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ARTICLES

Single-particle survival in gated trapping

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Any chemical reaction $A^*+B\rightarrow C$ whose progress is modulated by another reaction of the form $A^*\rightleftarrows A$ is said to be gated. The gating reaction $A^*\rightleftarrows A$ represents a reversible fluctuation from a active state A^* to an inactive state A that does not react with B. Reversibly blocked chemical reactions, conformational fluctuations in proteins, and reactions occurring within biomembranes or involving biological molecules have all been studied recently in contexts related to gating. This paper gives a unified, general formalism for calculating trapping rates and mean survival times of gated reactions. It also presents and solves some gating models. Although most of its explicit formulas are for problems with a single particle moving in the presence of a single gated, static trap, the method of solution is formally applicable to problems involving several particles and several point traps, even when the gating kinetics are non-Markovian. Those cases give integral equations that cannot be solved in closed form, however. This paper's results also include the bimolecular rate constant for a gated ligand binding to a gated protein. [S1063-651X(96)02509-3]

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I. INTRODUCTION

Any chemical reaction $A^*+B\rightarrow C$ whose progress is modulated by another reaction of the form $A^*\rightleftarrows A$ is said to be gated. The gating reaction $A^*\rightleftarrows A$ represents a reversible fluctuation from an active state A^* to an inactive state A that does not react with B. In some situations, a fourth species D may be responsible for the interconversion: $A^*+D\rightleftarrows A$. When other effects due to the blocker D can be neglected, however, this reversible chemical blocking is completely equivalent to gating. Several recent papers have investigated gating [1], dynamic trapping [2,3], or other related problems [4].

Early studies of gating [5,6] derived Smoluchowski mean-field rate constants [7–9] for a ligand binding to a gated protein. Gating has also been studied in other biological contexts, e.g., reactions occurring within biomembranes [3] or small molecules migrating through heme proteins [4]. Medical therapies also can involve blocking chemical reactions, and in fact the failure of an HIV blocker in clinical trials (e.g., [10]) originally motivated the present investigation. Although most gating and blocking models do not change the universality class of a chemical reaction [11] (e.g., they rarely change algebraic asymptotics into exponential ones), they are worthy of study because they can have profound practical implications, particularly in medical therapy, just by changing effective reaction rate constants.

This paper gives a unified, general formalism for calculating trapping rates and mean survival times for a restricted class of gated reactions. Our original motivation, which was to determine bimolecular Smoluchowski mean-field rate constants [7–9] for a particular class of gated reactions, led this paper to focus on the survival of a single moving particle in the presence of a single, gated, static trap. Much of the paper therefore assumes that particle movement and gating are independent, although this restriction is inessential in our method of solution. The method combines particle movement and gating into a single Markov process whose states are ordered pairs containing both the particle position and the gating state at time t [1–3,12,13]. Methods commonly used for analyzing Markovian trapping then furnish a solution [14].

The plan of this paper follows. Section II gives a formalism for solving both ungated and gated trapping in Markovian systems. Section III then describes some gating Green's functions, which are used to derive trapping rates, rate constants, and mean survival times for the corresponding gating models. One of these formulas determines the rate constant for a gated ligand binding to a gated protein. The Discussion then delineates the range of our solutions and several problems for future consideration.

II. GENERAL SURVIVAL RESULTS

The main result in this section is Eq. (2), an integral equation for the propagator $p(\mathbf{r},t|\mathbf{r}_0)$ in gated trapping. Gating solutions are obtained from Eq. (2) by incorporating both particle movement and the gating state into a general formalism for solving Markovian trapping. Results are conveniently divided into two cases, depending on whether or not

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the particle movement yields an equilibrium probability density in the absence of traps.

Let $G(\mathbf{r},t|\mathbf{r}_0)$ be any Green's function that describes time-homogeneous Markovian particle movement in a space without traps. Thus $G(\mathbf{r},t|\mathbf{r}_0)$ is the probability density that a particle initially at position $\mathbf{r}_0$ will be at position $\mathbf{r}$ at time t later. The initial condition for a continuous volume V (as opposed to the one for a lattice) is $G(\mathbf{r},0|\mathbf{r}_0)=\delta(\mathbf{r}-\mathbf{r}_0)$, where $\delta(\mathbf{r}-\mathbf{r}_0)$ is a Dirac δ function. Also, since there is no trapping $G(\mathbf{r},t|\mathbf{r}_0)$ satisfies a normalization condition $\int_V G(\mathbf{r},t|\mathbf{r}_0)d\mathbf{r}\equiv 1$ for all t. (This paper uses ''$\equiv$'' to denote equality for all values of a variable. In this case, e.g., the equation holds for all $t\geqslant 0$.)

