THE JOURNAL OF PHYSICAL CHEMISTRY A

ARTICLE

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Single Molecule Diffusion and the Solution of the Spherically Symmetric Residence Time Equation

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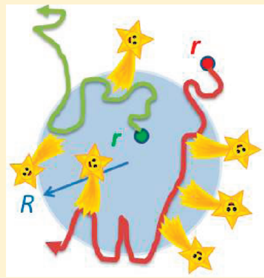
ABSTRACT: The residence time of a single dye molecule diffusing within a laser spot is propotional to the total number of photons emitted by it. With this application in mind, we solve the spherically symmetric "residence time equation" (RTE) to obtain the solution for the Laplace transform of the mean residence time (MRT) within a d-dimensional ball, as a function of the initial location of the particle and the observation time. The solutions for initial conditions of potential experimental interest, starting in the center, on the surface or uniformly within the ball, are explicitly presented. Special cases for dimensions 1, 2, and 3 are obtained, which can be Laplace inverted analytically for $d = 1$ and 3. In addition, the analytic short- and long-time asymptotic behaviors of the MRT are derived and compared with the exact solutions for $d = 1$, 2, and 3. As a demonstration of the simplification afforded by the RTE, the Appendix obtains the residence time distribution by solving the Feynman−Kac equation, from which the MRT is obtained by differentiation. Single-molecule diffusion experiments could be devised to test the results for the MRT presented in this work.



INTRODUCTION

When a laser beam is focused onto a tiny volume element (e.g., 1 fl) in a solution containing a very low (subnanomolar) concentration (c) of a fluorophore, fluorescence bursts can be observed.[1−8] These photonic fluctuations are largely due to a single dye molecule that diffuses (diffusion coefficient D) in and out of the laser focus, until it eventually escapes to large distances from it (Figure 1). Under steady-state illumination, for an idealized scenario in which the laser spot is a three-dimensional ball of radius R, which is uniformly illuminated, dye molecules arrive at its surface with the diffusion-control rate coefficient[9] $4\pi DRc$, which determines the waiting time between bursts. Once on the surface, the particle resides in the ball for an average duration $R^2/3D$,[2,10] which determines the average burst duration (hence also the average number of photons emitted).[2] A more detailed theoretical discussion can be found in section IV of ref 11.

Consequently, under steady-state conditions it suffices to consider particles starting on the surface of the sphere (those starting within the sphere contribute only a fast initial transient). Their mean residence time (MRT) within a three-dimensional ball (B_3) for an infinite observation time ($t \to \infty$), denoted here by $\langle \tau_{B_3}(\infty|R)\rangle$, is thus a fundamental quantity relevant for analyzing fluorescence bursts from a single freely diffusing dye molecule. More generally, the distribution of the number of emitted photons[11,12] is related to the distribution, $F_\tau(\infty|R)$, of the residence time τ (see Appendix). Interestingly, not only a spot of light can be generated but also a "spot of protons", namely a spatial pH jump.[13] Dyes diffusing through this spot will change their protonation state, and this could be detected spectroscopically.

We have previously evaluated these quantities for $t \to \infty$ and an arbitrary starting point r.[14] Setting $r = R$ in eq 3.16 of ref 14 (with the evident change of notations) indeed yields $\langle \tau_{B_3}(\infty|R)\rangle = R^2/3D$, as suggested earlier by Eigen.[10]

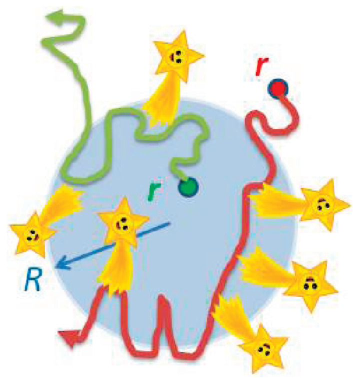


Figure 1. Schematic depiction of the residence time scenario. When the trajectory of the diffusing particle resides within the spherical domain of radius R, it is photoexcited by a continuous illumination source, resulting in photon emission (yellow stars). Thus the total number of photons emitted is proportional to the particle's residence time within the domain. The red trajectory starts outside the domain, whereas the green one starts inside it.

Single molecule diffusion experiments can be performed also on surfaces, membranes,[15] or filaments,[16,17] and these depend on the MRT for dimensions $d = 2$ or 1, respectively. For example, one-dimensional single-molecule motion occurs when motor proteins move along cellular filaments such as myosin on actin or kinesin/dynein on microtubules. In the so-called "single-motor assay", the filament is attached to a glass surface and the motor protein is

Special Issue: Victoria Buch Memorial

Received: October 18, 2010
Revised: December 24, 2010
Published: February 09, 2011

monitored via the fluorescence of a fused fluorescent dye.[16] Evidently, this involves an additional biasing force in the diffusion equation, which is outside the scope of the present article. Interestingly, however, it was recently found that single myosin Va molecules *diffuse* along microtubules (Figure 4 in ref 17), so that the equations below (for $d = 1$) may be relevant to such experiments.

Consequently, it is not sufficient to obtain the MRT in three-dimensions.[14] Recently, $\langle \tau_{B_d}(\infty|r)\rangle$ for arbitrary dimensionality, d, was obtained in eqs 10 and 11 of ref 18 (one equation is valid for $r \le R$ and the other for $r \ge R$). Here we obtain the most general solution, $\langle \tau_{B_d}(t|r)\rangle$, for an arbitrary observation time, t, arbitrary starting point, r, and arbitrary d. In the special case that $r = R$, it is proportional to the average number of emitted photons from the onset of a burst ($t = 0$) and up to time t. This quantity is thus particularly relevant to experiments in which single bursts can be clearly identified.

A different initial condition may be relevant for anticipated two-wavelength experiments, in which a laser pulse at one wavelength initiates a fast irreversible chemical reaction within the laser spot, and a second wavelength is used to probe the products of this reaction. For example, a spatial pH jump[13] could protonate all dye molecules within B_d, creating a uniform concentration of protonated dyes there. A second (continuous) laser could selectively excite the protonated form, whose emitted photons would be collected in such experiments. If the spots of the two lasers overlap, the total number of photons collected between the initiating pulse ($t = 0$) and time t should be proportional to $\langle \tau_{B_d}(t|B_d)\rangle$, the MRT when starting uniformly within B_d. If, however, the first spot is considerably smaller, one could approximate the pH jump as occurring at the origin, so that the relevant MRT would be $\langle \tau_{B_d}(t|0)\rangle$.

This scenario closely resembles reversible geminate recombination, which has been studied experimentally for excited-state proton transfer,[19−21] and also studied with considerable theoretical detail.[22−25] The presence of a specified molecule inside B_d is analogous to the bound state, but its entry and exit from this region do not involve additional rate coefficients, as it occurs diffusively. We therefore expect that the ubiquitous power-law decay of the geminate recombination binding probability, as $(4Dt)^{-d/2}$, will characterize also the long time behavior of the probability to reside within B_d, $P_{B_d}(t)$. Because $P_{B_d}(t)$ is just the time derivative of the MRT, it is also obtainable from the present analysis.

Much before the interest of the physical-chemistry community in residence times,[26] "occupation times" have been investigated by mathematicians, notably Paul Lévy[27] and Marc Kac.[28,29] They have considered the more general problem of calculating "Brownian functionals" defined along random-walk trajectories. Since then, the topic has become a textbook subject in random walks and diffusion theory.[30−34] Recently there has been growing interest in the application of Brownian functionals to various problems in physics, chemistry and economics.[14,35−43]

The canonical route for calculating the residence time probability density, $F_\tau(t|r)$, employs the Feynman−Kac (FK) formula[37] for $S_k(t|r)$, its Laplace transform (LT) with respect to τ. A similar equation has been derived for the generating function of the distribution of the number of emitted photons from a freely diffusing molecule; see eq 5.4 in ref 12. The various residence time moments (the first one being the MRT) can be generated from this equation by differentiation with respect to k. This is demonstrated in the Appendix.

