) = (2NJ/H_{pp})e^{(q-q_s)^2/l_s^2} \int_{q-q_s}^{\infty} dq e^{-(q-q_s)^2/l_s^2}$ , where  $l_s^2 = H_{pp}(q_s,0)/NH_{pq}(q_s,0)$ . Indeed, away from the saddle point  $q_s$  it possesses the following asymptotics:

$$\pi(q) = \begin{cases} \frac{J}{(q - q_s)H_{pq}} & q - q_s \gg l_s \\ \frac{2NJl_s \sqrt{\pi}}{H_{pp}} e^{(q - q_s)^2/l_s^2} & q_s - q \gg l_s. \end{cases} \quad (12)$$

The first line matches with the relaxation solution (8) at  $q \approx q_s$ , as it should. The second line is to be matched with the activation solution Eqs. (3), (6), and (7), which in the vicinity of  $q=q_s$  takes the form

$$\pi(q) = e^{-NS(q_s) - S_1(q_s)} e^{-N(q - q_s)^2 S''(q_s)/2}. \quad (13)$$

To relate the  $q$ -dependent exponential factors here and in the second line of Eq. (12), one may differentiate the identity  $H(q, p_a(q))=0$  over  $q$  to find

$$H_q + H_p p'_a = 0, \quad H_{qq} + H_p p''_a + (H_{pp} p'_a + 2H_{pq}) p'_a = 0. \quad (14)$$

Employing that  $p'_a = S''$  and  $H(q,0) = H_p(q_{0,s},0) = 0$ , one finds

$$S''(q_{0,s}) = -\frac{2H_{pq}(q_{0,s},0)}{H_{pp}(q_{0,s},0)} = -\frac{2 \sum_r r w'_r(q_{0,s})}{\sum_r r^2 w_r(q_{0,s})}, \quad (15)$$

and therefore  $S''(q_s) = -2/Nl_s^2$ . This establishes the equality of the exponential factors in Eqs. (12) and (13). Comparing the preexponential coefficients one finds for the escape current

$$J = \frac{H_{pp}(q_s,0)}{2} \sqrt{\frac{|S''(q_s)|}{2\pi N}} e^{-NS(q_s) - S_1(q_s)}. \quad (16)$$

One can employ now the normalization condition (10) to find the escape rate  $E_0 = 1/\tau$ . To this end we notice that the bulk of the QSD is centered around  $q_0$  and approximates the integral by a Gaussian one. As a result one finds for the escape time

$$\tau = \frac{4\pi}{H_{pp}(q_s, 0)} \frac{e^{S_1(q_s) - S_1(q_0)}}{\sqrt{|S''(q_s)|S''(q_0)}} e^{N[S(q_s) - S(q_0)]}, \quad (17)$$

where  $S(q_s) - S(q_0)$  and  $S_1(q_s) - S_1(q_0)$  are fully determined by Eqs. (6) and (7). It is important to mention that the corresponding integrals are free of singularities and can be straightforwardly evaluated for any given reaction scheme. Equation (17) is the main result of the present paper.

For analytically tractable examples it is useful to notice that with the help of identities in Eq. (14), one may partially integrate Eq. (7) to obtain

$$S_1(q_s) - S_1(q_0) = \ln \sqrt{\frac{S''(q_0)}{|S''(q_s)|}} + \Delta, \quad (18)$$

$$\Delta = \int_{q_0}^{q_s} dq \left[ \frac{H_{qq}}{2H_q} - \frac{\sum_r u_r (e^{rpa} - 1)}{H_p} \right].$$

Employing Eq. (15), one may somewhat simplify Eq. (17) to cast it in the following form:

$$\tau = \frac{2\pi e^\Delta}{H_{pq}(q_s, 0)} e^{N[S(q_s) - S(q_0)]}. \quad (19)$$

Below we illustrate the usefulness of Eqs. (17) and (19) on a few examples.

$r_1 - r_2$  reactions. Consider a reaction scheme where the step variable  $r$  may acquire only two values  $r_1$  and  $r_2$ . The corresponding reaction rates are  $W_{r_{1,2}}(n) = N w_{r_{1,2}}(q)$ , where we have omitted possible subleading terms  $u_{r_{1,2}}$  for brevity. The Hamiltonian takes the form

$$H(q, p) = w_{r_1}(q)(e^{r_1 p} - 1) + w_{r_2}(q)(e^{r_2 p} - 1), \quad (20)$$

and the activation trajectory is given by the solution of the following algebraic equation for  $e^{pa}$ :

$$\frac{e^{r_1 p a} - 1}{e^{r_2 p a} - 1} = - \frac{w_{r_2}(q)}{w_{r_1}(q)}. \quad (21)$$

