Green's functions and first passage time distributions for dynamic instability of microtubules

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It is shown that the dynamic instability process describing the self-assembly and/or disassembly of microtubules is a continuous version of a variant of persistent random walks described by the *generalized* telegrapher's equation. That is to say, a microtubule is likely to undergo stochastic traveling waves in which catastrophe and rescue events cannot propagate faster than v_- and v_+, respectively. For this stochastic process, analytic expressions for Green's functions of position and velocity of a microtubule and exact solutions for the first passage time distributions of a microtubule to the nucleating site are obtained. It is shown that, in the $\omega \to \infty$ limit, where ω^{-1} is the persistence time, the dynamic instability process can be described by a diffusion process in the presence of a drift term that, in fact, is the steady-state velocity of the microtubule. As a result, the catastrophe time distribution (i.e., the distribution of microtubule lifetimes to the nucleating site) exhibits a power law with an exponential cutoff as $F(t|x_0) \sim t^{-3/2} e^{-t/\tau_c}$, where τ_c is the time scale at which the drift term and the diffusive term are comparable. [S1063-651X(97)06812-8]

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I. INTRODUCTION

Microtubules (MTs) are polarized long protein fibers made of asymmetric tubulin dimers ($\alpha\beta$) that involve several forms of cellular activities, for example, cell division, transport network, and determination of cellular shapes. Nucleated MTs (e.g., as nucleated from the centrosome during the mitosis) are tightly attached to the nucleated site by their minus ends and MTs exchange tubulin dimers between the soluble and polymer pools at their free plus ends using the dynamic instability mechanism. For instance, within the cell, the MT meshwork can be rapidly remodeled into totally new configurations as a consequence of guanosine triphosphate (GTP) hydrolysis and turnover rates afforded by dynamic instability. The term ''dynamic instability'' was introduced by Mitchison and Kirschner [1] to describe and provide an explanation of the self-assembly and/or disassembly process of MTs. The dynamic instability is defined by an adsorption of free GTP tubulins [which are later converted into guanosine diphosphate (GDP)] in the growing phase that increases the MT length and a loss of GDP tubulins in the shrinking phase that shorten the MT, with infrequent random switches between these two states. The result is that the growing MT will persist in the growing phase, but once it undergoes a change to a shrinking state, it will continue to shrink. The transition from the growing phase to the shrinking phase is called a catastrophe and the reverse transition a rescue.

From the physical and mathematical standpoint, Dogterom and Leibler [2] proposed model equations to describe and capture the main essential features of the dynamic instability of MTs. Although other theoretical attempts describing the MT dynamics are available in the literature, such as the two-state model by Hill [3], the Dogterom and Leibler model has been used by several authors in order to describe various aspects of MT dynamics and are often called the basic equations for the dynamic instability mechanism.

My aim in this paper is to point out that, rather than being a unique feature of MT motions, the dynamic instability belongs to a class of stochastic processes frequently encountered in physics, chemistry, and biology. Indeed, it is shown that the dynamic instability is a continuous space version of a variant of persistent random walks described by the telegraph process, which, in the high-frequency limit of alternating MT phases, becomes a simple diffusion process with a drift term. The persistent random walk and its continuous limit, the telegrapher's equation, are known in the literature since their introduction by Taylor [5] as an attempt to describe the turbulent diffusion and by Goldstein [6] for the propagation of electromagnetic waves in conducting media. Most of the telegrapher's equations encountered in the literature deal with the situation where speeds of the walker in either directions are the same and the interconverting frequencies between these velocities are also equal. For this case, solutions of the telegrapher's equation subjected to a variety of boundary conditions have been studied by Masoliver *et al.* [7]. Meanwhile, in the dynamic instability of MTs, both the forward and backward velocities are different as well for the interconverting frequencies. This results in an additional convective term and a cross derivative with respect to the position and time in the telegrapher equation. For such a generalized telegrapher equation, analytical solutions with appropriate initial and boundary conditions are derived.

Moreover, it has been shown recently by Bicout and Szabo [8] that the persistent random walk can be regarded as a simple model for the dynamics in phase space and so the Wang-Uhlenbeck boundary conditions problem [4] can be solved exactly. As a generalization to these results, analytic expressions for the first passage time distributions of a MT to the nucleating site (origin) are calculated.

The rest of the paper is organized as follows. In Sec. II, I present the essence of the theoretical model proposed by

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Dogterom and Leibler, establish the equivalence between the dynamic instability and the telegraph process, and derive the corresponding boundary-free Green's functions. The derivation of first passage time distributions of a MT to the nucleating site is outlined in Sec. III. In Sec. IV the reduced Green's function (obtained in averaging over the equilibrium distribution of initial velocity) is evaluated and the moments of the time-dependent position of the MT-free end are analyzed. The diffusion limit of the dynamic instability mechanism is discussed in Sec. V and the catastrophe time distribution (or the distribution of MT lifetime to the nucleating site) is calculated. Some remarks on the qualitative resemblance of the dynamic instability and the fractional Brownian motion are presented in Sec. VI.

II. UNRESTRICTED GREEN'S FUNCTIONS

The Dogterom-Leibler model [2] assumes that MTs are rigid linear polymers having one end anchored to a nucleating flat surface. All MTs, whatever their length, are sufficiently far apart to be considered as independent and they grow, by their free end, perpendicularly to the nucleating planar surface. As a simple model of single-stranded polymer, the MT free end is either in the growing phase (phase ''+''), in which the MT grows with the average speed v_+, or in the shrinking phase (phase ''−''), in which the MT shrinks with the average speed v_-, with random transitions between these two macroscopic states. The frequency of switching from the growth to shrinkage is f_+ (the catastrophe frequency) and for the reverse switching from the shrinkage to growth is f_- (also called the rescue frequency). The overall rate of growth is controlled by both v_+ and f_+ which depend on the local concentration of free tubulin dimers near the MT's tip, while v_- and f_- can be supposed as constants. For simplicity, the position $x(t)$ of the MT free end is singled out as the only relevant coordinate for the dynamics (i.e., one-dimensional problem), so that it is possible to define the probability densities $P_+(x,t)$ and $P_-(x,t)$ of finding at time t the MT in the phases + and −, respectively, with its free end at a distance x. (Later on x, up to an additive constant, will be identified to the MT length.) Neglecting the free tubulin concentration variations in the MT dynamic process, the dynamic instability's equations governing the time evolution of $P_+(x,t)$ and $P_-(x,t)$ are [2]

$$\frac{\partial}{\partial t}\begin{pmatrix} P_+ \\ P_- \end{pmatrix} = \mathbf{L}\begin{pmatrix} P_+ \\ P_- \end{pmatrix}, \tag{2.1a}$$

$$\mathbf{L} = \begin{pmatrix} -v_+\frac{\partial}{\partial x} - f_+ & f_- \\ f_+ & v_-\frac{\partial}{\partial x} - f_- \end{pmatrix}. \tag{2.1b}$$

Equations (2.1a) describes the evolution of the state variable $x(t)$ that obeys the dynamical equation

$$\frac{dx}{dt} = v(t), \tag{2.2}$$

where the stochastic velocity $v(t)$ is a dichotomous Markov noise that takes values v_+ with probability g_+ and $-v_-$ with probability g_-. The switches of $v(t)$, $-v_- \underset{f_+}{\overset{f_-}{\rightleftarrows}} v_+$, are Poisson processes such that the respective probabilities can be described by the first-order kinetic equations

$$\frac{d}{dt}\begin{pmatrix} g_+ \\ g_- \end{pmatrix} = \begin{pmatrix} -f_+ & f_- \\ f_+ & -f_- \end{pmatrix}\begin{pmatrix} g_+ \\ g_- \end{pmatrix} \tag{2.3}$$

for which the solutions are

$$g_+(t) = \frac{f_-}{\omega} + \left[g_+(0) - \frac{f_-}{\omega} \right] e^{-\omega t}, \tag{2.4a}$$

$$g_-(t) = \frac{f_+}{\omega} + \left[g_-(0) - \frac{f_+}{\omega} \right] e^{-\omega t}, \tag{2.4b}$$

with $g_+(0)$ and $g_-(0)$ the initial conditions and such that $g_+(t) + g_+(t) = 1$ for all times, expressing the conservation of the total probability. ω^{-1} (with $\omega = f_+ + f_-$) denotes the mean time between switches of $v(t)$, i.e., the average time during which $v(t)$ keeps the same value. ω^{-1} is also called the persistence time to emphasize the fact that during that time the MT persists on average in the same growing or shrinking phase. Defining the instantaneous average velocity as

$$\langle v(t) \rangle = v_+ g_+(t) - v_- g_-(t), \tag{2.5}$$

one can show that the velocity relaxation (or correlation) function reads

$$\frac{\langle v(t) \rangle - \langle v(\infty) \rangle}{\langle v(0) \rangle - \langle v(\infty) \rangle} = e^{-\omega t}, \tag{2.6}$$

where the mean time ω^{-1} between switches of $v(t)$ is also the velocity relaxation time. For time scales longer than ω^{-1}, the average velocity relaxes towards $\langle v(\infty) \rangle$ which is, in fact, the steady-state average velocity (henceforth denoted by V) given by

$$\langle v(\infty) \rangle = V = \frac{v_+ f_-}{\omega} - \frac{v_- f_+}{\omega}. \tag{2.7}$$