However, when only the MRT is required, the FK route becomes unnecessarily tedious. A more direct procedure involves the solution of the "residence time equation" (RTE).[18] In ref 18, its spherically symmetric solution was obtained for $t \to \infty$. Here we solve it for arbitrary t and in any dimensionality. The initial condition is either an arbitrary distance, r, or one of the experimentally relevant initial conditions: Starting on the surface of B_d, its center, or uniformly within its volume. We obtain the special solutions for $d = 1$, 2, and 3, as well as the asymptotic behavior at short and long times. While fragments of this solution can be found in the literature,[14,29,34,39,41] a systematic and comprehensive discussion is unavailable elsewhere. It appears that the progress in single molecule diffusion makes such an exposition timely and, hopefully, also useful.

■ RESIDENCE TIME EQUATION

In this section we review the derivation of the RTE[18] − a partial differential equation for the MRT as a function of the observation time, t, and the initial position of the particle, $\mathbf{r}$, within a d-dimensional Euclidean space. We assume that the particle obeys a "normal" diffusion equation with a diffusion coefficient D. Its probability density to be by time t at point $\mathbf{r}'$ given that it was initially ($t = 0$) at $\mathbf{r}$, is denoted by $p(\mathbf{r}',t|\mathbf{r})$. This Green's function obeys the so-called "backward diffusion equation" in the initial coordinate:

$$\frac{\partial p(\mathbf{r}',t|\mathbf{r})}{\partial t} = D\Delta_d\, p(\mathbf{r}',t|\mathbf{r}) \tag{1}$$

where Δ_d is the d-dimensional Laplacian in the initial variable $\mathbf{r}$. The initial condition for this partial differential equation (PDE) is $p(\mathbf{r}',0|\mathbf{r}) = \delta(\mathbf{r}'-\mathbf{r})$, where $\delta(z)$ is the Dirac delta function. The solution of this PDE is equivalent to an average over an infinitely large ensemble of random trajectories.

From the Green's function, one may define the MRT within a volume element V as[26]

$$\langle \tau_V(t|\mathbf{r})\rangle \equiv \int_V \mathrm{d}\mathbf{r}' \int_0^t p(\mathbf{r}',t'|\mathbf{r})\, \mathrm{d}t' \tag{2}$$

where $\langle ...\rangle$ denotes averaging over an ensemble of random trajectories. In the above expression, the infinitesimal residence time, dt, is averaged with respect to the probability of residing in V at time t, which is

$$P_V(t|\mathbf{r}) \equiv \int_V p(\mathbf{r}',t|\mathbf{r})\, \mathrm{d}\mathbf{r}' = \partial\langle \tau_V(t|\mathbf{r})\rangle/\partial t \tag{3}$$

By performing the integrations on eq 1 first, one obtains the RTE:

$$\frac{\partial\langle \tau_V(t|\mathbf{r})\rangle}{\partial t} = D\Delta_d\langle \tau_V(t|\mathbf{r})\rangle + \Theta_V(\mathbf{r}) \tag{4}$$

Here $\Theta_V(\mathbf{r}) \equiv \int_V \delta(\mathbf{r}'-\mathbf{r})\, \mathrm{d}\mathbf{r}'$ is the characteristic function of the domain V, which equals 1 if $\mathbf{r} \in V$ and 0 otherwise. Thus if $D = 0$, the MRT is just t for a particle inside V and 0 otherwise. The initial condition is evidently $\langle \tau_V(0|\mathbf{r})\rangle = 0$. Continuity conditions (of the solution and its first derivative) are imposed on the surface of V, and boundary conditions − at the boundaries of the diffusion space. Equations for the higher moments can also be derived,[18] but these are not dealt with in the present work. [The second moment for a finite diffusion space is discussed in ref 42].

The RTE simplifies for spherical symmetry. We thus assume that the domain V is a d-dimensional ball (B_d) of radius R, centered on the origin. The solution now depends only on a single spatial coordinate, the radial distance $r \equiv |\mathbf{r}|$. The spherically symmetric Laplacian,

$$\Delta_d = r^{1-d} \frac{\partial}{\partial r} r^{d-1} \frac{\partial}{\partial r} \tag{5a}$$

can be written in an alternative form, which makes the connection with the Bessel equation more transparent:

$$\Delta_d = r^{1-d/2} \left[\frac{\partial^2}{\partial r^2} + \frac{1}{r}\frac{\partial}{\partial r} - \frac{1}{r^2}\left(1 - \frac{d}{2}\right)^2 \right] r^{d/2-1} \tag{5b}$$

The boundary conditions are zero flux at the origin, $r^{d-1}\partial\langle\tau_{B_d}(t|r)\rangle/\partial r \to 0$ as $r \to 0$, and a vanishing MRT when starting infinitely far away, $\langle\tau_{B_d}(t|r)\rangle \to 0$ as $r \to \infty$. In addition, we shall impose continuity conditions on the solution and its first derivative at $r = R$.

GENERAL SOLUTION FOR THE MRT IN A SPHERICAL DOMAIN

The general solution for the time-dependent MRT (for arbitrary d) can be obtained only in Laplace space, where the LT of a function $f(t)$ is defined by $\hat{f}(s) \equiv \int_0^\infty \exp(-st) f(t)\, dt$. The LT of eq 4, with the spherically symmetric Laplacian of eq 5b, is

$$\left\{ \alpha^{-2} r^{1-d/2} \left[\frac{\partial^2}{\partial r^2} + \frac{1}{r}\frac{\partial}{\partial r} - \frac{1}{r^2}\left(1 - \frac{d}{2}\right)^2 \right] r^{d/2-1} - 1 \right\} \langle\hat{\tau}_{B_d}(s|r)\rangle = -s^{-2} H(R - r) \tag{6}$$

where $\alpha \equiv (s/D)^{1/2}$ (abbreviations are collected in the Appendix). Inside of B_d, this ordinary differential equation is inhomogeneous, possessing the special solution s^{-2}. Indeed, eq 5a implies that $\Delta_d f = 0$ for any function f that is independent of r. It remains to find the general solution to the homogeneous equation, where the right-hand side (rhs) is replaced by 0.

Changing the dependent variable to $r^{d/2-1}\langle\hat{\tau}_{B_d}(s|r)\rangle$, yields a modified Bessel equation of order $\nu = d/2 - 1$ in the independent variable αr. The boundary conditions eliminate one or the other linearly independent solutions, so that the solution is proportional to the modified Bessel functions[44] $I_{d/2-1}(\alpha r)$ for $r < R$ and $K_{d/2-1}(\alpha r)$ for $r > R$. [Note that $K_\nu(x) = K_{-\nu}(x)$]. The two integration constants are determined by matching the solution and its derivative at $r = R$, giving

$$s^2\langle\hat{\tau}_{B_d}(s|r)\rangle = 1 - \left(\frac{R}{r}\right)^{d/2} \alpha r K_{d/2}(\alpha R)\, I_{d/2-1}(\alpha r) \qquad r \le R \tag{7a}$$

$$s^2\langle\hat{\tau}_{B_d}(s|r)\rangle = \left(\frac{R}{r}\right)^{d/2} \alpha r I_{d/2}(\alpha R)\, K_{1-d/2}(\alpha r) \qquad r \ge R \tag{7b}$$

Thus the LT of the time-dependent MRT for a spherically symmetric domain is obtained in a straightforward manner from the RTE for any dimensionality or initial location of the diffusing particle. Moreover, it is simultaneously the solution for the LT of the residence probability, because $\hat{P}_{B_d}(s|r) = s\langle\hat{\tau}_{B_d}(s|r)\rangle$. Although eq 7 is the most general form of the desired solution, various special cases are of interest. These will be discussed in the remainder of this work.