As a result, the following identity holds along the activation trajectory:

$$\begin{aligned} \frac{H_{qq}}{H_q} &= \frac{w_{r_1}''(q)(e^{r_1 p a} - 1) + w_{r_2}''(q)(e^{r_2 p a} - 1)}{w_{r_1}'(q)(e^{r_1 p a} - 1) + w_{r_2}'(q)(e^{r_2 p a} - 1)} \\ &= \frac{w_{r_1} w_{r_2}'' - w_{r_1}'' w_{r_2}}{w_{r_1} w_{r_2}' - w_{r_1}' w_{r_2}} = \frac{d}{dq} \ln(w_{r_1} w_{r_2}' - w_{r_1}' w_{r_2}). \end{aligned}$$

The fixed points satisfy  $r_1 w_{r_1}(q_{0,s}) = -r_2 w_{r_2}(q_{0,s})$ , while  $H_{pq}(q_{0,s}, 0) = r_1 w_{r_1}'(q_{0,s}) + r_2 w_{r_2}'(q_{0,s})$ . Employing Eqs. (18) and (19), one finds for the switching time

$$\tau = 2\pi \sqrt{\left| \frac{w_{r_1}(q_s)}{w_{r_1}(q_0)} \right|} \frac{e^{N[S(q_s) - S(q_0)]}}{\sqrt{|H_{pq}(q_s, 0)H_{pq}(q_0, 0)|}}, \quad (22)$$

where  $w_{r_1}(q_s)/w_{r_1}(q_0) = w_{r_2}(q_s)/w_{r_2}(q_0)$  and the action is given by Eq. (6).

In the particular case of *single-step* reactions,  $r_{1,2} = \pm 1$ , Eq. (21) may be solved explicitly,  $e^{pa(q)} = w_-(q)/w_+(q)$ . The fixed points are given by  $w_+(q_{0,s}) = w_-(q_{0,s})$  and according to Eq. (15)  $H_{pq}(q_{0,s}, 0) = -S''(q_{0,s})w_+(q_{0,s})$ . Employing Eq. (22), the switching rate of the single-step reaction schemes may be written as

$$\tau = \frac{2\pi}{w_\pm(q_0)} \frac{\exp\left[-\int_{q_0}^{q_s} dq \left(\frac{u_+}{w_+} - \frac{u_-}{w_-}\right)\right]}{\sqrt{|S''(q_s)|S''(q_0)}} e^{N[S(q_s) - S(q_0)]}, \quad (23)$$

where

$$S(q_s) - S(q_0) = \int_{q_0}^{q_s} dq \ln(w_-(q)/w_+(q)), \quad (24)$$

and we have included subleading terms in the rates  $u_\pm(q)$ , according to Eq. (18) [11]. In the particular case of reaction rates having only leading terms ( $u_\pm = 0$ ), Eq. (23) coincides with the results of Doering *et al.* [4], who showed it to be the large  $N$  asymptotics of the exact result for the single-step reactions [3]. In general, the  $u_r$  terms can substantially modify the prefactor [9] (see below).

Demographic explosion. Consider a single-step model [7,9]  $A \rightleftharpoons \emptyset$  with the relative rates 1 and  $N(1 - \delta^2)/2$ , where  $0 < \delta < 1$ , and  $2A \rightarrow 3A$  with the relative rate  $1/N$ . The corresponding transition rates are

$$W_-(n) = n, \quad W_+(n) = \frac{N(1 - \delta^2)}{2} + \frac{n(n-1)}{2N}.$$

The rescaled rates are  $w_- = q$  and  $w_+ = (1 - \delta^2 + q^2)/2$  while  $u_- = 0$  and  $u_+ = -q/2$  and the two rescaled fixed points are  $q_{0,s} = 1 \mp \delta$ . Employing Eq. (23), one finds for the escape time from the metastable state centered at  $n = N(1 - \delta)$  toward  $n \rightarrow \infty$

$$\tau = \frac{2\pi}{\delta} \frac{1 + \delta}{1 - \delta} e^{N[S(1+\delta) - S(1-\delta)]}, \quad (25)$$

in perfect agreement with the recent result of Meerson and Sasorov [9]. This example is specially interesting because it shows the importance of the subleading terms  $u_r$ . Disregarding these terms, one obtains a prefactor proportional to  $(1 - \delta)^{-1/2}$  instead of the correct one  $(1 - \delta)^{-1}$ . This constitutes an arbitrarily large error in the limit  $\delta \rightarrow 1$ , where the action  $S(2) - S(0)$  remains bounded.

