Properties of the generalized master equation: Green's functions and probability density functions in the path representation

Ophir Flomenbom and Robert J. Silbey
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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The Green's function for the master equation and the generalized master equation in path representation is an infinite sum over the length of path probability density functions (PDFs). In this paper, the properties of path PDFs are studied both qualitatively and quantitatively. The results are used in building efficient approximations for Green's function in 1D, and are relevant in modeling and in data analysis. © *2007 American Institute of Physics*.
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I. INTRODUCTION

Random walks in one-dimensional (1D) lattices appear in the description of a wide variety of problems in biology, chemistry, and physics.[1–15] In the evolving field of single molecules,[16–38] the data are made from stochastic events, and random walks constitute the adequate description for its modeling. Examples include enzymatic activity,[30–32] conformational changes of biopolymers,[26–29] dynamics of ion channels,[18–20] and motor proteins.[23–25] In some of these examples, 1D random walks are used.

Formulation of a Markovian random walk is conventionally made in terms of the master equation.[1–5,14] When the random walk has nonexponential waiting time probability density functions (WT-PDFs), the generalized master equation[10,11] (GME) is used. A random walk that obeys the GME is equivalent to a continuous time random walk[6–9] and has a corresponding path representation.[12,13] Analytical and numerical results of random walks in 1D lattices can be found in books[1–7] and in papers.[8–15] For the single molecule measurements mentioned above, the modeling and the analysis of the data are usually done in terms of the master equation and GME.[39–73]

Recent works showed that the path representation of the Green's function of the GME can provide interesting and useful new results.[12,13] Particularly, closed-form solutions for Green's functions in arbitrarily inhomogeneous 1D chains were given by using the path representation of the Green's function. This paper uses the same path representation of the Green's function but studies paths PDFs. Path PDFs supply more information on the dynamics than the information contained in the Green's function of the process. Path PDFs are useful in analytical studies of the GME, in modeling, in data analysis, and in building approximations for the Green's function. The analysis in this paper qualitatively tracks the origin of path PDFs and also quantifies it. Then, asymptotic analysis of path PDFs allows the construction of approximations for Green's functions in 1D. The main results in this paper include: (i) A path PDF is built from an ensemble of paths all have the same length, but which can differ in composition. (ii) A path PDF of order $2n$ is built from c^n paths, where c is smaller than the system length, but not smaller than two. (iii) A path PDF for an invariant chain is monopeaked in time. (iv) A path PDF contributes to the Green's function in the vicinity of its peak(s). (v) The Green's function at time t can be well approximated by a packet of $\sqrt{t}$ path PDFs.

The paper is laid out as follows: in Sec. II, the GME and the path representation of a general semi-Markovian random walk in 1D are introduced. The general closed-form solutions for Green's function of Refs. 12 and 13 are given and are used in expressing the Green's functions for related systems, such as circular chains. In Sec. III, we turn to simple examples and analyze path PDFs and Green's function for chains with a few states and for an invariant chain with L states. In Sec. IV, we conclude and discuss the use of our formalism and results in applications, and the extensions of our approximation scheme for the Green's function to higher dimensions.

II. THE GENERALIZED MASTER EQUATION AND THE PATH REPRESENTATION

A. The generalized master equation

This section presents the GME and the path representation of the Green's function. Then, the solution for the Green's function of Refs. 12 and 13 is given, and new results for related systems are obtained.

The most general semi-Markovian random walk in a 1D lattice of L states (a 1D random walk is one with only nearest neighbor transitions) is described by the state- and direction-dependent WT-PDFs, $\psi_{i\pm1i}(t)=\omega_{i\pm1i}\varphi_{i\pm1i}(t)$ for transitions between states i and $i\pm1$, with the normalization conditions $\int_0^\infty \varphi_{kj}(t)dt=1$ for all k and $\Sigma_k \omega_{kj}=1$, both valid for all j (Fig. 1). The system can also include state- and direction-dependent irreversible trapping WT-PDFs, $\psi_{Ii}(t)=\omega_{Ii}\varphi_{Ii}(t)$, with trap states $I=i+L$, $i=1,2,\ldots,L$. For any choice of the WT-PDFs, the stochastic trajectory generated by the dynamics consists of uncorrelated waiting times when each state has a distinct observable value.[39,41,43] This property, combined with the occurrence of the nonexponential distributed waiting times in the trajectory, defines (here) semi-

Markovian dynamics. The Green's function $G_{ij}(t;L)$ for semi-Markovian dynamics obeys the GME,[7,10,11]

$$\partial G_{ij}(t;L)/\partial t = -[K_{i+1i}(t) + K_{i-1i}(t)]^{*} G_{ij}(t;L) + K_{ii-1}(t)^{*} G_{i-1j}(t;L) + K_{ii+1}(t)^{*} G_{i+1j}(t;L) - K_{Ii}(t)^{*} G_{ij}(t;L), \quad i = 1, \ldots, L, \tag{1}$$

subject to the delta initial condition

$$\lim_{t\to 0} G_{ij}(t;L) = \delta_{ij}\delta(t).$$

Thus, $G_{ij}(t;L)$ gives the probability to occupy state i at time t given occupying state j at time 0. In Eq. (1),

$$f(t)^{*} g(t) = \int_0^t f(t-x)g(x)dx.$$

The so-called memory kernel $K_{ij}(t)$ is related in Laplace space ($\bar{g}(s)=\int_0^\infty g(t)e^{-st}dt$) to the WT-PDFs by

$$\bar{K}_{ij}(s) = \bar{\psi}_{ij}(s)/\bar{\Psi}_j(s),$$

where,

$$\bar{\Psi}_j(s) = \sum_k \bar{\Psi}_{kj}(s) = \left(1 - \sum_k \bar{\psi}_{kj}(s)\right)s^{-1}.$$

The GME, Eq. (1), can be written in matrix notation

$$\partial \mathbf{G}(t;L)/\partial t = \mathbf{K}(t)^{*}\mathbf{G}(t;L),$$

where Eq. (1) is recovered when taking the i,j element of the matrices in each side of the equality. The GME in Eq. (1) reduces to the Markovian master equation with a sink for exponential WT-PDFs, $\psi_{ij}(t)=a_{ij}e^{-a_j t}$, $a_j=\Sigma_k a_{kj}$ valid for any j, leading to delta kernels $K_{ij}(t)=a_{ij}\delta(t)$. Heavy tailed WT-PDFs with state- and direction-independent powers, $\psi_{ij}(t)\sim a_{ij}t^{-1-\beta}$, $0<\beta<1$ for all i and j, lead to the fractional master equation. For biophysical related systems, the GME in Eq. (1) was previously used in describing the dynamics of ion channels[51,52] and motor proteins.[47,48]

B. The path representation

A less familiar formulation of semi-Markovian random walks, but a very useful one, employs path PDFs for representing Green's functions. The path PDFs in this representation give detailed information on the random walk that is complementary to the information contained in the Green's function. Path PDFs are also the building blocks in approximations for Green's functions. In the current study, this aspect is utilized in Sec. III. The path representation of the Green's function is given by

$$G_{ij}(t;L) = \int_0^t \Psi_i(t-\tau)\sum_{n=0}^{\infty} w_{ij}(\tau, 2n+\gamma_{ij};L)d\tau. \tag{2}$$

The sum in the large parentheses defines $W_{ij}(t;L)$, which is the PDF of reaching state i exactly at time t when starting at state j exactly at time 0. In Eq. (2), $w_{ij}(t,2n+\gamma_{ij};L)$ is the path PDF of length $2n+\gamma_{ij}$ ($\gamma_{ij}=|i-j|$) that connects states $j\to i$ in time t. In this paper we analyze the $w_{ij}(t,2n+\gamma_{ij};L)$ or its convoluted counterpart

$$g_{ij}(t,2n+\gamma_{ij};L) = \int_0^t w_{ij}(\tau,2n+\gamma_{ij};L)\Psi_i(t-\tau)d\tau.$$

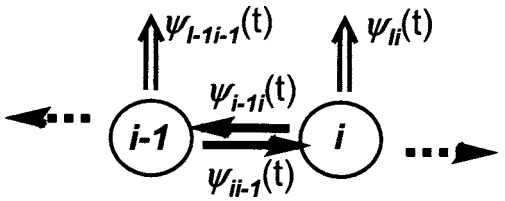

FIG. 1. A part of a semi-Markovian chain with only nearest neighbor transitions and directional WT-PDFs, $\psi_{i\pm 1i}(t)=\omega_{i\pm 1i}\varphi_{i\pm 1i}(t)$ and $\psi_{Ii}(t)=\omega_{Ii}\varphi_{Ii}(t)$. A way to simulate such a process is to first draw a random number out of a uniform density that determines the propagation direction according to the transition probabilities, and then to draw a random time out of the relevant WT-PDF.