As a specific example, $G(\mathbf{r},t|\mathbf{r}_0)$ could be the Green's function for particle diffusion in a potential $\phi(\mathbf{r})$. This particular $G(\mathbf{r},t|\mathbf{r}_0)$ satisfies the evolution equation $\partial G/\partial t=\mathcal{L}G$, where $\mathcal{L}$ is the second-order linear differential operator $\mathcal{L}f(\mathbf{r})=-(\nabla_{\mathbf{r}}\cdot\mathbf{J})f(\mathbf{r})$, and $\mathbf{J}$ is the flux defined by the vector-valued operator $\mathbf{J}f(\mathbf{r})=-e^{-\beta\phi(\mathbf{r})}D(\mathbf{r})\nabla_{\mathbf{r}}[e^{\beta\phi(\mathbf{r})}f(\mathbf{r})]$.

The presence of traps introduces sink terms into the evolution equation. If, e.g., each position $\mathbf{r}$ has a trap of strength $c(\mathbf{r})\geqslant 0$ associated with it, the evolution equation $\partial G/\partial t=\mathcal{L}G$ becomes $\partial p/\partial t=\mathcal{L}p-c(\mathbf{r})p$. Here, $p(\mathbf{r},t|\mathbf{r}_0)$ is the probability density that a particle initially at position $\mathbf{r}_0$ will be at position $\mathbf{r}$, untrapped, at time t later. The propagator $p(\mathbf{r},t|\mathbf{r}_0)$ satisfies the same initial condition as the Green's function $G(\mathbf{r},t|\mathbf{r}_0)$, $p(\mathbf{r},0|\mathbf{r}_0)=\delta(\mathbf{r}-\mathbf{r}_0)$, but does not satisfy a normalization condition, since in general $\int_V p(\mathbf{r},t|\mathbf{r}_0)d\mathbf{r}\leqslant 1$.

A system with gated traps has, in addition to the above particle-trap structure, a gating state $\mathbf{q}$ that evolves in a gating state space $\Omega_Q=\{\mathbf{q}_1,\mathbf{q}_2,\ldots,\mathbf{q}_N\}$, where N is finite. Above, the strength of an ungated trap depended only on the particle position $\mathbf{r}$. In contrast, the strength of a gated trap can now also depend on the gating state $\mathbf{q}_i$. Thus, when the gating state becomes $\mathbf{q}_i$, the strength of the trap at position $\mathbf{r}$ becomes $c_i(\mathbf{r})$, $i=1,2,\ldots,N$. The gated trap strengths $c_i(\mathbf{r})=c(\mathbf{q}_i,\mathbf{r})$ are therefore a function of the ''gated state'' of the system $\mathbf{x}=(\mathbf{q},\mathbf{r})$, an ordered pair specifying both the gating state and particle position. The gated state $\mathbf{x}$ evolves in a ''gated state space'' $\Omega=\Omega_Q\times V$. Note carefully that the preceding used the terms ''gating state'' and ''gated state'' to distinguish between $\mathbf{q}$ and $\mathbf{x}=(\mathbf{q},\mathbf{r})$.

Gating models can be either stochastic or deterministic. One example of a stochastic model, Poisson gating, has two gating states, one active and the other blocked. The active state $\mathbf{q}_1=(+)$ permits trapping, whereas the blocked state $\mathbf{q}_2=(-)$ inhibits it completely. In Poisson gating, the interconversions $(-)\underset{\beta_0}{\overset{\alpha_0}{\rightleftharpoons}}(+)$ are Poisson processes with rate constants α_0 and β_0. For brevity, the gated states $\mathbf{x}=(\pm,\mathbf{r})$ will be abbreviated to $\mathbf{r}_\pm$ in the following.

