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First passage time distribution for the 1D diffusion of particles with internal degrees of freedom

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Abstract

Proteins searching for their targets on DNA do so by non-specifically adsorbing and sliding along DNA. It became known recently that the proteins simultaneously undergo some internal conformational changes (partial folding and unfolding), such that in some of the sub-states their ability to recognize the target site is enhanced at the expense of diffusivity which is suppressed. We analyze the probability distribution of the first passage times of these proteins into the target taking into account the internal sub-states of proteins. We show that there are two distinct scaling regimes: one is diffusion controlled and the other is absorption controlled.

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(Some figures in this article are in colour only in the electronic version)

1. Introduction and formulation of the model

1.1. Specific problem: DNA search

First passage is one of the most classical problems in probability theory, with vast applications in physics, particularly in chemical and biological physics [1]. As almost everything in probability theory, it started historically with gambling, specifically—with the famous gambler's ruin problem: given the initial amount of money x_0, what is the probability distribution of the time t when the gambler loses everything? In the modern language, this problem can be described in terms of a random search along the 1D linear configuration space, parametrized by the amount of remaining money x, with an absorbing boundary condition at $x = 0$. The solution of this problem is available in the textbooks (see, e.g., [2]) for a variety of cases—when x is considered as either a discrete or a continuous variable, when randomness is either biased or unbiased, etc.

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This classical search model naturally arises when one thinks of proteins searching their target sites on DNA. Indeed, it was realized a long time ago by many authors [3–9] that, for instance, transcription factor proteins identify their respective specific sites on DNA through a process which involves as one of its stages the random walk (sliding) along DNA while protein is non-specifically attached to DNA. This problem continues to attract significant attention [10–16]. Most of the efforts are directed at the understanding of combination between 3D diffusion and 1D diffusion along DNA. Here, we would like to make a step back and to consider more attentively just the 1D aspect of the problem. We, therefore, assume that DNA is completely straight and desorption from DNA into the surrounding solution does not happen.

Very recently, following the insights from both experiment [17] and theory [12, 18] it became clear that even in this simplified 1D formulation there are two inter-related aspects of the problem which were not completely understood. One aspect is the problem of ‘overshooting’—the possibility that protein does arrive at the right place, but fails to bind to it because the final recognition rate is not fast enough. The second aspect is that most searching proteins, while adsorbed non-specifically on the DNA, have in fact two distinct conformational states, and two corresponding modes of behavior: the search mode and the recognition mode; in the former, protein ‘reading heads’ are not in contact with the base pairs, protein is rather loosely adsorbed on DNA and can slide along it; in the latter, protein is in quite tight connection to DNA, including its base pairs, and it can hardly, if at all, slide along DNA. It is only in the recognition mode that protein can realize final binding of the target site. In fact, it is hypothesized [12] that the two-state proteins are the evolutionary invention to address the overshooting problem (see also [18]).

For this system, the biologically relevant question is that of the first passage time: when first protein not only arrives at the target site, but also makes strong binding to it. In the works [12, 18], certain results were obtained on the *mean* first passage time. Here, we undertake to look at the probability distribution of the first passage time for two-state proteins sliding along DNA.

In this work, we make no effort to connect our theoretical findings with the real experimental data; part of it was done in paper [18], and another part will be done elsewhere. Here we concentrate on the challenging theoretical question of finding the relevant probability distribution; the fact that many of the distributions we obtain have fat power law tails opens up the possibility that the experimentally relevant is not mean, but most probable first passage time.

1.2. General problem: reaction coordinate and other degrees of freedom

In fact, our problem can also be viewed from a more general perspective. One important generalization of the first passage time paradigm comes when a one-dimensional random walk along some coordinate x is considered over a complex energy landscape, $U(x)$. The corresponding Fokker–Planck equation is an effective method to address such problems and to obtain the Green’s function—a probability distribution $P_t(x|x_0)$ for a random walker to be located at x at time t given that the walk started at x_0 at $t = 0$. The distribution of first passage times can then be determined from the Green’s function, as the corresponding probability current through the boundary.

Kramers developed a theory of chemical reaction rates based on this approach [19]. For instance, his theory has been applied with good results to single-molecule studies of forced protein ligand–receptor unbinding or even protein unfolding (see, e.g., [20]). A central assumption of the Kramers method concerns the neglect of internal degrees of freedom other than the reaction coordinate x. It is assumed that these internal degrees may alter quite significantly the effective energy landscape associated with the motion along the reaction coordinate x, but—it is assumed—they do not change the system dynamics in any other fundamental way, such that we still deal with a one-dimensional first passage problem.

The point that we want to emphasize is that the problem can be rendered effectively 1D for two fundamentally different reasons. In some cases, the problem is one dimensional by the very geometry of the system. For instance, the statistics of escape times of a DNA molecule trapped by a 'nanopore' is a first-passage-time problem characterized by a linear sequence of intermediate states along the 'translocation coordinate' (see, e.g., [21] and references therein). Another such example is the already-mentioned search for the specific site on DNA. In some other cases, notably—for problems involving activation over a very steep energy barrier where the reaction coordinate is the direction of steepest descent—the 1D behavior is enforced by the energy landscape. Finding such a one-dimensional representation is sometimes possible [22, 23], but in general it represents a difficult task [24]; see reference list in [25] for the path-sampling techniques in addressing this problem. For instance, the grand protein folding problem is a first passage-type problem, its main question is to find (at least the mean or preferably the whole distribution of) the time of first arrival to the folded state starting from a completely unfolded one. In such complex cases, finding a 'good' reaction coordinate is quite problematic, and the adjective 'good' is usually meant to indicate exactly that all other coordinates only contribute to the effective energy landscape.

While identification of the reaction coordinate is fully recognized as a difficult task, the possible role of internal degrees of freedom other than the reaction coordinate is, in general, not well understood. It is therefore the aim of this paper to demonstrate explicitly, for the very simple model, that Kramers-like reduction to one dimension can lead to qualitatively incorrect conclusions for the first-passage-time probability density.

1.3. The models

The main model addressed in this paper is depicted in figure 1(A). In the general context of DNA search, this model focuses on the 'sliding' stage, when protein has already found some place on DNA and non-specifically adsorbed to it. Our model is, therefore, 'almost' purely 1D. Namely, protein can diffuse along the 1D lattice of DNA sites with spacing a ($a = 0.34$ nm), but it can also at every site x change its internal state, which we will call 'spin' and denote by σ. Spin σ can have two values which we denote by + for the 'upper' or mobile state and $-$ for the 'lower' or recognition state. For simplicity, we assume that the mobility in the lower state is not only small, but also zero. Thus, 'spin' in this model is the only internal degree of freedom of diffusing molecules. In addition, we assume that there is a 'target site' at $x = 0$ such that if protein arrives at $x = 0$ point and flips to the lower state, then it can—with the rate constant Ω—recognize the target site and irreversibly attach to it. In this sense, the target site acts as a sink of probability. Our goal is to find the probability distribution of the recognition time, or the first passage time into the sink; more specifically, we want to know the role of internal degree of freedom—the 'spin'—in this distribution.

Note that our model is characterized by three (or even four) distinct time scales: one of them is the typical time of diffusion from the starting point x_0 to the sink, $x_0^2/4D$, where D is the diffusion coefficient; another time scale is $1/\Omega$, which is determined by the final recognition rate; one or two more time scales arise from the rates of conversion between 'spin' states + and $-$, we denote them by $\omega_\pm$ and $\omega_\mp$.

To address the role of internal degree of freedom, we must make comparison with the reduced, Kramers style, purely 1D model. It is depicted in figure 1(B). In this model, protein

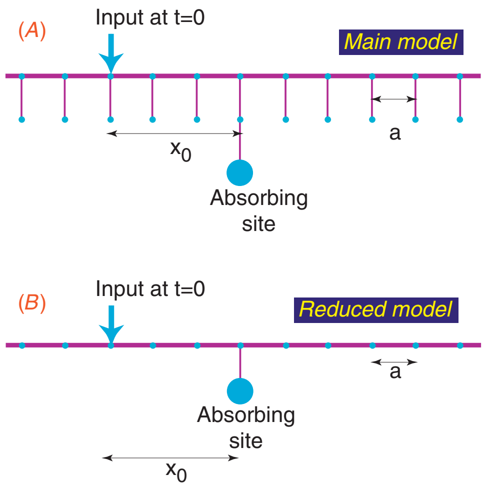

Figure 1. Schematic representation of the graphs corresponding to the two models considered in this work. For the full model (A), lower line of sites and upper line of sites correspond to the states with $\sigma = -$ and $\sigma = +$, respectively. A particle can move right, left or down (or stay still) if it is in the upper state +, while in the lower state − it can only either stay or go. In the reduced model (B), there is just one internal state for the particle at every x, so it performs the usual random walk along x.

just diffuses (possibly with a re-normalized diffusion constant) until it reaches the target site at $x = 0$ where it can get irreversibly absorbed with some (possibly re-normalized) rate Ω. Unlike our original model, the reduced model involves only two time scales, $x_0^2/4D$ and $1/\Omega$. Note that the latter time scale describes the possibility of overshoot, because if protein does reach $x = 0$ point, but does not stay there long enough compared to $1/\Omega$, it has a good chance to escape unabsorbed, which means it will have to perform one (or several) more tours of search. This model was already addressed in the literature [26]; to make our paper self-contained, we will present here the full solution of this problem, including some details not sufficiently emphasized before.

To conclude the introduction of models, it is useful to recall the classical result [2] for the first-passage-time distribution for the random walks on the semi-infinite line $x > 0$. This can be considered just one more (and final) step of simplification from our full model with three time scales (figure 1(A)) to a reduced model with two time scales (figure 1(B))—and now to a model with just one time scale: if the walker starts from the point $x = x_0$ at time $t = 0$, then the probability that it hits the $x = 0$ point for the first time at time t reads

$$Q(t) = \frac{x_0}{\sqrt{4\pi D t^3}} \, \mathrm{e}^{-x_0^2/4Dt}, \tag{1}$$

where D is the relevant diffusion coefficient. There is indeed only one characteristic time scale, $\sim x_0^2/4D$—the typical diffusion time over the distance x_0; we can interpret it as a 'waiting time' because the probability of reaching the boundary is exponentially small at $t \ll x_0^2/4D$. However, the decay of probability $Q(t)$ at large times is *not* associated with this time scale, it is actually the scale-free, power law $\sim t^{-3/2}$. This fat tail of the distribution implies that even the average first passage time, not to mention higher moments, is infinite (diverges) in this model. We will have to see how this plays out in our more sophisticated and more realistic models.

1.4. The main equations

Let us start with the reduced model. Denote $P(x, t)$ the occupation probability of the site x at time t. Then, our reduced model is described by the equation

$$\frac{\partial P}{\partial t} = D\Delta_a P + \delta(t)\Delta(x - x_0) - \Omega\Delta(x)P. \tag{2}$$

Here, Δ_a is the discrete lattice Laplacian operator:

$$\Delta_a P(x) = \frac{P(x + a) - 2P(x) + P(x - a)}{a^2}, \tag{3}$$

while $\Delta(x)$ is the Kronecker delta-function, D is the 1D diffusion coefficient of the protein and Ω is the absorption rate by the target site. We assume that at $t < 0$ there are no particles or $P(x, t) = 0$ at every x. This equation describes the following: at time $t = 0$, one particle is brought into the system at the point $x = x_0$ (the source term $+\delta(t)\Delta(x - x_0)$), then the probability distribution of this particle evolves with time and slowly sinks into the absorbing site at $x = 0$ (the sink term $-\Omega\Delta(x)P$). Thus, the current of probability away from the system is given by

$$Q(t) = \Omega P(x, t)|_{x=0}. \tag{4}$$

This $Q(t)$ represents the probability density distribution of the first passage time—the quantity of our interest.