EXPERIMENTALLY RELEVANT INITIAL CONDITIONS

As discussed in the Introduction, current experimental setups excite the fluorophore with a single wavelength from a continuous or pulsed laser. As steady-state conditions are established, dye molecules impinge upon the surface of the sphere at a constant rate, so that only the MRT from the surface is of interest.[2] Setting $r = R$ in eq 7 one obtains

$$s^2\langle\hat{\tau}_{B_d}(s|R)\rangle = Z I_{d/2}(Z)\, K_{1-d/2}(Z) \tag{8}$$

where $Z \equiv \alpha R = (sR^2/D)^{1/2}$.

Alternately, caged molecules may be released in the laser spot by a short laser pulse and their fluorescence monitored by a second (continuous) laser. In the simplest scenario, this creates a uniform concentration of molecules within B_d. The average fluorescence signal from such decaged dye molecules would be proportional to the MRT, which is averaged over this volume element:

$$\langle\hat{\tau}_{B_d}(s|B_d)\rangle = \frac{1}{V_d}\int_0^R \langle\hat{\tau}_{B_d}(s|r)\rangle \frac{2\pi^{d/2}}{\Gamma(d/2)} r^{d-1}\, dr = \frac{d}{R^d}\int_0^R \langle\hat{\tau}_{B_d}(s|r)\rangle r^{d-1}\, dr \tag{9}$$

Here $V_d = \pi^{d/2}R^d/\Gamma(1+d/2)$ is the volume of B_d and $\Gamma(x)$ is the Euler Gamma function, which obeys the recurrence relation $\Gamma(x+1) = x\Gamma(x)$. Using the definite integral[44] $\int_0^R x^\nu I_{\nu-1}(x)\, dx = R^\nu I_\nu(R)$, we obtain

$$s^2\langle\hat{\tau}_{B_d}(s|B_d)\rangle = 1 - dI_{d/2}(Z)\, K_{d/2}(Z) \tag{10}$$

If the probe pulse has a much wider spot than the release pulse (but they nevertheless share the same center-point), one could approximate the initial condition as a delta-function at the origin. Because $x^{-\nu}I_\nu(x) \to 2^{-\nu}/\Gamma(\nu+1)$ as $x \to 0$, eq 7a reduces to

$$s^2\langle\hat{\tau}_{B_d}(s|0)\rangle = 1 - 2(Z/2)^{d/2} K_{d/2}(Z)/\Gamma(d/2) \tag{11}$$

It is useful to have the LTs for these special cases, because sometimes they can be inverted more easily than the general case.

ONE, TWO, AND THREE DIMENSIONS

Although eq 7 is valid for any dimensionality, it is useful to write down the specific expressions for $d = 1$, 2, and 3. In particular, for $d = 1$ and 3 the Bessel functions are of half-integer order, and these can be written more compactly using hyperbolic functions,[44] allowing analytic inversion into the time domain. In these cases the Laplace inverse can be conveniently written in terms of the repeated integrals of the coerror function, so we first summarize some useful properties of these functions.

Repeated Integrals of the Coerror Function. The nth repeated coerror integral is defined by $\mathrm{i}^n\mathrm{erfc}(x) \equiv \int_x^\infty \mathrm{i}^{n-1}\mathrm{erfc}(x')\, dx'$. These functions obey the recursion relation[44]

$$\mathrm{i}^n\mathrm{erfc}(x) = -\frac{x}{n}\mathrm{i}^{n-1}\mathrm{erfc}(x) + \frac{1}{2n}\mathrm{i}^{n-2}\mathrm{erfc}(x) \tag{12}$$

for $n = 1, 2, 3, \ldots$, where $\mathrm{i}^0\mathrm{erfc}(x) \equiv \mathrm{erfc}(x)$ is the complementary error ("coerror") function, and $\mathrm{i}^{-1}\mathrm{erfc}(x) \equiv 2\exp(-x^2)/\pi^{1/2}$ is its derivative. From this relation, the first three functions are obtained as follows:

$$\mathrm{i}^1\mathrm{erfc}(x) = -x\,\mathrm{erfc}(x) + \mathrm{e}^{-x^2}/\sqrt{\pi} \tag{13a}$$

$$4\mathrm{i}^2\mathrm{erfc}(x) = (1+2x^2)\,\mathrm{erfc}(x) - 2x\mathrm{e}^{-x^2}/\sqrt{\pi} \tag{13b}$$

$$12\mathrm{i}^3\mathrm{erfc}(x) = -x(3+2x^2)\,\mathrm{erfc}(x) + 2(1+x^2)\mathrm{e}^{-x^2}/\sqrt{\pi} \tag{13c}$$

In particular, $\mathrm{i}^n\mathrm{erfc}(0) = 1/\pi^{1/2}$, $1/4$, and $1/(6\pi^{1/2})$ for $n = 1, 2$, and 3, respectively.

A useful LT involving the repeated integrals of the coerror function is given by

$$\int_0^\infty (4t)^{n/2}\mathrm{i}^n\mathrm{erfc}\left(\frac{x}{\sqrt{4Dt}}\right)\mathrm{e}^{-st}\,\mathrm{d}t = \frac{\mathrm{e}^{-\sqrt{s/D}x}}{s^{1+n/2}} \tag{14}$$

see Appendix V in ref 45. This relation will be used repeatedly below to generate time-domain results.

One Dimension. In one dimension, eq 7 depicts the LT of the MRT in the interval $[-R, R]$ for diffusion on the infinite line, and the particle placed initially (with equal probabilities) at $+r$ or $-r$ (we assume that $r \geq 0$). This solution is also applicable for the interval $[0, R]$ when diffusion takes place on the positive half-line. It is rewritten in terms of hyperbolic functions as

$$s^2\langle\hat{\tau}_{\mathrm{B}_1}(s|r)\rangle = 1 - \cosh(\alpha r)\,\mathrm{e}^{-\alpha R} \qquad r \leq R \tag{15a}$$

$$s^2\langle\hat{\tau}_{\mathrm{B}_1}(s|r)\rangle = \sinh(\alpha R)\,\mathrm{e}^{-\alpha r} \qquad r \geq R \tag{15b}$$

Using eq 14 with $n = 2$ we get

$$\langle\tau_{\mathrm{B}_1}(t|r)\rangle = t - 2t\left[\mathrm{i}^2\mathrm{erfc}\left(\frac{R-r}{\sqrt{4Dt}}\right) + \mathrm{i}^2\mathrm{erfc}\left(\frac{R+r}{\sqrt{4Dt}}\right)\right] \quad r \leq R \tag{16a}$$

$$\langle\tau_{\mathrm{B}_1}(t|r)\rangle = 2t\left[\mathrm{i}^2\mathrm{erfc}\left(\frac{r-R}{\sqrt{4Dt}}\right) - \mathrm{i}^2\mathrm{erfc}\left(\frac{r+R}{\sqrt{4Dt}}\right)\right] \quad r \geq R \tag{16b}$$

The second repeated coerror integral is given explicitly in eq 13b.