V is the key quantity to distinguish the two different dynamics of MT growth [2]. In the ''unlimited'' regime the MT continuously grows in the course of time with the average speed $V > 0$, while in the dynamic instability regime (also called the ''limited'' or ''bounded'' regime) that holds for $V < 0$, the system of MT is characterized by an equilibrium distribution of MT lengths. Roughly speaking, when $V > 0$ the catastrophe events are rare and the MT grows on average, whereas for $V < 0$ the catastrophe events become so frequent that there is a balance between growth and shrinking rates that gives a steady-state length of MT. The transition between these two regimes takes place at the threshold $V = 0$ where the MT is likely to experience a symmetric random walk. Thus, depending upon the local value of V, a MT can successively experience different growth regimes. It is then important for the characterization of each regime to determine the Green's function that describes the time evolution of the free end MT for arbitrary values of V. For that purpose, we start from the pair of coupled first-order equations (2.1a). By combining them, one can show that the dynamic instability equations can be rewritten as a generalized telegrapher's equation (uncoupled second-order equation) as

$$\frac{\partial^2 P_i}{\partial t^2}+\omega\frac{\partial P_i}{\partial t}=-\Delta v\frac{\partial^2 P_i}{\partial t\partial x}+\omega D\frac{\partial^2 P_i}{\partial x^2}-\omega V\frac{\partial P_i}{\partial x},\quad i=\pm, \tag{2.8}$$

where $\Delta v=v_+-v_-$ is the difference between the growth and shrinkage velocities and $D=v_+v_-/\omega$ is the effective diffusion coefficient. Equation (2.8) shows that the telegraph process, which originates from a persistent random walk, is the underlying stochastic process for the dynamic instability. The propagation of the MT free end is partially wavelike and partially diffusive. Notice that Eq. (2.8) differs from the telegrapher's equation commonly encountered in the literature by the presence of a convective term and a cross derivative with respect of position and time. Since Eq. (2.8) is a hyperbolic equation [the discriminant $(\Delta v)^2+4\omega D=(v_++v_-)^2>0$], the MT growing or shrinking waves cannot propagate faster than v_+ and $-v_-$, respectively. The MT free end is therefore confined within the ''light cone'' $-v_-t<x<v_+t$ at any time. Moreover, since P_+ and P_- satisfy the same telegrapher's equation, the only way to make the difference between them is to look for initial and boundary conditions. In that respect, the complete description of a MT will be obtained from the knowledge of the Green's functions $\Pi_{ij}(x,t|x_0)$ (with $i,j=-,+$), which is the probability density that a MT initially in phase j with length x_0 will be found in phase i with length x at time t later. In what follows, we focus on the unrestricted (boundary-free) Green's functions. In order to derive expressions for the four Green's functions $\Pi_{ij}(x,t|x_0)$ that satisfy the telegrapher's equation in Eq. (2.8), we consider the two different sets of initial conditions.

A. Microtubule initially in the growing phase

At $t=0$ the MT is in the phase + [i.e., $g_+(0)=1$ and $g_-(0)=0$] and has length x_0, which corresponds to the conditions

$$\Pi_{++}(x,t=0|x_0)=\delta(x-x_0), \tag{2.9a}$$

$$\Pi_{-+}(x,t=0|x_0)=0. \tag{2.9b}$$

Since the telegrapher's equation is a second-order equation we need a second initial condition for the time derivative of the Green's function. This is obtained by substituting Eqs. (2.9) into Eq. (2.1a) to give

$$\left.\frac{\partial\Pi_{++}}{\partial t}\right|_{t=0}=-v_+\frac{\partial}{\partial x}\delta(x-x_0)-f_+\delta(x-x_0), \tag{2.10a}$$

$$\left.\frac{\partial\Pi_{-+}}{\partial t}\right|_{t=0}=f_+\delta(x-x_0). \tag{2.10b}$$

Laplace transforming Eq. (2.8), we get

$$\mathbf{T}\begin{pmatrix}\hat\Pi_{++}\\ \hat\Pi_{-+}\end{pmatrix}=\begin{pmatrix}-s-f_-+v_-\dfrac{\partial}{\partial x}\\ -f_+\end{pmatrix}\delta(x-x_0), \tag{2.11}$$

where the operator $\mathbf{T}$ is given by

$$\mathbf{T}=\omega D\frac{\partial^2}{\partial x^2}-(\omega V+\Delta v s)\frac{\partial}{\partial x}-s(s+\omega) \tag{2.12}$$

and the Laplace transform $\hat p(s)$ of any function $p(t)$ is defined as $\hat p(s)=\int_0^\infty e^{-st}p(t)\,dt$. Let $\hat G_0(x,s|x')$ be the Green's function associated with $\mathbf{T}$ and satisfying the differential equation

$$\mathbf{T}\hat G_0(x,s|x')=\delta(x-x'). \tag{2.13}$$

Once $\hat G_0(x,s|x')$ is known, the Green's functions $\hat\Pi_{++}$ and $\hat\Pi_{-+}$ can be obtained from the integral

$$\begin{pmatrix}\hat\Pi_{++}\\ \hat\Pi_{-+}\end{pmatrix}=\int_{-\infty}^{\infty}dx'\;\hat G_0(x,s|x')\begin{pmatrix}-s-f_-+v_-\dfrac{\partial}{\partial x'}\\ -f_+\end{pmatrix}\times\delta(x'-x_0). \tag{2.14}$$

On the other hand, one can show that the solution of Eq. (2.13) is written

$$\hat G_0(x,s|x')=\frac{1}{\omega D(\lambda_2-\lambda_1)}[\mathcal{H}(x'-x)e^{\lambda_1(x-x')}+\mathcal{H}(x-x')e^{\lambda_2(x-x')}], \tag{2.15}$$

where $\mathcal{H}(\;)$ is the Heaviside step function defined as $\mathcal{H}(x)=0$ for $x<0$ and $\mathcal{H}(x)=1$ for $x>0$ and the s-dependent eigenvalues λ_1 and λ_2 are

$$\left.\begin{matrix}\lambda_1\\ \lambda_2\end{matrix}\right\}=\frac{\omega V+\Delta v s}{2\omega D}\pm\left[\left(\frac{\omega V+\Delta v s}{2\omega D}\right)^2+\frac{s(s+\omega)}{\omega D}\right]^{1/2}. \tag{2.16}$$

Substituting Eq. (2.15) into Eq. (2.14), we find

$$\hat\Pi_{++}(x,s|x_0)=\frac{s+f_--\lambda_1 v_-}{\omega D(\lambda_1-\lambda_2)}\mathcal{H}(x_0-x)e^{\lambda_1(x-x_0)}+\frac{s+f_--\lambda_2 v_-}{\omega D(\lambda_1-\lambda_2)}\mathcal{H}(x-x_0)e^{\lambda_2(x-x_0)} \tag{2.17}$$

and

$$\hat\Pi_{-+}(x,s|x_0)=\frac{f_+}{\omega D(\lambda_1-\lambda_2)}\mathcal{H}(x_0-x)e^{\lambda_1(x-x_0)}+\frac{f_+}{\omega D(\lambda_1-\lambda_2)}\mathcal{H}(x-x_0)e^{\lambda_2(x-x_0)}. \tag{2.18}$$