C. General solutions for the Green's function for 1D chains

Although many results for random walks in 1D lattices appear in the literature,[1–15] only recently were closed-form solutions for the Green's function of a semi-Markovian random walk in an *arbitrarily inhomogeneous* 1D lattice of L states given.[12,13] The solutions were found using the path representation of the Green's function, Eq. (2). The solution for $\bar{G}_{ij}(s;L)$ in terms of the input WT-PDFs reads[12,13] in Laplace space

$$\bar{G}_{ij}(s;L) = \bar{\Gamma}_{ij}(s)\frac{\bar{\Phi}(s;\tilde{L})}{\bar{\Phi}(s;L)}\bar{\Psi}_i(s) \equiv \bar{W}_{ij}(s;L)\bar{\Psi}_i(s), \tag{3}$$

where $\tilde{L}=L-\gamma_{ij}$. In Eq. (3),

$$\bar{\Gamma}_{ij}(s) = \prod_{k=j}^{i\mp 1} \bar{\psi}_{k\pm 1k}(s), \quad i\neq j, \quad \bar{\Gamma}_{ii}(s) = 1, \tag{4}$$

is the path PDF of direct transitions connecting the initial and final states. [The plus (minus) sign in the WT-PDF state index in Eq. (4) corresponds to the case $i>j$ ($i<j$).] The factor $\bar{\Phi}(s;\tilde{L})/\bar{\Phi}(s;L)$ originates from all possible transitions between the initial and final states. $\bar{\Phi}(s;L)$ depends only on the system size L,

$$\bar{\Phi}(s;L) = 1 + \sum_{i=1}^{[L/2]} (-1)^i \bar{h}(s,i;L), \tag{5}$$

where $[L/2]$, which appears in the upper limit in the sum in Eq. (5), is the floor operation (round towards zero) [Eq. (1) is valid for $L>1$, where, $\bar{\Phi}(s;1)=1$], and

$$\bar{h}(s,i;L) = \prod_{j=1}^{i} \sum_{k_j=k_{i-1}+2}^{L-1-2(i-j)} \bar{\psi}_{k_j k_{j+1}}(s)\bar{\psi}_{k_j+1k_j}(s), \quad k_0 = -1. \tag{6}$$

$\bar{\Phi}(s;\tilde{L})$ in Eq. (3) has the same form as $\bar{\Phi}(s;L)$ but is calculated on the lattice $\tilde{L}$. Lattice $\tilde{L}$ is constructed from the origi-

nal lattice by removing the states i and j and the states between them, and connecting the obtained two fragments. The connection between the two fragments is virtual. Namely, the WT-PDFs in the interface between the two fragments are identical zero. Only such a lattice can be used to calculate the required quantity $\bar{\Phi}(s;\tilde{L})$ in Eq. (3). For cases in which a fragment has a single state, this fragment is excluded, and lattice $\tilde{L}$ contains just the longer fragment. When both fragments contain one state, $\bar{\Phi}(s;\tilde{L})=1$.

D. General solutions for related systems

The analytical solutions for the Laplace transform of the Green's function, Eqs. (3)–(6), are useful for analyzing many aspects of semi-Markovian random walks in 1D chains. Clearly, the Green's function in the time domain is obtained by inverting its Laplace transform back into the time domain, but Eqs. (3)–(6) are also useful in calculating moments and correlation functions. When the first passage time PDF $\bar{F}_{ij}(s;L)$ (exit through substrate i to trap I) is needed, we simply replace $\bar{\Psi}_i(s)$ in Eq. (3) with $\bar{\psi}_{Ii}(s)$. Simple combinations of Green's functions in Eqs. (3)–(6) give the Green's function for a random walk with a special WT-PDF for the first transition, the Green's functions for a random walk in a circular 1D chain, and joint PDFs in space and time with more than two pairs of conjugated (space-time) arguments. These combinations are given below.

(1) Green's function for a random walk with a special WT-PDF for the first transition. Consider a process with a special WT-PDF for the first event. Such a WT-PDF is denoted by a star. Also, the corresponding Green's function for such a process is denoted by a star. For example, $\psi^*_{j'j}(t)$ is a special WT-PDF for making the first transition in the process from state j to state j', and $\bar{G}^*_{ij}(s;L)$ is the corresponding Green's function. Special WT-PDFs for first events are used when the process has been taking place before the observation starts.[7] The Green's function $\bar{G}^*_{ij}(s;L)$ is given by a simple combination of the "standard" Green's functions $\bar{G}_{ik}(s;L)s$,

$$\bar{G}^*_{ij}(s;L)=\sum_k \bar{G}_{ik}(s;L)\bar{\psi}^*_{kj}(s)+\bar{\Psi}^*_j(s)\delta_{ij}, \tag{7}$$

where,

$$\bar{\Psi}^*_j(s)=\sum_k (1-\bar{\psi}^*_{kj}(s))s^{-1}.$$

Because after the first event took place the random walk is equivalent to a standard random walk, Eq (7) is originated from a simple factorization of a path into two segments, one segment contains the first transition, and the second segment contains all other transitions. The second additive in the Eq. (7) represents no transition.

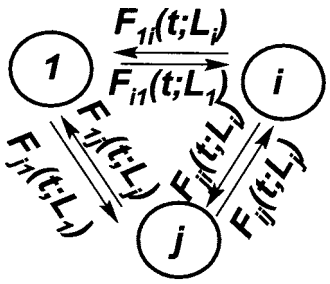

FIG. 2. A circular three-state chain. The system is characterized by the waiting time PDFs, here denoted by $F_{mn}(t;L_n)$, where $m,n=1,i,j$ and $m\neq n$.

(2) Green's functions for a random walk in a circular 1D chain. The second special case corresponds to a random walk in a circular 1D chain with L states. A circular chain is obtained from a linear L-state chain by connecting states 1 and L. We denote the Green's function for a circular 1D chain by substituting L with L^* in the Green's function chain length argument; so we write $\bar{G}_{ij}(s;L^*)$. $\bar{G}_{ij}(s;L^*)$ is calculated by a two-step mapping of the circular L-state chain to a two-state chain with correction. First, we construct from the circular L-state 1D chain, a circular three-state chain (Fig. 2). (In Fig. 2 and in the following discussion, $i<j$, without a loss of generality.) The WT-PDFs in the circular three-state chain are the first passage time PDFs calculated in linear 1D fragments taken out of the *original* circular chain. The fragments are made of the following states: states $j+1$ through $i-1$ consist the first fragment denoted by L_1, states 2 through $j-1$ consist the second fragment denoted by L_i, and states $i+1$ through L consist the third fragment denoted by L_j. The fragments correspond, respectively, to states 1, i, and j in the reduced circular three-state chain. The first passage time PDFs are found by modifying the expression in Eq. (3) and changing the sticking probability to the trapping WT-PDF. Using the above mapping and a second reduction scheme given below, $\bar{G}_{ij}(s;L^*)$ is given by

$$\bar{G}_{ij}(s;L^*)=\frac{\bar{\zeta}_{(1i)j}(s)}{1-\bar{\phi}_+(s)\bar{\phi}_-(s)}\bar{\Psi}_i(s). \tag{8}$$

Equation (8) results from a second mapping of the circular three-state chain into a two-state chain with correction. This is captured by the factor $(1-\bar{\phi}_+(s)\bar{\phi}_-(s))^{-1}$, where $\bar{\phi}_+(s)$ and $\bar{\phi}_-(s)$ in Eq. (8) are given by

$$\bar{\phi}_+(s)=\bar{F}_{1j}(s;L_j)+\bar{F}_{ij}(s;L_j)$$

and

$$\bar{\phi}_-(s)=\frac{\bar{F}_{1j}(0;L_j)(\bar{F}_{j1}(s;L_1)+\bar{F}_{i1}(s;L_1)\bar{F}_{ji}(s;L_i))+\bar{F}_{ij}(0;L_j)(\bar{F}_{ji}(s;L_i)+\bar{F}_{1i}(s;L_i)\bar{F}_{j1}(s;L_1))}{1-\bar{F}_{i1}(s;L_1)\bar{F}_{1i}(s;L_i)}.$$

Namely, state + corresponds to the initial state j, and state − is made from the states 1 and i. However, this mapping of the circular three-state chain into a two-state chain is an imperfect one. This fact is represented by the correction factor $\bar{\zeta}_{(1i)j}(s)$ and is the reason that we first mapped the circular L-state chain onto a circular three-state chain. $\bar{\zeta}_{(1i)j}(s)$ in Eq. (8) is given by

$$\bar{\zeta}_{(1i)j}(s) = \frac{\bar{F}_{ij}(s;L_j) + \bar{F}_{1j}(s;L_j)\bar{F}_{i1}(s;L_1)}{1 - \bar{F}_{i1}(s;L_1)\bar{F}_{1i}(s;L_i)}$$

and contains information on internal transitions in state −. Note that the Green's function for a circular L-state chain with a special WT-PDF for the first event, $\bar{G}^*_{ij}(s;L^*)$, is nothing but

$$\bar{G}^*_{ij}(s;L^*) = \sum_k \bar{G}_{ik}(s;L^*)\bar{\psi}^*_{kj}(s) + \bar{\Psi}^*_j(s)\delta_{ij}. \tag{9}$$

A circular 1D chain has been used to describe motor proteins activity.[49] The results of this section can be a starting point for a more general treatment of such systems.