Note that in this model, particles can visit the target site and fail to be absorbed because they are adsorbed by the origin with some finite rate constant Ω. Only in the limit, $\Omega \to \infty$, are all particles absorbed at this point, which is equivalent to the imposed absorbing boundary condition $P(x, t)|_{x=0} = 0$; this limit is, therefore, the most usual first passage problem. We consider a general case of arbitrary Ω, in which particles may 'overshoot'—visit the absorbing point one or more times, but escape non-absorbed. This is the reduced model illustrated in figure 1(*B*).

Let us now turn to our full model. If we denote $P_+(x, t)$ and $P_-(x, t)$ occupation numbers of the + and − states at the site x at time t, we can write the following equations:

$$\begin{aligned} \frac{\partial P_+}{\partial t} &= D\Delta_a P_+ - \omega_\pm P_+ + \omega_\mp P_- + \delta(t)\Delta(x - x_0), \\ \frac{\partial P_-}{\partial t} &= \omega_\pm P_+ - \omega_\mp P_- - \Omega\Delta(x)P_-. \end{aligned} \tag{5}$$

One can treat these equations as coupled diffusion–reaction equations or as a master equation of chemical dynamics on the graph in figure 1(*A*). In this case, D is the 1D diffusion coefficient of the protein in the + state, $\omega_\pm$ and $\omega_\mp$ are the rates of conformational transitions between the + and − states, and Ω is still the final recognition rate.

For the initial condition, we assume $P_+ = P_- = 0$ at $t < 0$ and at every x. Then, these equations describe the following scenario: at $t = 0$, one particle is placed into the upper (+) state at x_0 (the last term in the first equation, the source). Then, the probability flows through the graph and eventually all probability flows out through the absorbing site (the last term of the second equation, the sink). At the beginning, there is a certain probability current downward, from state + to state −, in the vicinity of x_0. But later on there is a reflux, or current upward, from the − state to the + state, because all the probability eventually has to go to $x = 0$ and down to the absorbing site. Thus,

$$Q(t) = \Omega P_-(x, t)|_{x=0} \tag{6}$$

is the probability current into the absorbing site. In other words, this is the probability density of the first passage time. This is the quantity that we would like to address.

In this paper, we will concentrate mostly on a restricted version of this problem, namely, we will pre-average over the starting point x_0: we will assume that at $t = 0$ there appears a certain density of proteins ρ, the same everywhere along x, but only in the $\sigma = +$ state. We will calculate first passage-time probability density $\overline{Q}(t)$ for this case.

To conclude this section, we point out that the two models are closely related. Under some conditions, there might be local *'chemical' equilibrium* between upper and lower states. For instance, this would happen if conformation conversion rates, $\omega_{\pm}$ and $\omega_{\mp}$, are much higher than all other rates, but this also happens under many other more realistic circumstances, as we shall see below. If this equilibrium is established, then we can reduce the coupled equations (5) to a single equation like (2) with some effective parameters $\tilde{D}$ and $\tilde{\Omega}$—see below.

We would like to mention that the models with two sub-states, not completely dissimilar to our model in figure 1(A), are considered also in the context of molecular motors (see, e.g., the textbook [27] and references therein).

2. Analysis of reduced model

2.1. Mathematical solution

We solve for the probability density distribution of first passage time $Q(t)$ for the reduced model by first re-writing equations (2) and (4) in the form

$$\frac{\partial P}{\partial t} = D\Delta_a P + \delta(t)\Delta(x - x_0) - Q(t)\Delta(x). \tag{7}$$

Then we can Fourier transform this equation with respect to x (remembering that for discrete lattice of x the wave number k is restricted to one cell of the reciprocal lattice: $-\pi/a < k < \pi/a$) and Laplace transform it with respect to t. This produces the solution in the form

$$P_{ks} = \frac{\mathrm{e}^{\imath k x_0} - Q_s}{s + D_k}, \tag{8}$$

where s is the Laplace variable and $D_k = 2D(1 - \cos ka)/a^2$. We can now write the inversion of the Fourier transform and, after that, we can determine Q from the self-consistency condition (4). We skip a few lines of straightforward algebra and obtain for the Laplace transformed Q (that is, $Q_s = \int_0^\infty \mathrm{e}^{-ts} Q(t)\,\mathrm{d}t$)

$$Q_s = \frac{F_s}{K_s + 1/\Omega}, \tag{9}$$

where

$$F_s = \frac{a}{2\pi}\int_{-\pi/a}^{\pi/a} \frac{\mathrm{e}^{\imath k x_0}}{s + D_k}\,\mathrm{d}k, \tag{10}$$

and

$$K_s = \frac{a}{2\pi}\int_{-\pi/a}^{\pi/a} \frac{1}{s + D_k}\,\mathrm{d}k. \tag{11}$$

Further simplification is achieved under the assumption $s \ll D/a^2$. Indeed, since at $s = 0$ the above integrals diverge at $k = 0$, at small s they are dominated by the small k region, where $D_k \simeq Dk^2$. Upon replacing D_k with Dk^2, one can also continue integration over k to infinity. This then yields

$$Q_s \simeq \frac{\exp\left[-\sqrt{x_0^2 s/D}\right]}{1 + \frac{\sqrt{4sD}}{a\Omega}} \qquad \text{at} \quad s \ll \frac{D}{a^2}. \tag{12}$$

Note that this result does not depend on the sign of the initial coordinate x_0, which is physically natural.

Computing the inverse Laplace transform from here is somewhat tricky, but possible. The calculation is described in some details in appendix A. As to the result, it will be convenient to write it parallel with some physical explanations.

2.2. Physical explanations

To write the final formula for the probability distribution of the first passage time $Q(t)$, it will be convenient to re-scale the time and coordinate variables. Specifically, we introduce the characteristic length X and characteristic time T such that

$$X = \frac{D}{a\Omega}, \qquad T = \frac{D}{a^2\Omega^2}. \tag{13}$$

Further, we introduce the dimensionless initial coordinate $\xi = |x|/X$ and dimensionless time $\tau = t/T$. Then, dimensionless probability density distribution $\theta(\tau) = TQ(t)$ must be normalized such that $\int_0^\infty \theta(\tau)\,\mathrm{d}\tau = 1$. We are now prepared to write the result for the inverse Laplace transform of equation (12) (derived in appendix A), in terms of the dimensionless probability density $\theta(\tau)$:

$$\begin{aligned}\theta(\tau) &= \frac{\mathrm{e}^{-\frac{\xi^2}{4\tau}}}{\sqrt{4\pi\tau}} \int_0^\infty \mathrm{e}^{-\eta}\left[1 - \mathrm{e}^{-\frac{\eta|\xi|+\eta^2}{\tau}}\right] \mathrm{d}\eta \\ &= \frac{\mathrm{e}^{-\frac{\xi^2}{4\tau}}}{\sqrt{4\pi\tau}} \left[1 - \frac{\sqrt{\pi\tau}}{2}\,\mathrm{e}^{\frac{(\xi+\tau)^2}{4\tau}}\,\mathrm{Erfc}\left(\frac{\xi+\tau}{2\sqrt{\tau}}\right)\right].\end{aligned} \tag{14}$$

As explained in appendix A, formula (14) is asymptotically exact at $t \gg a^2/D$—on a time scale longer than the time of 'diffusion' between neighboring sites. Obviously, smaller time scales do not make sense at all within our model, so the solution obtained is exact for the model under all physically relevant conditions.

To gain an insight into the distribution equation (15), we first present in figure 2 its numerically calculated plots for three different values of initial distance ξ. In order to make the plots for different values of ξ better comparable, we present the distribution against the variable τ/ξ^2 and we plot the quantity $\theta(\tau)\xi^2$ which is properly normalized against τ/ξ^2.

Mathematically, the distribution $\theta(\tau)$ has the following interesting properties:

- As a function of τ, the probability reaches maximum at τ_m which, roughly, scales with the square of initial distance, which is natural for the diffusion process.
- Specifically, the ratio τ_m/ξ^2 does not change very much at all, it only goes from $1/2$ when $\xi \to 0$ to $1/6$ when $\xi \to \infty$.
- More accurately, time of maximal probability is asymptotically equal to $\tau_m/\xi^2 \simeq 1/2 - \xi/4$ when $\xi \ll 1$ and to $\tau_m/\xi^2 \simeq 1/6 + 2/(3\xi)$ when $\xi \gg 1$.
- The height of the maximum (in proper units) approaches a constant, $\theta_{\max}\xi^2 \simeq \sqrt{54/\pi e^3}(1 - 4/\xi)$ when the starting point is far away, $\xi \gg 1$, while it goes like $\theta_{\max}\xi^2 \simeq \xi/\sqrt{2\pi e} - \xi^2\,\mathrm{Erfc}(1/\sqrt{2})/4$ when $\xi \ll 1$. Since the whole probability density is normalized, there is a very long tail of the distribution at small ξ.
- In terms of time dependence, probability density has the following asymptotic behavior. If we start far away, $\xi \gg 1$, then

$$\theta(\tau) \simeq \begin{cases} \dfrac{1}{\sqrt{4\pi\tau}}\,\mathrm{e}^{-\xi^2/4\tau} & \text{when} \quad \tau \ll \xi \\ \dfrac{\xi}{\sqrt{4\pi\tau^3}}\,\mathrm{e}^{-\xi^2/4\tau} & \text{when} \quad \tau \gg \xi. \end{cases} \tag{15}$$

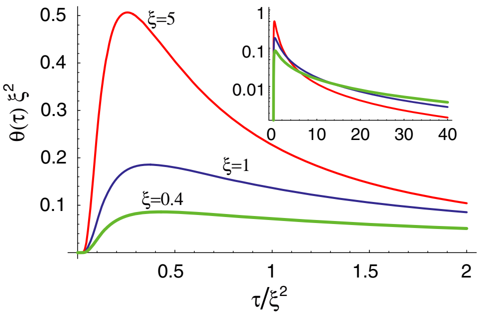

Figure 2. The distribution of first passage time for the reduced model in a reduced dimensionless form, as $\theta(\tau)\xi^2$ against τ/ξ^2; equation (14) is plotted numerically for three different values of initial distance ξ, namely $\xi = 5, \xi = 1$ and $\xi = 0.4$. The height of the maximum approaches $\sqrt{54/\pi e^3} \approx 0.925$ when $\xi \to \infty$. In the opposite limit, when ξ is small, the height of the maximum gets very small, proportional to ξ. Note, however, that all distributions are normalized to one, so the distributions at small ξ, exemplified here by $\xi = 0.4$, have particularly long tails. In the inset, the same distributions are shown in the semi-log scale and over wider range of time to demonstrate the very long tails.

- If, on the other hand, we start very near the sink, $\xi \ll 1$, then

$$\theta(\tau) \simeq \begin{cases} \dfrac{1}{\sqrt{4\pi\tau}}\,\mathrm{e}^{-\xi^2/4\tau} & \text{when} \quad \tau \ll 1 \\ \dfrac{2}{\sqrt{4\pi\tau^3}}\,\mathrm{e}^{-\xi^2/4\tau} & \text{when} \quad \tau \gg 1. \end{cases} \tag{16}$$

- Scaling regimes of probability density are summarized in figure 3.
- 'Half-absorption' time, $\tau_{1/2}$, is defined according to $\int_0^{\tau_{1/2}} \theta(\tau)\,\mathrm{d}\tau = \int_{\tau_{1/2}}^{\infty} \theta(\tau)\,\mathrm{d}\tau = 1/2$. This quantity behaves in the following way: at $\xi \ll 1$ we have $\tau_{1/2} \simeq 2$, while at $\xi \gg 1$ we obtain $\tau_{1/2} \simeq \xi^2/4\alpha^2$, where $\alpha \approx 0.48$ is the root of the equation $\mathrm{Erf}(\alpha) = 1/2$. That means, at small ξ only a tiny fraction of probability gets absorbed before the maximum, while at large ξ this fraction is about 1/6.