As a specific example of gated trapping, superimposing Poisson gating on the evolution equation $\partial p/\partial t=\mathcal{L}_p-c(\mathbf{r})p$ makes trap strengths switch from $c(\mathbf{r}_+)=c(\mathbf{r})$ in the $(+)$ state to $c(\mathbf{r}_-)=0$ in the $(-)$ state. If $\mathbf{x}_0=(\mathbf{q}_0,\mathbf{r}_0)$ is the initial system state, define $p_\pm(\mathbf{r},t|\mathbf{x}_0):=p(\mathbf{r}_\pm,t|\mathbf{x}_0)$, where '':='' denotes a definition. The ungated evolution equation $\partial p/\partial t=\mathcal{L}p-c(\mathbf{r})p$ becomes a pair of coupled equations,

$$\frac{\partial p_+}{\partial t}=\mathcal{L}p_+-c(\mathbf{r})p_+-\beta_0p_++\alpha_0p_-,$$

$$\frac{\partial p_-}{\partial t}=\mathcal{L}p_-+\beta_0p_+-\alpha_0p_-, \tag{1}$$

that display the particle movement, the trapping, and the gating interconversion.

For a general gated system, let the gated Green's function $G(\mathbf{x},t|\mathbf{x}_0)$ be the probability density that a system initially in state $\mathbf{x}_0$ will be in state $\mathbf{x}$ at time t later. Particle survival in the presence of gated traps will now be related to $G(\mathbf{x},t|\mathbf{x}_0)$, under the assumption that the gated state $\mathbf{x}=(\mathbf{q},\mathbf{r})$ evolves as a Markov process. A formalism for calculating Markovian particle survival with ungated traps already exists [14] and can be applied directly to gated traps, if the positional Green's function $G(\mathbf{r},t|\mathbf{r}_0)$ in the original formalism is replaced by the gated Green's function $G(\mathbf{x},t|\mathbf{x}_0)$. The formalism is given below for the gated Green's function $G(\mathbf{x},t|\mathbf{x}_0)$, but the original formalism can be recovered by substituting positional Green's functions $G(\mathbf{r},t|\mathbf{r}_0)$ for gated Green's functions $G(\mathbf{x},t|\mathbf{x}_0)$ everywhere, changing $\mathbf{x}$'s to $\mathbf{r}$'s, and replacing Ω by V.

When traps are present (gated or not), the formula

$$p(\mathbf{x},t|\mathbf{x}_0)=G(\mathbf{x},t|\mathbf{x}_0)-\int_0^t dT\int_\Omega d\mathbf{X} \times G(\mathbf{x},t-T|\mathbf{X})c(\mathbf{X})p(\mathbf{X},T|\mathbf{x}_0) \tag{2}$$

gives the probability that a system initially in state $\mathbf{x}_0$ will be in state $\mathbf{x}$, with the particle untrapped, at time t later [15]. Equation (2) indicates that the state $\mathbf{X}$ has a trap of strength $c(\mathbf{X})$ associated with it.

As an example without gating (change $\mathbf{x}$'s to $\mathbf{r}$'s everywhere), when the Green's function $G(\mathbf{r},t|\mathbf{r}_0)$ satisfies the evolution equation $\partial G/\partial t=\mathcal{L}G$ ($\mathcal{L}$ being the second-order linear differential operator defined above), Eq. (2) for $p(\mathbf{r},t|\mathbf{r}_0)$ is equivalent to the evolution equation $\partial p/\partial t=\mathcal{L}p-c(\mathbf{r})p$ with the initial condition $p(\mathbf{r},0|\mathbf{r}_0)=\delta(\mathbf{r}-\mathbf{r}_0)$.

As an example with gating, Eq. (2) for $p(\mathbf{x},t|\mathbf{x}_0)$ is equivalent to Eq. (1), when the gated trap strengths in Eq. (2) are taken as $c(\mathbf{X})=c(\mathbf{R})$ for $\mathbf{X}=\mathbf{R}_+$, with gating in the $(+)$ state, and $c(\mathbf{X})=0$ for $\mathbf{X}=\mathbf{R}_-$, with gating in the $(-)$ state.