(3) Joint PDFs in space and time with more than two pairs of conjugated (space-time) arguments. For semi-Markovian random walks, PDFs of joint space-time arguments with more than two argument pairs are also given by combinations of Green's functions. We focus on the three space-time variable pairs PDF, $G_{kji}(t+\tau+t_0, t+t_0|t_0;L)$, which is the PDF for occupying state k at time $t+\tau+t_0$ and state j at time $t+t_0$, given that the random walk started at state i exactly at time t_0. In what follows we take $t_0=0$, suppress the initial time argument, and write explicitly only the elapsed time in the third time argument. Thus, we compactly write $G_{kji}(\tau,t;L)$. The double Laplace transform of $G_{kji}(\tau,t;L)$ ($\tau\to u$ and $t\to s$) is given by simple combinations of the Green's function in Eq. (3),

$$\hat{\bar{G}}_{kji}(u,s;L) = \bar{W}_{ji}(s;L)\sum_z \hat{\bar{A}}_{zj}(u,s)\hat{G}_{kz}(u;L), \tag{10}$$

where z is any state that is directly connected to state j. In Eq. (10), we introduce the double Laplace transform of the "adaptor" function[12]

$$\hat{\bar{A}}_{n'n}(u,s) = \frac{\bar{\psi}_{n'n}(s) - \hat{\psi}_{n'n}(u)}{u-s},$$

for a transition between state n and state n'. $\hat{\bar{A}}_{n'n}(u,s)$ is the double Laplace transform of the joint backward and forward recurrence time PDFs. For occupying state n at time t, the backward recurrence time is the time elapsed from the last transition into state n, and the forward recurrence time is the time that will pass until a transition from state n will take place. Each of these times has a corresponding PDF. The adaptor function is thus the joint PDF of the backward and forward recurrence time PDFs. Only for the Markovian case, $\hat{\bar{A}}_{n'n}(u,s)=\bar{\Psi}_n(s)\hat{\psi}_{n'n}(u)$, leading to the well-known factorization of higher order propagators for Markovian processes into a product of Green's functions. Note that for a random walk with a special initial WT-PDF, $\hat{\bar{G}}^*_{kji}(u,s;L)$ is obtained from Eq. (10) when replacing $\bar{W}_{ji}(s;L)$ by $\bar{W}^*_{ij}(s;L)$, where $\bar{W}^*_{ij}(s;L)$ is obtained from Eq. (7) with $\bar{G}^*_{ij}(s;L) = \bar{W}^*_{ij}(s;L)\bar{\Psi}_i(s)$. For the circular L-state chain, $\hat{\bar{G}}_{kji}(\tau,t;L^*)$ is also obtained from Eq. (10) when replacing $\bar{W}_{ji}(s;L)$ by $\bar{W}_{ji}(s;L^*)$ and $\hat{G}_{kj-1}(u;L)$ by $\hat{G}_{kj-1}(u;L^*)$, where $\bar{W}_{ji}(s;L^*)$ is obtained from Eq. (8), with $\bar{G}_{ij}(s;L^*)=\bar{W}_{ij}(s;L^*)\bar{\Psi}_i(s)$. For $\hat{\bar{G}}^*_{kji}(u,s;L^*)$, Eq. (9) is first used for replacing $\bar{W}_{ji}(s;L)$ by $\bar{W}^*_{ji}(s;L^*)$ in Eq. (10), but the second substitution is the same as the second substitution in $\hat{\bar{G}}_{kji}(\tau,t;L^*)$.

III. PROPERTIES OF PATH PDFs

A. A two-state semi-Markov chain

This section finds properties of path PDFs, and studies their implications on the Green's function. This is done by studying two-, three-, and four-state chains, and an invariant L-state chain.

The simplest 1D chain consists of two states with no sink terms. The chain is referred to as a two-state semi-Markovian chain and is characterized completely by the WT-PDFs $\psi_{21}(t)$ and $\psi_{12}(t)$ (Fig. 3). Although a two-state semi-Markovian chain is the simplest 1D chain, the behavior of its associated path PDFs gives a good indication for the behavior of path PDFs for larger chains. The path PDFs express $\bar{W}_{21}(s;2)$ and $\bar{G}_{21}(s;2)$ as

$$\bar{W}_{21}(s;L) = \sum_{n=0}^{\infty} \bar{w}_{21}(s,2n+1;2) \tag{11}$$

and

$$\bar{G}_{21}(s;L) = \sum_{n=0}^{\infty} \bar{g}_{21}(s,2n+1;2), \tag{12}$$

where

$$\bar{g}_{21}(s,2n+1;2) = \bar{w}_{21}(s,2n+1;2)\bar{\Psi}_2(s). \tag{13}$$

For a two-state chain, the path PDF $\bar{w}_{21}(s,2n+1;2)$ consists of a single path of $2n+1$ transitions (Appendix A). Denoting by $N(2n;L)$ the number of paths with n double transitions that connect the edge states in a L-state chain, then, for this example, $N(2n;2)=1$. $N(2n;L)$ is further discussed in later sections. The expression for $\bar{w}_{21}(s,2n+1;2)$ reads (Appendix A)

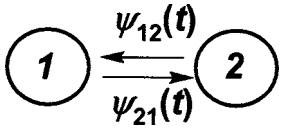

FIG. 3. A two-state semi-Markovian chain characterized by the WT-PDFs $\psi_{21}(t)$ and $\psi_{12}(t)$.

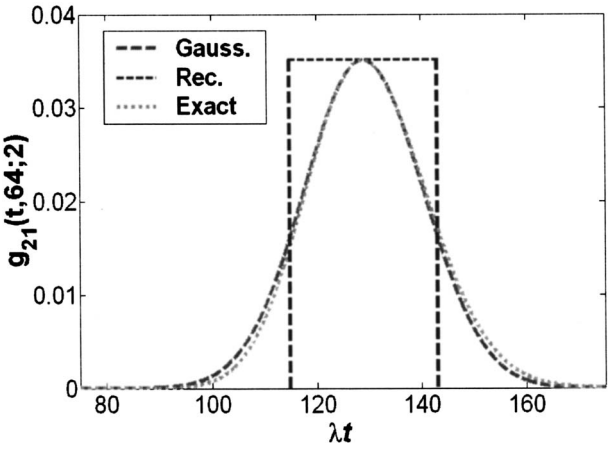

FIG. 4. $g_{21}(t,64;2)$ as a function of λt, for $dt=0.1$ and $\lambda=0.5$. The exact expression in Eq. (16) (dotted curve), the Gaussian approximation (dashed curve), and the rectangular approximation are shown.