As a check, one can easily verify that

$$\int_{-\infty}^{\infty}[\hat{\Pi}_{++}(x,s|x_0)+\hat{\Pi}_{-+}(x,s|x_0)]dx=\frac{1}{s}. \quad (2.19)$$

Inverting next these Laplace transform expressions [see the Appendix for the details of calculations] we finally obtain

$$\Pi_{++}(x,t|x_0)=\delta\left(t-\frac{x-x_0}{v_+}\right)\frac{e^{-f_+t}}{v_+}+\left[\mathcal{H}\left(t+\frac{x-x_0}{v_-}\right)+\mathcal{H}\left(t-\frac{x-x_0}{v_+}\right)\right]\frac{f_-}{v_++v_-}\left(\frac{z_-}{z_+}\right)^{1/2}\times e^{(z_++z_-)/2}I_1(\sqrt{z_+z_-}), \quad (2.20)$$

$$\Pi_{-+}(x,t|x_0)=\left[\mathcal{H}\left(t+\frac{x-x_0}{v_-}\right)+\mathcal{H}\left(t-\frac{x-x_0}{v_+}\right)\right]\frac{f_+}{v_++v_-}\times e^{(z_++z_-)/2}I_0(\sqrt{z_+z_-}), \quad (2.21)$$

in which we have defined dimensionless variables

$$z_+=\frac{2f_-}{v_++v_-}(x-x_0-v_+t), \quad (2.22a)$$

$$z_-=\frac{2f_+}{v_++v_-}(x_0-x-v_-t) \quad (2.22b)$$

and $I_0(\ )$ and $I_1(\ )$ are the modified Bessel functions of order zero and one, respectively. The dependence of Π_{ij} upon z_- and z_+ is characteristic of traveling waves moving with the speed v_- in the negative-x direction and with v_+ in the positive-x direction.

B. Microtubule initially in the shrinking phase

In this case the initial conditions are

$$\Pi_{+-}(x,t=0|x_0)=0, \quad (2.23a)$$

$$\Pi_{--}(x,t=0|x_0)=\delta(x-x_0) \quad (2.23b)$$

and the initial time derivatives are

$$\left.\frac{\partial\Pi_{+-}}{\partial t}\right|_{t=0}=f_-\delta(x-x_0), \quad (2.24a)$$

$$\left.\frac{\partial\Pi_{--}}{\partial t}\right|_{t=0}=v_-\frac{\partial}{\partial x}\delta(x-x_0)-f_-\delta(x-x_0). \quad (2.24b)$$

The Laplace transform of the Green's functions satisfies the differential equation

$$\mathbf{T}\begin{pmatrix}\hat{\Pi}_{+-}\\ \hat{\Pi}_{--}\end{pmatrix}=\begin{pmatrix}-f_-\\ -s-f_+-v_+\dfrac{\partial}{\partial x}\end{pmatrix}\delta(x-x_0). \quad (2.25)$$

As outlined above, one can show that

$$\hat{\Pi}_{+-}(x,s|x_0)=\frac{f_-}{\omega D(\lambda_1-\lambda_2)}\mathcal{H}(x_0-x)e^{\lambda_1(x-x_0)}+\frac{f_-}{\omega D(\lambda_1-\lambda_2)}\mathcal{H}(x-x_0)e^{\lambda_2(x-x_0)} \quad (2.26)$$

and

$$\hat{\Pi}_{--}(x,s|x_0)=\frac{s+f_++\lambda_1v_+}{\omega D(\lambda_1-\lambda_2)}\mathcal{H}(x_0-x)e^{\lambda_1(x-x_0)}+\frac{s+f_++\lambda_2v_+}{\omega D(\lambda_1-\lambda_2)}\mathcal{H}(x-x_0)e^{\lambda_2(x-x_0)}. \quad (2.27)$$

One still has the conservation of the probability density

$$\int_{-\infty}^{\infty}[\hat{\Pi}_{+-}(x,s|x_0)+\hat{\Pi}_{--}(x,s|x_0)]dx=\frac{1}{s}. \quad (2.28)$$

Proceeding as above to invert the Laplace transform solutions, we find

$$\Pi_{+-}(x,t|x_0)=\left[\mathcal{H}\left(t+\frac{x-x_0}{v_-}\right)+\mathcal{H}\left(t-\frac{x-x_0}{v_+}\right)\right]\frac{f_-}{v_++v_-}\times e^{(z_++z_-)/2}I_0(\sqrt{z_+z_-}), \quad (2.29)$$

$$\Pi_{--}(x,t|x_0)=\delta\left(t+\frac{x-x_0}{v_-}\right)\frac{e^{-f_-t}}{v_-}+\left[\mathcal{H}\left(t+\frac{x-x_0}{v_-}\right)+\mathcal{H}\left(t-\frac{x-x_0}{v_+}\right)\right]\frac{f_+}{v_++v_-}\times\left(\frac{z_+}{z_-}\right)^{1/2}e^{(z_++z_-)/2}I_1(\sqrt{z_+z_-}). \quad (2.30)$$

Some relations between Green's functions

One can realize by simple examination that the Green's functions derived above are symmetric each others. For example, Π_{ji} is obtained from Π_{ij} by changing into Π_{ij} the variables f_+ and z_+ by f_- and z_-, respectively, and vice versa. In addition, these are related through the detailed-balance-like relations as

$$z_+[\Pi_{++}(x,t|x_0)-\Pi_{++}(x,0|x_0)]=z_-[\Pi_{--}(x,t|x_0)-\Pi_{--}(x,0|x_0)] \quad (2.31a)$$

$$f_+\Pi_{+-}(x,t|x_0)=f_-\Pi_{-+}(x,t|x_0). \quad (2.31b)$$

C. Absorbing and reflecting boundary conditions

We now sketch the boundary conditions we have to use when one is interested in the problem of MT evolution in the presence of absorbing and/or reflecting boundary conditions.

To derive these conditions one can forget for the moment the initial state of the MT so that we can work with the probability density P_+ and P_-. Nonetheless, the position of the boundary relative to the initial MT position x_0 needs to be specified. One has, for example, the following conditions.

1. Absorbing boundary condition at $x=a\leqslant x_0$

For a MT starting from the position $x_0>a$, the point $x=a$ is absorbing if the probability of finding a MT at $x=a$ with velocity v_+ is zero, i.e,

$$P_+(x=a,t)=0. \tag{2.32}$$

Such a boundary condition was previously introduced by Wang and Uhlenbeck [4] when dealing with the Kramers-Klein equation. Although Eq. (2.32) sufficiently specifies the absorbing boundary condition, one often wants (for practical reasons) to have an additional requirement for the phase $-$. This can be achieved, for example, in substituting Eq. (2.32) into Eq. (2.1a). However, it convenient to emphasize that the resulting condition as obtained is fragile and depends on the differential equation we are using, so its use requires some cautions.

2. Reflecting boundary condition at $x=a\leqslant x_0$

The presence of a reflecting barrier means that no ''particle'' can pass beyond $x=a$, i.e., the MT length cannot be smaller than a. This imposes the conservation of probability density:

$$\int_a^\infty [P_+(x,t)+P_-(x,t)]dx=1. \tag{2.33}$$

As a consequence, we have

$$\int_a^\infty \frac{\partial^n}{\partial t^n}[P_+(x,t)+P_-(x,t)]dx=0, \quad n\geqslant 1. \tag{2.34}$$

By adding now the coupled equation (2.1a) and next using relation (2.34) in the summed equation with the assumption $P_\pm(\infty,t)=0$, we obtain an equation for a reflecting barrier

$$v_-P_-(x=a,t)=v_+P_+(x=a,t). \tag{2.35}$$

This is equivalent to saying that the total flux $[J(x,t)=v_+P_+(x,t)-v_-P_-(x,t)]$ of MTs across the barrier at $x=a$ is zero, so that the weighted probabilities of finding a MT at $x=a$ are both equal. Here also the similar boundary condition is encountered when dealing with the Kramers-Klein equation [4].