Equation (2) is basically a mass balance equation and as such has a combinatorial interpretation. Because the system is Markovian, the Chapman-Kolmogorov relation

$$G(\mathbf{x},t|\mathbf{x}_0)=\int_\Omega G(\mathbf{x},t-T|\mathbf{X})G(\mathbf{X},T|\mathbf{x}_0)d\mathbf{X} \tag{3}$$

holds for any time T with $0\leqslant T\leqslant t$. In Eq. (2) for partial trapping, the system state $[p(\mathbf{x},t|\mathbf{x}_0)]$ follows the evolution of the corresponding conservative system $[G(\mathbf{x},t|\mathbf{x}_0)]$ until it is killed by trapping and becomes a ''ghost.'' Because of the Chapman-Kolmogorov Eq. (3), the integrand in Eq. (2) represents the trajectories of ghosts that would have been in state x at time t but instead passed through a trap at $\mathbf{X}$ and were lost at time T. The rate of loss per unit volume is $c(\mathbf{X})p(\mathbf{X},T|\mathbf{x}_0)$.

Equation (2) can solve many ungated radiation boundary problems for a particle moving on a line [14]. As shown below, it can also solve many gating problems. Symmetries can sometimes reduce a problem on a d-dimensional continuum ($d>1$) to a problem on a line. When trapping surfaces do indeed reduce to trapping points, the following analysis is applicable. It also applies with minor changes to reaction-diffusion systems on d-dimensional lattices ($d\geqslant 1$), where all bodies are represented as geometric points. Since the analysis applies to problems on d-dimensional lattices, it retains boldface vector notation.

First, let us specialize $c(\mathbf{x})$ in Eq. (2) to a linear combination of δ functions: $c(\mathbf{x})=\sum_{i=1}^{M}\kappa_i\delta(\mathbf{x}-\mathbf{a}_i)$. When κ_j is finite, the term $\kappa_i\delta(\mathbf{x}-\mathbf{a}_i)$ represents the strength of a partially absorbing point trap $\mathbf{a}_i$. Solutions for fully absorbing points can be derived by taking limits $\kappa_i\to\infty$ in the following solutions for partially absorbing points. For M partially absorbing point traps,

$$p(\mathbf{x},t|\mathbf{x}_0)=G(\mathbf{x},t|\mathbf{x}_0)-\int_0^t dT\sum_{i=1}^{M} G(\mathbf{x},t-T|\mathbf{a}_i) \times\kappa_i p(\mathbf{a}_i,T|\mathbf{x}_0). \tag{4}$$

As an example, without gating (see the beginning of the section for notation), when $G(\mathbf{r},t|\mathbf{r}_0)$ is the ungated Green's function for diffusion with reflecting boundaries in a potential $\phi(\mathbf{r})$, $p(\mathbf{r},t|\mathbf{r}_0)$ in Eq. (4) provides a solution for the evolution equation $\partial p/\partial t=\mathcal{L}p$ with the initial condition $p(\mathbf{r},0|\mathbf{r}_0)=\delta(\mathbf{r}-\mathbf{r}_0)$ and the radiation boundary conditions $[(\mathbf{n}\cdot\mathbf{J})p(\mathbf{r},t|\mathbf{r}_0)]_{\mathbf{r}=\mathbf{a}_i}=\kappa_i p(\mathbf{a}_i,t|\mathbf{r}_0)$, $i=1,2,\ldots,N$, where $\mathbf{n}$ is a unit normal into the partially absorbing surface at $\mathbf{r}=\mathbf{a}_i$ away from the diffusion region. (Both the sign of $\mathbf{J}$ and the normal direction are the opposite of those in Ref. [6].) The radiation boundary condition is consistent with the mass balance interpretation, since it forces the loss term $\kappa_i p(\mathbf{a}_i,t|\mathbf{r}_0)$ in Eq. (4) to equal the rate of flow $[(\mathbf{n}\cdot\mathbf{J})p(\mathbf{r},t|\mathbf{r}_0)]_{\mathbf{r}=\mathbf{a}_i}$ across the absorbing surface at $\mathbf{r}=\mathbf{a}_i$, just as a mass balance interpretation requires.

As a corresponding example with gating, Poisson gating changes the ungated evolution into a pair of coupled equations, $\partial p_+/\partial t=\mathcal{L}p_+-\beta_0p_++\alpha_0p_-$ and $\partial p_-/\partial t=\mathcal{L}p_-+\beta_0p_+-\alpha_0p_-$. p_+ satisfies a radiation boundary condition; p_- a reflecting one. Again, however, Eq. (2) remains formally the same, if it sets the trap strengths $c(\mathbf{X})=0$ whenever $\mathbf{X}=\mathbf{R}_-$, with gating in the blocked $(-)$ state.

