Asymptotic analysis of jumping times in multiscale stochastic systems

R. E. Lee DeVille*

June 3, 2011

Abstract

It is a typical phenomenon in the dynamics of multiscale stochastic systems that noise induces large jumps in phase space, usually by switching between metastable structures. We consider a class of problems which arise in determining large jumps in multiscale SDE, and develop asymptotic approximations for the locations of these jumps. The moments of these times are related to those obtained in extreme value statistics. We also present an application relating to the dynamics of motor proteins. Counterintuitively, we observe that adding noise to the slow process will affect the mean, but not the variance, of the jumping location.

Keywords: Self-induced stochastic resonance, Stochastic resonance, Large deviations, Multiscale asymptotics, Molecular motors, Gumbel distribution, Fisher-Tippett distribution, Extreme Value distribution

1 Introduction

There is a particular asymptotic problem which frequently arises in computing where "jumps" occur in stochastic multiscale systems. We first present a specific formulation of the problem, and then present two applications which motivate consideration of this problem. In Section 2 we present a development of the asymptotic series of interest, and in Section 3 we compare the asymptotic expansions with direct numerical simulations of the stopping problem.

1.1 Problem formulation

Let X_t^ϵ be a solution to the SDE given by

$$dX_t^\epsilon = b(X_t^\epsilon)\,dt + \sqrt{\epsilon}\sigma(X_t^\epsilon)\,dW_t, \quad X_0 = x_0, \quad X_t \in \mathbb{R}, \tag{1}$$

and define a rate:

$$\kappa(x) = \nu(x)e^{\rho(x)/\epsilon}, \tag{2}$$

where $b, \sigma, \nu, \rho \colon \mathbb{R} \to \mathbb{R}$ are C^1, $b(x) > b_* > 0$, $\nu(x) > \nu_* > 0$, $\rho'(x) > 0$ and $\rho(x)$ has a single root, and $0 < \epsilon \ll 1$. Consider a random variable $\zeta > 0$ — the "stopping time" — whose law is given by

$$\lim_{\Delta t \to 0} (\Delta t)^{-1}\mathbb{P}^{x_0}(\zeta \in (0, \Delta t]) = \kappa(x_0).$$

*Department of Mathematics, University of Illinois, Urbana IL 61801, rdeville@illinois.edu

We are interested in characterizing the random variable X_ζ^ϵ asymptotically as $\epsilon \to 0$.

Specifically, we compute $m_{p,j}$, $p = 1, 2, \dots, j = 0, 1, 2, \dots$, so that the following asymptotic series are well-formed:

$$\mathbb{E}^{x_0}[X_\zeta^\epsilon] = \sum_{j=0}^{n} \epsilon^j m_{1,j}, \tag{3}$$

$$\mathbb{E}^{x_0}[(X_\zeta^\epsilon - \mathbb{E}^{x_0}[X_\zeta^\epsilon])^p] = \sum_{j=0}^{n} \epsilon^j m_{p,j}, \quad p > 1. \tag{4}$$

In this problem we have chosen $b(x), \rho'(x)$ positive. Since the drift $b(x)$ is positive, the diffusion tends to move to the right ($\mathbb{E}^{x_0}[X_t^\epsilon]$ is increasing in t), and, as X_t^ϵ increases, the diffusion becomes much more likely to be killed. Thus, $\mathbb{P}^{x_0}(\zeta < \infty) = 1$. Moreover, the probability distribution of the stopping location drops off very rapidly in the positive-x direction; in fact, as we show in Section 2.2, it decays as an iterated exponential. Finally, we remark on one counter-intuitive result arising from this analysis: increasing the amplitude of the noise significantly changes the mean of X_ζ^ϵ but not its variance. This is, of course, the exact opposite of what happens for the mean and variance of X_t^ϵ, and is due to the strong spatial dependence of the stopping rate.

1.2 Motivation

We present two multiscale problems in which the problem (1, 2) arises. In Section 1.2.1, we show that in the correct scaling limit, determining the jumping times amongst attracting slow manifolds in singularly-perturbed SDEs will generically give rise to the problem (1, 2). In Section 1.2.2, we show that (in certain models) determining the gait of a molecular motors is a problem equivalent to (1, 2).

In both contexts, the SDE (1) corresponds to the "slow" subsystem and the jumping rate in (2) corresponds to the jumps in the "fast" subsystem which are governed by a large deviation timescale.

1.2.1 Jumping times for singularly-perturbed SDE

We follow the exposition of [8] in describing the phenomenon of *self-induced stochastic resonance*, first identified in [25] (see also [17]). Consider the singularly-perturbed SDE:

$$dx = f(x,y)\,dt + \sqrt{\epsilon}h(x,y)\,dW_t^{(x)}, \tag{5}$$

$$dy = \alpha g(x,y)\,dt + \sqrt{\alpha\epsilon}k(x,y)\,dW_t^{(y)}, \tag{6}$$

where $0 < \alpha, \epsilon \ll 1$, $f, g, h, k \in C^2(\mathbb{R}^n \times \mathbb{R})$, and h is uniformly bounded below, $x \in \mathbb{R}^n, y \in \mathbb{R}$. Here we have n "fast" variables and one "slow" variable.

