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Residence time densities for non-Markovian systems. (I). The two-state system

M. Boguñá[a], A.M. Berezhkovskii[b,1], G.H. Weiss[a,*]

[a] *Mathemat. & Statist. Comput. Lab., Division of Computer Research and Technology, National Institutes of Health, Bldg. 12 A Room 2007, Bethesda, MD 20892, USA*

[b] *National Institute of Child Health and Human Development, National Institutes of Health, Bldg. 12 A Room 2007, Bethesda, MD 20892, USA*

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Abstract

We study dynamical system which makes transitions between two states at random times. We analyze properties of the cumulative time τ spent by the system in a given state up to time T. When the probability density for the residence time in a single sojourn in the given state differs from a negative exponential the system will be non-Markovian. Simple analytical expressions are derived for the Laplace transform with respect to T of moments of the cumulative residence time. An exact Fourier–Laplace transform of the probability densities for τ at a fixed T are also found. It can be inferred from this expression, that at sufficiently large T the probability densities tend towards a Gaussian. The parameters that define the Gaussian are also given.

1. Introduction

Recently developed experimental techniques generally referred to as single-molecule spectroscopy (SMS) has attracted much attention from researchers in biophysics, chemistry and physics as reviewed in Refs. [1–6]. These techniques allow one to follow the evolution in time of the state of a single molecule which undergoes a conformational change. This should be contrasted with traditional techniques that have been used to

* Corresponding author. Fax: +1-301-402-4544.

E-mail address: ghw@helix.nih.gov (G.H. Weiss)

[1] Permanent address: Karpov Institute of Physical Chemistry, 10 Vorontsovo Pole Street, 103064 Moscow K-64, Russia.

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study the kinetic behavior of such systems in the bulk. Such measurements can only provide information which is ensemble-averaged.

A key quantity in the analysis of the results of some SMS experiments is the fraction of time which a single molecule spends in different states when measurements are made for a time T [7–13]. The record of the state of the system during the observation time T will be referred to as its trajectory. Because the times at which transitions between states are made are random the cumulative time spent in any particular state is also random, the properties of this time being described by a probability density. An exact solution for the probability densities for a two-state system has been derived for the Markovian case in which the times between transitions are negative exponential [12]. In the present paper, we generalize the theory to allow for non-Markovian jumps between the two states as a background for analyzing systems having more than two states [14]. It will be shown that there are subtleties in the formulation of the two-state non-Markovian system that do not arise in the analysis of Markovian systems. In the following paper we show that the analogous multistate systems can, in essence, be reduced to the two-state system provided that only the cumulative residence time in one of the states is of interest.

Another application area in which the cumulative residence time in one of the two states gives useful physical information is in the theory of chromatography [15]. In this application, a molecule passing through a chromatography column can either be in a freely mobile state, or is in an entangled state, in which it does not move until it untangles. The cumulative residence time can be directly related to the observed concentration profile. The original formulation of the theory assumed that transitions between the two states were Markovian. A later formulation allowed for non-Markovian transitions [16]. This formulation was shown to produce results in excellent agreement with data obtained in gel electrophoresis [17].

The probability density of the cumulative residence time in one out of a discrete number of states has also been extensively discussed in the literature of probability theory [18–23]. Its extension to a continuum of states where the analogous quantity is known as the local time is discussed in Refs. [24–28]. Applications of the cumulative time spent in a single state, in addition to SMS, have been made in biology [29,30], and physics [31–34].

This paper is organized in the following fashion: First, we present some general expressions for the propagator that describes transitions between two states of the system. These propagators are then used to calculate the Laplace transform of the moments of the cumulative residence time. After that, we derive exact expressions for the Fourier–Laplace transform of the probability densities for the cumulative residence time. A simple argument suggests that the asymptotic form of the probability density (in the limit $T \to \infty$) should be Gaussian. This limiting behavior has also been found in earlier work, for example as in Refs. [10,11] among others, but without the generality of the present treatment.