Many equations in this paper involve Laplace transforms, which will be denoted by carets, i.e., $\hat{f}(s):=\int_0^\infty e^{-st}f(t)dt$. Transform Eq. (4) and then set $\mathbf{x}=\mathbf{a}_i$ $(i=1,2,\ldots,M)$. The convolution property of Laplace transforms [16] yields M simultaneous linear equations. These can be solved for $\hat{p}(\mathbf{a}_i,s|\mathbf{x}_0)$ in terms of $\hat{G}(\mathbf{x},s|\mathbf{x}_0)$ and $\hat{G}(\mathbf{a}_i,s|\mathbf{a}_j)$ $(i,j=1,2,\ldots,M)$ and then back substituted to obtain

$$\hat{p}(\mathbf{x},s|\mathbf{x}_0)=\hat{G}(\mathbf{x},s|\mathbf{x}_0)-[\kappa_j\hat{G}(\mathbf{x},s|\mathbf{a}_j)] \times[\delta_{ij}+\kappa_j\hat{G}(\mathbf{a}_i,s|\mathbf{a}_j)]^{-1}[\hat{G}(\mathbf{a}_i,s|\mathbf{x}_0)]. \tag{5}$$

The final three factors are, respectively, $1\times M$, inverse $M\times M$, and $M\times 1$ matrices. (Ref. [14] gives a detailed derivation of Eq. (5).) Here, $\delta_{ij}:=1$ for $i=j$, 0 otherwise.

Beyond $M=1$ or 2, the matrix inversion becomes tedious. Most of this paper therefore considers $M=1$, a single trap, only. For $M=1$, Eq. (5) yields

$$\hat{p}(\mathbf{x},s|\mathbf{x}_0)=\hat{G}(\mathbf{x},s|\mathbf{x}_0)-\frac{\kappa\hat{G}(\mathbf{x},s|\mathbf{a}_+)\hat{G}(\mathbf{a}_+,s|\mathbf{x}_0)}{1+\kappa\hat{G}(\mathbf{a}_+,s|\mathbf{a}_+)}. \tag{6}$$

For gated trapping with $M=1$, $\mathbf{x}=\mathbf{a}_+=(+,\mathbf{a})$ denotes a single trap at $\mathbf{r}=\mathbf{a}$, which can trap only when the system is in a single active state $\mathbf{q}=(+)$. For ungated trapping, the $(+)$ is redundant, so then we write $\mathbf{a}_+=\mathbf{a}$.

The probability the particle survives to time t if it starts at $\mathbf{r}_0$ is

$$S(t|\mathbf{x}_0):=\int_\Omega p(\mathbf{X},t|\mathbf{x}_0)d\mathbf{X}. \tag{7}$$

Since $\int_\Omega G(\mathbf{x},t|\mathbf{x}_0)d\mathbf{x}\equiv 1$ implies $\int_\Omega\hat{G}(\mathbf{x},s|\mathbf{x}_0)d\mathbf{x}=s^{-1}$, Eqs. (6) and (7) give

$$\hat{S}(s|\mathbf{x}_0)=s^{-1}\left[1-\frac{\kappa\hat{G}(\mathbf{a}_+,s|\mathbf{x}_0)}{1+\kappa\hat{G}(\mathbf{a}_+,s|\mathbf{a}_+)}\right]. \tag{8}$$

The presentation now splits into two cases, depending on whether or not particle movement without trapping has an equilibrium probability distribution.

A. Systems without an equilibrium probability distribution

As a specific example, three-dimensional Brownian motion has no equilibrium probability distribution, since $\lim_{t\to\infty}G(\mathbf{r},t|r_0)=0$ for all positions $\mathbf{r}$. Under the Brownian motion, however, a uniform unit density evolves into a well-defined equilibrium density $\rho(\mathbf{r})=\lim_{t\to\infty}\int_V G(\mathbf{r},t|\mathbf{R})d\mathbf{R}$ [which happens to be $\rho(\mathbf{r})\equiv 1$]. Under any motion, and in gating applications, if the equilibrium density exists, it is defined by $\rho(\mathbf{x}):=\lim_{t\to\infty}\int_V G(\mathbf{x},t|\mathbf{X})d\mathbf{R}$, where $\mathbf{X}=(\mathbf{Q},\mathbf{R})$. The integral is specifically over V and not Ω, because $\rho(\mathbf{x})$ needs to evolve from a unit *spatial* concentration. Thus $\rho(\mathbf{x})$ needs to be independent of the initial gating state(s) $\mathbf{Q}$, but this is usually the case in applications. The ungated situation does not suffer this complication, because then $\mathbf{X}=\mathbf{R}$ and $\Omega=V$.