Without noise ($\epsilon = 0$), this problem is the classical singularly-perturbed ODE. For simplicity of exposition, assume that there exists an interval $I \subset \mathbb{R}$, so that for each $y \in I$,

$$\frac{dx}{dt} = f(x,y)$$

has a finite number of attracting fixed points and that the union of the closures of their basins of attraction is all of $\mathbb{R}^n$. We will index these as $x_1(y), \dots, x_n(y)$; these are all smooth functions on some subinterval of I by the Implicit Function theorem, and these define smooth 1-D submanifolds of R^{n+1}. We denote these manifolds as S_j. (These are typically called "attracting slow manifolds".) After a rescaling of time we obtain the system

$$\begin{aligned} \alpha \frac{dx}{dt} &= f(x, y), \\ \frac{dy}{dt} &= g(x, y). \end{aligned} \tag{7}$$

From standard results in singular perturbation theory [29, 27, 31], we know that the trajectories of (7) will spend most of their time tracking the S_j, and the evolution is given by the slow variables restricted to the slow manifold. (More precisely, it can be shown that the trajectories typically lie in an $O(\alpha)$ neighborhood of the slow manifolds, and the flow is $O(\alpha)$ close to the restriction.) The system will switch between different slow manifolds when the trajectory "falls off" one of them.

Now consider the case with noise ($\epsilon > 0$). It is now possible for a trajectory to leave a neighborhood of a slow manifold earlier than it would in the deterministic system. First consider the case $\alpha = 0$, so that the system becomes (5) with y as a fixed parameter; since y is fixed, the attracting slow manifold is just an attracting fixed point. Consider an initial condition x_0 near $S_j(y)$ and denote by $\tau_j^\epsilon(y)$ as the (random) first passage time out of the basin of attraction of this fixed point. By Wentzell-Friedlin theory [18], there exists a function $I_j(y)$ such that

$$\lim_{\epsilon \to 0} \epsilon \log \tau_j^\epsilon(y) = I_j(y).$$

Since $\alpha > 0$, y is actually slowly-varying so that we have to match timescales. The combined problem was originally studied in [17, 25], where it was shown that in the limit

$$\epsilon \log \alpha^{-1} \to \beta > 0, \tag{8}$$

trajectories near S_j will move along S_j under the restricted dynamics until such time that $I_j(y) \leq \beta$, at which time the trajectory jumps to a neighborhood of a different slow manifold (which manifold it will be can also be determined by the theory of [18]).

To see why this should be true, notice that if $I_j(y) > \beta$, then the time it takes the fast system to escape the basin of attraction of $x_j(y)$ is roughly $e^{I_j(y)/\epsilon} \gg e^{\beta/\epsilon} = \alpha^{-1}$. The jump timescale of the fast system is much longer than the slow evolution, so we are likely to not see a jump before the slow system changes. On the other hand, if $I_j(y) < \beta$, then $e^{I_j(y)/\epsilon} \ll \alpha^{-1}$, meaning that we are very likely to see a jump before the slow system changes. In particular, if we have a slow manifold S_j such that the slow flow along this manifold is in the direction of decreasing $I_j(y)$, then in the limit (8) the system will move along S_j until it reaches the point where $I_j(y) = \beta$, at which time it will jump away with probability one.

All of the above is correct in the limit (8); in particular, and the next natural question to ask is what the corrections to this jump location are when ϵ is small but positive. Certainly, when ϵ is small, we expect the jump location to be near where it is when $\epsilon = 0$, so we want to develop this location in an asymptotic series around the $\epsilon = 0$ location. The local dynamics near the slow manifold S_j will be, in the absence of jumping away,

$$dy = \alpha G_j(y)\, dt + \sqrt{\alpha\epsilon} K_j(y)\, dW_t^{(y)}, \tag{9}$$

where G_j, K_j can be computed exactly [6] (in fact, K_j is simply the projection of k onto S_j, and G_j is the projection of g onto S_j plus an $O(\epsilon)$ "Itô correction" related to the curvature of S_i). If we ignore correlations, then the system will "jump away" from S_j with rate

$$\nu_j(y)e^{-I_j(y)/\epsilon}. \tag{10}$$

Here we have explicitly written down the "prefactor" $\nu_j(y)$ because it plays a role in the asymptotics; in general, this ν_j can be determined from the Kramers-Eyring formula [24, 4]. After rescaling time in (9, 10) by α in the limit (8), we obtain (1) and (2), with $b = G_j, \sigma = K_j, \rho = \beta - I_j$.