To gain more insight into these properties of the probability density distribution $\theta(\tau)$, it is useful to understand the nature of the characteristic length X and the characteristic time T. Over the time $\sim T$, a particle smears due to diffusion over a distance $\sim\sqrt{DT}$, which represents $\sim\sqrt{DT}/a$ sites, and, therefore, the particle spends on each site the time $t_a \sim T/(\sqrt{DT}/a) = \sqrt{Ta^2/D}$. If this time were smaller than $1/\Omega$, the chances of absorption would be marginal, so the sink is virtually transparent on this time scale. Conversely, if $t_a \gg 1/\Omega$, the absorption is nearly a certainty, so the sink is completely non-transparent. Therefore, the important cross-over occurs when $t_a \sim 1/\Omega$, which is exactly the time T defined in equation (13). Similarly, distance X is such that the particle starting closer to the sink has good chances to pass through non-absorbed, while the particle which starts further away is nearly certainly absorbed. In other words, on length and time scales exceeding X and T, the sink acts as a perfect absorber which can be replaced by the absorbing boundary condition; on length and time scales smaller than X and T the sink is almost perfectly transparent.

This consideration now suggests the following view. Suppose that first the particle starts much farther away from the sink than X: $x_0 \gg X$ (or $\xi \gg 1$). Then, typical diffusion trajectories will all absorb in the sink. Therefore, one expects that probability density distribution $Q(t)$ should be the same as in the classical first passage problem based on the absorbing boundary condition [2]. The only trajectories which have a chance to pass

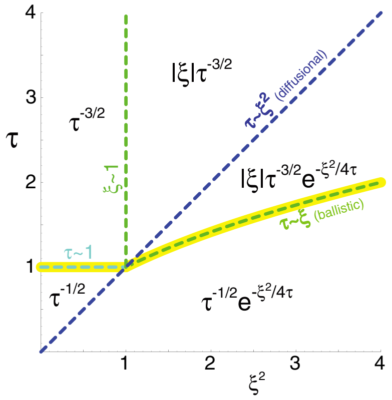

Figure 3. Diagram of scaling regimes for the probability distribution of the first passage time for the reduced model. Axes: unitless time $\tau = t/T$ against squared unitless initial distance ξ^2, where $\xi = |x_0|/X$. Both equations of cross-over lines and the behavior of probability density $\theta(\tau)$ for each regime are indicated in the diagram. The thick line separates the absorption-limited regime when X-wide region around the sink is effectively transparent (below the line) and the diffusion-limited regime when it is effectively a perfect absorbent (above the line).

through the sink are the exponentially rare 'ballistic' ones in which particle moves with the speed x_0/t exceeding $a\Omega$, that is, spending less time than $1/\Omega$ time on each site, which means $x_0/t \gg a\Omega$ or $\xi \gg \tau$. These trajectories are almost not affected by the sink and, therefore, their contribution to the diffusion current into the sink, to the leading order, equals the unperturbed density at the $x = 0$ site, which is simply the Green function of free diffusion, multiplied by Ω. To summarize, we expect

$$Q(t) \simeq \begin{cases} \dfrac{a\Omega}{\sqrt{4\pi Dt}}\,\mathrm{e}^{-x_0^2/4Dt} & \text{when} \quad t \ll x_0/(a\Omega) \\ \dfrac{x_0}{\sqrt{4\pi Dt^3}}\,\mathrm{e}^{-x_0^2/4Dt} & \text{when} \quad t \gg x_0/(a\Omega). \end{cases} \tag{17}$$

This is exactly the above-derived result of equation (15).

Consider now the case when the particle starts very close to the target site, $x_0 \ll X$. At the very beginning, we still have an almost unperturbed diffusion, which yields for $Q(t)$ the Green function of free diffusion multiplied by Ω. However, this regime continues only to $t \sim T$. If the particle was not absorbed by that time, then it must have spread over a distance about X and, therefore, the sink becomes absorbing from that time on. That produces results looking similar to equation (17), except that the cross-over happens at $t \sim T$ and the initial distance ξ must be replaced by X in the long time part of the result, and that is exactly equation (16).

We can conclude that there are two basic regimes; we can call them diffusion-limited regime and absorption-limited regime. In the diffusion-limited regime, which takes place when both $t > x_0/(a\Omega)$ and $t > T$, the dominant problem is to deliver the particle by diffusion into the region of a target; in the absorption-limited regime, the main problem is to spend sufficiently long time on the target site to get absorbed. Not surprisingly then the expression for probability in the diffusion-limited regime contains no Ω. The cross-over between these two regimes is marked by a thick line in figure 3.

2.3. Averaging over the initial position

It is of physical interest to consider also a slightly different problem in which the particle arrives at the initial moment at a random place on the x-axis. For the proteins searching for their targets on DNA, this formulation is the most natural, because protein can land on any place on DNA at random.

In this case, we are interested in the quantity $\overline{Q}(t)$, which is the average of $Q(t)$ over all initial positions:

$$\overline{Q}(t) = \int_{-\infty}^{+\infty} Q(t)\,\mathrm{d}x_0. \tag{18}$$

To compute $\overline{Q}(t)$ we can either directly integrate the result (14) over ξ, or integrate equation (12) over x_0, and then invert the Laplace transform afterward. One way or the other, we arrive at the answer:

$$\overline{Q}(t) = a\Omega\frac{2}{\sqrt{\pi}}\int_0^{\infty} \mathrm{e}^{-u\sqrt{\tau}-u^2}\,\mathrm{d}u = a\Omega\,\mathrm{e}^{\tau/4}\,\mathrm{Erfc}(\sqrt{\tau}/2) \tag{19}$$

with the following asymptotic behavior:

$$\overline{Q}(t) \simeq \begin{cases} a\Omega\left(1-\sqrt{\dfrac{a^2\Omega^2 t}{\pi D}}\right) & \text{for} \quad t \ll T \\ \sqrt{\dfrac{4D}{\pi t}} & \text{for} \quad t \gg T. \end{cases} \tag{20}$$

The small time, absorption-limited result is understood by the argument that at very small time the current into the sink is created only by the particles which happen to be initially on or very near the target. The long-time, diffusion-limited (and Ω-independent) result is rationalized by the idea that over time t the sink collects particles from the length $\sim\sqrt{Dt}$ which means that $\int_0^t \overline{Q}(t')\,\mathrm{d}t'$ should grow like $\sqrt{t}$.

3. Analysis of the full model

3.1. General analysis

Let us now consider our more sophisticated model, figure 1(A). It is described by equations (5) and (6); they are solved pretty much in the same way as equations (2)–(4) before (for completeness, the explicit expressions for P_+ and P_- are derived in appendix B). The result for the Laplace transformed probability distribution of the first passage time reads

$$Q_s = \frac{F_s}{K_s + 1/\Omega}, \tag{21}$$

where K_s and F_s are given by the following cumbersome, but exact expressions:

$$K_s = \frac{1}{s+\omega_\mp} + \frac{\omega_\pm\omega_\mp}{s+\omega_\mp} \times [s^2 + s(\omega_\pm+\omega_\mp)]^{-1/2}\left[s^2 + s(\omega_\pm+\omega_\mp) + \frac{4D}{a^2}(s+\omega_\mp)\right]^{-1/2} \tag{22}$$

and

$$F_s = \frac{a}{2\pi}\int_{-\pi/a}^{\pi/a} \frac{\omega_\pm\,\mathrm{e}^{-\imath k x_0}}{s^2 + s(\omega_\pm+\omega_\mp) + D_k(s+\omega_\mp)}\,\mathrm{d}k, \tag{23}$$

where $D_k = 2D(1-\cos ka)/a^2$. Similar to the reduced model, the expression for F_s can be dramatically simplified under the non-restrictive condition that the diffusion rate is much larger than the rates of conversion between the sub-states + and −: $D/a^2 \gg \omega_\pm, \omega_\mp, \Omega, s$. Then, D_k can be approximated as Dk^2, integration then can be pulled to infinity, with the result

$$F_s = \frac{\omega_\pm \exp\left[-|x_0|\sqrt{\frac{s^2+s(\omega_\pm+\omega_\mp)}{D(s+\omega_\mp)}}\right]}{\sqrt{\frac{4D}{a^2}(s+\omega_\mp)[s^2+s(\omega_\pm+\omega_\mp)]}}. \tag{24}$$

Physically, F_s describes the diffusion from the source and has nothing to do with the sink; this justifies the approximation in which granularity, or a is ignored in F_s (except as an overall factor a).

As a (weak, but valuable) test of their validity, the above results do satisfy the normalization condition $Q_s|_{s\to 0} = 1$; this happens because both F_s and K_s diverge at small s as $1/\sqrt{s}$, with the same coefficient.

3.2. *Simplified asymptotic expressions of Q_s*

Let us now look at the possible simplifications of the results (21) based on (22) and (24). We assume

$$\omega_{\mp} \ll \omega_{\pm} \ll \frac{D}{a^2}. \tag{25}$$

To begin with, we can simplify Q_s to the following level:

$$Q_s = \frac{\left(1 + \frac{s}{\omega_{\mp}}\right) \exp\left[-\sqrt{\frac{s(s+\omega_{\pm})}{D(s+\omega_{\mp})} x_0^2}\right]}{1 + \frac{s+\omega_{\mp}+\Omega}{\Omega\omega_{\mp}\omega_{\pm}} \sqrt{\frac{4D}{a^2} s(s+\omega_{\pm})(s+\omega_{\mp})}}. \tag{26}$$

Then, we have several different regimes for the Laplace variable s.

3.2.1. $s \ll \omega_{\mp}$: *'chemical' equilibrium approximation.*

In this case

$$Q_s \simeq \frac{\exp\left[-\sqrt{x_0^2 s\omega_{\pm}/D\omega_{\mp}}\right]}{1 + \left[\frac{1}{\omega_{\mp}} + \frac{1}{\Omega}\right]\sqrt{\frac{4sD\omega_{\mp}}{a^2\omega_{\pm}}}}. \tag{27}$$

This maps on the result (12) for the reduced model, with the physically transparent substitutions $D \to \tilde{D} = D\omega_{\mp}/\omega_{\pm} \ll D$ and $1/\Omega \to 1/\tilde{\Omega} = 1/\omega_{\mp} + 1/\Omega$. This corresponds to the situation when there is 'chemical' equilibrium between the sub-states + and − at every x, then the fraction of time the particle spends in the + state is equal to $\omega_{\mp}/\omega_{\pm}$ and since a particle can diffuse only while in the + state, we get the effective diffusion coefficient $\tilde{D}$. The detailed analysis of biophysical consequences of this approximation was given in the work [18]. Of course, the time-dependent $Q(t)$ can also be directly taken from the solution of the reduced model:

$$Q(t) = \frac{a^2\tilde{\Omega}^2\, \mathrm{e}^{-\frac{\tilde{\xi}^2}{4\tilde{\tau}}}}{\tilde{D}\sqrt{4\pi\tilde{\tau}}} \left[1 - \frac{\sqrt{\pi\tilde{\tau}}}{2}\, \mathrm{e}^{\frac{(\tilde{\xi}+\tilde{\tau})^2}{4\tilde{\tau}}}\, \mathrm{Erfc}\left(\frac{\tilde{\xi}+\tilde{\tau}}{2\sqrt{\tilde{\tau}}}\right)\right], \tag{28}$$

where

$$\tilde{\tau} = \frac{a^2\tilde{\Omega}t}{\tilde{D}}, \qquad \tilde{\xi} = \frac{a\tilde{\Omega}|x_0|}{\tilde{D}}. \tag{29}$$