The equilibrium density satisfies

$$\rho(\mathbf{x})\equiv\int_\Omega G(\mathbf{x},t|\mathbf{x}_0)\rho(\mathbf{x}_0)d\mathbf{x}_0 \tag{9}$$

for all $t\geqslant 0$.

As an example of an equilibrium density, for diffusion in a potential with $\lim_{t\to\infty}\phi(\mathbf{r})=0$, $\rho(\mathbf{r})=e^{-\beta\phi(\mathbf{r})}$ is stationary, since $\mathcal{L}\rho(\mathbf{r})=\nabla_{\mathbf{r}}.\{e^{-\beta\phi(\mathbf{r})}D(\mathbf{r})=\nabla_{\mathbf{r}}[e^{\beta\phi(\mathbf{r})}\rho(\mathbf{r})]\}\equiv 0$. In the corresponding diffusion with Poisson gating $(-)\underset{\beta_0}{\overset{\alpha_0}{\rightleftharpoons}}(+)$, the equilibrium probability of the $(+)$ state is $\rho_{pg}(+)=\alpha_0(\alpha_0+\beta_0)^{-1}$, whereas the equilibrium probability of the $(-)$ state is $\rho_{pg}(-)=\beta_0(\alpha_0+\beta_0)^{-1}$. Thus as $t\to\infty$, $\rho_{pg}(\mathbf{r}_+)=\rho_{pg}(+)e^{-\beta\phi(\mathbf{r})}$ and $\rho_{pg}(\mathbf{r}_-)=\rho_{pg}(-)e^{-\beta\phi(\mathbf{r})}$, independent of the initial gating state(s) $\mathbf{Q}$, as required.

A transformation of Eq. (9) yields

$$s^{-1}\rho(\mathbf{x})=\int_\Omega \hat{G}(\mathbf{x},s|\mathbf{x}_0)\rho(\mathbf{x}_0)d\mathbf{x}_0. \tag{10}$$

The rate of trapping starting from the equilibrium density $\rho(\mathbf{x})$ is

$$k(t)=(d/dt)\int_\Omega [1-S(t|\mathbf{x}_0)]\rho(\mathbf{x}_0)d\mathbf{x}_0. \tag{11}$$

The asymptotic rate of trapping $k_\infty=\lim_{t\to\infty}k(t)$, if it exists, provides a rate constant for mean-field approximations to chemical kinetics. The transform of Eq. (11), standard Laplace transform identities [16], and Eqs. (8) and (10) then yield

$$\hat{k}(s)=s\int_\Omega [s^{-1}-\hat{S}(s|\mathbf{x}_0)]\rho(\mathbf{x}_0)d\mathbf{x}_0$$

$$=s^{-1}\,\frac{\kappa\rho(\mathbf{a}_+)}{1+\kappa\hat{G}(\mathbf{a}_+,s|\mathbf{a}_+)}. \tag{12}$$

Standard theorems [17] show $k_\infty=\lim_{t\to\infty}k(t)=\lim_{s\to 0}s\hat{k}(s)$. Since many gating results are more easily phrased in terms of characteristic times k_∞^{-1} than rates k_∞, define $\hat{\lambda}(s):=[s\hat{k}(s)]^{-1}$. Thus Eq. (12) implies $k_\infty^{-1}=\hat{\lambda}(0)$, where

$$\hat{\lambda}(s)=\frac{1+\kappa\hat{G}(\mathbf{a}_+,s|\mathbf{a}_+)}{\kappa\rho(\mathbf{a}_+)}. \tag{13}$$

Some problems may require an untransformed expression for $k_\infty^{-1}=\hat{\lambda}(0)$:

$$k_\infty^{-1}=\frac{1+\kappa\displaystyle\int_0^\infty G(\mathbf{a}_+,t|\mathbf{a}_+)dt}{\kappa\rho(\mathbf{a}_+)}. \tag{14}$$