We note that it is no longer strictly correct to describe the jumping process by a "rate" since it will now retain a memory as y slowly evolves, if we are not in the limit (8). To take all of these dependencies and corrections to the rate into account requires an analysis comparable to that done in [9]; the dependence in particular adds significant complication to the theory, but clearly the solution to the problem considered in this paper is a better approximation to the correct answer than the limiting process (which cannot identify anything but the jump location as $\epsilon \to 0$).

1.2.2 Molecular motors

Motor proteins are nanometer-sized engines capable of generating motion at the microscopic level (for reviews see e.g. [2, 30]). Many different types of motor proteins exist in eucaryotic cells; these proteins move various organelles and vesicles from one place to another. Other types of motor proteins are also responsible for cell division and muscle contraction. Typically, motor proteins bind to filament tracks made of actin or microtubules, and move along them using the energy generated by hydrolysis (and thus the motion of the motor can be modeled by a one-dimensional process). The part of the motor protein which binds to the track is called the "motor head", and this is the part of the motor which hydrolyzes ATP. The rest of the protein is referred to as the "tail domain"; it is this part of the protein which binds to the load on which the motor protein performs work. The hydrolysis process is part of a complicated cycle during which the motor protein experiences conformational changes together with binding and unbinding to the track, the net effect of which is the motion by one step (typically a few nanometers long).

A wide variety of mathematical models have been proposed for motor proteins and, consistent with the observation that the motors operate in the thermal bath of the solvent, these models typically have a stochastic component. One particular class of models which has shown a remarkable degree of success is that due to Fisher and Kolomeisky [15, 16, 23]. In this model, the motor is located at a discrete set of sites along its track, and steps forward or backward as a Markov jump process. The rates of the jumps depend on the force applied by the cargo, which in turn depends on the distance between the cargo and the motor. More specifically, when a motor is located at position m, and a cargo at position c, the rate at which a motor "steps forward" is given by the formula

$$\rho(m, c) = \rho_0 \exp(-LF(m - c)/k_B T), \tag{11}$$

where F is the force between cargo and motor, L a characteristic length associated to the motor's step size, k_B Boltzmann's constant, T temperature, and ρ_0 the "zero separation stepping rate". Using the appropriate rescaling (see [11, Appendix A] for details), one can write this as

$$\tilde{\rho}(\tilde{m}, \tilde{c}) = \rho_0 \exp(\phi(\tilde{m} - \tilde{c})/\epsilon), \tag{12}$$

where $\epsilon = k_B T/\kappa L^2$ and $\kappa = F'(0)$ is the linear spring constant corresponding to F. We can see for fixed $\tilde{m}$, (12) has precisely the same form as (2). Moreover, the diffusion coefficient of the cargo is $\sqrt{C\epsilon}$ for some fixed constant C (for details of this derivation, see [10, Section 3]), and thus the motion of the cargo is governed by an SDE with the same scalings as (1). The stopping of the diffusion corresponds to the motor's stepping forward one step, at which time the system is reset with new initial conditions. In practice, this model is more complicated, since there are several conformational changes which can take place at any given time (e.g. the motor can step forward or backward), but in the idealization of there being only one such conformational change, (1, 2) is a reasonable model for the dynamics of a motor-cargo complex.

For the parameters corresponding to the specific protein myosin-V, the nondimensional parameter ϵ is likely in the range $(0.1, 0.6)$ [11, Appendix A]. The author (and collaborators) [11, 12, 10] have shown that the $\epsilon \to 0$ limit gives a reasonably good approximation for the dynamics of a motor-cargo system, which is reasonable since ϵ is "small". However, since ϵ is "not too small", asymptotic corrections will be significant. In fact, it was shown in [11] that these corrections are necessary to give a useful answer, but there they had to be computed by hand for that case. A need for a general approach to these asymptotics directly motivates the current study.

2 Asymptotic Analysis

In this section, we present an asymptotic analysis of (1, 2). We first start with the simpler case of $\sigma \equiv 0$ in Section 2.1 for two reasons: it is amenable to a particularly clean solution, and it inspires the correct scaling for the full problem. We consider the full problem in Section 2.2.

2.1 Deterministic slow subsystem

Let us first consider the simpler case of (1, 2) where we chose $\sigma \equiv 0$, so that the diffusion is replaced by an ODE (this is very similar to an analysis performed in [7]). Define the cumulative probability distribution $P(t) = \mathbb{P}(\zeta > t)$. Then

$$\frac{dP}{dt} = -P(t)\nu(y(t))e^{\rho(y(t))/\epsilon} \tag{13}$$

and changing variables with respect to y, using $dy/dt = b(y)$, we obtain

$$\frac{dP}{dy} = -P(y)\frac{\nu(y)e^{\rho(y)/\epsilon}}{b(y)}. \tag{14}$$

Solving for $P(y)$, using the boundary condition that $P(-\infty) = 1$, gives

$$P(y) = \exp\left(-\int_{-\infty}^{y} \frac{\nu(z)}{b(z)} e^{\rho(z)/\epsilon}\, dz\right). \tag{15}$$