Combining Eqs. (2.32) and (2.35) yields the radiation boundary condition

$$J(x=a,t)=\kappa P_+(x=a,t), \quad x_0>a, \tag{2.36}$$

where κ is the absorption rate. The purely reflecting and absorbing boundary conditions correspond to $\kappa=0$ and $\kappa\to\infty$ limits, respectively. All the above conditions can also be derived in the case where $x_0<a$ or when x_0 lies between two barriers.

III. FIRST PASSAGE TIME DISTRIBUTIONS

One of the problems where the boundary conditions are very important is the calculation of the mean lifetime or the evaluation of the full distribution of lifetimes of a MT in the presence of an absorbing barrier. Here we outline how first passage time distributions that a MT initially at x_0 and in either states $+$ and $-$ reaches the absorbing nucleating site at $x=0$ for the first time. To this end, we need to compute first the survival probabilities that provides the complete dynamical description of the fate of the MT. Denoting by $S_+(t|x_0)$ and $S_-(t|x_0)$ the survival probabilities that a MT starting out at $x_0>0$ in states $+$ and $-$, respectively, and propagating in the whole available space has not yet reached at time t the absorbing barrier at $x=0$, one can show that $S_+(t|x_0)$ and $S_-(t|x_0)$ obey the coupled set of differential equations

$$\frac{\partial}{\partial t}\begin{pmatrix} S_+ \\ S_- \end{pmatrix}=\mathbf{L}^\dagger\begin{pmatrix} S_+ \\ S_- \end{pmatrix}, \tag{3.1a}$$

$$\mathbf{L}^\dagger=\begin{pmatrix} v_+\dfrac{\partial}{\partial x_0}-f_+ & f_+ \\ f_- & -v_-\dfrac{\partial}{\partial x_0}-f_- \end{pmatrix}, \tag{3.1b}$$

with the initial condition $S_+(0|x_0)=S_-(0|x_0)=1$. Since the initial position $x_0>0$, one requires that the ''particle'' must not only reach the barrier but also be moving in the right direction, say, in the negative-x direction (or moving with velocity $-v_-$) to satisfy the absorbing condition. In this case, the adjoint boundary condition to Eq. (2.32) reads

$$S_-(t|x_0)=0 \quad \text{if } x_0=0. \tag{3.2}$$

This implies that the survival probability of a MT at $x_0=0$ but in the growing phase is nonzero and has to be determined. Laplace transforming Eq. (3.1a), we get

$$\frac{\partial}{\partial x_0}\begin{pmatrix} \hat{S}_+ \\ \hat{S}_- \end{pmatrix}=\mathbf{M}\begin{pmatrix} \hat{S}_+ \\ \hat{S}_- \end{pmatrix}+\begin{pmatrix} \dfrac{-1}{v_+} \\ \dfrac{1}{v_-} \end{pmatrix}, \tag{3.3}$$

in which we have used the initial condition $S_+(0|x_0)=S_-(0|x_0)=1$ and introduced the matrix $\mathbf{M}$ defined by

$$\mathbf{M}=\begin{pmatrix} \dfrac{s+f_+}{v_+} & -\dfrac{f_+}{v_+} \\ \dfrac{f_-}{v_-} & -\dfrac{s+f_-}{v_-} \end{pmatrix}. \tag{3.4}$$

The s-dependent eigenvalues q_1 and q_2 of $\mathbf{M}$ are

$$\left.\begin{matrix} q_1 \\ q_2 \end{matrix}\right\} = -\frac{[v_+f_- - v_-f_+ + (v_+ - v_-)s]}{2v_+v_-} \pm \left\{ \left[\frac{[v_+f_- - v_-f_+ + (v_+ - v_-)s]}{2v_+v_-} \right]^2 + \frac{s(s+f_+ + f_-)}{v_+v_-} \right\}^{1/2}, \tag{3.5}$$

and the corresponding eigenvectors $\mathbf{u}_1$ and $\mathbf{u}_2$ are

$$\mathbf{u}_{1,2} = \begin{pmatrix} 1 \\ c_{1,2} \end{pmatrix}, \quad c_{1,2} = \frac{f_-}{s + f_- + q_{1,2}v_-}. \tag{3.6}$$

It follows that the general solution of Eq. (3.3) is therefore

$$\begin{pmatrix} \hat{S}_+(s|x_0) \\ \hat{S}_-(s|x_0) \end{pmatrix} = \frac{1}{s}\begin{pmatrix} 1 \\ 1 \end{pmatrix} + Ae^{q_1x_0}\begin{pmatrix} 1 \\ c_1 \end{pmatrix} + Be^{q_2x_0}\begin{pmatrix} 1 \\ c_2 \end{pmatrix}, \tag{3.7}$$

where A and B are unknown constants. Since probabilities $\hat{S}_\pm(s|x_0)$ might be bounded as $x\to\infty$, this requires us to have $A=0$. The remaining constant B is obtained in using the boundary condition in Eq. (3.2). We find

$$\hat{S}_+(s|x_0) = \frac{1}{s}\left[1 - \left(\frac{s + f_- + v_-q_2}{f_-} \right) e^{q_2x_0} \right], \tag{3.8a}$$

$$\hat{S}_-(s|x) = \frac{1}{s}[1 - e^{q_2x_0}]. \tag{3.8b}$$

It may be interesting, as a check, to consider the two limiting cases. When $f_-=0$, i.e., once the MT is in state $-$, it stays there until it disappears at the nucleating site. In this case both the survival probabilities are equal to one, $S_\pm(t|x_0)=1$, up to the time $t=x_0/v_-$, after which they are zero. Conversely, for $f_+=0$, i.e., once the MT starts in state $+$, it stays there forever so that $S_+(t|x_0)=1$ for all times and $S_-(t|x_0)=1-\mathcal{H}(t-x_0/v_-)e^{-f_-t}$.

Let us return to the survival probabilities and note that q_2 can be expressed in term of steady-state velocity V [cf. Eq. (2.7)], the difference of velocities Δv, and the diffusion coefficient D as $q_2(s) = -[\omega V + \Delta v s + \sqrt{(\omega V + \Delta v s)^2 + 4\omega D s(s+\omega)}]/2\omega D$. Thus, depending on the sign of V, we have $q_2(0)=0$ for $V\leqslant 0$ and $q_2(0) = -V/D$ for $V>0$. It follows that as $t\to\infty$, the survival probabilities decrease to zero when $V\leqslant 0$ and to a finite value less than one for $V>0$, meaning that in the latter situation once the MT has been nucleated it never shrinks back to the nucleating site. This allows us to define the escape probabilities that a MT starting out from x_0 never reaches the nucleating site as $\epsilon_\pm(x_0) = S_\pm(\infty|x_0)$. Multiplying by s Eqs. (3.8a) and (3.8b) and taking next the $s\to 0$ limit, we find

$$\epsilon_+(x_0) = \begin{cases} 0, & V\leqslant 0 \\ 1 - \left(\frac{v_-f_+}{v_+f_-} \right) \exp\left[-\frac{Vx_0}{D} \right], & V>0, \end{cases} \tag{3.9a}$$

$$\epsilon_-(x_0) = \begin{cases} 0, & V\leqslant 0 \\ 1 - \exp\left[-\frac{Vx_0}{D} \right], & V>0. \end{cases} \tag{3.9b}$$