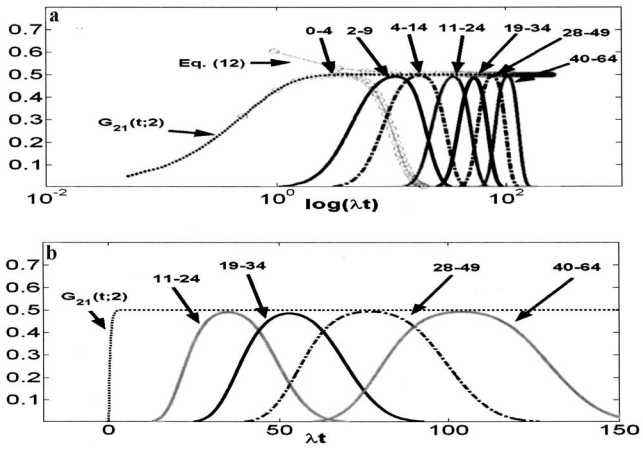

FIG. 5. The Green's function in Eq. (18), the expression in Eq. (19) that uses the rectangular approximation, and packets of path PDFs (the size of each packet is shown at the base of the arrow pointing on the packet). Panel (a) shows, on a linear-log scale, that the approximation of a packet of path PDFs is valid only at the maximum of the packet, where panel (b) emphasizes that the packet width increases at large times (the width of the packet scales as $\sqrt{t}$). Here, $\lambda=0.5$ and $dt=0.1$ with appropriate arbitrary units.

$$\bar{w}_{21}(s,2n+1;2)=\bar{\psi}_{21}(s)(\bar{\psi}_{12}(s)\bar{\psi}_{21}(s))^n$$
$$=\bar{\psi}_{21}(s)(\bar{h}(s,1;2))^n, \tag{14}$$

where $\bar{h}(s,1;2)=\bar{\psi}_{12}(s)\bar{\psi}_{21}(s)$, can be obtained from Eq. (6). By substituting Eq. (14) into Eqs. (11) and (12), the geometric series is summed to give $\bar{W}_{21}(s;L)=\bar{\psi}_{21}(s)(1-\bar{\psi}_{12}(s)\bar{\psi}_{21}(s))^{-1}$ and $\bar{G}_{21}(s;L)=\bar{\psi}_{21}(s)(1-\bar{\psi}_{12}(s)\bar{\psi}_{21}(s))^{-1}\bar{\Psi}_2(s)$, as is well known for a two-state system, e.g., Ref. 7. Choosing, for simplicity, an invariant system, namely, $\bar{\psi}_{21}(s)=\bar{\psi}_{12}(s)=\lambda/(\lambda+s)$, the inversion of Eq. (14) into the time domain leads to

$$w_{21}(t,2n+1;2)=\lambda e^{-\lambda t}(\lambda t)^{2n}/(2n)!, \tag{15}$$

which has units of inverse time and

$$g_{21}(t,2n+1;2)=e^{-\lambda t}(\lambda t)^{2n+1}/(2n+1)!. \tag{16}$$

When substituting Eqs. (15) and (16) into the corresponding transformed Eqs. (11) and (12), one gets

$$W_{21}(t;2)=\lambda e^{-\lambda t}\sum_{n=0}^{\infty}(\lambda t)^{2n}/(2n)!=\lambda e^{-\lambda t}\cosh(\lambda t) \tag{17}$$

and

$$G_{21}(t;2)=e^{-\lambda t}\sum_{n=0}^{\infty}(\lambda t)^{2n+1}/(2n+1)!=e^{-\lambda t}\sinh(\lambda t). \tag{18}$$

We proceed by addressing the question "how many path PDFs contribute to the Green's function at time t?" This will also allow determining the time for which an approximation that truncates Eq. (18) after N terms,

$$G_{21}(t;2|N)=e^{-\lambda t}\sum_{n=0}^{N}(\lambda t)^{2n+1}/(2n+1)!,$$

is still valid. We first go back to Eq. (16) that expresses $g_{21}(t,2n+1;2)$ as a gamma density of order $2n+1$, whose peak occurs at $t_{\max}=(2n+1)/\lambda$. Asymptotic (large n) expansion of the factorial appearing in the denominator of the gamma density shows that the amplitude of $g_{21}(t,2n+1;2)$ at $t_{\max}$ scales as $n^{-1/2}$ and that around $t=t_{\max}$, $g_{21}(t,2n+1;2)$ can be approximated by the Gaussian

$$g_{21}(t,2n+1;2)\approx\frac{1}{\sqrt{2\pi(2n+1)}}e^{-(t-t_{\max})^2/2[(2n+1)/\lambda^2]}.$$

The Gaussian part can be further approximated by a rectangular of height 1 and width $2\sqrt{a}\sqrt{2n+1}/\lambda(\equiv 2\sigma_n)$ centered around $t_{\max}$, where $a=\pi/2$ chosen such that the rectangular approximation has the same area under it as of the gamma density in Eq. (16). The exact expression for $g_{21}(t,2n+1;2)$ [Eq. (16)], the Gaussian approximation, and the rectangular approximation are shown in Fig. 4 for $n=64$. The area under the Gaussian between the intersection times with the rectangular approximation is ~80% of its total area.

Using the rectangular approximation for the Gaussian part in the path representation of the Green's function leads to

$$G_{21}(t;2)\approx(2\pi)^{-1/2}\sum_{s=t-\sigma_n}^{t+\sigma_n}(2s+1)^{-1/2}$$
$$\approx(1/2)[1+\pi/(16\lambda t)]+o[(\lambda t)^{-2}]. \tag{19}$$

The final expression is obtained when taking the continuum limit of the sum and expanding the outcome of the resulting integral up to second order in $1/(\lambda t)$. Similar to the behavior of the exact expression in Eq. (18), the approximation for the Green's function is bounded for large t. Moreover, the approximation and the exact expression agree at large t, which is a consequence of the value of a, $a=\sqrt{\pi/2}$.

Instead of the rectangular approximation, one can substitute the gamma densities of Eq. (15) into Eq. (19) and perform the partial summation numerically. The outcome is shown in Fig. 5. Also shown are the analytical solution $G_{21}(t;2)$ and the approximation in Eq. (19). Figure 5 shows that the partial summation around $\lambda t\approx 2n$ of a packet of about $2\sqrt{\pi/2}\sqrt{2n}$ path PDFs is such that the packet reaches the correct value at time λt [up to a second order in $1/(\lambda t)$].

Although this analysis follows Eq. (19) that originates from an asymptotic expansion, the packet of path PDFs well approximates the Green's function even for small n. Figure 5(b) shows that the width of the packet centered around $\lambda t \approx 2n$ increases with t (it scales as $\sqrt{t}$), but the approximation is valid only at its peak. Additionally, we can conclude from this analysis that the approximation $G_{21}(t;2|N)$ is valid for times $t \approx t_N - \sqrt{a^2 t_N/\lambda}$, where $t_N \equiv 2N/\lambda$.

Summarizing, the Green's function at time $t \approx (2n+1)/\lambda$ can be built from about $\sqrt{2\pi t/\lambda}$ path PDFs centered around $g_{21}(t,2n+1;2)$. Path PDFs that are not part of the packet do not contribute to the Green's function at this time [within the $1/(\lambda t)^2$ approximation]. In light of these results it is straightforward to correctly compare the contribution of successive path PDFs to the Green's function at time t. From Eq. (16) the ratio of successive path PDFs is found to obey $g_{21}(t,2m+1;2)/g_{21}(t,2m-1;2)=(\lambda t/2m)^2$, so, at large enough time (denote by $t_{\gg}$) the path PDF of order $2m+1$ has a larger amplitude than the path PDF of order $2m-1$ (large times mean $t_{\gg} \gg t_{\max} \approx 2m/\lambda$). However, this result does not mean that the $2m+1$ order path PDF is important to the approximation for the Green's function at time $t_{\gg}$. The packet analysis shows that a $2m+1$ path PDF contributes to the Green's function for times satisfying $t_{\max} - \sqrt{t_{\max}/\lambda} \leqslant t \leqslant t_{\max} + \sqrt{t_{\max}/\lambda}$. Thus, asymptotic (large t) analysis should be done with care when comparing the contribution of successive path PDFs to the Green's function at time t, and should use the Gaussian approximation for path PDFs.

B. The three-state chain

In this section, we study the three-state system in Fig. 6, with $\psi_{ij}(t) \equiv \varphi_{ij}(t)\omega_{ij}$ and no trapping WT-PDFs. The analysis deals with path PDFs that construct $\bar{W}_{13}(s;3)$ via the path representation

$$\bar{W}_{13}(s;3) = \sum_{n=0}^{\infty} \bar{w}_{13}(s,2n+2;3).$$

As opposed to path PDFs for the two-state chain, $\bar{w}_{13}(s,2n+2;3)$ $(n>0)$ is built from more than one path. There are two types of degeneracy of paths that contribute to a given path PDF: one type corresponds to paths of different sequences of $2n+2$ transitions that connect states 1 and 3. The second type corresponds to all the permutations of the sequence of states visited in the path that result in a connected path. When saying that a path contributes to a path PDF, we mean that its associated single-path PDF contributes to the path PDF, so a path PDF is a sum over single-path PDFs of the same length. The single-path PDFs that correspond to the first type of degeneracy are, in principle, different functions of the time, but those that correspond to the second type lead to the same single-path WT-PDF. The reason is that $w_{13}(t,2n+2;3)$ contains one time argument, so its Laplace transform is insensitive to the order in which the states are visited. Note that the above classification of path types is relevant for any length chain.