Consider $\epsilon \to 0$. Define y_0 such that $\rho(y_0) = 0$ (this is unique by the assumptions of the problem). If $y < y_0$, then the exponent in the inner exponential is negative for all z in the domain of integration, and thus the integrand is exponentially small, meaning that $P(y) \to 1$. Similarly, if $y > y_0$, then for some z in the domain of integration, the exponent in the inner exponential is positive for some of the domain. Therefore the integrand is exponentially large, making the integral exponentially large, meaning $P(y) \to 0$. So we have

$$\lim_{\epsilon \to 0} P(y) = \begin{cases} 1, & y < y_0, \\ 0, & y > y_0. \end{cases}$$

In the limit, $P(y)$ is a Heaviside function which jumps at the zero of ρ. Now we compute the $O(\epsilon)$ asymptotics for $\epsilon > 0$. Recall (14) and consider the expansion

$$y = y_0 + \epsilon(z + z_0), \tag{16}$$

where z_0 remains to be determined and $\rho(y_0) = 0$. Changing variables in (14) gives

$$\begin{aligned} \frac{dP}{dz} &= -\epsilon \frac{P(z)\nu(y_0 + \epsilon(z + z_0))}{b(y_0 + \epsilon(z + z_0))} e^{\rho'(y_0)(z+z_0)+O(\epsilon)} \\ &= -\epsilon P(z) \frac{\nu(y_0 + \epsilon z_0)}{b(y_0 + \epsilon z_0)} e^{\rho'(y_0)z} e^{\rho'(y_0)z_0} + O(\epsilon^2). \end{aligned} \tag{17}$$

We want to choose z_0 to match powers of ϵ, namely

$$e^{\rho'(y_0)z_0} = \epsilon^{-1}, \quad \text{or } z_0 = \frac{\log \epsilon^{-1}}{\rho'(y_0)},$$

so we expand around

$$y^* = y_0 + \epsilon z_0 = y_0 + \frac{\epsilon \log \epsilon^{-1}}{\rho'(y_0)}.$$

Thus

$$\frac{dP}{dz} = -Ae^{Bz}P(z) + O(\epsilon), \quad A := \frac{\nu(y^*)}{b(y^*)}, \quad B := \rho'(y_0).$$

The "inner expansion" of the cdf is

$$\frac{dP}{dz} = -Ae^{Bz}P(z), \tag{18}$$

where we impose the boundary conditions $P(-\infty) = 1, P(\infty) = 0$. We can solve this by integration to get

$$P(z) = \exp\left(-\int_{-\infty}^{z} Ae^{B\zeta}\, d\zeta\right) \text{ or } P(z) = \exp\left(-\frac{A}{B}e^{Bz}\right). \tag{19}$$

From this, we can determine (see Appendix A)

$$m_1 = -\frac{\gamma + \log(A/B)}{B}, \quad m_2 = \frac{\pi^2}{6B^2},$$

and thus

$$\begin{aligned} \langle Y^\epsilon \rangle &= y_0 + \frac{\epsilon \log \epsilon^{-1}}{\rho'(y_0)} - \epsilon \frac{\gamma + \log(\nu(y^*)/b(y^*)\rho'(y_0))}{\rho'(y_0)} + o(\epsilon), \\ \left|(Y^\epsilon - \langle Y^\epsilon \rangle)^2\right| &= \epsilon^2 \frac{\pi^2}{6\rho'(y_0)^2} + o(\epsilon^2), \end{aligned}$$

where γ is the Euler–Mascheroni constant.

2.2 Stochastic slow subsystem

We consider (1, 2), where σ can now be nonzero. Performing the same inner expansion as in (16), i.e.

$$y = y_0 + \epsilon(z + z_0) = y^* + \epsilon z, \quad t = \epsilon\tau,$$

gives the rescaled SDE

$$dZ_\tau = b(y^*)\,d\tau + \sigma(y^*)\,dW_\tau + O(\epsilon). \tag{20}$$

The rate rescales as

$$\begin{aligned}\kappa(y)\,dt &= \epsilon\kappa(y^* + \epsilon z)\,d\tau \\ &= \epsilon\nu(y^*)\exp(\rho'(y_0)z_0)\exp(\rho'(y_0)z)\,d\tau \\ &= \nu(y^*)\exp(\rho'(y_0)z)\,d\tau.\end{aligned} \tag{21}$$

(We can, of course, exchange y_0 and y^* anywhere; this will only lead to a correction at yet higher order, since $y^* = y_0 + \epsilon\log\epsilon^{-1}$. Thus we switch back and forth at this order as is convenient.) We will write (20, 21) as

$$dZ_t = \mu\,dt + \sigma\,dW_t, \tag{22}$$

$$k(z) = \nu e^{\rho z}, \tag{23}$$

and the coefficients of the diffusion no longer depend on space. We will write $p^{z_0}(Z_\zeta = z)$ to denote the stopping location of problem (22, 23) with initial condition $Z_0 = z_0$. We want to determine the density $p^{-\infty}(Z_\zeta = z)$.