Fokker-Planck Hamiltonian. Consider a dissipative particle under the influence of a multiplicative Gaussian noise (understood in the sense of Itô [3]). The corresponding Fokker-Planck equation is  $\dot{P} = \hat{H}P$ , where

$$\hat{H}(q, \hat{p}) = \hat{p}^2 D(q) - \hat{p} V'(q), \quad (26)$$

here  $D(q) > 0$  is a coordinate-dependent diffusion coefficient and  $\hat{p} = -\partial_q$ . Since this is a normally ordered operator, cf. Eq. (1), one may employ the theory developed above. Following the WKB approximation one substitutes  $\hat{p} \rightarrow p$  and employs Eq. (19). The stationary points are defined by the condition

$V'(q_{0,s})=0$  and the activation trajectory is given by  $p_a(q) = V'(q)/D(q)$ . As a result  $S(q_s) - S(q_0) = \int_{q_0}^{q_s} dq V'(q)/D(q)$  and  $H_{pq}(q_s, 0) = -V''(q_s) > 0$ . There are no subleading terms here,  $u_r = 0$ , and therefore

$$\Delta = \int_{q_0}^{q_s} dq \frac{H_{qq}}{2H_q} = \frac{1}{2} \ln \left| \frac{V''(q_s)D(q_s)}{V''(q_0)D(q_0)} \right|,$$

where we have made use of  $V'(q_0) = V'(q_s) = 0$ . Using this equality again one finds  $S''(q_{0,s}) = V''(q_{0,s})/D(q_{0,s})$ , and finally, plugging all together in Eq. (19), one obtains

$$\tau = \frac{2\pi}{\sqrt{V''(q_0)|V''(q_s)|}} \sqrt{\frac{D(q_s)}{D(q_0)}} \exp \left[ \int_{q_0}^{q_s} dq V'(q)/D(q) \right], \tag{27}$$

in agreement with previous calculations [2]. Assuming a constant diffusion coefficient  $D(q) = T$  (i.e., additive noise), one recovers Kramers result [1]. Notice that the role of  $N$  is played by  $1/T$ .

Higher moments of noise. Consider now Kramers problem of a dissipative particle subject to a white non-Gaussian noise. The corresponding Hamiltonian reads

$$H(q, p) = \epsilon_k p^k + T p^2 - p V'(q). \tag{28}$$

Here  $k=3, 4, \dots$  and  $\epsilon_{3,4,\dots}$  is the third, fourth, etc. (i.e., first nonvanishing beyond the second) irreducible moment of the noise correlation function. This type of noise appears as, e.g., higher-order corrections in the Kramers-Moyal expansion of the master equation [3]. Assuming that the higher moments are much smaller than the second one [12] and proceeding as in the last case, we find

$$\tau = \frac{2\pi}{\sqrt{|V''(q_s)|V''(q_0)}} e^{[V(q_s) - V(q_0)]/T} \times \exp \left\{ -\frac{\epsilon_k}{T^k} \int_{q_0}^{q_s} [V'(q)]^{k-1} dq + O(\epsilon_k^2) \right\}. \tag{29}$$

As can be seen, the prefactor remains unchanged and the whole contribution coming from the higher-order noise concentrates in an extra “phase.” Note that  $\epsilon_k$  is necessarily positive for even  $k$  (in order to keep the noise real) but it can be either positive or negative for odd  $k$ . For the escape processes under consideration  $V(q_s) > V(q_0)$ , and so the integral term in the extra phase is positive, which implies that even moments of noises only contribute to reduce the escape time, while the odd ones can reduce or increase the switching time, depending on the sign of the corresponding moment.

To conclude, we have calculated the escape rate from a metastable state whose dynamics is described by a general multistep master equation. We found a relatively simple analytical result for the switching rates between metastable states (but not for absorbing phase transitions, as, e.g., extinction) of an arbitrary single-species reaction scheme. We have shown that the general formula found here reduces to known results for single-step reactions and Fokker-Planck equations, with either additive or multiplicative noises. This technique can be used to improve the accuracy with which phenomena as chemical stochastic resonance has been studied [8]. A further clarification of the physics of these systems could be possibly achieved this way.

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 [10] In so doing we neglect the back current from the state centered at  $q'_0$ , see Fig. 1, toward  $q_0$ . This is appropriate at times shorter than the (exponentially long) escape time from  $q'_0$ .  
 [11] Notice that the equation of motion along the activation trajectory  $\dot{q} = H_p(q, p_a(q)) = w_- - w_+ = -H_p(q, 0)$  is the time-reversal partner of the relaxation motion. This is a consequence of the fact that the single-step reactions satisfy the detailed balance condition. We are indebted to M. Dykman for discussion of this point.  
 [12] Here, weakness is to be understood in the sense that the  $O(\epsilon_k^2)$  terms in the exponent may be disregarded. This is the case when  $\epsilon_k^2(k-1) \int_{q_0}^{q_s} [V'(q)]^{2k-3} dq \ll T^{2k-1}$ .