2. Description of non-Markovian transitions

A standard approach used to study the kinetics of two-state Markovian systems is to write a set of two linear differential equations for the populations of the two states. When the system is non-Markovian the evolution of the system is more conveniently described in terms of integral equations.

We denote the two states by S_1 and S_2. If there is a change of state at some time t, say from S_2 to S_1 then we shall say that this initiates a single sojourn in S_1. If the immediately following change from S_1 to S_2 occurs at time $t+\tau$ then we say that the sojourn time in S_1 is equal to τ. We will assume that τ is a random variable, and that the probability density describing its properties is $\psi_1(\tau)$. Similarly, the probability density for the duration of a single sojourn in S_2 will be denoted by $\psi_2(\tau)$. Thus, the two-state system is symbolically represented in terms of the probability densities as

$$S_1 \underset{\psi_2(t)}{\overset{\psi_1(t)}{\rightleftarrows}} S_2 \,. \tag{2.1}$$

The standard approach to studying the kinetics of the two-state system, formulated in terms of rate equations for the populations of the two states, is applicable when $\psi_i(t)=k_i\exp(-k_i t)$, $i=1,2$. The sojourn-time densities can also be thought of as being the probability densities for the first-passage times for exiting the state. For future analysis, we will also need the probability that a single sojourn in state i lasts for more than a time t. This probability will be denoted by $\Psi_i(t)$ which is equal to

$$\Psi_i(t) = \int_t^\infty \psi_i(\xi)\,\mathrm{d}\xi \,. \tag{2.2}$$

Our further analysis requires knowing the probability density for the time to the first change of state. The time at which one begins to observe the system, $t=0$, need not necessarily coincide with the beginning of a sojourn in either of the states. If we suppose that the system is initially in S_i and the time to the immediately following sojourn termination is equal to t, then all the information that is available is that the observed sojourn time must exceed t. Let $\psi_i^{(0)}(t)$ be the required probability density function for such an incomplete sojourn. This function should then have the form $\psi_i^{(0)}(t) = A\Psi_i(t)$ where A is a constant to be determined from the requirement that $\psi_i^{(0)}(t)$ should be normalized to 1. This fixes the value of A as being equal to $1/\langle t_i\rangle$ where $\langle t_i\rangle$ is the average duration of a single sojourn in S_i:

$$\langle t_i\rangle = \int_0^\infty t\psi_i(t)\,\mathrm{d}t = \int_0^\infty \Psi_i(t)\,\mathrm{d}t \,. \tag{2.3}$$

These moments will be assumed to be finite. Hence the expression for $\psi_i^{(0)}(t)$ is

$$\psi_i^{(0)}(t) = \frac{\Psi_i(t)}{\langle t_i\rangle} \,. \tag{2.4}$$

This expression also appears in the monograph by Cox [35] as well as in a paper by Tunaley [36]. Only for the choice $\psi_i(t)=k_i\exp(-k_i t)$ will the probability densities for the complete and incomplete sojourns coincide, that is, only in the Markovian case will it be true that $\psi_i^{(0)}(t)=\psi_i(t)$.

3. Propagators

Statistical properties of two-state systems have been discussed in the literature, cf., for example, see Ref. [35]. To keep our exposition self-contained we derive some of the results in the form required for further analysis. One of the key quantities needed in our derivations is the propagator $G_{ij}(t)$ which is the probability that the system is in S_i at time t conditional on being in S_j at $t=0$. The kinetic behavior of the two-state system is described by a set of four propagators. We will see that all of them can be expressed in terms of the equilibrium probabilities

$$P_{\mathrm{eq}}(i) = \frac{\langle t_i \rangle}{\langle t_1 \rangle + \langle t_2 \rangle}, \quad i = 1, 2 \tag{3.1}$$

and a single relaxation function $R(t)$ whose Laplace transform will be calculated later.

In the non-Markovian case the propagators can be calculated by solving a set of integral equations. To derive such an equation for $G_{11}(t)$ we introduce the function $g_{12}(t)$ which is the probability that a system that begins a sojourn in S_2 at $t=0$ is in S_1 at time $t>0$. The distinction between this function and $G_{12}(t)$ is in how the initial state of the system is formulated.