3.2.2. $s \gg \omega_{\mp}$: *irreversible approximation.*

Although $s \gg \omega_{\mp}$, but we do not specify so far the relation between s and $\omega_{\pm}$ or Ω; of course, we still assume $s \ll D/a^2$. In this case, equation (26) is reduced to

$$Q_s = \frac{\frac{s}{\omega_{\mp}} \exp\left[-\sqrt{x_0^2(s+\omega_{\pm})/D}\right]}{1 + \frac{s+\Omega}{\Omega\omega_{\mp}\omega_{\pm}} s\sqrt{\frac{4D}{a^2}(s+\omega_{\pm})}}. \tag{30}$$

Here, it can be proven that we must neglect the unity in the denominator, despite the fact that we do not assume anything about Ω:

$$\frac{s+\Omega}{\Omega\omega_\mp\omega_\pm}s\sqrt{\frac{4D}{a^2}(s+\omega_\pm)} = \underbrace{\left(1+\frac{s}{\Omega}\right)}_{>1}\underbrace{\frac{s}{\omega_\mp}}_{\gg 1}\sqrt{\underbrace{\frac{4D}{a^2\omega_\pm}}_{\gg 1}\underbrace{\left(1+\frac{s}{\omega_\pm}\right)}_{>1}} \gg 1. \tag{31}$$

Neglect of the unity in the denominator yields significant simplification: at $\omega_\mp \ll s \ll D/a^2$, we have

$$Q_s = \frac{\omega_\pm\Omega\exp\left[-\sqrt{x_0^2(s+\omega_\pm)/D}\right]}{(s+\Omega)\sqrt{\frac{4D}{a^2}(s+\omega_\pm)}}. \tag{32}$$

Remarkably, this result does not depend on $\omega_\mp$ at all. This motivates the following interpretation. At the very beginning of the process, there are some transitions from + to −, but, to the first approximation, no transitions from − to +, simply because particles are initially placed in the + state, and there are no particles in the − state. In other words, at very small time t the transitions from + to − can be considered as effectively irreversible.

Indeed, the inversion of the Laplace transform (32) yields

$$Q(t) = \int_0^t \frac{\Omega\omega_\pm a}{\sqrt{4\pi Dt'}}\,\mathrm{e}^{-\Omega t+(\Omega-\omega_\pm)t'-\frac{x_0^2}{4Dt'}}\,\mathrm{d}t', \tag{33}$$

which, together with

$$P_+(x,t)|_{x=0} = \sqrt{\frac{a^2}{4\pi Dt}}\,\mathrm{e}^{-\omega_\pm t-\frac{x_0^2}{4Dt}}, \tag{34}$$

represents the exact solution of the 'irreversible' approximation of equation (5):

$$\begin{aligned}
\frac{\partial P_+}{\partial t} &= D\Delta_a P_+ - \omega_\pm P_+ + \delta(t)\Delta(x-x_0),\\
\frac{\partial P_-}{\partial t} &= \omega_\pm P_+ - \Omega\Delta(x)P_-,\\
Q(t) &= \Omega P_-(x,t)|_{x=0}\,.
\end{aligned} \tag{35}$$

The result (32) can also be somewhat more simplified for further restricted ranges of s. If $\omega_\mp \ll s \ll \omega_\pm$, then

$$Q_s \simeq \sqrt{\frac{a^2\omega_\pm}{4D}}\frac{\exp\left[-\sqrt{x_0^2\omega_\pm/D}\right]}{1+\frac{s}{\Omega}}, \tag{36}$$

while if $\omega_\pm \ll s \ll D/a^2$, then

$$Q_s \simeq \sqrt{\frac{a^2\omega_\pm^2}{4Ds}}\frac{\exp\left[-\sqrt{x_0^2 s/D}\right]}{1+\frac{s}{\Omega}}. \tag{37}$$

3.3. *Physical explanation*

We have obtained two limiting results for Q_s, equations (27) and (32). They match smoothly at $s \sim \omega_\mp$. In this sense, the problem is completely solved in terms of Q_s.

Furthermore, the result for Q_s has direct physical meaning, as was pointed out to us by Leonid Mirny. Suppose that proteins not only diffuse but also die, and their death rate is independent of their state vis-a-vis DNA; for instance, the most natural ‘death’ in this context would be desorption from DNA. That means, protein obeys the ‘radioactive decay’ law and the probability for the protein to survive till time t is e^{-t/t^*}, where t^* is the characteristic decay time. Then, the probability for the protein to reach the target at time t is going to be $Q(t)\,\mathrm{e}^{-t/t^*}$, and the total probability for the given protein to reach the target during its life-time is $\int_0^\infty Q(t)\,\mathrm{e}^{-t/t^*}\,\mathrm{d}t$, which is nothing else but the Laplace transform Q_s taken at $s = 1/t^*$. This motivates considering Q_{1/t^*} as a function of t^*. Formula (26) gives, in this case,

$$Q_{1/t^*} = \frac{\left(1 + \frac{1}{t^*\omega_\mp}\right)\exp\left[-\sqrt{\frac{(1+t^*\omega_\pm)}{(1+t^*\omega_\mp)}\frac{x_0^2}{Dt^*}}\right]}{1 + \frac{1+t^*\omega_\mp+t^*\Omega}{t^{*\,3}\Omega\omega_\mp\omega_\pm}\sqrt{\frac{4Dt^*}{a^2}(1+t^*\omega_\pm)(1+t^*\omega_\mp)}}, \tag{38}$$

with the obvious asymptotic behavior.

We should realize that although asymptotic expressions for Q_s, equations (27) and (32), cross-over smoothly into one another at $s \sim \omega_\mp$, the two limiting expressions for $Q(t)$, equations (28) and (33), do not match. One of them is valid at $t \ll 1/\omega_\pm$ while the other is valid at $t \gg 1/\omega_\mp$. That means, there is some intermediate physical regime, which has to do with the dispersion of effective diffusion constant, because it must fall from D to a much smaller $\tilde{D}$. This new physical regime is when there is already some non-negligible reflux from the lower states to the upper ones, but not yet equilibrium between the two. Mathematically, this transient regime arises from the essential singularity of Q_s at $s = -\omega_\mp$ (due to the factor $s+\omega_\mp$ sitting in the denominator under the square root in the exponential). We have not found any simple expression for $Q(t)$ covering this intermediate transient regime.

4. Averaging over initial position for the full model

As in the case of the reduced model, let us now consider the case when a particle starts at the random point x_0, so that we want to find the average $\overline{Q}(t)$ defined in full analogy with equations (18), i.e., $\overline{Q}_s = \int_{-\infty}^{\infty} Q_s\,\mathrm{d}x_0$. Using equations (21), (22) and (24), we easily obtain

$$\overline{Q}_s = \frac{a\omega_\pm\Omega(s+\omega_\mp)\sqrt{\frac{s^2+s(\omega_\pm+\omega_\mp)+\frac{4D}{a^2}(s+\omega_\mp)}{s^2+s(\omega_\pm+\omega_\mp)}}}{(s+\Omega')\sqrt{[s^2+s(\omega_\pm+\omega_\mp)][s^2+s(\omega_\pm+\omega_\mp)+\frac{4D}{a^2}(s+\omega_\mp)]}+\Omega\omega_\pm\omega_\mp}, \tag{39}$$

where $\Omega' = \Omega + \omega_\mp$.

Inverting the Laplace transform for equation (39) is not easy; we do that in appendix C in various limits. Here, we present the results for the most interesting case of strong diffusion, in which the diffusion rate $d = 4D/a^2$ is assumed much larger than the final absorption rate Ω. As discussed also in detail in [18], this case is also most realistic for the real protein–DNA system, where $d = 4D/a^2$ is usually in a megahertz range, while Ω is not more than a few kilohertz.

More specifically, we concentrate on the limit $\omega_\mp \ll \Omega < \omega_\pm \ll d \equiv D/a^2$. The result for this limit reads

$$\overline{Q}(t) \simeq \frac{\Omega\omega_\pm\omega_\mp}{\Omega'\omega}\,\mathrm{e}^{\frac{\Omega^2\omega_\pm^2\omega_\mp^2}{\Omega'^2\omega\sigma_1\sigma_2}t}\,\mathrm{Erfc}\left(\sqrt{\frac{\Omega^2\omega_\pm^2\omega_\mp^2}{\Omega'^2\omega\sigma_1\sigma_2}t}\right) - \frac{\omega_\pm^2\Omega}{\omega(\omega_\pm-\Omega)}\,\mathrm{e}^{-\omega t} + \frac{\omega_\pm\Omega^2}{\Omega'(\omega_\pm-\Omega)}\,\mathrm{e}^{-\Omega' t}, \tag{40}$$

where $\omega = \omega_\pm + \omega_\mp$, $\Omega' = \Omega + \omega_\mp$, $d = 4D/a^2$, while σ_1 and σ_2 are the two roots of the quadratic equation $\sigma(\sigma-\omega) - d(\sigma-\omega_\mp) = 0$.

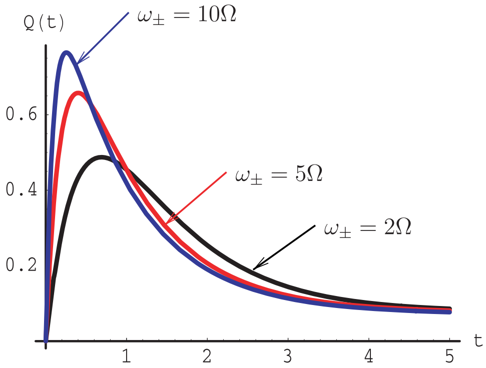

Figure 4. The distribution of the first passage time. The data used are: $\Omega = 1, d = 100\Omega, \omega_\mp = 0.1\Omega$, while $\omega_\pm = 2\Omega, 5\Omega, 10\Omega$ as labeled in the figure.

The first term in $\overline{Q}(t)$ essentially plays the same role as $\overline{Q}(t)$ in the reduced model (equation (19)), which has its maximum at $t = 0$ and then decays monotonically. The lack of particles at the absorption site at the initial moment for the full model, however, results in the presence of two other terms in $\overline{Q}(t)$ of the full model. Overall, we have $\overline{Q}(t) = 0$, which is a property of the full model different from the reduced one.

At small times, $\overline{Q}(t)$ for the full model grows, and does so linearly in time. Specifically, when $t \ll 1/\omega$, we obtain $\overline{Q}(t) \simeq \omega_\pm \Omega t$. At larger times, $\overline{Q}(t)$ goes through a peak. The maximum is reached, to the first order in the above-specified parameters, at

$$t_m \simeq \frac{\ln \frac{\omega_\pm}{\Omega}}{\omega_\pm - \Omega}. \tag{41}$$

An interesting fact is that this time of maximum does not depend on the diffusion rate d, suggesting that the maximum originates from the dynamics of the inter-conversion between the + and − states of 'local particles'—those which happen to be at the absorption site from the very beginning. This is fundamentally different from the reduced model (before averaging over x_0), in which the maximum of $Q(t)$ is due to the diffusion delivering particles to the absorption site. When $\omega_\pm$ and Ω are very close, $\omega_\pm \to \Omega$, we have $t_m \simeq 1/\Omega$, and t_m decreases when $\omega_\pm$ increases.

In figure 4, we make a numerical plot of the average distribution of the first passage time $\overline{Q}(t)$. It is worth pointing out that $\overline{Q}(t)$ is not normalized to one (unlike $Q(t)$) since the initial distribution of particles along x is uniform, not just one particle.