For $n=0$, $\bar{w}_{13}(s,2;3)$ consists of one path, $\bar{w}_{13}(s,2;3) = \bar{\psi}_{23}(s)\bar{\psi}_{12}(s) = \bar{\Gamma}_{13}(s)$. For $n=1$, $\bar{w}_{13}(s,4;3)$ consists of two

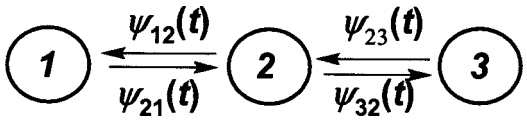

FIG. 6. A three-state chain. The system is characterized by the waiting time PDFs $\psi_{21}(t)$, $\psi_{12}(t)$, $\psi_{32}(t)$, and $\psi_{23}(t)$.

paths, each of which occurs once, $\bar{w}_{13}(s,4;3) = \bar{\Gamma}_{13}(s) \times (\bar{\psi}_{32}(s)\bar{\psi}_{23}(s) + \bar{\psi}_{21}(s)\bar{\psi}_{12}(s))$. The expression in the parentheses equals to $\bar{h}(s,1;3)$, see Eq. (6). For $n=2$, there are four paths that contribute to $\bar{w}_{13}(s,6;3)$, three of which are distinct: two paths of the sequences (the order in which the states are visited is written from left to right) 3232321 and 3212121 occur once, and one path with two permutations, with the sequences 3212321 and 3232121. $\bar{w}(s,6;3)$ is given by

$$\bar{w}_{13}(s,6;3) = \bar{\Gamma}_{13}(s)(\bar{\psi}_{32}(s)\bar{\psi}_{23}(s) + \bar{\psi}_{21}(s)\bar{\psi}_{12}(s))^2 = \bar{\Gamma}_{13}(s)(\bar{h}(s,1;3))^2.$$

Using a recursion relation (Appendix A), one finds that the expression for $\bar{w}_{13}(s,2n+2;3)$ for any n reads

$$\bar{w}_{13}(s,2n+1;3) = \bar{\Gamma}_{13}(s)(\bar{h}(s,1;3))^n. \tag{20}$$

Summing Eq. (20) over n gives $\bar{W}_{13}(s;3)$,

$$\bar{W}_{13}(s;3) = \sum_{n=0}^{\infty} \bar{w}_{13}(s,2n+1;3) = \bar{\Gamma}_{13}(s)/[1-\bar{h}(s,1;3)].$$

As opposed to the two-state chain, the general result for $\bar{W}_{13}(s;3)$ is less familiar, and can be found useful in modeling and in data analysis.

The previous section showed that the Green's function at time t can be constructed from a packet of path PDFs whose size is proportional to $\sqrt{t}$, and the same is valid for the three-state chain as well. This follows by comparing Eq. (20) to Eq. (14): choosing a symmetric Markovian invariant system $(\omega_{12}=0.5)$, Eq. (20) leads to $g_{13}(t,2n+2;3) = (1/2)e^{-\lambda t}(\lambda t)^{2n+2}/(2n+2)!$, which is a very similar functional form to that of $g_{12}(t,2n+1;2)$ given by Eq. (16). Therefore the results for the three-state Green's function, both analytically and numerically, are very similar to the results of the two-state chain.

We continue the analysis by quantifying the various contributions to the path PDFs. For this purpose, we note that Eq. (20) originates from

$$\bar{w}_{13}(s,2n+2;3s) = \bar{\Gamma}_{13}(s)\sum_{k=0}^{n} (\bar{\psi}_{12}(s)\bar{\psi}_{21}(s))^k (\bar{\psi}_{32}(s)\bar{\psi}_{23}(s))^{n-k} \binom{n}{k}, \tag{21}$$

as can be shown by counting of paths. Each term in the sum in Eq. (21) corresponds to a path with degeneracy $\binom{n}{k}$. Considering an invariant system (in WT-PDFs) with $\omega_{12}=q$, Eq. (21) can be rewritten as

$$\bar{w}_{13}(s,2n+2;3)=\bar{\Gamma}_{13}(s)(\bar{\varphi}^2(s))^n\sum_{k=0}^{n}(q)^k(p)^{n-k}\binom{n}{k}$$

$$\equiv\bar{\Gamma}_{13}(s)(\bar{\varphi}^2(s))^n S(2n+3;3).$$

Here, $S(2n+2;3)$ is the amplitude factor. [In $S(2n+\gamma_{1L};L)$, L is the chain length.] For the invariant three-state chain, the amplitude factor is unity, namely, $S(2n+2;3)=\Sigma_{k=0}^{n}(q)^k(p)^{n-k}\binom{n}{k}=1$, because $p+q=1$. Each term in $S(2n+2;3)$ consists of the probability of a path, $p^{n-k}q^k$, multiplied by the number of times it occurs, $\binom{n}{k}$. As $S(2n+2;3)$ is unity, the probability that a path connecting states 3 and 1 has k transitions between states 1 and 2, given that in total there are $2n+2$ transitions in the path, is $p^{n-k}q^k\binom{n}{k}$. From the amplitude factor, one calculates the total number of paths that contribute to $\bar{w}_{13}(s,2n+2;3)$,

$$N(2n;3)=\sum_{k=0}^{n}\binom{n}{k}=2^n,$$

because the number of paths must be independent of the probability of each path. Note that for $L=2,3$, $N(2n;L)$ obeys the scaling

$$N(2n;L)=(L-1)^n,\quad L=2,3.$$

Additionally, for both chain lengths, $S(2n+\gamma_{1L};L)$ is unity, and $\bar{w}_{1L}(s,2n+\gamma_{1L};L)$ is proportional to the nth power of $\bar{h}(s,1;L)$. These relationships do not hold for larger chains, but from the above we conclude that the lower bound on $N(2n;L)$ for any chain with $L\geqslant 3$ states is 2^n, because $N(2n;L)$ must be an increasing function of L for a fixed $n>0$. In fact, $N(2n;L)$ must obey $N(2n;L-1)\leqslant N(2n;L)\leqslant N(2n;L+1)$. The next section shows that the upper bound on $N(2n;L)$ must be smaller than $(L-1)^n$ for $L>3$.

C. The four-state chain

This section studies a four-state chain with no trapping WT-PDFs. The system is described by the set of six WT-PDFs, $\psi_{i\pm1i}(t)=\omega_{i\pm1i}\varphi_{i\pm1i}(t)$, see Fig. 7. The analysis mainly aims at calculating $N(2n;4)$. The first step in the analysis obtains a general expression for $\bar{w}_{14}(s,2n+3;4)$,

$$\bar{w}_{14}(s,2n+3;4)=\bar{\Gamma}_{14}(s)\sum_{j=0}^{[n/2]}(-1)^j(\bar{h}(s,1;4))^{n-2j}(\bar{h}(s,2;4))^j\binom{n-j}{j}. \quad (22)$$

In Eq. (22)

$$\bar{h}(s,1;4)=\bar{\psi}_{21}(s)\bar{\psi}_{12}(s)+\bar{\psi}_{32}(s)\bar{\psi}_{23}(s)+\bar{\psi}_{43}(s)\bar{\psi}_{34}(s)$$

and

$$\bar{h}(s,2;4)=\bar{\psi}_{21}(s)\bar{\psi}_{12}(s)\bar{\psi}_{43}(s)\bar{\psi}_{34}(s),$$

as can be obtained from the definition for $\bar{h}(s,i;L)$ in Eq. (6). Equation (22) is derived by finding and solving the recursion relation for $\bar{w}_{14}(s,2n+3;4)$ (Appendix A). Note that the solution of Eq. (22) is given by (Appendix B)

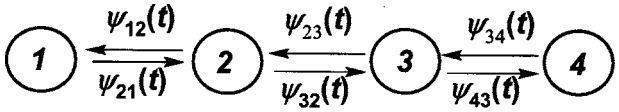

FIG. 7. A four-state chain. The system is characterized by the waiting time PDFs $\psi_{21}(t)$, $\psi_{12}(t)$, $\psi_{32}(t)$, $\psi_{23}(t)$, $\psi_{43}(t)$, and $\psi_{34}(t)$.