Figure 2 depicts the behavior of this solution as a function of t for various values of r. Clearly, $\langle\tau_{\mathrm{B}_1}(t|r)\rangle < t$, decreasing with increasing r. When $r < R$, the short time behavior of $\langle\tau_{\mathrm{B}_1}(t|r)\rangle$ is like t (black dashed line), whereas when $r = R$ it is $t/2$ (dash-dot line), because from the boundary the particle can step with equal probabilities left or right. When $r > R$, it starts off with a delay due to the time required to diffuse from r into the residence interval. Figure 2B shows this function to longer times on a log−log scale. Because for $d < 2$ the random walk is recurrent, returning to the specified interval with unit probability, the MRT becomes independent of the initial location of the particle as $t \to \infty$, though the approach to the dashed line is slower for larger r values.

Returning to the experimentally relevant initial conditions, we note that when $r = R$, we get $\langle\hat{\tau}_{\mathrm{B}_1}(s|R)\rangle = [1-\exp(-2Z)]/(2s^2)$, which is eq 57 in ref 39. [As before, we use the abbreviation $Z \equiv (sR^2/D)^{1/2}$]. From eq 14, its Laplace inverse is

$$\langle\tau_{\mathrm{B}_1}(t|R)\rangle = \frac{t}{2}[1 - 4\mathrm{i}^2\mathrm{erfc}(2z)] \tag{17}$$

where $z \equiv R/(4Dt)^{1/2}$. This result, of course, can be obtained also by setting $r = R$ in eq 16 and noting that $\mathrm{i}^2\mathrm{erfc}(0) = 1/4$. Thus, initially, the particle spends equal time inside and outside the interval, and this explains the leading $t/2$ term. The solution when

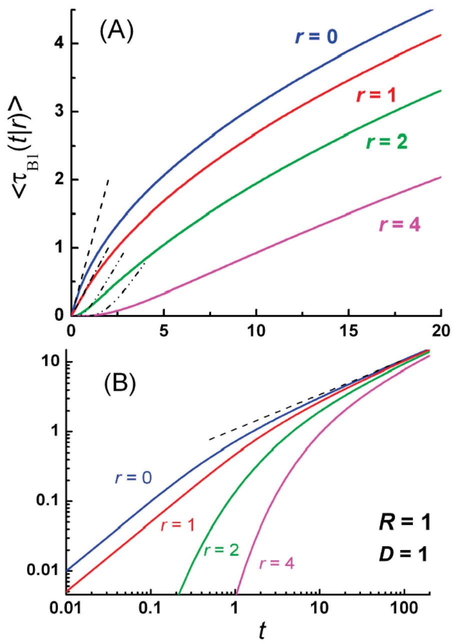


Figure 2. Time dependence of the mean residence time in the interval $[-R, R]$ for a particle diffusing on the line, starting from various initial positions, r (indicated). Here $D = 1$ and $R = 1$. The MRT was evaluated here in two equivalent routes: (i) from eqs 16 and 13b, using MatLab (TM); (ii) by performing the double integral in eq 2. In the latter case, the spatial integral was performed numerically over the "Special region" in the "Variables" menu of our Windows application for solving the Spherically Symmetric Diffusion Problem (SSDP ver. 2.66[46]), whereas the temporal integral was performed using MatLab's trapezoidal numerical integration. (A) Short times, linear scale. Dash and dash-dot lines depict the functions t and $t/2$. Dash-dot-dot lines are the short-time approximation from eq 36b. (B) Longer times on a log−log scale. The dashed black line is the universal long-time asymptotics of eq 42.

starting at the origin has a similar structure

$$\langle\tau_{\mathrm{B}_1}(t|0)\rangle = t[1 - 4\mathrm{i}^2\mathrm{erfc}(z)] \tag{18}$$

except that now it begins as t, and the $\mathrm{i}^2\mathrm{erfc}$ term varies faster with time.

For a uniform distribution inside the interval one gets

$$s^2\langle\hat{\tau}_{\mathrm{B}_1}(s|\mathrm{B}_1)\rangle = 1 - \sinh(Z)\,\mathrm{e}^{-Z}/Z \tag{19}$$

This can be verified by setting $d = 1$ in eq 10 or by integrating eq 15a. It inverts as

$$\langle\tau_{\mathrm{B}_1}(t|\mathrm{B}_1)\rangle = t\left[1 - \frac{1}{3\sqrt{\pi}\,z} + \frac{2}{z}\,\mathrm{i}^3\mathrm{erfc}(2z)\right] \tag{20}$$

where the third repeated integral of the coerror function is given in eq 13c.

Two Dimensions. This geometry is relevant for a single-molecule diffusing on a planar membrane on which a circular laser spot is focused. Equation 7 now reduces to

$$s^2\langle\hat{\tau}_{\mathrm{B}_2}(s|r)\rangle = 1 - \alpha R\,K_1(\alpha R)\,I_0(\alpha r) \qquad r \leq R \tag{21a}$$

$$s^2\langle\hat{\tau}_{\mathrm{B}_2}(s|r)\rangle = \alpha R\,I_1(\alpha R)\,K_0(\alpha r) \qquad r \geq R \tag{21b}$$

These relations can be inverted only numerically. Alternatively, the MRT can be calculated numerically from the double integral

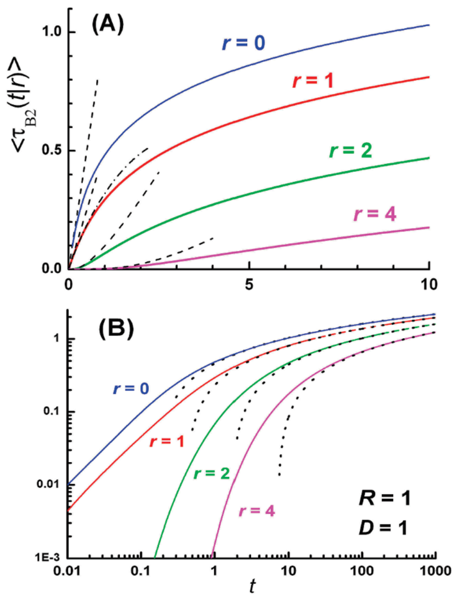


Figure 3. Time dependence of the mean residence time in the unit circle for a particle diffusing in the plane, starting from various indicated values of r, for $D = 1$ and $R = 1$. Calculated from the double integral of eq 2; see legend of Figure 2 for detail. For $r = 0$ the MRT was calculated also from eq 25, and this revealed that the double integral computation is accurate to about 2% (less than can be resolved in the figure). (A) Short times, linear scale. The dashed black lines depict the short-time approximation from eq 36. The dash-dot line is from eq 39 (for $r = 1$). (B) Longer times, log−log scale. Dotted black lines show the long-time approximation from eq 52 with $\gamma(r) = 0.46, 0.23, -0.13$, and -0.49 for $r = 0, 1, 2$, and 4, respectively.

of eq 2. We have used this to produce Figure 3, showing the MRT in the unit circle for different initial distances, r, of the particle from the origin.

In the special case that the particle starts on the perimeter of the circle one obtains

$$s^2\langle\hat{\tau}_{B_2}(s|R)\rangle = ZI_1(Z)\,K_0(Z) \tag{22}$$

whereas for a uniform initial distribution within the circle we get

$$s^2\langle\hat{\tau}_{B_2}(s|B_2)\rangle = 1 - 2I_1(Z)\,K_1(Z) \tag{23}$$

These LT's do not appear to be invertible in terms of familiar special functions.