In the expression of $\overline{Q}(t)$, there is the characteristic quantity, $\Omega^2\omega_\pm^2\omega_\mp^2/\Omega'^2\omega\sigma_1\sigma_2 \simeq \omega_\pm\omega_\mp/d$, with the dimension of rate. For the time of order of the inverse of this characteristic rate, $t \sim d/(\omega_\pm\omega_\mp)$, the number of particles absorbed is

$$\int_0^{\frac{\mathrm{d}}{\omega_\pm\omega_\mp}} \overline{Q}(t)\,\mathrm{d}t \simeq \frac{\Omega d}{\Omega'\omega} \simeq \frac{d}{\omega}. \tag{42}$$

This can be understood from the following argument. Since $d/(\omega_\pm\omega_\mp) \gg 1/\omega_\mp$, at the time of order of $d/(\omega_\pm\omega_\mp)$, there is nearly complete equilibrium between + and − states and, therefore, diffusion on this time scale is described by the effective diffusion coefficient $\tilde{D}$, so the distance of diffusion over time t is $\sqrt{\tilde{D}t} \simeq (d/\omega_\pm)a \simeq (d/\omega)a$, and formula (42) simply gives the number of particles collected over this distance during the time $\sim d/(\omega_\pm\omega_\mp)$.

5. Conclusion

We study the first passage time distribution for the model of diffusion of particles with internal degrees of freedom. For this model, there are four essential rate constants: $\omega_{\pm}, \omega_{\mp}, \Omega$ and D/a^2. We calculate the probability flux delivered into the absorption site for two types of initial conditions, when the particle starts at the known distance x_0 from the absorption site, or when the particle starts anywhere along the line. We consider two models. The reduced model is different from the classical 1D first passage problem in only a seemingly minor respect that it allows the overshoot—fruitless arrival at the right place when particles diffuse away before they get absorbed. Even in this case, as one could see from the results of the paper [26] and as we show explicitly, there is non-trivial behavior, with two significantly different regimes, diffusion dominated and absorption dominated. In the former, the search time is spent mostly diffusing to the target; in the latter, the search time is spent mostly wandering rather close to the target and waiting for a successful absorption act. Our second model accounts also, on the simplest level, for the fluctuations of the internal states of particles. In this case, we found that the first arrival at the target is controlled by the complex interplay between diffusion dynamics and 'chemical' conversion between the sub-states. For this model, we obtain the first passage time distributions with long power law tails; this hints at the possibility that the experimentally relevant search time might not be the mean but the most probable first passage time. We discuss elsewhere the biophysical consequences of this model [18].

Acknowledgments

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Appendix A. Inverting the Laplace transform for the reduced model

In this section, we describe the contour integration which leads to equation (15).

In general, inverting the Laplace transform involves evaluation of the integral

$$Q(t) = \frac{1}{2\pi\imath}\int_{\mathcal{C}} \mathrm{e}^{st} Q_s \,\mathrm{d}s, \tag{A.1}$$

where integration path $\mathcal{C}$ in the complex plane s runs from negative imaginary infinity to positive imaginary infinity and must be to the right of every and all singularities of Q_s (see figure A1).

We are only interested in the time range, $t \gg a^2/D$, because on shorter time scales of less than one jump between neighboring sites, our model fails along with the diffusion language. As soon as $t \gg a^2/D$, because of the factor e^{st}, the integral over s is dominated by the region of the complex plane where $|s| \ll D/a^2$. But in this region, equation (12) is asymptotically exact, so it is sufficient to derive the expression for $Q(t)$, equation (15) which is asymptotically exact at $t \gg a^2/D$, that is, whenever the model itself makes physical sense.

Inspection of expression (12) for Q_s indicates that it has a branch point at $s = 0$ and, accordingly, there should be a branch cut which we choose to place along the negative real s-axis. Then, we can deform the integration contour to go along the two sides of the branch cut, as shown in figure A1. As a result, denoting $\sigma = -s$ on the negative real s, we can write

$$Q(t) = \frac{1}{2\pi\imath}\int_0^{\infty} \mathrm{e}^{-\sigma t}\left[Q_{-\sigma\,(\mathrm{below})} - Q_{-\sigma\,(\mathrm{above})}\right] \mathrm{d}\sigma, \tag{A.2}$$

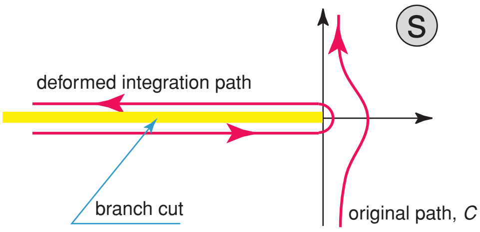

Figure A1. Integration path for equation (A.2). Explanations in the text.

where subscripts 'above' and 'below' refer to the corresponding sides of the branch cut. Remembering that $\sqrt{s} = \imath\sqrt{\sigma}$ on the upper side of the branch cut (where $s = -\sigma + \imath 0$) and $\sqrt{s} = -\imath\sqrt{\sigma}$ on the lower side (where $s = -\sigma - \imath 0$), we get after simple manipulations

$$Q(t) = \frac{1}{\pi}\int_0^\infty \frac{\sin\sqrt{\frac{x_0^2\sigma}{D}} + \sqrt{\frac{4D\sigma}{a^2\Omega^2}}\cos\sqrt{\frac{{x_0}^2\sigma}{D}}}{1+\frac{4D\sigma}{a^2\Omega^2}}\,\mathrm{e}^{-\sigma t}\,\mathrm{d}\sigma. \tag{A.3}$$

We now introduce the integration variable, $\eta = \sqrt{x_0^2\sigma/D}$, and also use the dimensionless parameters ξ and τ defined right after equation (13). Then we get

$$\begin{aligned}
Q(t) &= \frac{2D}{\pi x_0^2}\int_0^\infty \frac{\eta\sin\eta + \frac{2}{\xi}\eta^2\cos\eta}{1+\frac{4}{\xi^2}\eta^2}\,\mathrm{e}^{-\frac{\tau}{\xi^2}\eta^2}\,\mathrm{d}\eta\\
&= \frac{D\xi}{2\pi x_0^2}\int_{-\infty}^\infty \frac{\eta^2\,\mathrm{e}^{\imath\eta} - \frac{\imath\xi}{2}\eta\,\mathrm{e}^{\imath\eta}}{\eta^2+\frac{\xi^2}{4}}\,\mathrm{e}^{-\frac{\tau}{\xi^2}\eta^2}\,\mathrm{d}\eta\\
&= \frac{D\xi}{2\pi x_0^2}\int_{-\infty}^\infty \left(1-\frac{\frac{\imath\xi}{2}}{\eta+\frac{\imath\xi}{2}}\right)\mathrm{e}^{\imath\eta-\frac{\tau}{\xi^2}\eta^2}\,\mathrm{d}\eta\\
&= \frac{D\xi^2\,\mathrm{e}^{-\frac{\xi^2}{4\tau}}}{x_0^2\sqrt{4\pi\tau}} - \frac{\imath D\xi^2}{4\pi x_0^2}\int_{-\infty}^\infty \frac{\mathrm{e}^{\imath\eta-\frac{\tau}{\xi^2}\eta^2}}{\eta+\frac{\imath\xi}{2}}\,\mathrm{d}\eta\\
&= \frac{D\xi^2\,\mathrm{e}^{-\frac{\xi^2}{4\tau}}}{x_0^2\sqrt{4\pi\tau}} - \frac{D\xi^2}{4x_0^2}\,\mathrm{e}^{\frac{\tau+2\xi}{4}}\,\mathrm{Erfc}\left(\frac{\xi+\tau}{\sqrt{4\pi}}\right)\\
&= \frac{a^2\Omega^2\,\mathrm{e}^{-\frac{\xi^2}{4\tau}}}{D\sqrt{4\pi\tau}}\left[1-\frac{\sqrt{\pi\tau}}{2}\,\mathrm{e}^{\frac{(\xi+\tau)^2}{4\tau}}\,\mathrm{Erfc}\left(\frac{\xi+\tau}{\sqrt{4\tau}}\right)\right].
\end{aligned} \tag{A.4}$$

Appendix B. Explicit solutions for densities in the full model

Explicit formulae for both $P_+(k,t)$ and $P_-(k,t)$ are relatively simple in the Fourier representation (note that k is restricted to one cell of the reciprocal lattice: $-\pi/a < k < \pi/a$). The solutions are expressed in terms of the k-dependent eigenvalues of the symmetric matrix:

$$\begin{pmatrix} -D_k - \omega_\pm & \sqrt{\omega_\pm\omega_\mp} \\ \sqrt{\omega_\pm\omega_\mp} & -\omega_\mp \end{pmatrix}, \tag{B.1}$$

where, once again, we denote for simplicity $D_k = 2D(1-\cos ka)/a^2$. These eigenvalues are λ_+ and λ_-; they are given by

$$\lambda_\pm = -\frac{\omega_\pm + \omega_\mp + D_k}{2} \pm \sqrt{\left(\frac{\omega_\pm + \omega_\mp + D_k}{2}\right)^2 - D_k\omega_\mp}. \tag{B.2}$$

In terms of the eigenvalues, the solutions read

$$P_+(k,t) = \frac{\mathrm{e}^{\imath kx_0}[(\lambda_+ + \omega_\mp)\,\mathrm{e}^{\lambda_+ t} - (\lambda_- + \omega_\mp)\,\mathrm{e}^{\lambda_- t}] - \omega_\mp \int_0^t Q(t')[\mathrm{e}^{\lambda_+(t-t')} - \mathrm{e}^{\lambda_-(t-t')}]\,\mathrm{d}t'}{\lambda_+ - \lambda_-}, \tag{B.3}$$

$$P_-(k,t) = \frac{\mathrm{e}^{\imath kx_0}\omega_\pm[\mathrm{e}^{\lambda_+ t} - \mathrm{e}^{\lambda_- t}] + \int_0^t Q(t')[(\lambda_- + \omega_\mp)\,\mathrm{e}^{\lambda_+(t-t')} - (\lambda_+ + \omega_\mp)\,\mathrm{e}^{\lambda_-(t-t')}]\,\mathrm{d}t'}{\lambda_+ - \lambda_-}. \tag{B.4}$$

Appendix C. Inverting the Laplace transform for the full model

C.1. General considerations: no approximations

We have computed $\overline{Q}_s$ for real positive s, equation (39), and now we need to construct its analytic continuation to all complex s in order to perform the integration and invert the Laplace transform. For the reasons explained in appendix C, it is convenient to re-write $\overline{Q}_s$ in the form

$$\overline{Q}_s = \frac{\omega_\pm\Omega(s+\omega_\mp)\frac{\sqrt{s+\sigma_1}\sqrt{s+\sigma_2}}{\sqrt{s}\sqrt{s+\omega}}}{(s+\Omega')\sqrt{s}\sqrt{s+\omega}\sqrt{s+\sigma_1}\sqrt{s+\sigma_2} + \Omega\omega_\pm\omega_\mp}, \tag{C.1}$$

where $\omega = \omega_\pm + \omega_\mp$ and $\Omega' = \Omega + \omega_\mp$, $d = 4D/a^2$, while $s_{1,2} = -\sigma_{1,2}$ are the roots of

$$s(s+\omega) + d(s+\omega_\mp) = 0, \tag{C.2}$$

$$s_{1,2} = -\frac{d+\omega}{2}\left[1 \mp \sqrt{1 - \frac{4d\omega_\mp}{(d+\omega)^2}}\right]. \tag{C.3}$$

It is easy to see that $s_{1,2}$ are both real and negative. For simplicity the constant coefficient a in equation (C.1) has been ignored.