$$\bar{w}_{14}(s,2n+3;4)=\bar{\Gamma}_{14}(s)2^{-n-1}\frac{(\bar{h}(s,1;4)+\bar{d}(s))^{n+1}-(\bar{h}(s,1;4)-\bar{d}(s))^{n+1}}{\bar{d}(s)},$$

where $\bar{d}(s)=\sqrt{\bar{h}^2(s,1;4)-4\bar{h}(s,2;4)}$. Only when $\bar{h}^2(s,1;4)\gg 4\bar{h}(s,2;4)$ for a given s, the path PDF has the form $\bar{w}_{14}(s,2n+3;4)\propto(\bar{h}(s,1;4))^n$, but this result does not hold in general. [The scaling $\bar{w}_{1L}(s,2n+\gamma_{1L};L)\propto(\bar{h}(s,1;L))^n$ holds for all invariant chains when s goes to zero as discussed in the next section.] Summing $\bar{w}_{14}(s,2n+3;4)$ over n leads to the expression for $\bar{W}_{14}(s;4)$,

$$\bar{W}_{14}(s;4)=\sum_{n=0}^{\infty}\bar{w}(s,2n+3;4)$$

$$=\bar{\Gamma}_{14}(s)/[1-\bar{h}(s,1;4)+\bar{h}(s,2;4)].$$

The general expression for $\bar{W}_{14}(s;4)$ is not familiar but can be used in modeling and in data analysis.

Examining in detail the expression for path PDF in Eq. (22), we notice that it contains negative terms. This means that not all the terms in the sum correspond to actual paths. In fact, the negative terms compensate for paths that are over counted in the positive terms in the sum, which means that not all the positive terms also correspond to actual paths. [This behavior is in contrast to the terms in the sums for $\bar{w}_{1L}(s,2n+\gamma_{1L};L)$ for $L=2,3$, where all the terms represent actual paths.] We continue the analysis for an invariant system, for which Eq. (22) is written as

$$\bar{w}_{14}(s,2n+3;4)=\bar{\Gamma}_{14}(s)(\bar{\varphi}(s))^{2n}S(2n+3;4), \quad (23)$$

where the amplitude factor is given by

$$S(2n+3;4)=\sum_{j=0}^{[n/2]}(q+pq+p)^{n-2j}(-qp)^j\binom{n-j}{j}. \quad (24)$$

Equation (23) holds also for an inhomogeneous four-state chain with state-dependent transition probabilities but state-independent WT-PDFs, where for such chains Eq. (24) is modified by adjusting the expressions in the parentheses in the sum. Performing the summation in Eq. (24) gives (Appendix B)

$$S(2n+3;4)=\frac{1}{1-pq}(1-pq^{-(n+1)}). \quad (25)$$

The amplitude factor in Eq. (24) is asymptotically a constant of time (as $n\sim t$), which means that the packet approximation for the smaller chain Green's functions is valid for the four-state chain as well. From the amplitude factor, the expression for $N(2n;4)$ follows

$$N(2n;4) = \sum_{j=0}^{[n/2]} (3)^{n-2j}(-1)^j \binom{n-j}{j}, \tag{26}$$

because the number of paths must be independent of the transition probabilities, but the three additives in the first factor in the sum for the amplitude factor represent distinct paths. Note that each term in the sum for the amplitude factor is a product of a term associated with the number of paths [see Eq. (26)] with a term associated with the local potential. The solution of Eq. (26) reads (Appendix B)

$$N(2n;4) = \frac{1}{\sqrt{5}}((1+\phi)^{n+1} - (1-1/\phi)^{n+1}), \tag{27}$$

where $\phi = 1.618,\ldots$ is the golden ratio (Appendix B). The number of paths associated with $\bar{w}_{14}(s,2n+3;4)$ is always an integer and is smaller than $3^n (= (L-1)^n|_{L=4})$ for $n>1$, but scales as $N(2n;4) \sim (1+\phi)^n$.

D. An invariant *L*-state chain

This section considers an invariant L state chain with probability p to jump to the left and derives an asymptotic expression, in the path length n, for the path PDFs. Firstly, note that the expression for path PDFs for an invariant chains reads

$$\bar{w}_{1L}(s,2n+\gamma_{1L};L) = \bar{\Gamma}_{1L}(s)(\bar{\varphi}(s))^{2n} S(2n+\gamma_{1L};L)$$

This equation can be written as

$$\bar{w}_{1L}(s,2n+\gamma_{1L};L) = (\bar{\varphi}(s))^{2n+L-1} p^{L-2} S(2n+\gamma_{1L};L).$$

We show below that the factor $p^{L-2}S(2n+\gamma_{1L};L)$ can be approximated by $2P_L(\mathrm{ss})$, leading to the general expression for path PDFs for invariant chains

$$\bar{w}_{1L}(s,2n+\gamma_{1L};L) \approx (\bar{\varphi}(s))^{2n+L-1} 2P_L(\mathrm{ss}). \tag{28}$$

In Eq. (28), $P_L(\mathrm{ss})$ is the probability to occupy state L at steady state. The approximation in Eq. (28) is valid as long as it is sensible to use steady state probabilities. [This is always the case when $\varphi(t)$ has a finite first moment.] To support the approximation form, first note that the amplitude factor $S(2n+\gamma_{1L};L)$ cannot decay to zero faster than $n^{-1/2}$, otherwise the probability at steady state vanishes, but cannot also be an increasing function of n, otherwise the probability will increase without bound. Then, when assuming $p^{L-2}S(2n+\gamma_{1L};L) \sim$ const, namely, when the amplitude factor is independent of n for large n, $p^{L-2}S(2n+\gamma_{1L};L)$ must be equal to $2P_L(\mathrm{ss})$ from consistency demands. To show this, we sum $\bar{w}_{1L}(s,2n+\gamma_{1L};L)$ over n and multiply the result by $\bar{\Psi}_L(s)$. The expression must lead to $P_L(\mathrm{ss})$ when taking the limit of $s \to 0$, which means that $p^{L-2}S(2n+\gamma_{1L};L) \approx 2P_L(\mathrm{ss})$. Now, in the specific case of a four-state chain, it was shown that the amplitude factor is a sum of a constant and function of n that decays to zero exponentially fast with n. Moreover, the constant fulfills $(p^{L-2}S(2n+\gamma_{1L};L) \approx 2P_L(\mathrm{ss}))_{L=4}$. We rely on this result in postulating that $S(2n+\gamma_{1L};L) \approx$ const for any L asymptotically in n, and by this justify the form of the approximation for path PDFs for invariant chains given by Eq. (28).

IV. CONCLUDING REMARKS

The master equation and the GME are frequently used in modeling processes in biology, chemistry, and physics. Recently, the Laplace transform of the Green's function $G_{ij}(t;L)$ for a 1D *arbitrarily* inhomogeneous semi-Markovian random walk in a chain of L states was found in closed form in terms of the input WT-PDFs.[12,13] In this paper, we analyzed path PDFs, denoted by $w_{ij}(t,2n+\gamma_{ij};L)$, in the path representation of $G_{ij}(t;L)$. It was shown that the path PDF $\bar{w}_{ij}(s,2n+\gamma_{ij};L)$ is built from two types of degeneracy: (a) different paths of the same length of $2n+\gamma_{ij}$ transitions and (b) all the permutations of the sequence of states in a given path that result in a connected path. It was further shown that, independent of the origin of the degeneracy, the number of paths that contribute to the path PDF that connects the edge states, calculated as a function of the system length L and the length of the path $2n+\gamma_{1L}$, $N(2n;L)$, is bounded by $N(2n;L-1) \leqslant N(2n;L) \leqslant (L-1)^n$ and is not less than 2^n for $L \geqslant 3$. Thus $N(2n;L)$ grows exponentially with the length of the path and as a power law with the length of the system. Note that $N(2n;L)$ characterizes any 1D random walk, namely, $N(2n;L)$ is independent of the chain details but its length. It was also shown that path PDFs are mono-peaked in time.