As an example without gating, consider three-dimensional Brownian motion in the presence of a partially absorbing sphere of radius a. The spherically symmetric Laplacian $\nabla^2 f=r^{-2}(\partial/\partial r)(r^2\partial f/\partial r)$ specifies the problem mathematically: the spherically symmetric reflecting Green's function $G_{3D}(r,t|r_0)$ satisfies $\partial G/\partial t=D\nabla^2 G$ for $r>a$, and has a reflecting boundary $[\partial G/\partial r]_{r=a}=0$ at the spherical surface. Standard tables [18] contain $G_{3D}(r,t|r_0)$, and other tables [16] contain its Laplace transform

$$\hat{G}_{3D}(r,s|r_0)=\frac{1}{8\pi Drr_0\sqrt{s/D}}\times\left[e^{-|r-r_0|\sqrt{s/D}}+e^{-(r+r_0-2a)\sqrt{s/D}}\,\frac{a\sqrt{s/D}-1}{a\sqrt{s/D}+1}\right]. \tag{15}$$

Without trapping, the equilibrium density starting from an initial uniform unit density is $\rho(r)\equiv 1$. On the other hand, a radiation boundary condition at the sphere's surface gives $D[\partial p/\partial r]_{r=a}=k_{eq}(4\pi a^2)^{-1}p$ in the usual notation [6], which is equivalent to a trapping strength $c(r)=k_{eq}(4\pi a^2)^{-1}\delta(r-a)$ everywhere on the spherical surface $r=a$. In Eq. (2), spherical symmetry and the radial δ function make the inner spatial integral $\int_V d\mathbf{R}\,G(\mathbf{r},t-T|\mathbf{R})c(\mathbf{R})p(\mathbf{R},T|\mathbf{r}_0)=k_{eq}G(r,t-T|a)p(a,T|r_0)$. Spherical symmetry therefore reduces the sphere to a single "point" trap along the radial coordinate. Formally, the strength $\kappa_i\delta(\mathbf{r}-\mathbf{a}_i)$ of this trap is $k_{eq}\delta(r-a)$, and formal substitution into the equations following Eq. (2) makes Eq. (13) yield

$$\hat{\lambda}_{3D}(s)=k_{eq}^{-1}+(4\pi Da)^{-1}(1+a\sqrt{s/D})^{-1}. \tag{16}$$

The known result [6] $k_{3D\infty}^{-1}=k_{eq}^{-1}+(4\pi R_0 D)^{-1}$ follows directly from Eq. (16) and the general relation $k_\infty^{-1}=\hat{\lambda}(0)$.

B. Systems with an equilibrium probability distribution

As an example without gating, consider diffusion in a one-dimensional harmonic potential $\phi(r)=(1/2)cr^2$. The particle movement has the evolution equation $\partial G/\partial t=D\partial/\partial r(\partial G/\partial r+\beta crG)$, and an equilibrium probability distribution $\rho(\mathbf{r})=\lim_{t\to\infty}G(\mathbf{r},t|\mathbf{r}_0)$ exists [14].

In general, let $\rho(\mathbf{x})=\lim_{t\to\infty}G(\mathbf{x},t|\mathbf{x}_0)$ be the relevant equilibrium probability density, so $\int_\Omega\rho(\mathbf{x})d\mathbf{x}=1$. We implicitly assume, as is usual in cases of physical interest, that $\rho(\mathbf{x})$ is independent of the initial state $\mathbf{x}_0$.

The probability that a particle starting in the equilibrium probability distribution survives to time t is $S(t)=\int_\Omega S(t|\mathbf{x}_0)\rho(\mathbf{x}_0)d\mathbf{x}_0$, where $S(t|\mathbf{x}_0)$ is given in Eq. (7). Equations (8), (10), and (13) therefore show that $\hat{S}(s)=\int_\Omega\hat{S}(s|\mathbf{x}_0)\rho(\mathbf{x}_0)d\mathbf{x}_0$ equals

$$\hat{S}(s)=s^{-1}\left[1-\frac{s^{-1}\kappa\rho(\mathbf{a}_+)}{1+\kappa\hat{G}(\mathbf{a}_+,s|\mathbf{a}_+)}\right]=s^{-1}\left[1-\frac{s^{-1}}{\kappa\hat{\lambda}(s)}\right]. \tag{17}$$

Equation (17) relates $\hat{S}(s)$ and $\hat{\lambda}(s)$ if a equilibrium probability distribution exists. Note that although $\rho(\mathbf{x})$ has different normalizations depending on whether or not an equilibrium probability distribution exists, Eq. (13) always defines $\hat{\lambda}(s)$ formally.