To derive the integral equation we note that if the system is in S_1 at $t=0$ it can be in S_1 at $t>0$ in one of two ways. Either the system remains in S_1 for the entire time t or else a transition is made to S_2 at some time $\xi < t$, and the system returns to S_1 at least once thereafter, being in S_1 at time t. These two possibilities can be incorporated into the single equation

$$G_{11}(t) = \Psi_1^{(0)}(t) + \int_0^t \psi_1^{(0)}(\xi) g_{12}(t-\xi)\,\mathrm{d}\xi \tag{3.2}$$

in which $\Psi_1^{(0)}(t) = \int_t^\infty \psi_1^{(0)}(\xi)\,\mathrm{d}\xi$. The Laplace transform of this equation is

$$\hat{G}_{11}(s) = \hat{\Psi}_1^{(0)}(s) + \hat{\psi}_1^{(0)}(s)\hat{g}_{12}(s) \tag{3.3}$$

leaving only the problem of calculating $\hat{g}_{12}(s)$ to complete the derivation.

The probability $g_{12}(t)$ also satisfies an integral equation of convolution form. To find this equation we define a cycle time as being the sum of a complete sojourn time in S_1, i.e., the period of time from a transition $S_2 \to S_1$ to the immediately following transition $S_1 \to S_2$, plus a complete sojourn time in S_2. Let $\varphi(t)$ be the probability density for a single cycle time, that is,

$$\varphi(t) = \int_0^t \psi_1(\xi)\psi_2(t-\xi)\,\mathrm{d}\xi \tag{3.4}$$

or $\hat{\varphi}(s) = \hat{\psi}_1(s)\hat{\psi}_2(s)$. The equation satisfied by the function $g_{12}(t)$ can be written in terms of $\varphi(t)$ as

$$g_{12}(t) = \int_0^t \psi_2(\xi)\Psi_1(t-\xi)\,\mathrm{d}\xi + \int_0^t \varphi(\xi) g_{12}(t-\xi)\,\mathrm{d}\xi\,, \tag{3.5}$$

where the first term on the right-hand side of this equation accounts for the possibility that during the time t there is only a single sojourn in S_2 of duration ξ, following

which the system remained in S_1 for a time $t-\xi$ or greater. The second term on the right accounts for the possibility that there was at least one cycle lasting a time ξ.

The solution to Eq. (3.5) in the transform domain is therefore

$$\hat{g}_{12}(s)=\frac{\hat{\psi}_2(s)\hat{\Psi}_1(s)}{1-\hat{\psi}_1(s)\hat{\psi}_2(s)}=\frac{\hat{\psi}_2(s)[1-\hat{\psi}_1(s)]}{s[1-\hat{\psi}_1(s)\hat{\psi}_2(s)]} \tag{3.6}$$

which is to be inserted into Eq. (3.3) to furnish the solution

$$\hat{G}_{11}(s)=\hat{\Psi}_1^{(0)}(s)+\frac{\hat{\psi}_1^{(0)}(s)\hat{\psi}_2(s)\hat{\Psi}_1(s)}{1-\hat{\psi}_1(s)\hat{\psi}_2(s)}\,. \tag{3.7}$$

In this expression $\hat{\psi}_1^{(0)}(s)$ is found from Eq. (2.4) to be

$$\hat{\psi}_1^{(0)}(s)=\frac{1-\hat{\psi}_1(s)}{s\langle t_1\rangle} \tag{3.8}$$

and

$$\hat{\Psi}_1^{(0)}(s)=\frac{1}{s}\left[1-\frac{1-\hat{\psi}_1(s)}{s\langle t_1\rangle}\right]\,. \tag{3.9}$$

When these are inserted into Eq. (3.7) one finds that

$$\hat{G}_{11}(s)=\frac{1}{s}\left[1-\frac{\{1-\hat{\psi}_1(s)\}\{1-\hat{\psi}_2(s)\}}{s\langle t_1\rangle\{1-\hat{\psi}_1(s)\hat{\psi}_2(s)\}}\right]\,. \tag{3.10}$$