However, when the random walk starts at the center of the disk, the solution can be obtained analytically. Utilizing the fact that $I_0(0) = 1$, eq 21 reduces to

$$s^2\langle\hat{\tau}_{B_2}(s|0)\rangle = 1 - ZK_1(Z) \tag{24}$$

This, of course, can also be obtained by setting $d = 2$ in eq 11. Its Laplace inverse is

$$\langle\tau_{B_2}(t|0)\rangle = t[1 - z^2\Gamma(-1,z^2)] \tag{25}$$

where $\Gamma(a,x) \equiv \int_x^\infty \exp(-y)y^{a-1}\,dy$ is the (upper) incomplete Gamma function.[44] It is related to the exponential integral, $E_1(x) \equiv \int_x^\infty \exp(-y)y^{-1}\,dy$, by

$$\Gamma(-1,x) = \exp(-x)/x - E_1(x) \tag{26}$$

This provides a more practical way to calculate $\Gamma(a,x)$ when $a = -1$, because it is usually defined only for positive a.

The result in eq 25 can alternately be obtained by integrating the diffusion Green's function for $d = 2$ according to eq 2. A first, spatial, integration over the disk gives

$$\begin{aligned} P_{B_2}(t|0) &= \int_0^R \frac{\exp(-r'^2/4Dt)}{4\pi Dt}\,2\pi r'\,dr' \\ &= 1 - \exp(-z^2) \end{aligned} \tag{27}$$

A second, temporal, integration then gives the MRT: $\langle\tau_{B_2}(t|0)\rangle = \int_0^t P_{B_2}(t'|0)\,dt'$, from which eq 25 is obtained by a change of variables, $y = 1/t'$.

Three Dimensions. The three-dimensional problem depicts a freely diffusing single molecule in solution,[1−8] as discussed at length in the Introduction. The simplifying assumptions are that the laser spot is spherical and its intensity is uniform therein. In reality, the spot may assume other geometrical shapes (such as a cylinder) and the light density distribution may be nonuniform (e.g., Gaussian). Such technical complications are beyond the goals of the present exposition, which focuses on the simplest physical scenario.

For $d = 3$ the Bessel functions are of half-integer order and can thus be written in terms of hyperbolic functions.[44] Subsequently, eq 7 reduces to

$$1 - s^2\langle\hat{\tau}_{B_3}(s|r)\rangle = (1 + \alpha R)\sinh(\alpha r)e^{-\alpha R}/(\alpha r) \qquad r \le R \tag{28a}$$

$$s^2\langle\hat{\tau}_{B_3}(s|r)\rangle = [\alpha R\cosh(\alpha R) - \sinh(\alpha R)]e^{-\alpha r}/(\alpha r) \qquad r \ge R \tag{28b}$$

in agreement with eqs 8 and 9 in ref 41. These authors have inverted this LT as follows:

$$\langle\tau_{B_3}(t|r)\rangle = \langle\tau_{B_3}(\infty|r)\rangle + \phi(R,r,t) - \phi(-R,r,t) \tag{29}$$

The infinite time limit is given by[14] $D\langle\tau_{B_3}(\infty|r)\rangle = R^2/2 - r^2/6$ for $r \le R$ and $R^3/(3r)$ for $r \ge R$ (see below), and the function ϕ is defined as

$$\begin{aligned} \phi(R,r,t) &= \frac{t}{3\sqrt{\pi}\,z'}[1 + (z+z')(z'-2z)]\,e^{-(z+z')^2} \\ &\quad + t\left(\frac{1}{2} + \frac{z'^2}{3} - \frac{2z^3}{3z'} - z^2\right)\operatorname{erf}(z+z') \end{aligned} \tag{30}$$

where $z \equiv R/(4Dt)^{1/2}$ and $z' \equiv r/(4Dt)^{1/2}$. The time dependence of the MRT for various r values is demonstrated in Figure 4.

When starting on the surface of the sphere, one has

$$\langle\hat{\tau}_{B_3}(s|R)\rangle = [Z - 1 + (Z+1)\exp(-2Z)]/(2Zs^2) \tag{31}$$

By eq 14, its Laplace inverse is

$$\begin{aligned} \langle\tau_{B_3}(t|R)\rangle = t\Bigg[&\frac{1}{2} - \frac{2}{3}\sqrt{\frac{Dt}{\pi R^2}} + 2i^2\operatorname{erfc}\left(\frac{R}{\sqrt{Dt}}\right) \\ &+ 4\frac{\sqrt{Dt}}{R}\,i^3\operatorname{erfc}\left(\frac{R}{\sqrt{Dt}}\right)\Bigg] \end{aligned} \tag{32a}$$

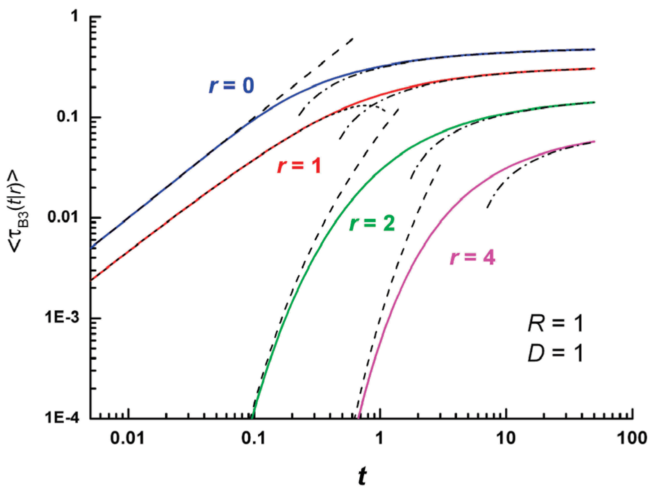


Figure 4. Time dependence of the mean residence time in the unit sphere for a particle diffusing in three-dimensional space, starting from various indicated values of r, for $D = 1$ and $R = 1$. Calculated from eq 29, or alternately from eq 32b and eq 33b for $r = 1$ and 0, respectively. In this three-dimensional case the numerical evaluation of the double integral of eq 2 did not produce accurate results, unlike the case of Figure 2. The short time asymptotics are shown by black dashed lines: eq 39 for $r = R = 1$ and eq 36 otherwise (where for $r = 0$ we just took the leading term, t). The long time asymptotics, eq 50, is shown by the black dash-dot lines. Note the log−log scale.

with explicit expressions for the repeated integrals of the coerror function in eqs 13b and 13c. Inserting these two relations, and substituting $z \equiv R/(4Dt)^{1/2}$, allows one to rewrite this result as

$$\langle \tau_{B_3}(t|R)\rangle = \frac{t}{2}\left\{1+\left(\frac{8z^2}{3}-1\right)\mathrm{erfc}(2z) + \frac{2}{3\sqrt{\pi}}\left[\left(\frac{1}{z}-2z\right)\exp(-4z^2)-\frac{1}{z}\right]\right\} \tag{32b}$$

This result is obtained also by inserting $z' = \pm z$ into eq 30. The two coefficients of erfc($2z$), namely $t/2$ and $4z^2t/3$, are the limiting behaviors when $t \to 0$ and $t \to \infty$, respectively (because the last term vanishes in both limits). The asymptotic behavior will be discussed in more detail below.