We follow the standard Greens function approaches [3, Sections 11,12,26], [20, Sec. 4.11], [21, Chapter 5], [26, Section 8.2] in solving this problem. Define

$$Lf := \frac{\sigma^2}{2}\frac{d^2f}{dx^2} + \mu\frac{df}{dx} - k(x)f,$$

and choose ϕ_0 to solve

$$L\phi_0 = 0, \quad \phi_0(-\infty) = 0, \quad \phi_0 \text{ decreasing}, \tag{24}$$

then

$$p^{-\infty}(Z_\zeta = z) = C\frac{d}{dz}\left(\frac{d\phi_0}{ds}\right), \tag{25}$$

where $s(z) := e^{-\frac{2\mu}{\sigma^2}z}$ and C is chosen to normalize. Also notice that since $L\phi_0 = 0$, we can also write

$$p^{-\infty}(Z_\zeta = z) = C'\frac{k(z)}{s(z)}\phi_0(z). \tag{26}$$

It is straightforward to solve $L\phi_0 = 0$, and we obtain

$$\phi_0(x) = e^{-\mu x/\sigma^2}K\left(\frac{2\mu}{\rho\sigma^2}, \frac{\sqrt{8\nu e^{\rho x}}}{\rho\sigma}\right), \tag{27}$$

where K is the hyperbolic Bessel function

$$K(\alpha, x) = \frac{\pi}{2\sin(\alpha\pi)}(i^\alpha J(-\alpha, ix) - i^{-\alpha}J(\alpha, ix))$$

and $J(\alpha, x)$ is the standard Bessel function. The asymptotics of K are [28, Chapter 5], [22, Chapter 6], [1, Sec. 9.6.]:

$$K(\alpha, x) \approx \sqrt{\frac{\pi}{2x}} e^{-x}, x \to \pm\infty, \quad K(\alpha, x) \approx \frac{\Gamma(\alpha)}{2} \left(\frac{2}{x}\right)^{\alpha}, x \to 0. \tag{28}$$

Thus we have that

$$\phi_0(x) \approx \exp(-e^{\rho x/2}), x \to \infty,$$

so decays like an iterated exponential for x large. Clearly, multiplying by an exponential and differentiating, or using formula (26), will not change the decay rate from an iterated exponential.

3 Numerical validation

In all that follows, we compare direct numerical simulation of either (1, 2) or (22, 23) to the asymptotic formula given by (25). Our method is as follows: we use a first-order Euler-Muriyama integrator for the SDE with fixed timestep Δt; at each step, compute $\kappa(x)\Delta t$ and $r \in U(0, 1)$, and if $r < \kappa(x)\Delta t$, the process is terminated. We then take an ensemble average of many copies of independent copies of this process. We first simulate (1, 2) directly, using a timestep of $\Delta t = 10^{-3}$

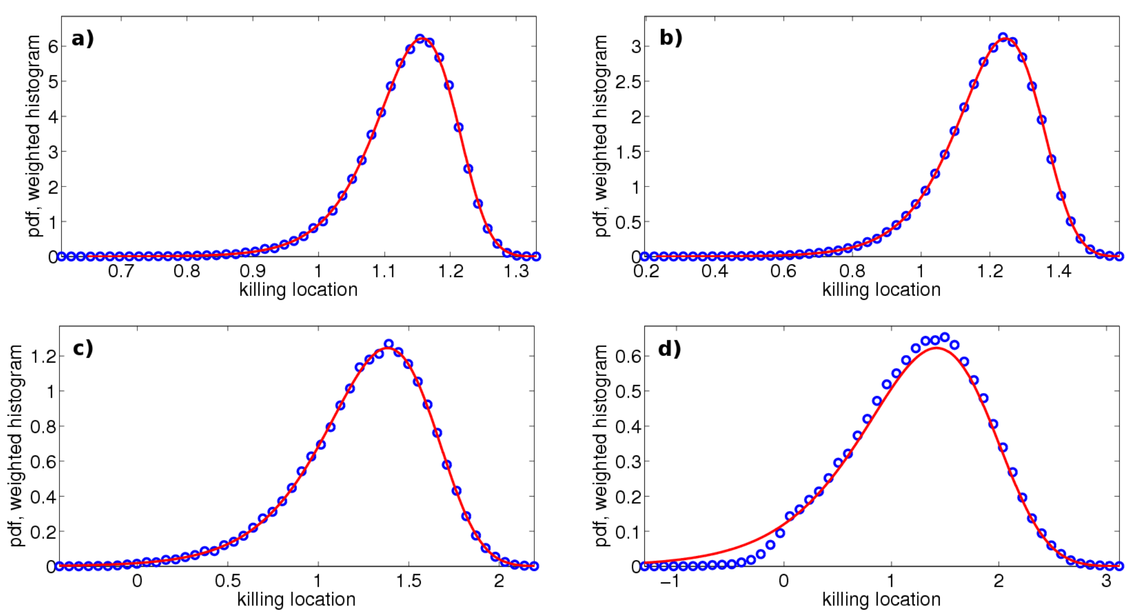

Figure 1: Simulations versus analysis for $\epsilon = .05$ (a),$\epsilon = .1$ (b), $\epsilon = .25$ (c), $\epsilon = .5$ (d) and the functions defined in (29). We obtain the pdf analytically from (25, 27) and this is plotted in solid red. The direct numerical simulation is given by blue data points.