The long-time behavior of $G_{11}(t)$ is related to the singular small-s behavior of $\hat{G}_{11}(s)$. We observe that in the small-s regime $\hat{\psi}_i(s)\approx 1-\langle t_i\rangle s+o(s)$ so that according to Eq. (3.10)

$$\lim_{s\to 0} s\hat{G}_{11}(s)=\frac{\langle t_1\rangle}{\langle t_1\rangle+\langle t_2\rangle}=P_{\mathrm{eq}}(1) \tag{3.11}$$

which shows that as t tends to infinity the propagator $G_{11}(t)$ approaches the equilibrium probability $P_{\mathrm{eq}}(1)$ as must be the case.

The remaining three propagators can all be found quite easily when $G_{11}(t)$ is known. It is evident that $G_{21}(t)=1-G_{11}(t)$ so that

$$\hat{G}_{21}(s)=\frac{[1-\hat{\psi}_1(s)][1-\hat{\psi}_2(s)]}{s^2\langle t_1\rangle[1-\hat{\psi}_1(s)\hat{\psi}_2(s)]}. \tag{3.12}$$

Similarly, $\hat{G}_{22}(s)$ and $\hat{G}_{12}(s)$ can be found by interchanging the subscripts 1 and 2 in Eqs. (3.10) and (3.12).

Two consequences of these relations, together with Eq. (3.1) are (a) that the probabilities $G_{12}(t)$ and $G_{21}(t)$ satisfy the condition of detailed balance in the form

$$G_{12}(t)P_{\mathrm{eq}}(2)=G_{21}(t)P_{\mathrm{eq}}(1) \tag{3.13}$$

and (b) that the propagators can all be expressed in terms of a single relaxation function, $R(t)$, which decreases monotonically from one to zero as a function of time. To

determine the form of this function we note that the propagators can be written in general form as

$$G_{ij}(t) = P_{\mathrm{eq}}(i) + [\delta_{ij} - P_{\mathrm{eq}}(i)]R(t)\,. \tag{3.14}$$

The Laplace transform of $R(t)$ is given by

$$\hat{R}(s) = \frac{1}{s}\left[1 - \left(\frac{\langle t_1\rangle + \langle t_2\rangle}{\langle t_1\rangle\langle t_2\rangle}\right)\frac{[1-\hat{\psi}_1(s)][1-\hat{\psi}_2(s)]}{s[1-\hat{\psi}_1(s)\hat{\psi}_2(s)]}\right]\,. \tag{3.15}$$

When the $\psi_i(t)$ are negative exponentials, $\psi_i(t)=k_i\exp(-k_i t)$, it is quite straightforward to invert the expression in Eq. (3.15) to find that

$$R(t) = \mathrm{e}^{-(k_1+k_2)t} \tag{3.16}$$

which is therefore the relaxation function for the Markovian case.

4. Cumulative residence times

We next discuss the theory of cumulative residence times. To formalize this notion consider a trajectory $\{\xi(t)\}$, $0\leqslant t < T$, where $\xi(t)$ is equal to 1 when the system is in S_1 and is equal to 2 when it is in S_2. The cumulative time spent by a trajectory $\{\xi(t)\}$ in S_i up to T is

$$\tau_i(T|\{\xi(t)\}) = \int_0^T \delta_{\xi(t),i}\,\mathrm{d}t \tag{4.1}$$

which is a functional of the trajectory depending parametrically on the observation time T, and the initial state S_j where $j=\xi(0)$. We seek to find the probability density for the cumulative residence time for a fixed T and the initial state S_j. This function will be denoted by $p_i(\tau|T|j)$. A formal expression for this function is

$$p_i(\tau|T|j) = \langle\delta(\tau - \tau_i(T|\{\xi(t)\}))\rangle_j \tag{4.2}$$

in which the subscript j indicates that the average is to be taken over all trajectories initially in S_j, which is say that $\xi(0)=j$.