When starting at the origin we take the limit $\sinh(x)/x \to 1$ as $x \to 0$ to obtain $\langle \hat{\tau}_{B_3}(s|0)\rangle = 1/s^2 - (Z + 1)\exp(-Z)/s^2$. This inverts to give

$$\langle \tau_{B_3}(t|0)\rangle = t[1-4z\,\mathrm{ierfc}(z)-4\,\mathrm{i}^2\mathrm{erfc}(z)] \tag{33a}$$

With the aid of eq 13 one can rewrite this as

$$\langle \tau_{B_3}(t|0)\rangle = t[1+(2z^2-1)\,\mathrm{erfc}(z)-2z\,\mathrm{e}^{-z^2}/\sqrt{\pi}\,] \tag{33b}$$

For a uniform initial distribution within the sphere one obtains

$$\langle \hat{\tau}_{B_3}(s|B_3)\rangle = \frac{1}{s^2}-\frac{3}{2Zs^2}\left[1-\frac{1}{Z^2}+\left(1+\frac{1}{Z}\right)^2\exp(-2Z)\right] \tag{34}$$

■ ASYMPTOTIC BEHAVIOR

The behavior of the solution in eq 7 is best clarified from its asymptotic limits $t \to 0$ and $t \to \infty$, which are discussed below.

Short Times. For short times one utilizes the $x \to \infty$ asymptotics: $I_\nu(x) \sim (2\pi x)^{-1/2}\mathrm{e}^x$ and $K_\nu(x) \sim (\pi/2x)^{1/2}\mathrm{e}^{-x}$ [see eqs 9.7.1 and eq 9.7.2 in ref 44 for the complete expansion]. For $s \to \infty$ one thus finds

$$1-s^2\langle \hat{\tau}_{B_d}(s|r)\rangle \sim \frac{1}{2}\left(\frac{R}{r}\right)^{(d-1)/2}\mathrm{e}^{-\alpha(R-r)} \qquad r \le R \tag{35a}$$

$$s^2\langle \hat{\tau}_{B_d}(s|r)\rangle \sim \frac{1}{2}\left(\frac{R}{r}\right)^{(d-1)/2}\mathrm{e}^{-\alpha(r-R)} \qquad r \ge R \tag{35b}$$

By eq 14, the Laplace inverse is then

$$\langle \tau_{B_d}(t|r)\rangle \sim t-2t\left(\frac{R}{r}\right)^{(d-1)/2}\mathrm{i}^2\mathrm{erfc}\left(\frac{R-r}{\sqrt{4Dt}}\right) \qquad r \le R \tag{36a}$$

$$\langle \tau_{B_d}(t|r)\rangle \sim 2t\left(\frac{R}{r}\right)^{(d-1)/2}\mathrm{i}^2\mathrm{erfc}\left(\frac{r-R}{\sqrt{4Dt}}\right) \qquad r \ge R \tag{36b}$$

For $d = 1$ this corresponds to neglecting the $\mathrm{i}^2\mathrm{erfc}[(r+R)/(4Dt)^{1/2}]$ terms in eq 16.

From eq 36 it is immediately evident that, irrespective of dimensionality, when starting inside the ball $\langle \tau_{B_d}(t|r)\rangle \sim t$ (because until its first exit, the particle moves entirely within B_d), whereas for $r = R$ one has $\langle \tau_{B_d}(t|R)\rangle \sim t/2$; namely, the particle initially spends half of its time inside and half outside B_d (because from the boundary, the particle can enter or exit the sphere with equal probabilities). When starting outside, $\langle \tau_{B_d}(t|r)\rangle$ rises with a delay determined from the second repeated integral of the coerror function.

For a uniform initial distribution within B_d, the LT in eq 10 involves a product of the form $K_\nu(Z)\,I_\nu(Z)$. Therefore, the exponential terms in the asymptotic expansion of the modified Bessel functions vanish identically, leaving a power series in $1/Z^2$. This gives

$$s^2\langle \hat{\tau}_{B_d}(s|B_d)\rangle \sim 1-\frac{d}{2Z}\left(1-\frac{d^2-1}{8Z^2}+\ldots\right) \tag{37}$$

which inverts to give a power series in t:

$$\langle \tau_{B_d}(t|B_d)\rangle \sim t\left[1-\frac{d}{3\sqrt{\pi}z}\left(1-\frac{d^2-1}{80z^2}+\ldots\right)\right] \tag{38}$$

For $d = 1$ all the correction terms involving $d^2 - 1$ vanish. This leaves a two-term series that corresponds to neglecting the $\mathrm{i}^3\mathrm{erfc}(2z)$ term in eq 20. The functions $\mathrm{i}^n\mathrm{erfc}(x)$ decay at large x proportional to $\exp(-x^2)$, which is faster than any power, and hence they can be neglected. Higher order terms will involve a factor of $d^2 - 9$; hence they vanish for $d = 3$ and the series ends here: $\langle \tau_{B_3}(t|B_3)\rangle \sim [1-(1-0.1z^{-2})/(\pi^{1/2}z)]t$. Indeed, for $d = 3$ eq 37 corresponds to the neglect of the $\exp(-2Z)$ term in eq 34.

Let us compare this to the case $r = R$, where the asymptotic expansion of the modified Bessel functions gives $s^2\langle \hat{\tau}_{B_d}(s|R)\rangle \sim [1-(d-1)/(2Z)]/2 + \ldots$. This is inverted as

$$\langle \tau_{B_d}(t|R)\rangle \sim \frac{t}{2}\left(1-\frac{d-1}{3\sqrt{\pi}z}+\ldots\right) \tag{39}$$

For $d = 3$, where the full analytic solution was found in eq 32a, it again corresponds to neglecting the i^nerfc terms. The improved approximation achieved by the $1/z$ correction term is demonstrated for $d = 2$ and 3 in Figures 3 and 4, respectively.

In comparison with eq 38, we have already noted that at short times the MRT for trajectories that start on the surface is multiplied by a factor 1/2, because of the two opposing directions along the surface normal: The inside move contributes to the MRT whereas the outside move does not. Now we see that the difference in the $1/z$ term is in the dimensionality, which reduces by 1 when starting on the surface as compared to starting within the volume of the sphere. One may tentatively interpret this term as due to trajectories that leave B_d by moving perpendicular to the surface normal. When $d = 1$, there is no such perpendicular direction, and the $1/z$ term in eq 39 vanishes, as implied also by the exact result in eq 17.

Long Times: $d < 2$. The behavior at long times depends more profoundly on the spatial dimension. The critical dimensionality is $d = 2$, because for $d < 2$ the random walk is recursive whereas for $d > 2$ it is transient. In the first case, the random walker will return with certainty to the origin, so that the long-time asymptotics must be independent of the initial location, r. Thus we can start from any of the two relations in eq 7. Employing the $x \to 0$ limit of the modified Bessel functions:[44]

$$I_\nu(x) \sim (x/2)^\nu/\Gamma(\nu+1) \tag{40a}$$

$$K_\nu(x) \sim (x/2)^{-|\nu|}\Gamma(|\nu|)/2 \tag{40b}$$

we obtain for $d < 2$ and $s \to 0$ that

$$\langle \hat{\tau}_{B_d}(s|r)\rangle \sim \frac{\Gamma(1-d/2)}{\Gamma(1+d/2)}\frac{(\alpha R/2)^d}{s^2} \tag{41}$$

Its Laplace inverse is

$$\langle \tau_{B_d}(t|r)\rangle \sim \frac{z^d t}{(1-d/2)\Gamma(1+d/2)} = \frac{V_d t}{(1-d/2)(4\pi D t)^{d/2}} \tag{42}$$

Because the random walk is recursive, the MRT increases indefinitely with t and is independent of r. In particular, for $d = 1$ (where $V_1 = 2R$) we get $\langle \tau_{B_1}(t|r)\rangle \sim 2R(t/(\pi D))^{1/2}$, in agreement with eq 61 in ref 39 and eq 42 in ref 43.