and taking 10^5 realizations, and present the computation in Figure 1. We took as functions

$$b(x) = \cos(x) + 2, \quad \sigma(x) = 1, \quad X_0^{\epsilon} = 0, \quad \nu = 3, \quad \rho(x) = 2x^2 - x - 1, \tag{29}$$

and show the results for various values of ϵ. We chose ρ to be increasing and zero at $x = 1$, so that in the limit $\epsilon \to 0$, we expect the system to jump w.p.1 at $x = 1$. The red curves are the theoretical prediction given by (25). For ϵ chosen small enough, the approximation is exact to the eye, and even gives a pretty fair fit for $\epsilon = 1/2$! Note that the process which computes the red curve is completely in closed form except for a numerical computation for the normalization.

Finally, we simulate the process for several values of σ to show the dependence of the first two moments of the jumping time on σ, with all other parameters held fixed; see Figure 2. Here we have chosen $\mu = 1, \nu = 1, \rho = 3$, and $Z_0 = -3$ in (22) and (23). All simulations use a timestep of $\Delta t = 10^{-3}$ and an ensemble of 10^5 trials; we have plotted these in blue dots. For the analytic approximation, we use (25, 27) for $\sigma > 0$ and the methods of Section 2.1 for $\sigma = 0$; we plot this in the red solid curve.

An interesting observation is that while both of the first two moments of the escape are monotonically increasing functions of σ, the mean changes dramatically, while the standard deviation saturates quickly (note that the mean changes by a factor of about six over this range, whereas the standard deviation changes by less than a factor of two). This is somewhat surprising: adding noise to the slow variable does not make the jumping location much more random, whereas it makes the mean of the process change significantly. We discuss this observation further in Section 4 below.

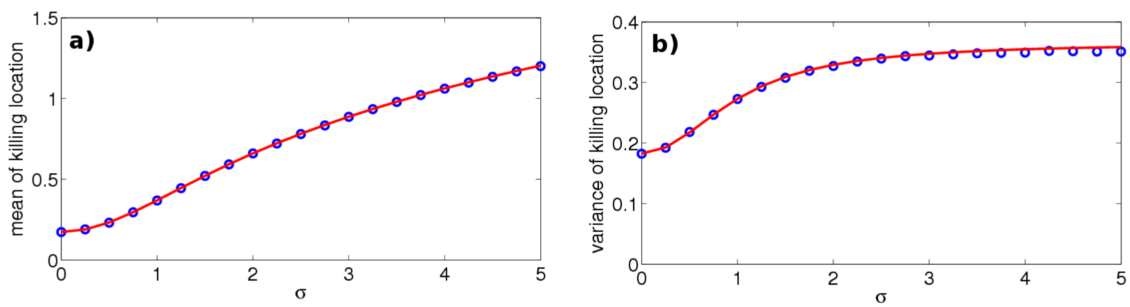

Figure 2: Mean and standard deviation for the stopping location in (22, 23) with $\mu = \nu = 1, \rho = 3$, $Z_0 = -3$. The red curve is the solution given by (25, 27), and the blue datapoints from direct simulations.

4 Conclusions

We have considered a general stopped diffusion problem with a small parameter and have derived the asymptotics for the stopping location. This problem arises directly in the study of the dynamics of motor proteins (see Section 1.2.2) and as an approximation for jumps away from a slow manifold in the general context of singularly-perturbed SDE (see Section 1.2.1). In particular, one can now compute asymptotics for motor protein models where the cargo is also subject to thermal fluctuations, extending the results of [11]. As described in Section 1.2.2, the model considered in this paper is the exact model which one would use to describe the motion of one motor on a one-dimensional filament. Interesting problems arise when one considers coupled collections of such motors, see [12, 13]; one could extend the analysis here to cases of that type.

As noted in Section 1.2.1, the current analysis gives a closer approximation for computing "jump locations" in singularly-perturbed SDE asymptotics; previous arguments were only applicable when the slow variable was deterministic (this was done in [7, 12, 11]). Thus the current method, while not the full solution for problems of this type, is an improvement over the current state of the art.

The distribution (19) is known as the Gumbel, Fisher–Tippett, or Extreme Value Distribution [14, 19] in various contexts. It can be obtained as a limit of the minimum order statistic of a sequence of n i.i.d. random variables. This is not a surprising connection, since it is the c.d.f. for the time of occurrence of the first of some sequence of events, but it is interesting that this law arises exactly without taking this limit.