4.1. Moments of the cumulative residence time

The formal expressions in Eqs. (4.1) and (4.2), together with a knowledge of the propagators, allow us to readily find the Laplace transform with respect to T of moments of the cumulative residence time. The first moment of the cumulative residence time can be written as

$$\langle\tau_i(T)\rangle_j = \int_0^T \langle\delta_{\xi(t),i}\rangle_j\,\mathrm{d}t\,. \tag{4.3}$$

But $\langle\delta_{\xi(t),i}\rangle_j$ is a path integral representation of the propagator

$$\langle\delta_{\xi(t),i}\rangle_j = G_{ij}(t)\,. \tag{4.4}$$

Hence the first moments can be expressed in terms of the propagator as

$$\langle \tau_i(T) \rangle_j = \int_0^T G_{ij}(t)\,\mathrm{d}t \tag{4.5}$$

as is otherwise obvious.

Essentially, the same formalism can be used to calculate the second and higher moments. The second moment can be written as

$$\begin{aligned}\langle \tau_i^2(T) \rangle_j &= \int_0^T \int_0^T \langle \delta_{\xi(t_1),i} \delta_{\xi(t_2),i} \rangle_j \,\mathrm{d}t_1\,\mathrm{d}t_2 \\ &= 2\int_0^T \mathrm{d}t_1 \int_0^{t_1} \langle \delta_{\xi(t_1),i} \delta_{\xi(t_2),i} \rangle_j \,\mathrm{d}t_2\,,\end{aligned} \tag{4.6}$$

where the second line follows from the first by taking advantage of the symmetry of the integrand with respect to t_1 and t_2. The limits on the integral with respect to t_2 imply that $t_1 \geqslant t_2$, which allows us to write

$$\langle \delta_{\xi(t_1),i} \delta_{\xi(t_2),i} \rangle_j = G_{ii}(t_1 - t_2) G_{ij}(t_2)\,. \tag{4.7}$$

The relation in this equation shows that

$$\langle \tau_i^2(T) \rangle_j = 2\int_0^T \mathrm{d}t_1 \int_0^{t_1} G_{ii}(t_1 - t_2) G_{ij}(t_2)\,\mathrm{d}t_2\,. \tag{4.8}$$

This is equivalent to the Laplace transform

$$\langle \hat{\tau}_i^2(s) \rangle_j = \frac{2}{s} \hat{G}_{ii}(s) \hat{G}_{ij}(s)\,. \tag{4.9}$$

An extension of this proof to higher moments shows that for integer $n > 0$,

$$\langle \hat{\tau}_i^n(s) \rangle_j = \frac{n!}{s} [\hat{G}_{ii}(s)]^{n-1} \hat{G}_{ij}(s)\,. \tag{4.10}$$

The Laplace transform of the propagator in Eq. (3.14) is

$$\hat{G}_{ij}(s) = \frac{1}{s} P_{\mathrm{eq}}(i) + [\delta_{ij} - P_{\mathrm{eq}}(i)] \hat{R}(s)\,, \tag{4.11}$$

where $\hat{R}(s)$ is the Laplace transform of the relaxation function defined in Eq. (3.15). On substituting this into Eq. (4.10) we find

$$\begin{aligned}\langle \hat{\tau}_i^n(s) \rangle_j = \frac{n!}{s} &\left\{ \frac{1}{s} P_{\mathrm{eq}}(i) + [\delta_{ij} - P_{\mathrm{eq}}(i)] \hat{R}(s) \right\} \\ &\times \left\{ \frac{1}{s} P_{\mathrm{eq}}(i) + [1 - P_{\mathrm{eq}}(i)] \hat{R}(s) \right\}^{n-1}\,.\end{aligned} \tag{4.12}$$

We parenthetically note that the leading term in $(1/s)$ in each of the moments is independent of the initial state but that the correction terms will be influenced by it.