The asymptotic behavior of the residence probability can be obtain by differentiation with respect to time

$$P_{B_d}(t|r) \equiv \frac{\partial\langle \tau_{B_d}(t|r)\rangle}{\partial t} \sim \frac{V_d}{(4\pi D t)^{d/2}} \tag{43}$$

As anticipated in the Introduction, this decay is the same as that observed for reversible geminate recombination,[20−24] with the volume V_d playing the role of the equilibrium constant there.

Long Times: $d > 2$. When $d > 2$, the random-walk is transient, so that a maximal and time-independent MRT is obtained as $t \to \infty$. Using the Bessel asymptotics from eq 40, one finds that the $s \to 0$ limit for $r \geq R$ is given by

$$\langle \hat{\tau}_{B_d}(s|r)\rangle \sim \frac{1}{d(d-2)}\left(\frac{R}{r}\right)^d \frac{r^2}{Ds} \tag{44}$$

Its Laplace inverse is

$$D\langle \tau_{B_d}(\infty|r)\rangle = \frac{1}{d(d-2)}\left(\frac{R}{r}\right)^d r^2 \tag{45}$$

in agreement with eq 11a of ref 18. In particular,

$$D\langle \tau_{B_d}(\infty|R)\rangle = \frac{R^2}{d(d-2)} \tag{46}$$

Hence, $\langle \tau_{B_3}(\infty|R)\rangle = R^2/(3D)$, which is the result obtained by Eigen.[10]

For $r \leq R$, inserting the leading term of the Bessel asymptotics, eq 40, into eq 7 gives zero. Apparently higher terms in the asymptotic expansion should be employed. Alternately, one can solve the steady-state form of the RTE[18] to obtain

$$2D\langle \tau_{B_d}(\infty|r)\rangle = \frac{R^2}{d-2} - \frac{r^2}{d} \tag{47}$$

see eq 10a of ref 18. For $r = R$ it reproduces eq 46. By integration according to eq 9, one obtains

$$2D\langle \tau_{B_d}(\infty|B_d)\rangle = \frac{4R^2}{(d-2)(d+2)} \tag{48}$$

Hence $\langle \tau_{B_3}(\infty|B_d)\rangle = 2R^2/(5D)$, which is larger than $\langle \tau_{B_3}(\infty|R)\rangle = R^2/(3D)$. It is indeed expected that a transient random walk will reside longer in a domain when starting in its interior than on its surface.

For $d = 3$ one can show that the approach to the infinite-time limit also follows a $t^{-1/2}$ power law. This correction term to eq 47 is obtained by expanding the exponentials in eq 28a up to fourth order:

$$s^2\langle \hat{\tau}_{B_3}(s|r)\rangle \sim \frac{(\alpha R)^2}{2} - \frac{(\alpha r)^2}{6} - \frac{(\alpha R)^3}{3} + \ldots \tag{49}$$

By Laplace inversion, one obtains

$$\langle \tau_{B_3}(\infty|r)\rangle - \langle \tau_{B_3}(t|r)\rangle \sim \frac{R^3}{3D}\frac{1}{(\pi D t)^{1/2}} = \frac{2V_3 t}{(4\pi D t)^{3/2}} \tag{50}$$

where, for $r \leq R$ we have $D\langle \tau_{B_3}(\infty|r)\rangle = R^2/2 - r^2/6$. However, eq 50 is valid also for $r \geq R$, when $D\langle \tau_{B_3}(\infty|r)\rangle = R^3/(3r)$, because the general solution for $d = 3$ in eq 29 has the same functional form for $\langle \tau_{B_3}(\infty|r)\rangle - \langle \tau_{B_3}(t|r)\rangle$ irrespective of whether r is inside or outside B_d. This approximation is demonstrated as dash-dot lines in Figure 4. Here, too, partial differentiation with respect to t results in eq 43 (with $d = 3$), demonstrating the connection with the geminate recombination problem.

Long Times: $d = 2$. The two-dimensional case should be treated separately. Utilizing the small x limits:[44] $I_0(x) \sim 1$, $I_1(x) \sim x/2$, $K_0(x) \sim -\ln x$, and $K_1(x) \sim 1/x$, one obtains[29]

$$\langle \hat{\tau}_{B_2}(s|r)\rangle \sim -(R^2/4Ds)\ln s \tag{51}$$

irrespective of r. Darling and Kac[29] have inverted it using Karamatra's Tauberian theorem to obtain $\langle \tau_{B_2}(t|r)\rangle \sim (R^2/4D)\ln t$. In practice, this expression may not be very useful, because convergence to this asymptotic behavior is extremely slow. Figure 3 shows that better agreement with the (preasymptotic) long-time behavior is obtained when an empirical correction term, $\gamma(r)$, is added

$$\langle \tau_{B_2}(t|r)\rangle \sim (R^2/4D)\ln t + \gamma(r) \tag{52}$$

CONCLUSION

In this work we have obtained the general solution for the LT of the MRT within a d-dimensional ball, $\langle \tau_{B_d}(t|r)\rangle$, for arbitrary observation time, t, and starting point, r. Because present or anticipated experimental setups depend on the MRT from $r = R$, $r = 0$ or a uniform distribution within B_d, specific expressions were obtained for these initial conditions. Subsequently, specialized results were presented for dimensions 1, 2, and 3. For $d = 1$ and 3, the modified Bessel functions in eq 7 reduce to hyperbolic functions, which can then be inverted analytically. In addition, the analytic short- and long-time asymptotic behaviors were obtained (for arbitrary d) and compared with the exact solutions for $d = 1, 2$, and 3.

In single-molecule diffusion experiments, mostly the solution for $r = R$ and $t \to \infty$ was utilized thus far. The present theoretical exposition may pave the road for more extensive application of the MRT in analyzing experimental results. Since it is nowadays possible to identify the onset of fluorescence bursts, one could measure $\langle \tau_{B_d}(t|R)\rangle$ by collecting the emitted photons from the onset of a burst and up to an arbitrary time t, with subsequent averaging over all collected bursts.

Another anticipated experiment could prepare a constant concentration of a dye molecule within the laser spot, e.g., by the photorelease of caged reactants using an ultrafast laser pulse. Their diffusion out of the spot could then be followed by single-molecule fluorescence methods, a process somewhat analogous to reversible geminate recombination. The total number of photons emitted between the photorelease pulse and until some time t later, could be compared with expressions derived here for $\langle \tau_{B_d}(t|B_d)\rangle$ or $\langle \tau_{B_d}(t|0)\rangle$. The correct analysis of the diffusion process is, in turn, a first step before deconvoluting it from other processes of interest, such as fluorescence quenching and conformational changes.

SOLUTION OF THE FEYNMAN−KAC EQUATION

In this Appendix we consider $F_\tau(t|\mathbf{r})$, the probability density for residence time τ within V, for trajectories started at $\mathbf{r}$ and monitored for a duration t. Evidently, it is normalized so that $\int_0^t F_\tau(t|\mathbf{r})\, d\tau = 1$. This is the zeroth residence time moment. Its nth moment is given by

$$\langle \tau_V^n(t|\mathbf{r})\rangle = \int_0^t F_\tau(t|\mathbf{r})\tau^n \, d\tau \tag{53}$$

Define the LT of $F_\tau(t|\mathbf{r})$ with respect to τ by

$$S_k(t|\mathbf{r}) \equiv \int_0^t F_\tau(t|\mathbf{r}) \exp(-k\tau)\, d\tau \tag{54}$$

noting that the upper integration limit may be replaced by ∞, because $F_\tau(t|\mathbf{r}) = 0$ for $\tau > t$. As $t \to 0$, $\exp(-k\tau) \to 1$, and the last integral tends to the normalization condition, so that $S_k(0|\mathbf{r}) = 1$. Alternately, this follows because $F_\tau(t|\mathbf{r}) \to \delta(\tau)$ as $t \to 0$.