We see that when $V>0$ and such that $V \gg D/x_0$, most of MTs grow indefinitely regardeless their initial state, that is, the characteristic of the unbounded regime mentioned above. In general, for an arbitrary value of V, the survival probabilities start from one at $t=0$ and decrease to a certain finite value as $t\to\infty$. One may then define the "relaxation times," denoted by $\tau_\pm(x_0)$, that $S_\pm(t|x_0)$ relaxes toward $S_\pm(\infty|x_0)$:

$$\tau_\pm(x_0) = \int_0^\infty \left[\frac{S_\pm(t|x_0) - S_\pm(\infty|x_0)}{1 - S_\pm(\infty|x_0)} \right] dt, \tag{3.10}$$

in which we have used $S_\pm(0|x_0)=1$. When $S_\pm(\infty|x_0)=0$, i.e., when the escape probabilities are identically equal to zero, $\tau_\pm(x_0)$ reduce the time areas under $S_\pm(t|x_0)$. These are, by definition, the mean first passage times to $x=0$ for a MT initially at x_0 and in state $+$ or $-$. On the other hand, when the escape probabilities are nonzero, $\tau_\pm(x_0)$ represent the time areas between $S_\pm(t|x_0)$ and the line $1-S_\pm(\infty|x_0)$. In this case $\tau_\pm(x_0)$ denote the mean first passage times conditional that a MT, initially at x_0 and in state $+$ or $-$, has reached the absorbing boundary at $x=0$. In each case, the first passage time distributions, denoted by $F_\pm(t|x_0)$, can be related to the corresponding survival probabilities as

$$F_\pm(t|x_0) = -\frac{1}{1 - S_\pm(\infty|x_0)} \frac{dS_\pm(t|x_0)}{dt}$$

or

$$\hat{F}_\pm(s|x_0) = \frac{1 - s\hat{S}_\pm(s|x_0)}{1 - S_\pm(\infty|x_0)}. \tag{3.11}$$

A. Bounded regime $V\leqslant 0$

Here we have $\epsilon_\pm(x_0) = S_\pm(\infty|x_0) = 0$. Substituting Eqs. (3.8a) and (3.8b) into Eq. (3.11) yields

$$\hat{F}_+(s|x_0) = \left(\frac{s + f_- + v_-q_2}{f_-} \right) e^{q_2x_0}, \tag{3.12a}$$

$$\hat{F}_-(s|x_0) = e^{q_2x_0}. \tag{3.12b}$$

Using next the relation in Eq. (A9), and after some calculations, we finally end up with expressions

$$F_+(t|x_0) = \mathcal{H}\left(t - \frac{x_0}{v_-} \right) \frac{2f_+f_-}{v_+ + v_-} \frac{e^{-(z_+^0 + z_-^0)/2}}{z_+^0} \times \left\{ x_0 I_0(\sqrt{z_+^0 z_-^0}) + \frac{v_+}{f_+} \left(\frac{z_-^0}{z_+^0} \right)^{1/2} I_1(\sqrt{z_+^0 z_-^0}) \right\}, \tag{3.13a}$$

$$F_-(t|x_0)=\delta\left(t-\frac{x_0}{v_-}\right)e^{-f_-t}+\mathcal{H}\left(t-\frac{x_0}{v_-}\right)\frac{2f_+f_-}{v_++v_-}\frac{x_0}{\sqrt{z_+^0z_-^0}}\times e^{-(z_+^0+z_-^0)/2}I_1(\sqrt{z_+^0z_-^0}),\tag{3.13b}$$

where we have defined the dimensionless variables

$$z_+^0=\frac{2f_-}{v_++v_-}(v_+t+x_0),\tag{3.14a}$$

$$z_-^0=\frac{2f_+}{v_++v_-}(v_-t-x_0).\tag{3.14b}$$

Equations (3.13a) and (3.13b) represent the generalization of expressions previously derived in Ref. [8]. Note that as a direct reading of the boundary condition in Eq. (3.2), $F_-(t|0)=\delta(t)$ while $F_+(t|0)\neq\delta(t)$, meaning that the mean first passage time or the lifetime of a MT starting at the nucleating site with an outgoing velocity is nonzero.

The mean first passage times can be obtained from the relation in Eq. (3.10) as $\tau_\pm(x_0)=\hat{S}_\pm(0|x_0)$. By taking the $s\to0$ limit in Eqs. (3.8a) and (3.8a) we end up with the expressions

$$\tau_+(x_0)=-\frac{x_0}{V}-\frac{v_++v_-}{\omega V},\tag{3.15a}$$

$$\tau_-(x_0)=-\frac{x_0}{V}.\tag{3.15b}$$

Similar expressions were previously derived by Rubin [9] using a clever but complicated derivation based on the discrete two-phase model of dynamic instability proposed by Hill [3]. These times decrease when the velocity gets larger and diverge at $V=0$. Note that $\tau_+(0)\to1/f_+$ as $v_-\to\infty$ and $\tau_+(0)\to0$ as $f_+\to\infty$. In averaging next these lifetimes over the initial equilibrium velocity, we obtain the overall mean lifetime $\tau(x_0)$ to $x=0$ as

$$\tau(x_0)=g_-(\infty)\tau_-(x_0)+g_+(\infty)\tau_+(x_0)=-\frac{x_0}{V}-\frac{(v_++v_-)f_-}{\omega^2V}.\tag{3.16}$$

B. Unbounded regime $V>0$

Since now $\epsilon_\pm(x_0)=S_\pm(\infty|x_0)\neq0$, direct application of the relation in Eq. (3.11) straightforwardly leads to

$$\hat{F}_+(s|x_0)=\left[\frac{v_+(s+f_-+v_-q_2)}{v_-f_+}\right]\exp\left\{\left(\frac{V}{D}+q_2\right)x_0\right\},\tag{3.17a}$$

$$\hat{F}_-(s|x_0)=\exp\left\{\left(\frac{V}{D}+q_2\right)x_0\right\}.\tag{3.17b}$$

The time-dependent $F_+(t|x_0)$ and $F_-(t|x_0)$ are then obtained by multiplying Eqs. (3.13a) and (3.13b) by $(v_+f_-/v_-f_+)\exp(Vx_0/D)$ and $\exp(Vx_0/D)$, respectively. As above, we still have $F_-(t|0)=\delta(t)$ and $F_+(t|0)\neq\delta(t)$. Deriving Eqs. (3.17a) and (3.17b) with respect to s and taking the $s\to0$ limit, we obtain the expressions for the conditional mean first passage times as

$$\tau_+(x_0)=\left(\frac{1}{V}+\frac{\Delta v}{\omega D}\right)x_0+\frac{v_++v_-}{\omega V},\tag{3.18a}$$

$$\tau_-(x_0)=\left(\frac{1}{V}+\frac{\Delta v}{\omega D}\right)x_0.\tag{3.18b}$$

Except for the additional term $\Delta v/\omega D$ in these formulas, we see that both the ordinary and conditional mean first passage times are identical. Depending on the sign of Δv, it is possible for $|V|$ fixed to find a set of parameters $v_\pm$ and $f_\pm$ such that the conditional mean first passage times in the unbounded regime ($V>0$) are smaller or greater than the mean first passage times in the bounded regime ($V\leqslant0$); the equality in both regimes holding for $\Delta v=0$, i.e., $v_+=v_-$.

As above, the overall mean relaxation time is obtained in averaging these times over the equilibrium velocity distribution. We get

$$\tau(x_0)=\left(\frac{1}{V}+\frac{\Delta v}{\omega D}\right)x_0+\frac{(v_++v_-)f_-}{\omega^2V}.\tag{3.19}$$

IV. REDUCED GREEN'S FUNCTIONS AND MOMENTS

In practice one is often interested in following a MT prepared in the state where the initial velocity is chosen from the equilibrium velocity distribution, that is to say, that at $t=0$ the MT is in the state + with the probability $g_+(\infty)$ and in the state − with the probability $g_-(\infty)$. The reduced Green's function is then defined as

$$P_i(x,t|x_0)=\sum_j g_j(\infty)\Pi_{ij}(x,t|x_0),\tag{4.1}$$

where $P_i(x,t|x_0)$ denotes now the probability density that a MT initially of length x_0 will be found in phase i with length x at the time t later. Denoting next by $P(x,t|x_0)=P_+(x,t|x_0)+P_-(x,t|x_0)$ the probability density that at time t the MT free end is found at x given that it was initially at x_0, we have

$$P(x,t|x_0)=\frac{f_-}{\omega}[\Pi_{++}(x,t|x_0)+\Pi_{-+}(x,t|x_0)]+\frac{f_+}{\omega}[\Pi_{+-}(x,t|x_0)+\Pi_{--}(x,t|x_0)].\tag{4.2}$$

$P(x,t|x_0)$ satisfies the same telegrapher's equation that P_i and Π_{ij} do, i.e., Eq. (2.8), but with the initial conditions

$$P(x,t=0|x_0)=\delta(x-x_0),\tag{4.3a}$$

$$\left.\frac{\partial P}{\partial t}\right|_{t=0}=-V\frac{\partial}{\partial x}\delta(x-x_0).\tag{4.3b}$$