When s is small the singular behavior in this expression will be due to the term s^{-1} which appears in the brackets of both terms in Eq. (4.12). Further, the small-s behavior of $\hat{R}(s)$ can be determined by substituting the expansion

$$\hat{\psi}_i(s) \approx 1 - \langle t_i \rangle s + \frac{\langle t_i^2 \rangle}{2} s^2 - \cdots \tag{4.13}$$

into Eq. (3.15). In this way we find that

$$\lim_{s\to 0}\hat{R}(s)=\hat{R}(0)=\frac{1}{2}\frac{\sigma_1^2\langle t_2\rangle^2+\sigma_2^2\langle t_1\rangle^2}{\langle t_1\rangle\langle t_2\rangle(\langle t_1\rangle+\langle t_2\rangle)} \tag{4.14}$$

in which $\sigma_i^2=\langle t_i^2\rangle-\langle t_i\rangle^2$.

A consequence of this analysis is that the large-T behaviors of the first two moments are

$$\begin{aligned}\langle\tau_i(T)\rangle_j &\approx P_{\rm eq}(i)T+[\delta_{ij}-P_{\rm eq}(i)]\hat{R}(0)\,,\\ \langle\tau_i^2(T)\rangle_j &\approx [P_{\rm eq}(i)T]^2+2P_{\rm eq}(i)[1+\delta_{ij}-2P_{\rm eq}(i)]\hat{R}(0)T\,,\end{aligned} \tag{4.15}$$

so that the variance is

$$\sigma_\tau^2(T)=\langle\tau_i(T)\rangle_j-\langle\tau_i(T)\rangle_j^2\approx 2P_{\rm eq}(1)P_{\rm eq}(2)\hat{R}(0)T\,. \tag{4.16}$$

This expression is independent of i and j. Thus, the variance becomes a universal function at large T. After inserting the detailed expressions for the parameters on the right-hand side one finds that

$$\sigma_\tau^2(T)\approx\frac{\sigma_1^2\langle t_2\rangle^2+\sigma_2^2\langle t_1\rangle^2}{(\langle t_1\rangle+\langle t_2\rangle)^3}T \tag{4.17}$$

independent of the initial state.

4.2. The large-T form of the probability density

When T is sufficiently large there will have been many sojourns in both states. An argument suggested by the central-limit theorem would lead us to conclude that the asymptotic form of the probability density should be a Gaussian, which is to say that

$$p_i(\tau|T)=\frac{1}{\sigma_\tau(T)\sqrt{2\pi}}\exp\left\{-\frac{[\tau-P_{\rm eq}(i)T]^2}{2\sigma_\tau^2(T)}\right\}\,. \tag{4.18}$$

This is indeed correct and can be derived directly from results described later in this paper.

A slightly more informative version of this probability density is that which describes the behavior of the fraction of time spent in S_1. This fraction is $x=\tau/T$. The resulting probability density will be denoted by $h_i(x|T)$ which is found by an elementary transformation of $p_i(\tau|T)$ to be

$$h_i(x|T)=\frac{1}{\sigma_x(T)\sqrt{2\pi}}\exp\left\{-\frac{[x-P_{\rm eq}(i)]^2}{2\sigma_x^2(T)}\right\}\,, \tag{4.19}$$

where the variance, $\sigma_x^2(T)$, is

$$\sigma_x^2(T)=\frac{\sigma_\tau^2(T)}{T^2}=\frac{2P_{\rm eq}(1)P_{\rm eq}(2)\hat{R}(0)}{T}\,. \tag{4.20}$$

When $T\to\infty$ the variance $\sigma_x^2(T)$ goes to zero. Thus $h_i(x|T)$ has the property that

$$\lim_{T\to\infty}h_i(x|T)=\delta(x-P_{\rm eq}(i)) \tag{4.21}$$

which has the practical implication that an infinite record of a single trajectory can only furnish information about the equilibrium constant. It is therefore a form of ergodicity.