As regards the singularities of $\overline{Q}_s$, there are four branch points at $s = 0$, $s = -\sigma_1$, $s = -\omega$ and $s = -\sigma_2$ (always in that order). Given the analytic continuation rules discussed in appendix D, there are two branch cuts along the negative real s-axis, one from 0 to $-\sigma_1$ and another from $-\omega$ to $-\sigma_2$.

Now, we want to find the poles of $\overline{Q}_s$. The poles are given by the equation, Denominator = 0, or

$$(s+\Omega')\sqrt{s}\sqrt{s+\omega}\sqrt{s+\sigma_1}\sqrt{s+\sigma_2} = -\Omega\omega_\pm\omega_\mp. \tag{C.4}$$

This is a rather ugly equation. To simplify things, let us call it the brother equation and consider simultaneously also the sister equation of the form

$$(s+\Omega')\sqrt{s}\sqrt{s+\omega}\sqrt{s+\sigma_1}\sqrt{s+\sigma_2} = +\Omega\omega_\pm\omega_\mp. \tag{C.5}$$

By squaring either brother or sister equation, we obtain the sixth power polynomial equation

$$P(s) = C, \tag{C.6}$$

where

$$P(s) = (s+\Omega')^2 s(s+\omega)(s+\sigma_1)(s+\sigma_2) \tag{C.7}$$

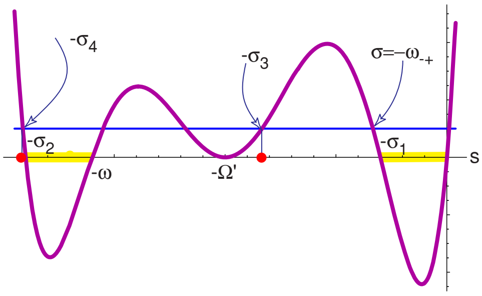

Figure C1. Graphical solution of the equation $P(s) = C$ (C.6) assuming C is small. That is guaranteed if $\omega_\mp$ is small compared to others.

and

$$C = (\omega_\mp(\Omega' - \omega_\mp)(\omega - \omega_\mp))^2. \tag{C.8}$$

The advantage of this polynomial equation is that we at least know that it has exactly six roots, and each of these six roots is either the solution of the brother equation or that of the sister equation; moreover, neither brother nor sister equation has any other roots.

Note that we know all six roots of the equation, $P(s) = 0$, and all of them are real. Based on that, we can quite plausibly sketch the plot of $P(s)$ for all real s; it is shown in figure C1, assuming for now that $\Omega' < \omega$, or $\Omega < \omega_\pm$. Then, the graphical solution of $P(s) = C$ is done by an obvious construction involving a horizontal line at the level C, as illustrated in figure C1. If C is small enough, all six roots are real, and it is then easy to decide which roots belong to brother and which to sister equations. In the figure, the roots of the brother equation are indicated by the blue arrows. One of them, which is immediately to the left of $-\sigma_1$, is equal to $s = -\omega_\mp$ as can be established by direct substitution; this root does not give rise to the pole of $\overline{Q}_s$, because there is a factor $s + \omega_\mp$ in the numerator. Therefore, we end up with two poles, both on the real negative s-axis, one to the right of $-\Omega'$ and the other to the left of $-\sigma_2$. They are marked by red dots in the figure.

With the singularities as described, it is now convenient to write the inverse Laplace transform in the form

$$\overline{Q}(t) = \overline{Q}_1(t) + \overline{Q}_2(t) + \overline{Q}_3(t) + \overline{Q}_4(t), \tag{C.9}$$

corresponding to

- near branch cut $\overline{Q}_1(t)$,
- far away branch cut $\overline{Q}_2(t)$,
- near pole $\overline{Q}_3(t)$,
- far away pole $\overline{Q}_4(t)$.

As far as branch cuts are concerned, their contributions can be written as follows:

$$\frac{1}{2\pi\imath}\int_{\text{cut}} \mathrm{e}^{-\sigma t}[\overline{Q}_{-\sigma\,(\text{below})} - \overline{Q}_{-\sigma\,(\text{above})}]\,\mathrm{d}\sigma, \tag{C.10}$$

where 'above' and 'below' refer to the corresponding sides of the real axis. Given our accepted rules of analytic continuation, we establish the signs of all involved square roots and obtain first for the near branch cut:

$$\overline{Q}_1(t) = \frac{1}{\pi}\int_0^{\sigma_1} \mathrm{e}^{-\sigma t}\frac{\Omega^2\omega_\pm^2\omega_\mp(\omega_\mp - \sigma)\sqrt{\frac{(\sigma_1-\sigma)(\sigma_2-\sigma)}{\sigma(\omega-\sigma)}}}{-P(-\sigma)+C}\,\mathrm{d}\sigma. \tag{C.11}$$

This is obviously positive definite. Similarly, for the far away branch cut reads

$$\overline{Q}_2(t) = -\frac{1}{\pi}\int_{\omega}^{\sigma_2} \mathrm{e}^{-\sigma t}\, \frac{\Omega^2\omega_\pm^2\omega_\mp(\sigma-\omega_\mp)\sqrt{\frac{(\sigma-\sigma_1)(\sigma_2-\sigma)}{\sigma(\sigma-\omega)}}}{-P(-\sigma)+C}\,\mathrm{d}\sigma. \tag{C.12}$$

This is negative definite. Finally,

$$\overline{Q}_{3,4}(t) = \mathrm{e}^{-\sigma_{3,4}t}\,\mathrm{Res}(\sigma_{3,4}), \tag{C.13}$$

where $-\sigma_3$ and $-\sigma_4$ are the two above-discussed poles, and the residues are those of $\overline{Q}_s$ in these poles. To calculate these residues, it is useful to write the expressions for $\overline{Q}_s$ most conveniently in the corresponding regions of the negative s-axis. Namely, between the two branch cuts (where we expect to find one of the poles, at σ_3) we can write

$$\overline{Q}_s = \frac{\omega_\pm\Omega(\omega_\mp-\sigma)\sqrt{\frac{(\sigma-\sigma_1)(\sigma_2-\sigma)}{\sigma(\omega-\sigma)}}}{\Omega\omega_\pm\omega_\mp-(\Omega'-\sigma)\sqrt{(\sigma-\sigma_1)(\sigma_2-\sigma)\sigma(\omega-\sigma)}}, \tag{C.14}$$

while in the region beyond the second branch cut (where we expect to find another pole, at σ_4) we get

$$\overline{Q}_s = \frac{\omega_\pm\Omega(\omega_\mp-\sigma)\sqrt{\frac{(\sigma-\sigma_1)(\sigma-\sigma_2)}{\sigma(\sigma-\omega)}}}{\Omega\omega_\pm\omega_\mp-(\sigma-\Omega')\sqrt{(\sigma-\sigma_1)(\sigma-\sigma_2)\sigma(\sigma-\omega)}}. \tag{C.15}$$

Note that these two expressions are different in terms of signs.

So far, we did not use any approximations.

C.2. Approximations

Since the calculation is quite cumbersome, it is methodically important to control how it works for the case of known results. In this case, the important trivial cases are no diffusion case ($d = 0$) and zero-time case ($t = 0$). We should emphasize that at $t = 0$ our full model is significantly different from the reduced one. In the reduced model, $\overline{Q}(t)$ has a certain finite value at $t = 0$ due to the positive probability that the particle happened to be at the target site $x = 0$ at $t = 0$ ($x_0 = 0$). In the full model, a particle can of course be on the $x = 0$ site at $t = 0$, but only in the sub-state +, while the current into the sink is from the sub-state −, where the initial density is zero. Therefore, $\overline{Q}(t)$ must be zero at $t = 0$. Establishing this in the results is very instructive, as we will see. Proving that $\overline{Q}(t = 0) = 0$ is not an important separate goal, because this fact is beyond a doubt physically. However, seeing it in the equations is an important component making sure that our much more challenging calculations for $t \neq 0$ make sense.

C.2.1. No diffusion case, $d = 0$. First we have to address this when $d = 0$. In this case, $\sigma_1 = 0$ and $\sigma_2 = \omega$. There are no branch cuts any more; they shrink to zero length each. Simplifications can be done while still at positive real s; therefore, there is no issue with analytic continuation of the square roots. Accordingly, things really simplify:

$$\begin{aligned}\overline{Q}_s|_{d=0} &= \frac{\omega_\pm\Omega(\omega_\mp-\sigma)}{\Omega\omega_\pm\omega_\mp-(\Omega'-\sigma)\sigma(\omega-\sigma)}\\ &= \frac{\omega_\pm\Omega}{\sigma^2-\sigma(\omega+\Omega)+\Omega\omega_\pm}\\ &= \frac{\omega_\pm\Omega}{\left(\sigma-\sigma_3^{(0)}\right)\left(\sigma-\sigma_4^{(0)}\right)}.\end{aligned} \tag{C.16}$$

This has obviously two poles, in accordance with the general consideration suggesting always two poles. The positions of the poles are given by

$$\sigma_{3,4}^{(0)} = \tfrac{1}{2}[\omega + \Omega \pm \sqrt{(\omega - \Omega)^2 + 4\Omega\omega_{\mp}}], \tag{C.17}$$

they are both obviously real as expected. The integration then yields two simple poles with their residues and with the overall minus sign due to the switch from s to σ. The result reads

$$\begin{aligned}\overline{Q}(t) &= \frac{\omega_{\pm}\Omega}{\sigma_3^{(0)} - \sigma_4^{(0)}}\left[\mathrm{e}^{-\sigma_4^{(0)}t} - \mathrm{e}^{-\sigma_3^{(0)}t}\right] \\ &= \frac{2\omega_{\pm}\Omega \sinh\left[\frac{\sqrt{(\omega-\Omega)^2+4\Omega\omega_{\mp}}}{2}t\right]}{\sqrt{(\omega - \Omega)^2 + 4\Omega\omega_{\mp}}}\,\mathrm{e}^{-\frac{\omega+\Omega}{2}t}.\end{aligned} \tag{C.18}$$

This is zero at $t = 0$ and is positive at $t > 0$. At small t, we get $\overline{Q}(t) \simeq \omega_{\pm}\Omega t$, as it should be. Overall, this is a very healthy looking formula.

C.2.2. No diffusion and small $\omega_{\mp}$. Just to simplify the appearance of the formula, we now assume $\omega_{\mp} \ll \omega, \Omega$. This yields to the first approximation,

$$\overline{Q}(t) = \frac{2\omega_{\pm}\Omega \sinh\left[\frac{\omega-\Omega}{2}t\right]}{\omega - \Omega}\,\mathrm{e}^{-\frac{\omega+\Omega}{2}t}. \tag{C.19}$$

This approximation breaks down at very long time, because we approximated the expression inside the sinh, so the condition is $t < (\omega - \Omega)/\Omega\omega_{\mp}$. Roughly that means $t < 1/\omega_{\mp}$, that is, the time beyond which the reflux from the lower to the upper state becomes important.