We may investigate the possibility of an equilibrium distribution that we denote by $P_{\rm eq}(x)$. Eliminating all time derivatives of P in Eq. (2.8) yields

$$D\frac{\partial^2 P_{\rm eq}}{\partial x^2}-V\frac{\partial P_{\rm eq}}{\partial x}=0. \tag{4.4}$$

To emphasize the one-to-one relation between x and the MT length, we can, without loss of generality, restrict x to take only positive values. This differential equation is easily solved with the conditions that the equilibrium distribution is bounded, i.e., $\lim_{x\to\infty}P_{\rm eq}(x)=0$, and the probability density is conserved, i.e., $\int_0^\infty P_{\rm eq}(x)dx=1$, or equivalently, in using the reflecting boundary condition in Eq. (2.35) for $a=0$. One finds that in the unlimited regime (i.e., $V\geqslant 0$) the equilibrium distribution does not exist, while in the bounded regime (i.e., $V<0$) the steady-state length distribution is an exponential given by:

$$P_{\rm eq}(x)=l^{-1}e^{-x/l}, \tag{4.5a}$$

$$l=-\frac{D}{V}=\frac{v_+v_-}{v_-f_+-v_+f_-}, \tag{4.5b}$$

where l is the average MT length that diverges at the threshold $V=0$, i.e., when $v_-f_+=v_+f_-$.

The statistics of the MT dynamics can also be characterized from the various moments of x, in particular their dependence on time t. The moments are defined as

$$m_n(t)=\int_{-\infty}^{\infty}(x-x_0)^nP(x,t|x_0)dx \tag{4.6}$$

plus the relations

$$\int_{-\infty}^{\infty}(x-x_0)^n\frac{\partial P}{\partial x}dx=-nm_{n-1}(t), \tag{4.7a}$$

$$\int_{-\infty}^{\infty}(x-x_0)^n\frac{\partial^2 P}{\partial x^2}dx=n(n-1)m_{n-1}(t). \tag{4.7b}$$

All moments can be obtained from the Laplace transform of Eq. (2.8) by multiplying by $(x-x_0)^n$ and integrating over x from $-\infty$ to ∞. We get for $n=0$ and $n=1$:

$$\hat{m}_0(s)=\frac{1}{s}\Leftrightarrow m_0(t)=1, \tag{4.8a}$$

$$\hat{m}_1(s)=\frac{V}{s^2}\Leftrightarrow m_1(t)=Vt, \tag{4.8b}$$

and for $n\geqslant 2$ the moments are given by the recurrence

$$\hat{m}_n(s)=\frac{s\Delta v+\omega V}{s(s+\omega)}n\hat{m}_{n-1}(s)+\frac{\omega D}{s(s+\omega)}n(n-1)\hat{m}_{n-2}(s) \tag{4.8c}$$

From an experimental standpoint, the most accessible quantity for any random walk process is the mean-square displacement

$$\langle\Delta x^2(t)\rangle=m_2(t)-[m_1(t)]^2=2D_{\rm app}\left\{t-\frac{1}{\omega}(1-e^{-\omega t})\right\} \tag{4.9a}$$

$$\simeq\begin{cases}\omega D_{\rm app}t^2 & \text{for } \omega t\ll 1\\ 2D_{\rm app}t & \text{for } \omega t\gg 1,\end{cases} \tag{4.9b}$$

in which we have introduced the apparent diffusion coefficient defined by

$$D_{\rm app}=D-\frac{V^2}{\omega}\left[1-\frac{\Delta v}{V}\right]=\frac{f_+f_-(v_++v_-)^2}{\omega^3}. \tag{4.10}$$

This expression of $\langle\Delta x^2(t)\rangle$ is very similar to the one we obtain for the classical Brownian motion. For small time scales compared to the velocity relaxation time ω^{-1}, $\langle\Delta x^2(t)\rangle\sim t^2$, which is characteristic of deterministic motion or a wave propagation process, and for large time scale, $\langle\Delta x^2(t)\rangle\sim t$, which is characteristic of Brownian diffusion process with the diffusion coefficient $D_{\rm app}$. The latter is the diffusion coefficient we will determine from the standard deviation based experiments. Due to the difference both in speeds v_- and v_+ and in frequencies f_- and f_+, the MT free end appears to diffuse with a smaller diffusion coefficient $D_{\rm app}\leqslant D$. This apparent diffusion coefficient, previously obtained by Dogterom and Leibler [2] as being the effective diffusion coefficient, reduces to D at the threshold $V=0$ or in the diffusion limit $\omega\to\infty$. All of this suggests the possibility to approximate the dynamic instability (or telegraph) process by a simple diffusion process. It worthwhile to note, however, that the difference between D and $D_{\rm app}$ indicates that taking the $t\to\infty$ limit (as in the usual telegraph process) in dynamic instability expressions does not lead to the correct diffusion limit.

V. DIFFUSION LIMIT OF THE DYNAMIC INSTABILITY

In order to gain more insight into the diffusion limit of the dynamic instability process, we focus again on the probability $P(x,t)=P_+(x,t)+P_-(x,t)$ that the MT free end is at x at time t and we consider in addition the probability flux, $J(x,t)=v_+P_+(x,t)-v_-P_-(x,t)$. From Eq. (2.1a) one can show that

$$\frac{\partial P}{\partial t}+\frac{\partial J}{\partial x}=0, \tag{5.1a}$$

$$\frac{\partial J}{\partial t}+\Delta v\frac{\partial J}{\partial x}+\omega J=-\omega D\frac{\partial P}{\partial x}+\omega VP. \tag{5.1b}$$

In combining together these equations, one can easily show that both $P(x,t)$ and $J(x,t)$ satisfy the same telegrapher's equation in Eq. (2.8). Equation (5.1a) expresses the conservation of the total probability density and Eq. (5.1b) describes the evolution of the probability flux. The integrated form of Eq. (5.1b) can be written as

$$J(x,t)=e^{-\omega t}J(x-\Delta v t,0)+\int_{-\infty}^{\infty}dx'\int_0^t dt' \times \delta[x-x'-\Delta v(t-t')]\omega e^{-\omega(t-t')} \times\left[-D\frac{\partial P}{\partial x'}+VP(x',t')\right]. \quad (5.2)$$

Using the fact that $\omega e^{-\omega(t-t')}\rightarrow\delta(t-t')$ as $\omega\rightarrow\infty$, it is easy show that

$$\lim_{\omega\rightarrow\infty}J(x,t)=\int_{-\infty}^{\infty}dx'\int_0^{\infty}dt'\,\delta(t-t')\,\delta(x-x') \times\left[-D\frac{\partial P}{\partial x'}+VP(x',t')\right] =-D\frac{\partial P}{\partial x}+VP(x,t), \quad (5.3)$$

which gives Fick's first law in the presence of a drift. This limit is the exact analog of the overdamped limit of the conventional Brownian motion. Combining Eqs. (5.1a) and (5.3) leads to the diffusion equation (also known as the Wiener process)

$$\frac{\partial P}{\partial t}=D\frac{\partial^2 P}{\partial x^2}-V\frac{\partial P}{\partial x}. \quad (5.4)$$

It is worthwhile to emphasize that the dynamic instability (or the telegraph process) is a velocity jump process in which the MT free end moves in a deterministic motion with a velocity randomly switching between two values according to a Poisson process, whereas its approximating diffusion process is a position jump process in which the MT stochastically moves from one position to another with the density distribution $\phi(t)$ for pausing time between jumps also governed by a Poisson process, i.e., $\phi(t)=\omega e^{-\omega t}$. Equivalently, Eq. (5.4) describes the evolution of the state variable $x(t)$ obeying the dynamical equation

$$\frac{dx}{dt}=V+\zeta(t), \quad (5.5)$$

where $\zeta(t)$ is the Gaussian stochastic velocity of mean zero and variance $\langle\zeta(t)\zeta(t')\rangle=2D\delta(t-t')$.