We finish with a comment on a seemingly paradoxical observation made above. As observed in Figure 2, increasing σ increases $\mathbb{E}[X_\zeta^\epsilon]$ without significantly changing the variance of X_ζ^ϵ. We might expect that the effect of increasing σ would instead do the opposite, which does happen for the random variable X_t^ϵ for any fixed t where the stopping time is ignored. However, this is not correct, and it is due to the strong asymmetry in the stopping rate. Speaking roughly, for fixed t, $\mathbb{E}[X_t^\epsilon]$ is independent of σ because we are just as likely to get a realization which moves "too slow" as one which moves "too fast" (relative to the mean drift). However, if a realization actually moves much faster than its mean, then it has a possibility of getting further before it survives, since the high rate has less time to work. On the other hand, if a realization moves slower than its mean, it spends more time where the rate is low, but since the rate is low it is unlikely to jump. Therefore, realizations of the diffusion which move "too fast" have a significantly different effect on the stopping location than ones which move "too slow", and this leads to a bias (and increase) in X_ζ^ϵ. Of course, this effect exploits the non-constant stopping rate and can only become apparent when the rate is a rapidly-varying function of space.

5 Acknowledgments

The author is indebted to Richard Sowers, Renming Song, Eric Vanden-Eijnden, and Alex Yong for helpful discussion on these topics.

References

[1] Milton Abramowitz and Irene A. Stegun. *Handbook of mathematical functions with formulas, graphs, and mathematical tables*, volume 55 of *National Bureau of Standards Applied Mathematics Series*. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C., 1964.

[2] Bruce Alberts, Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, and Peter Walter. *Molecular Biology of the Cell*. Garland Science, 4th edition, 2002.

[3] Andrei N. Borodin and Paavo Salminen. *Handbook of Brownian motion—facts and formulae*. Probability and its Applications. Birkhäuser Verlag, Basel, second edition, 2002.

[4] Anton Bovier, Michael Eckhoff, Véronique Gayrard, and Markus Klein. Metastability in reversible diffusion processes. I. Sharp asymptotics for capacities and exit times. *J. Eur. Math. Soc. (JEMS)*, 6(4):399–424, 2004.

[5] S. C. Chapman, G. Rowlands, and N. W. Watkins. Extremum statistics: a framework for data analysis. *Nonlinear Processes in Geophysics*, 9(5/6):409–418, 2002.

[6] Giovanni Ciccotti, Tony Lelievre, and Eric Vanden-Eijnden. Projection of diffusions on submanifolds: application to mean force computation. *Comm. Pure Appl. Math.*, 61(3):371–408, 2008.

[7] R. E. Lee DeVille, Cyrill B. Muratov, and Eric Vanden-Eijnden. Non-meanfield deterministic limits in chemical reaction kinetics far from equilibrium. *J. Chem. Phys.*, 124(23):Article No. 231102, June 2005.

[8] R. E. Lee DeVille, Cyrill B. Muratov, and Eric Vanden-Eijnden. Two distinct mechanisms of coherence in randomly perturbed dynamical systems. *Phys. Rev. E (3)*, 72(3):031105, 2005.

[9] R. E. Lee DeVille and Eric Vanden-Eijnden. A nontrivial scaling limit for multiscale Markov chains. *J. Stat. Phys.*, 126(1):75–94, 2007.

[10] R. E. Lee DeVille and Eric Vanden-Eijnden. Self-induced stochastic resonance for Brownian ratchets under load. *Commun. Math. Sci.*, 5(2):431–446, 2007.

[11] R. E. Lee DeVille and Eric Vanden-Eijnden. Regular gaits and optimal velocities for motor proteins. *Biophysical J.*, 95(6):2681–2691, September 15 2008.

[12] R. E. Lee DeVille and Eric Vanden-Eijnden. Regularity and synchrony in motor proteins. *Bull. Math. Biol.*, 70(2):484–516, 2008.

[13] Thomas A. J. Duke. Molecular model of muscle contraction. *Proceedings of the National Academy of Sciences of the United States of America*, 96(6):2770–2775, 1999.

[14] Michael Falk, Jürg Hüsler, and Rolf-Dieter Reiss. *Laws of small numbers: extremes and rare events*. Birkhäuser Verlag, Basel, extended edition, 2004.

[15] Michael E. Fisher and Anatoly B. Kolomeisky. The force exerted by a molecular motor. *Proceedings of the National Academy of Sciences*, 96:6597–6601, June 1999.

[16] Michael E. Fisher and Anatoly B. Kolomeisky. Simple mechanochemistry describes the dynamics of kinesin molecules. *Proceedings of the National Academy of Sciences*, 98(14):7748–7753, 2001.

[17] Mark I. Freidlin. On stable oscillations and equilibriums induced by small noise. *J. Statist. Phys.*, 103(1-2):283–300, 2001.