Knowledge of $S_k(t|\mathbf{r})$ allows one to calculate the nth residence time moment[14]

$$\langle \tau_V^n(t|\mathbf{r})\rangle = (-1)^n \left[\frac{\partial^n S_k(t|\mathbf{r})}{\partial k^n}\right]_{k=0} \tag{55}$$

The goal of the present Appendix is to show that this route yields the same expression for the MRT as eq 7.

Kac has shown[28] that $S_k(t|\mathbf{r})$ is the survival probability for diffusion with a uniform depletion rate constant, k, within the domain V (see also refs 30−32, 34, and 37):

$$\frac{\partial S_k(t|\mathbf{r})}{\partial t} = [D\Delta_d - k\,\Theta_V(\mathbf{r})]S_k(t|\mathbf{r}) \tag{56}$$

A closely related equation was derived for the generating function of the probability to observe N photons up to time t in a single molecule diffusion experiment; see eq 5.4 in ref 12. This attests to the close connection between the residence time and the single molecule problems.

For spherical symmetry, utilizing the initial condition $S_k(0|r) = 1$, one may write the LT of eq 56 as

$$\left\{ Dr^{1-d/2}\left[\frac{\partial^2}{\partial r^2} + \frac{1}{r}\frac{\partial}{\partial r} - \frac{1}{r^2}\left(1 - \frac{d}{2}\right)^2\right] r^{d/2-1} - kH(R-r) - s\right\}\hat{S}_k(s|r) = -1 \tag{57}$$

where $H(x)$ is the Heaviside function, which equals 1 if $x > 0$ and zero otherwise, and we have introduced the Laplacian from eq 5b. The boundary conditions are $r^{d-1}\partial\hat{S}_k(s|r)/\partial r \to 0$ as $r \to 0$, and $\hat{S}_k(s|r) \to 1$ as $r \to \infty$. A special solution for this inhomogeneous differential equation is, clearly, $\hat{S}_k(s|r) = 1/[s + kH(R-r)]$. We need to add to this the general solution of the homogeneous equation, for which the -1 on the rhs is replaced by 0.

Defining a function $f(r) \equiv r^{d/2-1}\hat{S}_k(s|r)$, and the independent variable $y \equiv ([s + kH(R-r)]/D)^{1/2} r$, we find that the homogeneous equation is transformed into

$$\left[\frac{\partial^2}{\partial y^2} + \frac{1}{y}\frac{\partial}{\partial y} - \frac{1}{y^2}\left(1 - \frac{d}{2}\right)^2 - 1\right] f(y) = 0 \tag{58}$$

This is a modified Bessel function of order $\nu = d/2 - 1$, whose linearly independent solutions are $I_{\pm\nu}(y)$ and $K_\nu(y)$. Because $K_\nu(y)$ diverges as $y \to 0$, it cannot play a role inside the sphere. Of the two functions $I_{\pm\nu}(y)$, the function $I_{d/2-1}(y)$ obeys the boundary condition at the origin because[44] $y^\nu d(y^{-\nu}I_\nu(y))/dy = I_{\nu+1}(y) \to 0$ as $y \to 0$. Outside the sphere the only solution is $K_\nu(y)$, which decays to 0 as $y \to \infty$ [so that $\hat{S}_k(s|r) \to s^{-1}$ as $r \to \infty$]. The functions $I_{\pm\nu}(y)$ diverge as $\exp(y)/y$, so they do not play a role there. Subsequently, the general solution to eq 57 is

$$\hat{S}_k(s|r) = \frac{1}{s+k} + r^{1-d/2} A I_{d/2-1}(\beta r) \qquad r \le R \tag{59a}$$

$$\hat{S}_k(s|r) = \frac{1}{s} + r^{1-d/2} B K_{1-d/2}(\alpha r) \qquad r \ge R \tag{59b}$$

where we have defined $\alpha \equiv (s/D)^{1/2}$ and $\beta \equiv [(s+k)/D]^{1/2}$. Cf. eqs 3 and 4 in ref 41.

The coefficients A and B are next obtained from the continuity of the solution and its first derivative at $r = R$. This yields

$$A = \frac{k R^{d/2-1}}{(s+k)\sqrt{s}} \frac{K_{d/2}(\alpha R)}{\Omega} \tag{60a}$$

$$B = -\frac{k R^{d/2-1}}{s\sqrt{s+k}} \frac{I_{d/2}(\beta R)}{\Omega} \tag{60b}$$

where the denominator, Ω, is given by

$$\Omega = \sqrt{s+k} K_{1-d/2}(\alpha R)\, I_{d/2}(\beta R) + \sqrt{s} K_{d/2}(\alpha R)\, I_{d/2-1}(\beta R) \tag{61}$$

Inserting into eq 59 gives the solution for $\hat{S}_k(s|r)$ for a ball in any dimensionality, d. This solution is known in the mathematical literature, and tabulated as eq 4−1.5.1 in Part II of ref 34.

In spite of the complex dependence of $\hat{S}_k(s|r)$ on k, the evaluation of the first derivative in eq 55 is simple because A and B are proportional to k. Thus $\hat{S}_k(s|r)$ has the form $kg(k)$ [where $g(k)$ is some function of k], so that the MRT is simply $-g(k)$. Utilizing the identity[44] $K_\nu(x)\, I_{\nu+1}(x) + K_{\nu+1}(x)\, I_\nu(x) = x^{-1}$ in evaluating the denominator, $\Omega(k{=}0) = D^{1/2}/R$, one obtains eq 7. By comparing this derivation to the solution for the MRT using the LT of the spherically symmetric RTE in eq 6, one can appreciate the considerable simplification afforded by the RTE.

■ ABBREVIATIONS

a. Scalars

$$\alpha \equiv \sqrt{s/D}$$

$$Z \equiv \alpha R = \sqrt{sR^2/D}$$

$$z \equiv R/\sqrt{4Dt}$$

$$V_d = \pi^{d/2} R^d / \Gamma(1 + d/2)$$

b. Special Functions

$$\Gamma(a,x) = \int_x^\infty y^{a-1} \mathrm{e}^{-y}\, \mathrm{d}y$$

$$\Gamma(x) = \Gamma(x,0) = \int_0^\infty y^{x-1} \mathrm{e}^{-y}\, \mathrm{d}y$$

$$E_1(x) = \Gamma(0,x) = \int_x^\infty y^{-1} \mathrm{e}^{-y}\, \mathrm{d}y$$

$$\mathrm{erfc}(x) = 1 - \mathrm{erf}(x) = \frac{2}{\sqrt{\pi}} \int_x^\infty \mathrm{e}^{-y^2}\, \mathrm{d}y$$

$$\mathrm{i}^n\mathrm{erfc}(x) = \int_x^\infty \mathrm{i}^{n-1}\mathrm{erfc}(y)\, \mathrm{d}y$$

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■ ACKNOWLEDGMENT

I thank Shai Carmi for comments on the manuscript. This research was supported by THE ISRAEL SCIENCE FOUNDATION (grant number 122/08). The Fritz Haber Center is supported by the Minerva Gesellschaft für die Forschung, München, FRG.

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