C.2.3. Weak diffusion case, $d \ll \omega$. Let us now consider the finite but small d case: suppose $d \ll \omega$. Also we know that $\omega_{\mp} < \omega$ (although at this moment we do not assume $\omega_{\mp} \ll \omega$). Then we have

$$\sigma_1 \simeq \frac{\omega_{\mp}}{\omega}d, \qquad \sigma_2 \simeq \omega + \frac{\omega_{\pm}}{\omega}d. \tag{C.20}$$

It is now convenient to remember equation (C.3) and to replace

$$(\sigma - \sigma_1)(\sigma - \sigma_2) = \sigma(\sigma - \omega) - d(\sigma - \omega_{\mp}), \tag{C.21}$$

because this form is well prepared to use expansion in powers of d. For instance, in the vicinity of pole 3 we write

$$\sqrt{\frac{\sigma(\omega - \sigma) + d(\sigma - \omega_{\mp})}{\sigma(\omega - \sigma)}} \simeq 1 + \frac{d}{2}\frac{\sigma - \omega_{\mp}}{\sigma(\omega - \sigma)}, \tag{C.22}$$

which assumes that d is small compared to even the smallest of $\omega_{\pm}$, $\omega_{\mp}$, Ω and their relevant combinations. Performing algebra and remembering that

$$\Omega\omega_{\pm}\omega_{\mp} - (\Omega' - \sigma)\sigma(\omega - \sigma) = \left(\sigma - \sigma_3^{(0)}\right)\left(\sigma - \sigma_4^{(0)}\right)(\omega_{\mp} - \sigma), \tag{C.23}$$

we obtain, to the first approximation in d:

In the vicinity of pole 3

$$\overline{Q}_s \simeq \frac{\frac{\omega_{\pm}\Omega}{\sigma_3^{(0)} - \sigma_4^{(0)}}\left[1 + \frac{d}{2}\frac{\sigma_3^{(0)} - \omega_{\mp}}{\sigma_3^{(0)}(\omega - \sigma_3^{(0)})}\right]}{\sigma - \sigma_3^{(0)} + \frac{d}{2}\frac{\Omega' - \sigma_3^{(0)}}{\sigma_3^{(0)} - \sigma_4^{(0)}}}, \tag{C.24}$$

and in the vicinity of pole 4

$$\overline{Q}_s \simeq \frac{\frac{\omega_\pm \Omega}{-\sigma_3^{(0)}+\sigma_4^{(0)}}\left[1 - \frac{d}{2}\frac{\sigma_4^{(0)}-\omega_\mp}{\sigma_4^{(0)}(\sigma_4^{(0)}-\omega)}\right]}{\sigma - \sigma_4^{(0)} - \frac{d}{2}\frac{\sigma_4^{(0)}-\Omega'}{\sigma_4^{(0)}-\sigma_3^{(0)}}}. \tag{C.25}$$

From the numerators of these equations, we read out the values of residues in the corresponding poles; from the denominators, we read out the positions of the poles. In general, the contributions of these poles read

$$\overline{Q}_3(t) + \overline{Q}_4(t) = \mathrm{Res}_3\, \mathrm{e}^{-\sigma_3 t} + \mathrm{Res}_4\, \mathrm{e}^{-\sigma_4 t}. \tag{C.26}$$

C.2.4. Weak diffusion case, $d \ll \omega$, at $t = 0$. Let us first concentrate on the $t = 0$ case. For this case, we just need the sum of residues. Upon some algebra, we have

$$\mathrm{Res}_3 + \mathrm{Res}_4 = \frac{d}{2}\left(\frac{\omega_\pm}{\omega_\mp} - 1\right). \tag{C.27}$$

This formula is obtained in linear order in small d, but does not involve any approximation in terms of $\omega_\mp$ being small. If we do assume additionally that $\omega_\mp$ is small, we should still require that d is smaller still: $d < \omega_\mp$, because, as we see, $\omega_\mp$ is in one place in the denominator, so $d < \omega_\mp$ is the requirement to justify the expansion in d.

Let us now look at the contributions of the branch cuts, formulae (C.11) and (C.12). Physically, the branch cuts describe diffusion, because simple poles produce just purely exponential time dependence, while more complex time dependence is due to branch cuts. Accordingly, it is not surprising that branch cuts disappear at $d = 0$. Now, when d is not zero but small, we want to have the linear terms in d; we immediately realize that the length of each branch cut is of order d. Therefore, the integrands have to be taken to the zeroth order in d. The most important thing to realize in this respect is that $P(-\sigma)$ is negligible compared to C in the denominator, because two of the factors involved in the definition of P are of order d each. Thus, we neglect P. Furthermore, the square root in the numerator is also simplified. The end result for $\overline{Q}_1$ reads

$$\overline{Q}_1(t = 0) \simeq \frac{1}{\pi}\int_0^{\sigma_1} \frac{\Omega^2\omega_\pm^2\omega_\mp^2\sqrt{\frac{\sigma_1-\sigma}{\sigma}}}{C}\,\mathrm{d}\sigma = \frac{\sigma_1}{2} \simeq \frac{\omega_\mp}{2\omega}d. \tag{C.28}$$

Similar calculation for another branch cut yields

$$\overline{Q}_2(t = 0) \simeq -\frac{1}{\pi}\int_\omega^{\sigma_2} \frac{\sigma - \omega_\mp}{\omega_\mp}\sqrt{\frac{\sigma_2 - \sigma}{\sigma - \omega}}\,\mathrm{d}\sigma \simeq -\frac{\omega_\pm^2}{2\omega\omega_\mp}d. \tag{C.29}$$

That counts all linear terms in d and does not involve any additional approximations in terms of small $\omega_\mp$ or anything else.

Combining all contributions together, we obtain $\overline{Q}(t = 0) = 0$, as it must be.

C.2.5. Weak diffusion case, $d \ll \omega$, and $t \neq 0$. Now let us consider the time dependence of $\overline{Q}(t)$. We also assume $\omega_\mp \ll \Omega \ll \omega_\pm$. First,

$$\begin{aligned}\overline{Q}_1(t) &\simeq \frac{1}{\pi}\int_0^{\sigma_1} \sqrt{\frac{\sigma_1}{\sigma} - 1}\,\mathrm{e}^{-\sigma t}\,\mathrm{d}\sigma \\ &= \frac{\sigma_1}{2}\left[I_0\left(\frac{\sigma_1 t}{2}\right) + I_1\left(\frac{\sigma_1 t}{2}\right)\right]\mathrm{e}^{-\frac{\sigma_1 t}{2}}\end{aligned}$$

$$\simeq \begin{cases} \dfrac{\sigma_1}{2} & \text{when} \quad t \ll \dfrac{1}{\sigma_1} \\ \sqrt{\dfrac{\sigma_1}{\pi t}} & \text{when} \quad t \gg \dfrac{1}{\sigma_1}, \end{cases} \tag{C.30}$$

where I_0 and I_1 are modified Bessel functions of the first kind, and the parameter σ_1 is related to the effective diffusion constant since $\sigma_1 \simeq \omega_\mp d/\omega \sim \tilde{D}/a^2$. Further,

$$\begin{aligned} \overline{Q}_2(t) &\simeq \frac{1}{\pi \omega_\mp} \int_\omega^{\sigma_2} (\omega_\mp - \sigma) \sqrt{\frac{\sigma_2 - \sigma}{\sigma - \omega}}\, \mathrm{e}^{-\sigma t}\, \mathrm{d}\sigma \\ &= -\frac{\sigma_2 - \omega}{2\omega_\mp} \exp\left(-\frac{\sigma_2 + \omega}{2} t\right) \left[\frac{1}{t} I_1\left(\frac{\sigma_2 - \omega}{2} t\right)\right. \\ &\quad \left. + \, \omega_\pm \left[I_0\left(\frac{\sigma_2 - \omega}{2} t\right) + I_1\left(\frac{\sigma_2 - \omega}{2} t\right)\right]\right] \\ &\simeq \begin{cases} -\dfrac{\omega_\pm^2 d}{2\omega_\mp \omega}\, \mathrm{e}^{-\omega t} & \text{when} \quad t \ll \dfrac{1}{\sigma_2 - \omega} \\ -\dfrac{\omega_\pm^{3/2} \sqrt{d}}{\sqrt{\pi \omega t}\, \omega_\mp}\, \mathrm{e}^{-\omega t} & \text{when} \quad t \gg \dfrac{1}{\sigma_2 - \omega}. \end{cases} \end{aligned} \tag{C.31}$$

The quantity, $\sigma_2 - \omega \simeq \omega_\pm d/\omega \simeq d \sim D/a^2$, is related to the 'bare' diffusion constant. Since $1/d \gg 1/\omega$, $\overline{Q}_2(t)$ can then be simply written as

$$\overline{Q}_2(t) \simeq \begin{cases} -\dfrac{\omega_\pm^2 d}{2\omega_\mp \omega}(1 - \omega t) & \text{when} \quad t \ll \dfrac{1}{\omega} \\ 0 & \text{when} \quad t \gg \dfrac{1}{\omega}. \end{cases} \tag{C.32}$$

Finally, $\overline{Q}_3(t) + \overline{Q}_4(t) = \mathrm{Res}_3\, \mathrm{e}^{-\sigma_3 t} + \mathrm{Res}_4\, \mathrm{e}^{-\sigma_4 t}$ with

$$\begin{aligned} \sigma_3 &\simeq \sigma_3^{(0)} + \frac{d\big(\sigma_3^{(0)} - \Omega'\big)}{2\big(\sigma_3^{(0)} - \sigma_4^{(0)}\big)}, \\ \sigma_4 &\simeq \sigma_4^{(0)} + \frac{d\big(\sigma_4^{(0)} - \Omega'\big)}{2\big(\sigma_4^{(0)} - \sigma_3^{(0)}\big)}, \\ \mathrm{Res}_3 &= \frac{\omega_\pm \Omega}{\sigma_4^{(0)} - \sigma_3^{(0)}} \left(1 - \frac{d\big(\sigma_3^{(0)} - \omega_\mp\big)}{2\sigma_3^{(0)}\big(\sigma_3^{(0)} - \omega\big)}\right), \\ \mathrm{Res}_4 &= \frac{\omega_\pm \Omega}{\sigma_3^{(0)} - \sigma_4^{(0)}} \left(1 - \frac{d\big(\sigma_4^{(0)} - \omega_\mp\big)}{2\sigma_4^{(0)}\big(\sigma_4^{(0)} - \omega\big)}\right). \end{aligned} \tag{C.33}$$

With the assumption of $\omega_\mp \ll \Omega \ll \omega_\pm$, $\sigma_3^{(0)} \to \Omega$, $\sigma_4^{(0)} \to \omega$. Therefore, $\sigma_3 \to \Omega$ and $\sigma_4 \to \omega$. We can then see that each of the two pole parts decays much faster than the first branch cut.

For small time t, $t \ll 1/\omega$, all terms in $\overline{Q}(t)$ are relevant, and this region is the linear region in t, $\overline{Q}(t) \simeq \Omega(\omega_\pm - d/2)t$.

On the other hand, when $t \gg 1/\Omega$, only the first branch cut part is relevant, $\overline{Q}(t) \sim \overline{Q}_1(t)$, which is similar to $\overline{Q}(t)$ in the reduced model.

In the middle region, $1/\omega \ll t \ll 1/\Omega$, $\overline{Q}_1(t) \sim \sigma_1/2$, and we can still neglect $\overline{Q}_2(t)$. The pole part $\overline{Q}_3(t) + \overline{Q}_4(t)$, however, is important. This term determines the peak position of $\overline{Q}(t)$—approximately at $\ln\big(\sigma_4^{(0)}/\sigma_3^{(0)}\big)/\big(\sigma_4^{(0)} - \sigma_3^{(0)}\big)$.