4.3. Derivation of the Fourier–Laplace transform of $p_i(\tau|T|j)$

In this subsection we derive the Fourier–Laplace transform of $p_i(\tau|T|j)$ defined by

$$\hat{p}_i(\omega|s|j) = \int_{-\infty}^{\infty} e^{i\omega\tau}\, d\tau \int_0^{\infty} e^{-sT} p_i(\tau|T|j)\, dT\,. \tag{4.22}$$

The derivation conceptually follows the ideas presented in Refs. [22,23]. As a first step of the derivation we introduce an auxiliary function $\rho_i(\tau|T|j)$ which is analogous to $p_i(\tau|T|j)$ except that the initial observation coincides with the beginning of a sojourn in S_j. The $\rho_i(\tau|T|j)$ can be found from a pair of coupled integral equations. For example, the $\rho_1(\tau|T|j)$ satisfy

$$\begin{aligned}
\rho_1(\tau|T|1) &= \Psi_1(T)\delta(\tau - T) + \int_0^T \psi_1(t)\rho_1(\tau - t|T - t|2)\, dt,\\
\rho_1(\tau|T|2) &= \Psi_2(T)\delta(\tau) + \int_0^T \psi_2(t)\rho_1(\tau|T - t|1)\, dt.
\end{aligned} \tag{4.23}$$

The first terms on the right-hand sides of these equations account for those trajectories in which the system never changes state during the time T, while the integral terms account for trajectories in which at least one change of state has been made.

The Fourier–Laplace transforms of the $\rho_1(\tau|T|j)$, defined as in Eq. (4.22), provides a set of two equations

$$\begin{aligned}
\hat{\rho}_1(\omega|s|1) &= \hat{\Psi}_1(s - i\omega) + \hat{\psi}_1(s - i\omega)\hat{\rho}_1(\omega|s|2)\,,\\
\hat{\rho}_1(\omega|s|2) &= \hat{\Psi}_2(s) + \hat{\psi}_2(s)\hat{\rho}_1(\omega|s|1)
\end{aligned} \tag{4.24}$$

which are easily solved:

$$\begin{aligned}
\hat{\rho}_1(\omega|s|1) &= \frac{\hat{\Psi}_1(s - i\omega) + \hat{\psi}_1(s - i\omega)\hat{\Psi}_2(s)}{1 - \hat{\psi}_1(s - i\omega)\hat{\psi}_2(s)}\,,\\
\hat{\rho}_1(\omega|s|2) &= \frac{\hat{\Psi}_2(s) + \hat{\Psi}_1(s - i\omega)\hat{\psi}_2(s)}{1 - \hat{\psi}_1(s - i\omega)\hat{\psi}_2(s)}\,.
\end{aligned} \tag{4.25}$$

When the $\hat{\rho}_i(\omega|s|j)$ are known one can calculate the joint transforms of $p_i(\tau|T|j)$ which are the probability densities taking the proper initial conditions into account.

As an example, the integral equation satisfied by $p_1(\tau|T|1)$ is

$$p_1(\tau|T|1) = \Psi_1^{(0)}(T)\delta(\tau - T) + \int_0^T \psi_1^{(0)}(t)\rho_1(\tau - t|T - t|2)\, dt\,. \tag{4.26}$$

The first term on the right-hand side accounts for trajectories that remain in S_1 for the entire time T, while the integral term accounts for all of the remaining trajectories. The joint transform of this probability density is therefore equal to

$$\hat{p}_1(\omega|s|1) = \hat{\Psi}_1^{(0)}(s - i\omega) + \hat{\psi}_1^{(0)}(s - i\omega)\hat{\rho}_1(\omega|s|2)\,. \tag{4.27}$$

An expansion of $\hat{p}_1(\omega|s|1)$ in the neighborhood of $(\omega,s)=(0,0)$ can be used to prove that $p_1(\tau|T|1)$ is asymptotically Gaussian as in Eq. (4.18). In the Markovian case, in which the $\psi_i(t)$ are exponential it is possible to invert the transforms to find $p_i(\tau|T|j)$ explicitly [12].

5. Discussion

In this paper we have shown how to calculate statistical properties of the time spent in one of a pair of states. An appeal to the central-limit theorem yields an asymptotic Gaussian approximation to the probability density of the sojourn time in S_i when the first two moments of the sojourn times are finite, and are given in Eq. (4.15). In the following paper we show how to reduce systems with three or more states, to an equivalent two-state system, provided that only the probability density for the fraction of time spent in one of the states is required. Formalism relating to problems requiring the joint probability density in several states can also be developed [37].

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