[18] Mark I. Freidlin and Alexander D. Wentzell. *Random perturbations of dynamical systems*. Springer-Verlag, New York, second edition, 1998.

[19] J. B. S. Haldane and S. D. Jayakar. The distribution of extremal and nearly extermal values in samples from a normal distribution. *Biometrika*, 50(1-2):89–94, 1963.

[20] Kiyosi Itô and Henry P. McKean, Jr. *Diffusion processes and their sample paths*. Springer-Verlag, Berlin, 1974. Second printing, corrected, Die Grundlehren der mathematischen Wissenschaften, Band 125.

[21] Ioannis Karatzas and Steven E. Shreve. *Brownian motion and stochastic calculus*, volume 113 of *Graduate Texts in Mathematics*. Springer-Verlag, New York, second edition, 1991.

[22] James P. Keener. *Principles of applied mathematics*. Perseus Books, Advanced Book Program, Cambridge, MA, revised edition, 2000. Transformation and approximation.

[23] Anatoly B. Kolomeisky and Michael E. Fisher. A simple kinetic model describes the processivity of myosin-V. *Biophysical Journal*, 84:1642–1650, 2003.

[24] B. J. Matkowsky and Z. Schuss. The exit problem for randomly perturbed dynamical systems. *SIAM J. Appl. Math.*, 33(2):365–382, 1977.

[25] Cyrill B. Muratov, Eric Vanden-Eijnden, and Weinan E. Self-induced stochastic resonance in excitable systems. *Phys. D*, 210(3-4):227–240, 2005.

[26] Bernt Øksendal. *Stochastic differential equations*. Universitext. Springer-Verlag, Berlin, sixth edition, 2003. An introduction with applications.

[27] Robert E. O'Malley, Jr. *Singular perturbation methods for ordinary differential equations*, volume 89 of *Applied Mathematical Sciences*. Springer-Verlag, New York, 1991.

[28] R. B. Paris and D. Kaminski. *Asymptotics and Mellin-Barnes integrals*, volume 85 of *Encyclopedia of Mathematics and its Applications*. Cambridge University Press, Cambridge, 2001.

[29] Donald R. Smith. *Singular-perturbation theory*. Cambridge University Press, Cambridge, 1985. An introduction with applications.

[30] Ronald D. Vale and Ronald A. Milligan. The way things move: Looking under the hood of molecular motor proteins. *Science*, 288:88–95, 2000.

[31] Ferdinand Verhulst. *Methods and applications of singular perturbations*, volume 50 of *Texts in Applied Mathematics*. Springer, New York, 2005. Boundary layers and multiple timescale dynamics.

A Exact Computation of Moments

Define

$$\begin{aligned} m_1 &= \int_{-\infty}^{\infty} xA\exp\left(Bx - \frac{A}{B}e^{Bx}\right)dx,\\ m_k &= \int_{-\infty}^{\infty} (x-m_1)^k A\exp\left(Bx - \frac{A}{B}e^{Bx}\right)dx. \end{aligned}$$

We will follow the standard approach for the Fisher-Tippett distribution, which is slightly modified for this case (see e.g. [5]). We start with the cumulants:

$$c_k := \int_{-\infty}^{\infty} x^k A\exp\left(Bx - \frac{A}{B}e^{Bx}\right)dx.$$

We make the change of variables

$$y = Ae^{Bx}/B, \quad dy = By\,dx,$$

so

$$c_k = \int_0^{\infty} (\log By/A)^k \frac{e^{-y}}{B^k}\,dy.$$

Recall that

$$\Gamma^{(n)}(1) = \int_0^{\infty} e^{-t}(\log t)^n\,dt,$$

and this gives

$$c_k = B^{-k}\sum_{j=0}^{k}\binom{k}{j}(\log B/A)^{k-j}\Gamma^{(j)}(1).$$

Finally, to obtain the kth moment, we write

$$m_k = \sum_{l=0}^{k}\binom{k}{l}(-m_1)^{k-l}c_l, \quad m_1 = c_1.$$

Working this out exactly for several cases, we can obtain, for example, that

$$m_1 = -\frac{\gamma + \log(A/B)}{B}, \quad m_2 = \frac{\pi^2}{6B^2}, \quad m_3 = -\frac{2\zeta(3)}{B^3},$$
$$m_4 = \frac{3\pi^4}{20B^4}, \quad m_5 = -\frac{10\pi^2\zeta(3) + 72\zeta(5)}{3B^5}, \quad m_6 = \frac{61\pi^6 + 6720\zeta(3)^2}{168B^6},$$

etc., where $\zeta(\cdot)$ is the Riemann Zeta function and γ is the Euler–Mascheroni constant:

$$\gamma := \lim_{n\to\infty}\left[\left(\sum_{k=1}^{n}\frac{1}{k}\right) - \ln n\right] \approx 0.57722.$$

The m_j can be computed exactly to any order. Notice that the third moment is always negative, and all moments higher than one depend only on $|\rho'(y_0)|$ and not ν, b.