C.2.6. Strong diffusion case ($d \gg \omega$) *and* $t = 0$. When diffusion is fast, and $d \gg \omega$, first of all we have to find σ_1 and σ_2:

$$\sigma_1 \simeq \omega_\mp - \frac{\omega_\pm \omega_\mp}{d}, \qquad \sigma_2 \simeq d + \omega_\pm. \tag{C.34}$$

Looking then at the expression for $\overline{Q}_1(t)$, formula (C.11), we first see that σ can be neglected in the expression $\sigma_2 - \sigma$, because σ_2 is larger than d and σ is smaller than $\omega_\mp$. Once we have done that, we see further that the $P(-\sigma)$ term in the denominator is large (contains the σ_2 factor), while the C term is much smaller (does not contain any σ_2). However, we cannot just neglect C, because then the remaining integral would diverge at small σ. From this, we conclude that our integral is dominated by the small σ region, which means that the integration can be continued to infinity and we can now neglect σ in all terms like $\Omega' - \sigma$, $\omega - \sigma$ and even $\sigma_1 - \sigma$; in all surviving terms, we can replace $\sigma_1 \simeq \omega_\mp$. Thus, we obtain

$$\begin{aligned}
\overline{Q}_1(t = 0) &\simeq \frac{1}{\pi} \int_0^{\sigma_1} \frac{\Omega^2 \omega_\pm^2 \omega_\mp (\omega_\mp - \sigma) \sqrt{\frac{(\sigma_1 - \sigma)\sigma_2}{\sigma(\omega - \sigma)}}}{(\Omega' - \sigma)^2 (\omega - \sigma)(\sigma_1 - \sigma)\sigma_2 \sigma + C} \,\mathrm{d}\sigma \\
&\simeq \frac{1}{\pi} \int_0^{\infty} \frac{\Omega^2 \omega_\pm^2 \omega_\mp^2 \sqrt{\frac{\omega_\mp \sigma_2}{\sigma \omega}}}{\Omega'^2 \,\omega \omega_\mp \sigma_2 \sigma + C} \,\mathrm{d}\sigma \\
&= \frac{\omega_\mp \Omega \omega_\pm}{\Omega' \omega}.
\end{aligned} \tag{C.35}$$

Importantly, we did not resort here to any approximations, except assuming $d \gg \omega$, no expansions in terms of any ω being small.

Now we address $\overline{Q}_2$. It is similar; it is also dominated by σ close to the lower limit, while the upper limit can be sent to infinity. To facilitate the calculation, it is convenient to introduce $\xi = \sigma - \omega$ as an integration variable. Then we write

$$\begin{aligned}
\overline{Q}_2(t = 0) &\simeq -\frac{1}{\pi} \int_0^{\sigma_2 - \omega} \frac{\Omega^2 \omega_\pm^2 \omega_\mp (\eta + \omega_\pm)^{3/2} \sqrt{\frac{\sigma_2}{\eta(\omega + \eta)}}}{(\omega - \Omega' + \eta)^2 (\omega + \eta)(\omega_\pm + \xi)\sigma_2 \eta + C} \,\mathrm{d}\eta \\
&\simeq -\frac{1}{\pi} \int_0^{\infty} \frac{\Omega^2 \omega_\mp \omega_\pm^{7/2} \sqrt{\frac{\sigma_2}{\eta \omega}}}{(\omega - \Omega')^2 \omega \omega_\pm \sigma_2 \eta + C} \,\mathrm{d}\eta \\
&\simeq -\frac{\omega_\pm^2 \Omega}{\omega\,(\omega_\pm - \Omega)}.
\end{aligned} \tag{C.36}$$

To address the pole contribution $\overline{Q}_3$, we should once again neglect σ in the expression, $\sigma_2 - \sigma$, in formula (C.14). Then, we see that the pole σ_3 is located close to Ω' and, therefore, σ should be replaced with Ω' in all terms except $(\Omega' - \sigma)$. We should also remember that $\Omega' - \sigma_1 \simeq \Omega' - \omega_\mp = \Omega$. That yields

$$\begin{aligned}
\overline{Q}_s &\simeq \frac{\omega_\pm \Omega (\omega_\mp - \sigma) \sqrt{\frac{(\sigma - \sigma_1)\sigma_2}{\sigma(\omega - \sigma)}}}{\Omega \omega_\pm \omega_\mp - (\Omega' - \sigma) \sqrt{(\sigma - \sigma_1)\,\sigma_2 \sigma\,(\omega - \sigma)}} \\
&\simeq -\frac{\omega_\pm \Omega^2 \sqrt{\frac{\Omega \sigma_2}{\Omega'(\omega - \Omega')}}}{\Omega \omega_\pm \omega_\mp - (\Omega' - \sigma) \sqrt{\Omega \sigma_2 \Omega'(\omega - \Omega')}} \\
&= -\frac{\omega_\pm \Omega^2 \big/ \Omega'(\omega_\pm - \Omega)}{\sigma - \Omega' + \frac{\omega_\pm \Omega \omega_\mp}{\sqrt{\Omega \Omega'(\omega_\pm - \Omega)\sigma_2}}}.
\end{aligned} \tag{C.37}$$

The position of the pole is read from the denominator of this formula; the pole is indeed close to Ω', because σ_2 is large. The value of the residue is read from the numerator. Incorporating the minus sign which is due to the $s \to -\sigma$ exchange, we find

$$\overline{Q}_3(t=0) \simeq \frac{\omega_\pm \Omega^2}{\Omega'(\omega_\pm - \Omega)}. \tag{C.38}$$

Finally, $\overline{Q}_4(t = 0) \simeq \mathcal{O}(d^{-7})$, it does not have the d-independent contribution, so it is negligible. Simple algebra (this time it is really simple!) shows that $\overline{Q}_1(t=0) + \overline{Q}_2(t=0) + \overline{Q}_3(t=0) = 0$, as it must be.

C.2.7. Strong diffusion case ($d \gg \omega$)*, and* $t > 0$*.* Now we can study $\overline{Q}(t)$. First, taking advantage of the dominance of $\sigma \to 0$ region in the integral of $\overline{Q}_1(t)$, we have

$$\begin{aligned}
\overline{Q}_1(t) &= \frac{1}{\pi}\int_0^{\sigma_1} \frac{\left(1-\frac{\sigma}{\omega_\mp}\right)\sqrt{\frac{(\sigma_1-\sigma)(\sigma_2-\sigma)}{\sigma(\omega-\sigma)}}\,\mathrm{e}^{-\sigma t}}{1+\frac{(\Omega'-\sigma)^2\sigma(\omega-\sigma)(\sigma_1-\sigma)(\sigma_2-\sigma)}{C}}\,\mathrm{d}\sigma \\
&\simeq \frac{1}{\pi}\sqrt{\frac{\sigma_1\sigma_2}{\omega}}\int_0^\infty \frac{\mathrm{e}^{-\sigma t}}{\sqrt{\sigma}\left(1+\frac{\Omega'^2\omega\sigma_1\sigma_2}{C}\sigma\right)}\,\mathrm{d}\sigma \\
&= \frac{\Omega\omega_\pm\omega_\mp}{\Omega'\omega}\,\mathrm{e}^{\frac{\Omega^2\omega_\pm^2\omega_\mp^2}{\Omega'^2\omega\sigma_1\sigma_2}t}\,\mathrm{Erfc}\left(\sqrt{\frac{\Omega^2\omega_\pm^2\omega_\mp^2}{\Omega'^2\omega\sigma_1\sigma_2}t}\right) \\
&\simeq \begin{cases} \dfrac{\Omega\omega_\pm\omega_\mp}{\Omega'\omega} & \text{when} \quad t \ll \dfrac{\Omega'^2\omega\sigma_1\sigma_2}{\Omega^2\omega_\pm^2\omega_\mp^2} \\[2ex] \dfrac{1}{a}\sqrt{\dfrac{4D_{\mathrm{eff}}}{\pi t}} & \text{when} \quad t \gg \dfrac{\Omega'^2\omega\sigma_1\sigma_2}{\Omega^2\omega_\pm^2\omega_\mp^2}. \end{cases}
\end{aligned} \tag{C.39}$$

By changing variable $\eta = \sigma - \omega$ and considering the dominance of $\eta \to 0$ region, we can get

$$\begin{aligned}
\overline{Q}_2(t) &= \frac{1}{\pi}\int_\omega^{\sigma_2} \frac{\left(1-\frac{\sigma}{\omega_\mp}\right)\sqrt{\frac{(\sigma-\sigma_1)(\sigma_2-\sigma)}{\sigma(\sigma-\omega)}}\,\mathrm{e}^{-\sigma t}}{1+\frac{(\Omega'-\sigma)^2\sigma(\sigma-\omega)(\sigma-\sigma_1)(\sigma_2-\sigma)}{C}}\,\mathrm{d}\sigma \\
&\simeq -\frac{\omega_\pm\sqrt{\frac{(\omega-\sigma_1)(\sigma_2-\omega)}{\omega}}\,\mathrm{e}^{-\omega t}}{\pi\omega_\mp}\int_0^\infty \frac{1}{\sqrt{\eta}\left[1+\frac{(\Omega'-\omega)^2\omega(\omega-\sigma_1)(\sigma_2-\omega)}{C}\eta\right]}\,\mathrm{d}\eta \\
&\simeq -\frac{\omega_\pm^2\Omega}{\omega(\omega_\pm-\Omega)}\,\mathrm{e}^{-\omega t}.
\end{aligned} \tag{C.40}$$

Using the expression for $\overline{Q}_3(t=0)$, $\overline{Q}_3(t)$ is easily obtained:

$$\overline{Q}_3(t) = \overline{Q}_3(t=0)\,\mathrm{e}^{-\sigma_3 t} \simeq \frac{\omega_\pm\Omega^2}{\Omega'(\omega_\pm-\Omega)}\,\mathrm{e}^{-\Omega' t}. \tag{C.41}$$

Finally, $\overline{Q}_4(t) = \overline{Q}_4(t=0)\,\mathrm{e}^{-\sigma_4 t}$ is negligible.

Appendix D. Analytic continuation

We have computed $\overline{Q}_s$ for real positive s, and our task is to find analytic continuation of this function to the entire complex plane in order to perform complex integration to invert the Laplace transform.

To see how this analytic continuation should be performed, consider a simpler example of a function defined for positive real s via the relation

$$f(s) = \sqrt{s(s+a)} = \sqrt{s}\sqrt{s+a}, \tag{D.1}$$

where $a \geqslant 0$ (real), and where we assume that for any positive real x, we take the positive value for $\sqrt{x}$.

Consider an example of $a = 3$ and let us compute $f(-4)$. One way to do it is

$$f(s) = \sqrt{(-4)(-4+3)} = \sqrt{4} = 2, \tag{D.2}$$

while the other way is

$$f(s) = \sqrt{-4} \times \sqrt{-4+3} = 2\imath \times \imath = -2. \tag{D.3}$$

So which one is right? In other words, which one of the two branches of the complex function represents the right analytic continuation if we start from positive values of square roots at positive real s?

To find an unambiguous solution, we have to choose the branch cut of the function $\phi(z) = \sqrt{z}$. We can do it arbitrarily, but once the choice is made, we cannot switch the rules as we go. Let us choose the branch cut along the negative real axis of z, and that rule then will have to be applied in all cases, whether $z = s$, or $z = s+a$, or $z = s(s+a)$. With this definition in mind, let us now find $f(s)$ for real negative s in the region $s < -a$. We choose to operate with the now obviously easier definition $f(s) = \sqrt{s}\sqrt{s+a}$ and consider $f(s)$ just above the real axis at $s < -a$. Above the real axis we are above the branch cuts for both square roots, yielding $f(s) = \imath\sqrt{|s|} \times \imath\sqrt{|s+a|} = -\sqrt{|s(s+a)|}$. The same answer is obtained for $f(s)$ just below the real axis at $s < -a$, which means that there is no branch cut in this region. Thus, the correct analytical continuation of $f(s)$ to negative real s at $s < -a$ reads

$$f(s) = -\sqrt{|s(s+a)|} \qquad \text{at} \quad s < -a. \tag{D.4}$$

This is nicely illustrated by the limit $a \to 0$, in which case we obtain $f(s) = -|s| = s$ for negative s, which is an obviously correct analytic continuation of $f(s)$ at positive s.

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