A. Restricted Green's function

The differential equation (5.4) is easier to use than Eq. (2.8) and it can be solved explicitly. One of the interesting situation for MTs corresponds to the case where x is restricted to the subspace $x\geqslant 0$ by imposing the reflecting boundary condition at $x=0$, i.e.,

$$\left.\left(D\frac{\partial P}{\partial x}-VP\right)\right|_{x=0}=0. \quad (5.6)$$

Thus, with the initial condition $P(x,t=0|x_0)=\delta(x-x_0)$, the solution of Eq. (5.4) is given by [10]

$$P(x,t|x_0)=\frac{1}{(4\pi Dt)^{1/2}}\left\{\exp\left[-\frac{(x-x_0-Vt)^2}{4Dt}\right]+\exp\left[-\frac{Vx_0}{D}\right]\exp\left[-\frac{(x+x_0-Vt)^2}{4Dt}\right]\right\} -\frac{V}{2D}\exp\left[\frac{Vx}{D}\right]\mathrm{erfc}\left[\frac{x+x_0+Vt}{\sqrt{4Dt}}\right], \quad (5.7)$$

where erfc[ ] is the complementary error function. Letting $t\rightarrow\infty$, we find that for $V\geqslant 0$, $P(x,t|x_0)\rightarrow 0$ as $t\rightarrow\infty$, whereas for $V<0$, $P(x,t\rightarrow\infty|x_0)=P_{\mathrm{eq}}(x)$, where the equilibrium distribution $P_{\mathrm{eq}}(x)$ is given by Eq. (4.5a).

B. The catastrophe time distribution

Another interesting quantity to determine is the density distribution of catastrophe time, i.e., the time at which a MT initially of length $x=x_0$ disappears for the first time in reaching the nucleating site at $x=0$. The mean catastrophe time is something like the mean lifetime of a MT or the mean first passage time to $x=0$ as discussed earlier in Sec. III In this respect, the catastrophe time distribution is identical to the first passage time distribution. Here we derive similar expressions for the survival probability, the first passage time distribution, and the mean first passage time in the diffusion limit. Thus $S(t|x_0)$ denotes the survival probability that a MT initially of length $x=x_0$ is still in the system at time t in the presence of the absorbing nucleating site at $x=0$. The catastrophe time distribution $F(t|x_0)$ is, for $V\leqslant 0$, the first passage time distribution to $x=0$ for an original MT of length $x=x_0$ and, for $V>0$, it is the conditional first passage time distribution that a MT starting out at x_0 has reached the origin $x=0$. Both $S(t|x_0)$ and $F(t|x_0)$ are related by the same relations in Eq. (3.11) (without the index $\pm$). In order to determine $S(t|x_0)$ we have to solve first Eq. (5.4) with the initial condition $P(x,t=0|x_0)=\delta(x-x_0)$ and subjected to the absorbing boundary condition at $x=0$, that is to say, $P(x,t|x_0)=0$ for x or $x_0=0$ (here the forward and adjoint boundary conditions are the same). With these conditions the solution of Eq. (5.4) is given by

$$P(x,t|x_0)=\frac{1}{(4\pi Dt)^{1/2}}\left\{\exp\left[-\frac{(x-x_0-Vt)^2}{4Dt}\right]-\exp\left[-\frac{Vx_0}{D}\right]\exp\left[-\frac{(x+x_0-Vt)^2}{4Dt}\right]\right\}. \quad (5.8)$$

The survival probability is therefore obtained by integrating Eq. (5.8) over x from 0 to ∞ as

$$S(t|x_0)=\int_0^{\infty}P(x,t|x_0)dx=\frac{1}{2}\mathrm{erfc}\left[\frac{-x_0-Vt}{\sqrt{4Dt}}\right]-\frac{1}{2}\exp\left[-\frac{Vx_0}{D}\right]\mathrm{erfc}\left[\frac{x_0-Vt}{\sqrt{4Dt}}\right]. \quad (5.9)$$

As discussed above, we may consider the escape probability that is obtained by taking the $t\to\infty$ limit in Eq. (5.9). We find

$$\epsilon(x_0)=\begin{cases}0, & V\leqslant 0\\ 1-\exp\left\{-\dfrac{Vx_0}{D}\right\}, & V>0.\end{cases} \tag{5.10}$$

This indicates that for $V>0$ catastrophe events are so rare that a MT has a certain probability of persisting in the system without touching the nucleating site, while for $V\leqslant 0$, $\epsilon(x_0)=0$, showing that a MT will surely collapse to $x=0$.

Using next Eq. (5.9) in the time derivative relation in Eq. (3.11), we get the catastrophe time distribution as

$$F(t|x_0)=\frac{x_0}{(4\pi Dt^3)^{1/2}}\exp\left[-\frac{(x_0-Vt)^2}{4Dt}\right]\times\begin{cases}1, & V\leqslant 0\\ \exp\left\{\dfrac{Vx_0}{D}\right\}, & V>0,\end{cases} \tag{5.11}$$

where the additional exponential term for $V>0$ take care of the normalization to one of $F(t|x_0)$. This expression represents the diffusion limit of Eqs. (3.13a) and (3.13b) for $V\leqslant 0$ and their analogous for $V>0$. For a time t fixed, $F(t|x_0)$ follows a shifted Wigner distribution (except for the additional exponential term for $V>0$) as a function of initial MT length. At the transition threshold $V=0$, $F(t|x_0)$ scales with time as a power law, $F(t|x_0)\sim t^{-3/2}$ for larger t, so that the catastrophe time distribution has no finite moments. When the diffusion is biased, i.e., $V\neq 0$, the distribution $F(t|x_0)$ has an exponential shoulder as $F(t|x_0)\sim t^{-3/2}e^{-t/\tau_c}$. The power law breaks down at about $t=\tau_c$, where τ_c is the cutoff time scale at which the drift term and the diffusive term are comparable, namely, $V\tau_c\sim\sqrt{D\tau_c}$. The precise expression of the cutoff time τ_c, obtained from Eq. (5.11), is

$$\tau_c=\frac{4D}{V^2}. \tag{5.12}$$

As a consequence of the limitation to the power law, the moments of the catastrophe time distribution are now finite. For that purpose, it is convenient to work with the Laplace transformed expression of $S(t|x_0)$:

$$\hat{S}(s|x_0)=\frac{1}{s}\left[1-\exp\left\{-\left(\frac{V+\sqrt{V^2+4Ds}}{2D}\right)x_0\right\}\right]. \tag{5.13}$$

By using this expression in Eq. (3.10), we find that the mean catastrophe time (equal to the mean first passage time to the nucleating site for the regime $V\leqslant 0$ or equal the conditional mean first passage time to the nucleating site for the regime $V>0$), denoted by $\tau_d(x_0)$, is simply given by

$$\tau_d(x_0)=\frac{x_0}{|V|}. \tag{5.14}$$

This manifestly shows that the time area under $S(t|x_0)$ in the the regime $V\leqslant 0$ (i.e., the mean first passage time to the nucleating site) is exactly identical to the time area comprised between $S(t|x_0)$ and the line $1-S(\infty|x_0)$ for $V>0$ (i.e., the conditional mean first passage time to the nucleating site). Notice that $\tau_d(x_0)$ corresponds to the diffusion limit, i.e., $\omega\to\infty$, of the mean lifetimes $\tau(x_0)$ given in Eqs. (3.16) and (3.19). It may be instructive to remark that the functional form of $F(t|x_0)$ is also found in other dynamical systems, for example, for the distribution of laminar phase duration in the on-off intermittency [11] and for the distribution of the size of the avalanche in the self-organized criticality [12].

In some instances, the dynamic instability of MTs can be seen as an example of the on-off intermittency if we identify the laminar phases to the elapsed times during which a MT has not yet touched the nucleating site. Note also that during the ''MT laminar phases'' the MT undergoes stochastic motion (governed by the telegraph process) like the on-off intermittency observable (which can undergo chaotic motion) does.

The term self-organized criticality was proposed [13] to refer to a generic state of driven systems that, evolving towards that state, may respond to a minor solicitation by a hierarchy of chain reactions that can propagate to an arbitrary subset of the system throughout the entire system. Such a concept can manifestly be used to characterize the dynamics of a MT, which, for any original length, can abruptly shrink to zero due to a catastrophe event or escape from zero thanks to a rescue event. Moreover, the connection between the dynamic instability of MTs and the self-organized criticality is supported by the possibility of mapping the avalanche propagation onto a random walk or a diffusion process.