It is well known[1–6] that for any kind of connectivity between the discrete states in the lattice, i.e., for any dimension, the Green's function of the random walk can be found according to the equation

$$G_{ij}(t;L) = \mathrm{ILT}([sI - K(s)]^{-1})_{ij},$$

where ILT stands for inverse Laplace transform. The numerical inversion of the kernel matrix with $(-s)$ added to the diagonal elements is easily done for the tridiagonal case (i.e., 1D), given not too large L. However, for inhomogeneous systems with many states (large L), numerical inversion can be unstable. This problem becomes worse in higher dimensions, where the kernel matrix contains many off-tridiagonal elements. For 1D chains of any length, the analytical solution in Eqs. (3)–(6) can be used, but in higher dimensions analytical solutions for arbitrarily inhomogeneous systems are missing. Then, approximations for $G_{ij}(t;L)$ are needed. Building approximations for $G_{ij}(t;L)$ in higher dimensions using the path PDF approach (i.e., finding *important* paths and their associated number as a function of t) can be useful in the analysis of the dynamics of interacting objects, which is a subject of great interest in physical systems (see, for example, Ref. 74). We note that the analysis given in this paper can be useful when building approximations for $G_{ij}(t;L)$ in higher dimensions. By considering $N(2n;L)$, one gets an indication of the complexity of (a simulation for obtaining) $G_{ij}(t;L)$. (Note that n and t are not independent.) However, for an inhomogeneous chain, not all paths in $N(2n;L)$ are necessarily equally important to the convergence of the associated path PDF. Moreover, not all path PDFs are important to the convergence of $G_{ij}(t;L)$. This was shown to be the case for the 1D two-state chain, where the approximation for $G_{1L}(t;L)$ sums over a packet of $\sqrt{t}$ analytically known path PDFs centered around the n order path

PDF, but holds true for all invariant chains. The situation is more involved for inhomogeneous chains, because both slow-transition short paths and fast-transition long paths can be equally important for obtaining $G_{ij}(t;L)$. [Here, we use the term "slow (fast) transitions" to indicate that in an inhomogeneous chain, some WT-PDFs have small (large) first moments relative to other WT-PDFs. This means that for a given t, paths that visit slow states may be shorter than paths that visit fast states, but still both path types are important to the convergence of the Green's function at time t.] In any case, it is clear from the analysis of the simple invariant case that a path PDF contributes to $G_{ij}(t;L)$ in the vicinity of its peak and that asymptotic analysis of path PDFs should be done with care when comparing the contributions of different path PDFs to $G_{ij}(t;L)$. The partial summation over path PDFs, where a path PDF enters the partial summation only in the vicinity of its peak, may be a good strategy to begin with in approaching the problem of building Green's function approximations in higher dimensions. Self-avoiding path PDFs in higher dimensions are 1D objects and are given by equation of the same type of Eq. (4). The difficulty lies in compiling the information from different paths. For non-self-avoiding paths, another difficulty is associated with the analysis of paths with intersection and U-turns.

Lastly, note that the dynamics of motor proteins[47,48] and of ion channels[51,52] has already been described by the 1D generalized master equation, Eq. (1). Of particular interest in modeling motor proteins are circular chains,[47–50] as shown in Fig. 2. The results of this paper, both the general expressions for Green's functions for circular chains and the results from the path PDF analysis, can be found useful in the analysis of data and in modeling these systems. Detailed investigation of such systems is a matter of future research.

ACKNOWLEDGMENT

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APPENDIX A: RECURSION RELATIONS FOR PATH PDFS FOR SMALL CHAINS

This appendix gives the recursion relations for the $\bar{w}_{1L}(s,2n+\gamma_{1L};L)s$ for $L=2,3,4$. For $L=2$, there is one path with exactly $2n+1$ transitions, which means that

$$\bar{w}_{12}(s,2n+1;2)=\bar{w}_{12}(s,2(n-1)+1;2)\bar{\psi}_{21}(s)\bar{\psi}_{12}(s). \tag{A1}$$

The associated initial condition with Eq. (A1) is given by $\bar{w}_{12}(s,0+1;2)=\bar{\psi}_{12}(s)=\bar{\Gamma}_{12}(s)$. [Recall that the path length in $\bar{w}_{12}(s,2(n-1)+1;2)$ is written in a way that emphasizes the contributions to the path from the back transitions, $2(n-1)$, and from the direct transitions, 1. This notation is also used in larger chains.] The recursion relation in Eq. (A1) and its associated initial condition lead to

$$\bar{w}_{12}(s,2n+1;2)=\bar{\psi}_{12}(s)(\bar{\psi}_{21}(s)\bar{\psi}_{12}(s))^n$$
$$=\bar{\Gamma}_{12}(s)(\bar{h}(s,1;2))^n, \tag{A2}$$

which is given in Eq. (14) in the main text. For $L=3$, the recursion relation for $\bar{w}_{13}(s,2n+2;3)$ reads

$$\bar{w}_{13}(s,2n+2;3)=\bar{w}_{13}(s,2(n-1)+2;3)\bar{h}(s,1;3), \tag{A3}$$

with the initial condition $\bar{w}_{13}(s,0+2;3)=\bar{\Gamma}_{13}(s)$. The resulting expression for $\bar{w}_{13}(s,2n+2;3)$ reads

$$\bar{w}_{13}(s,2n+2;3)=\bar{\Gamma}_{13}(s)(\bar{h}(s,1;3))^n. \tag{A4}$$

Equation (A4) is given in the main text in Eq. (20). For $L=4$, the recursion relation for $\bar{w}_{14}(s,2n+3;4)$ is more involved than that of the smaller chains. We find that the recursion relation reads

$$\bar{w}_{14}(s,2n+3;4)=\bar{w}_{14}(s,2(n-1)+3;4)\bar{h}(s,1;4)$$
$$-\bar{w}_{14}(s,2(n-2)+3;4)\bar{h}(s,2;4), \tag{A5}$$

with the initial conditions $\bar{w}_{14}(s,0+3;4)=\bar{\Gamma}_{14}(s)$ and $\bar{w}_{14}(s,2+3;4)=\bar{\Gamma}_{14}(s)\bar{h}(s,1;4)$. The resulting expression for $\bar{w}_{14}(s,2n+3;4)$ can be calculated by first performing a z transform (i.e., multiplying by z^n both sides of the equation and performing a summation over n) and then expanding the result in powers of z. The resulting expression for $\bar{w}_{14}(s,2n+3;4)$ is given in Eq. (22) in the main text.

APPENDIX B: THE FIBONACCI FUNCTION

This appendix gives the formula that was used in the calculations of sums in Sec. III B. The formula utilizes the expression of the Fibonacci function and its solution

$$F_n(a/4)=\sum_{k=0}^{[n/2]}\binom{n-k}{k}(a/4)^k=2^{-n}\frac{r_+^{n+1}-r_-^{n+1}}{r_+-r_-},$$

$$r_\pm=1\pm\sqrt{1+a}. \tag{B1}$$

$F_n(a)$ in Eq. (B1) is the Fibonacci function and solves the linear recursion relation $F_n(a)=aF_{n-1}(a)+F_{n-2}(a)$. $F_n(1)$ is the Fibonacci number also given by $F_n=[\phi^n/\sqrt{5}]$, where $[\cdot]$ is the round towards zero operation [as in the upper bound in the sum in Eq. (B1)] and the golden ration ϕ is the positive root of the equation $x^2-x-1=0$. The Fibonacci number can be found by solving the recursion relation $F_n=F_{n-1}+F_{n-2}$, with the initial conditions $F_0=F_1=1$.

[1] N. G. van Kampen, *Stochastic Processes in Physics and Chemistry*, revised and enlarged ed. (North-Holland, Amsterdam, 1992).
[2] S. Redner, *A Guide to First-Passage Process* (Cambridge University Press, Cambridge, UK, 2001).
[3] N. W. Goel and N. Richter-Dyn, *Stochastic Models in Biology* (Academic, New York, 1974).
[4] Z. Schuss, *Theory and Applications of Stochastic Differential Equations* (Wiley, New York, 1980).
[5] B. Hille, *Ion Channels of Excitable Membranes* (Sinauer, Sunderland, MA, 2001).
[6] G. H. Weiss, *Aspects and Applications of the Random Walk* (North-Holland, Amsterdam, 1994).
[7] D. R. Cox, *Renewal Theory* (Methuen, London, 1962).
[8] E. W. Montroll and G. H. Weiss, J. Math. Phys. **6**, 167 (1965).

[9] H. Scher and M. Lax, Phys. Rev. B **7**, 4491 (1973).
[10] V. M. Kenkre, E. W. Montroll, and M. F. Shlesinger, J. Stat. Phys. **9**, 45 (1973).
[11] J. Klafter and R. Silbey, Phys. Rev. Lett. **44**, 55 (1980).
[12] O. Flomenbom and J. Klafter, Phys. Rev. Lett. **95**, 098105 (2005).
[13] O. Flomenbom, J. Klafter, and R. J. Silbey, Phys. Rev. Lett. **97**, 178901 (2006).
[14] C. Van Den Broeck and M. Bouten, J. Stat. Phys. **45**, 1031 (1986).
[15] R. Metzler and J. Klafter, Phys. Rep. **339**, 1 (2000).
[16] W. E. Moerner and M. Orrit, Science **283**, 1670 (1999).
[17] S. Weiss, Science **283**, 1676 (1999).
[18] E. Neher and B. Sakmanm, Nature (London) **260**, 799 (1976).
[19] C. G. Nichols, Nature (London) **440**, 470 (2006).
[20] A. Mitra, R. Tascione, A. Auerbach, and S. Licht, Biophys. J. **89**, 3071 (2005).
[21] J. J. Kasianowicz, E. Brandin, D. Branton, and D. W. Deamer, Proc. Natl. Acad. Sci. U.S.A. **93**, 13770 (1996).
[22] L. Kullman, P. A. Gurnev, M. Winterhalter, and S. M. Bezrukov, Phys. Rev. Lett. **96**, 038101 (2006).
[23] R. J. Davenport, G. J. L. Wuite, R. Landick, and C. Bustamante, Science **287**, 2497 (2000).
[24] N. R. Forde, D. Izhaky, G. R. Woodcock, G. J. L. Wuite, and C. Bustamante, Proc. Natl. Acad. Sci. U.S.A. **99**, 11682 (2002).
[25] K. Adelman, A. La Porta, T. J. Santangelo, J. T. Lis, J. W. Roberts, and M. D. Wang, Proc. Natl. Acad. Sci. U.S.A. **99**, 13538 (2002).
[26] B. Schuler, E. A. Lipman, and W. A. Eaton, Nature (London) **419**, 743 (2002).
[27] H. Yang, G. Luo, P. Karnchanaphanurach, T. Louie, I. Rech, S. Cova, L. Xun, and X. S. Xie, Science **302**, 262 (2003).
[28] E. Rhoades, E. Gussakovsky, and G. Haran, Proc. Natl. Acad. Sci. U.S.A. **100**, 3197 (2003).
[29] X. Zhuang, H. Kim, M. J. B. Pereira, H. P. Babcock, N. G. Walter, and S. Chu, Science **296**, 1473 (2002).
[30] H. Lu, L. Xun, and X. S. Xie, Science **282**, 1877 (1998).
[31] L. Edman, Z. Földes-Papp, S. Wennmalm, and R. Rigler, Chem. Phys. **247**, 11 (1999).
[32] K. Velonia, O. Flomenbom, D. Loos, S. Masuo, M. Cotlet, Y. Engelborghs, J. Hofkens, A. E. Rowan, J. Klafter, R. J. M. Nolte, Angew. Chem., Int. Ed. **44**, 560 (2005).
[33] S. Nie, D. T. Chiu, and R. N. Zare, Science **266**, 1018 (1994).
[34] R. Shusterman, S. Alon, T. Gavrinyov, and O. Krichevsky, Phys. Rev. Lett. **92**, 048303 (2004).
[35] G. Zumofen, J. Hohlbein, and C. G. Hübner, Phys. Rev. Lett. **93**, 260601 (2004).
[36] A. E. Cohen and E. W. Moerner, Proc. Natl. Acad. Sci. U.S.A. **103**, 4362 (2006).
[37] R. M. Dickson, A. B. Cubitt, R. Y. Tsien, and W. E. Moerner, Nature (London) **388**, 355 (1997).
[38] I. Chung and M. G. Bawendi, Phys. Rev. B **70**, 165304 (2004).
[39] O. Flomenbom and R. J. Silbey, Proc. Natl. Acad. Sci. U.S.A. **103**, 10907 (2006).
[40] W. J. Bruno, J. Yang, and J. Pearson, Proc. Natl. Acad. Sci. U.S.A. **102**, 6326 (2005).
[41] O. Flomenbom, J. Klafter, and A. Szabo, Biophys. J. **88**, 3780 (2005).
[42] J. B. Witkoskie and J. Cao, J. Chem. Phys. **121**, 6361 (2004).
[43] O. Flomenbom and J. Klafter, Acta Phys. Pol. B **36**, 1527 (2005); J. Chem. Phys. **123**, 064903 (2005).
[44] J. Cao, Chem. Phys. Lett. **327**, 38 (2000).
[45] D. Colquhoun and A. G. Hawkes, Philos. Trans. R. Soc. London, Ser. B **300**, 1 (1982).
[46] F. Qin, A. Auerbach, and F. Sachs, Biophys. J. **79**, 1915 (2000).
[47] M. E. Fisher and A. B. Kolomeisky, Proc. Natl. Acad. Sci. U.S.A. **96**, 6597 (1999).
[48] A. B. Kolomeisky and M. E. Fisher, J. Chem. Phys. **113**, 10867 (2000).
[49] U. Seifert, Europhys. Lett. **70**, 36 (2005).
[50] Y. Kafri, D. K. Lubensky, and D. R. Nelson, Biophys. J. **86**, 3373 (2004).
[51] I. Goychuk and P. Hänggi, Phys. Rev. E **70**, 051915 (2004).
[52] G. L. Millhauser, E. E. Salpeter, and R. E. Oswald, Proc. Natl. Acad. Sci. U.S.A. **85**, 1503 (1988).
[53] O. Flomenbom and J. Klafter, Phys. Rev. E **68**, 041910 (2003); Biophys. J. **86**, 3576 (2004).
[54] M. O. Vlad, F. Moran, F. W. Schneider, and J. Ross, Proc. Natl. Acad. Sci. U.S.A. **99**, 12548 (2002).
[55] S. Yang and J. Cao, J. Chem. Phys. **117**, 10996 (2002).
[56] J. Wang and P. Wolynes, Phys. Rev. Lett. **74**, 4317 (1995).
[57] O. Flomenbom, K. Velonia, D. Loos, S. Masuo, M. Cotlet, Y. Engelborghs, J. Hofkens, A. E. Rowan, R. J. M. Nolte, M. Van der Auweraer, F. C. de Schryver, and J. Klafter, Proc. Natl. Acad. Sci. U.S.A. **102**, 2368 (2005); O. Flomenbom, J. Hofkens, K. Velonia, F. C. de Schryver, A. E. Rowan, R. J. M. Nolte, J. Klafter, and R. J. Silbey, Chem. Phys. Lett. **432**, 371 (2006).
[58] N. Agmon, J. Phys. Chem. B **104**, 7830 (2000).
[59] H. Qian and E. L. Elson, Biophys. Chem. **101**, 565 (2002).
[60] S. C. Kou, B. J. Cherayil, W. Min, B. P. English, and X. S. Xie, J. Phys. Chem. B **109**, 19068 (2005).
[61] I. V. Gopich and A. Szabo, J. Chem. Phys. **124**, 154712 (2006).
[62] J. Y. Sung and R. J. Silbey, Chem. Phys. Lett. **415**, 10 (2005).
[63] H. Qian and H. Wang, Europhys. Lett. **76**, 15 (2006).
[64] R. Granek and J. Klafter, Phys. Rev. Lett. **95**, 098106 (2005).
[65] J. W. Shaevitz, S. M. Block, and M. Schnitzer, Biophys. J. **89**, 2277 (2005).
[66] V. Barsegov and D. Thirumalai, Phys. Rev. Lett. **95**, 168302 (2005).
[67] F. Šanda and S. Mukamel, J. Chem. Phys. **108**, 124103 (2006).
[68] P. Allegrini, G. Aquino, P. Grigolini, L. Palatella, and A. Rosa, Phys. Rev. E **68**, 056123 (2003).
[69] E. Barkai, Y. Jung, and R. Silbey, Annu. Rev. Phys. Chem. **55**, 457 (2004).
[70] J. Tang and R. A. Marcus, J. Chem. Phys. **123**, 204511 (2005).
[71] S. Bianco, P. Grigolini, and P. Paradisi, J. Chem. Phys. **123**, 174704 (2005).
[72] F. L. H. Brown, Phys. Rev. Lett. **90**, 028302 (2003).
[73] G. Bel, Y. J. Zheng, and F. L. H. Brown, J. Phys. Chem. B **110**, 19066 (2006).
[74] P. G. Bolhuis, D. Chandler, C. Dellago, and P. L. Geissler, Annu. Rev. Phys. Chem. **53**, 291 (2002).