VI. CONCLUDING REMARKS

Fractional Brownian motion was introduced by Mandelbrot and Van Ness [14] as a generalization to a conventional Brownian motion so as to describe long-range correlated random walks. A particle undergoing such a kind of motion has a variance scaling with time like $\langle\Delta x^2(t)\rangle\sim t^{2H}$, where H is the Hurst exponent [15] such that $0<H<1$. The essential feature of the fractional Brownian motion is the manifestation of persistent and antipersistent trends in random walks with $H>1/2$ and $H<1/2$, respectively. By persistent we mean that an increase (a decrease) trend in the past tends on the average to be followed by an increase (a decrease) trend in the future, while the term antipersistent denotes the situation where an increase trend is followed by a decreasing one and vice versa. $H=1/2$ corresponds to the ordinary Brownian motion with independent steps of the walker.

It is obvious from the foregoing analysis that MTs undergo persistent random walks. Indeed, a MT initially in the growing phase will persist in that phase, but once it begins shrinking, it will continue to shrink. One would then be tempted to conclude that the dynamic instability of a MT is similar to a fractional Brownian motion with $H>1/2$. Meanwhile, this is not so since both the mean-square displacement of the MT given in Eq. (4.9b) and the catastrophe time distribution in Eq. (5.11) lead to a Hurst exponent of $H=1/2$ as for an ordinary Brownian motion. The similarity between the dynamic instability and the fractional Brownian motion is only qualitative. In fact, the persistent nature of the MT dynamics originates from its underlying persistent random walk in which one is given the probabilities of moving either in the same direction or in the reverse direction of the immediately preceding step. Such a process can be regarded as a two-step correlated random walk. The persistence of MT motions is also evidenced in the diffusion limit where the MT dynamics is analogous to that of a particle diffusing in a linear potential, namely, $U(x)=-V|x|$ [see, for example, Eq. (5.5)], where V is the steady-state velocity of a MT. Since in the absence of the diffusion the particle always moves in such a way as to minimize $U(x)$, we clearly see why an equilibrium distribution of MT lengths holds only when $V<0$, i.e., when the point $x=0$ is attractive.

In the meantime we have to note that since velocity switches are Poisson processes (or first-order kinetics) with constant frequencies, a MT is equally likely to undergo catastrophe and rescue events at any time, regardless of how long it has been growing or shrinking. The dynamic instability discussed here is then Markovian. However, it is possible that the MT dynamics exhibits memory effects. This may occur, for example, when the catastrophe frequency becomes a function of time depending on how long the MT has been growing [16,17]. Such a behavior can be modeled by considering, for example, non-first-order kinetics for the velocity transitions. It will be interesting to conduct similar studies as done above for such non-Markovian dynamics.

On the other hand, the diffusion coefficient D and the steady-state velocity V (thereby v_+ and v_- as well as f_+ and f_-) may become space dependent due to a special distribution of free tubulins, hence making the problem nonlinear. Here also, studying nonlinear effects on the dynamic instability is of a great interest to address the question of self-organization of MTs. Finally, for practical concerns, the diffusion approximation of the dynamic instability outlined above can provide a possible framework for investigating the non-Markovian and nonlinear dynamics of microtubules.

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APPENDIX A: INVERSION OF THE LAPLACE TRANSFORM OF $\hat{\Pi}_{ij}(x,s|x_0)$

To illustrate how Laplace transformed Green's functions $\hat{\Pi}_{ij}(x,s|x_0)$ are inverted we consider $\hat{\Pi}_{++}(x,s|x_0)$ for $x<x_0$:

$$\hat{\Pi}_{++}(x,s|x_0)=\frac{s+f_- -\lambda_1 v_-}{\omega D(\lambda_1-\lambda_2)}e^{\lambda_1(x-x_0)}, \quad x<x_0. \tag{A1}$$

In rewriting the eigenvalues λ_1 and λ_2 as

$$\left.\begin{matrix}\lambda_1\\ \lambda_2\end{matrix}\right\}=\frac{\omega V+\Delta v s}{2\omega D}\pm\left(\frac{v_+ + v_-}{2v_+v_-}\right)\sqrt{(s+b_1)(s+b_2)}, \tag{A2}$$

with

$$\left.\begin{matrix}b_1\\ b_2\end{matrix}\right\}=\frac{v_+f_- + v_-f_+\pm 2\sqrt{v_+v_-f_+f_-}}{v_+ + v_-}, \tag{A3}$$

$\hat{\Pi}_{++}(x,s|x_0)$ becomes

$$\hat{\Pi}_{++}(x,s|x_0)=\frac{e^{V(x-x_0)/2D}}{2v_+(v_+ + v_-)}\Bigg\{-(v_+ + v_-)e^{-ys}\times e^{-a\sqrt{(s+b_1)(s+b_2)}}+[(v_+f_- + v_-f_+)+(v_+ + v_-)s]e^{-ys}\frac{e^{-a\sqrt{(s+b_1)(s+b_2)}}}{\sqrt{(s+b_1)(s+b_2)}}\Bigg\}, \tag{A4}$$

where

$$a=\left(\frac{v_+ + v_-}{2v_+v_-}\right)(x_0-x), \tag{A5}$$

$$y=\frac{\Delta v}{2D\omega}(x_0-x). \tag{A6}$$

Next denoting by $p(t)=\mathcal{L}^{-1}[\hat{p}(s)]$ the inverse Laplace transform, we have

$$\mathcal{L}^{-1}[e^{-ys}]=\delta(t-y), \tag{A7}$$

$$\mathcal{L}^{-1}[se^{-ys}]=-\frac{\partial}{\partial y}\mathcal{L}^{-1}[e^{-ys}]=-\frac{\partial}{\partial y}\delta(t-y), \tag{A8}$$

$$\mathcal{L}^{-1}\left[\frac{e^{-a\sqrt{(s+b_1)(s+b_2)}}}{\sqrt{(s+b_1)(s+b_2)}}\right]=\mathcal{H}(t-a)e^{-(b_1+b_2)t/2}I_0\left(\frac{b_1-b_2}{2}\sqrt{t^2-a^2}\right), \tag{A9}$$

$$\mathcal{L}^{-1}[e^{-a\sqrt{(s+b_1)(s+b_2)}}]=-\frac{\partial}{\partial a}\mathcal{L}^{-1}\left[\frac{e^{-a\sqrt{(s+b_1)(s+b_2)}}}{\sqrt{(s+b_1)(s+b_2)}}\right]=\delta(t-a)e^{-(b_1+b_2)a/2}+\mathcal{H}(t-a)\frac{a(b_1-b_2)}{2\sqrt{t^2-a^2}}\times e^{-(b_1+b_2)t/2}I_1\left(\frac{b_1-b_2}{2}\sqrt{t^2-a^2}\right), \tag{A10}$$

where $I_0(\ )$ and $I_1(\ )$ are the modified Bessel functions of order zero and one, respectively, and the formula in Eq. (A9) is obtained from Ref. [18]. Using Eqs. (A7)–(A10), one obtains $\Pi_{++}(x,t|x_0)$ for $x<x_0$ as

$$\Pi_{++}(x,t|x_0) = \mathcal{H}(t-y)\mathcal{H}(t-y-a)e^{-(b_1+b_2)(t-y)/2}e^{V(x-x_0)/2D} \times\frac{b_1-b_2}{2v_+}\left[\frac{t-y-a}{t-y+a}\right]^{1/2} I_1\left(\frac{b_1-b_2}{2}\sqrt{(t-y)^2-a^2}\right). \tag{A11}$$

After some rearrangements, we find

$$\Pi_{++}(x,t|x_0)=\mathcal{H}\left(t+\frac{x-x_0}{v_-}\right)\frac{f_-}{v_++v_-}\left(\frac{z_-}{z_+}\right)^{1/2} \times e^{(z_++z_-)/2}I_1(\sqrt{z_+z_-}), \tag{A12}$$

where z_- and z_+ are defined in Sec. II. All Green's functions $\Pi_{ij}(x,t|x_0)$ are determined in this way.

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