Standard theorems [17] again imply that $\rho(\mathbf{x})=\lim_{t\to\infty}G(\mathbf{x},t|\mathbf{x}_0)=\lim_{s\to\infty}s\hat{G}(\mathbf{x},s|\mathbf{x}_0)$. Equation (8) shows that the average time to reaction [19,20] starting from a state $\mathbf{x}_0$ is

$$\tau(\mathbf{x}_0)=\int_0^\infty S(t|\mathbf{x}_0)dt=\hat{S}(0|\mathbf{x}_0)=\lim_{s\to 0}\left[\hat{\lambda}(s)-\frac{\hat{G}(\mathbf{a}_+,s|\mathbf{x}_0)}{\rho(\mathbf{a}_+)}\right] \tag{18}$$

(if the limit exists), where the final equality in Eq. (18) follows from evaluating Eq. (8) by continuity at $s=0$ and then using Eq. (13). An alternative, untransformed expression for $\tau(\mathbf{x}_0)$ is available from Eqs. (13) and (18)

$$\tau(\mathbf{x}_0)=\frac{1+\kappa\displaystyle\int_0^\infty[G(\mathbf{a}_+,t|\mathbf{a}_+)-G(\mathbf{a}_+,t|\mathbf{x}_0)]dt}{\kappa\rho(\mathbf{a}_+)}. \tag{19}$$

Similarly, because of Eq. (10), the mean survival time starting from equilibrium can be derived by averaging $\tau(\mathbf{x}_0)$ over the equilibrium probability distribution $\rho(\mathbf{x}_0)$

$$\tau=\int_{\Omega}\tau(\mathbf{x}_0)\rho(\mathbf{x}_0)d\mathbf{x}_0=\lim_{s\to 0}[\hat{\lambda}(s)-s^{-1}]. \tag{20}$$

The rest of the paper simply refers to τ as the "mean survival time."

As with $\tau(\mathbf{x}_0)$, an untransformed expression for τ is available

$$\tau=\frac{1+\kappa\int_0^{\infty}[G(\mathbf{a}_+,t|\mathbf{a}_+)-\rho(\mathbf{a}_+)]dt}{\kappa\rho(\mathbf{a}_+)}. \tag{21}$$

Consider again as an example diffusion in a one-dimensional harmonic potential $\phi(r)=(1/2)cr^2$, with a trap at $r=a=0$. The reflecting Green's function $G_H(r,s|r_0)$ satisfies $\partial G/\partial t=D\partial/\partial r(\partial G/\partial r+\beta crG)$ for $r>0$, with the boundary condition $[\partial G/\partial r]_{r=a=0}=0$. When length and time are rescaled so $D=\beta c=1$, the reflecting Green's function $G_H(a,s|a)=(1/\sqrt{2})(1/2s-1)![(1/2s-1/2)!]^{-1}$ [14]. Equation (13) then yields

$$\hat{\lambda}_H(s)=\kappa^{-1}\left(\frac{1}{2}\pi\right)^{1/2}+\frac{1}{2}B\left(\frac{1}{2},\frac{1}{2}s\right), \tag{22}$$

where $B(a,b)$ is the β function [16]. The known result [14] for the mean survival time $\tau_H=\kappa^{-1}(\frac{1}{2}\pi)^{1/2}+\ln 2$ then follows from Eqs. (20) and (22).

III. SURVIVAL RESULTS FOR SPECIFIC MODELS OF GATED TRAPPING

In accord with our original motivations, this section now gives solutions for several simplified models in which the system gating state **q** and particle position **r** change independently. Under this assumption, the positional Green's function $G(\mathbf{r},t|\mathbf{r}_0)$, describing the particle movement in the absence of trapping, is well defined without reference to the gating state **q** of the system.

Since the formalism in Sec. II applies to both ungated and gated systems, the usage of "G" there was deliberately ambiguous: "G" there denoted either a positional Green's function $G(\mathbf{r},t|\mathbf{r}_0)$ (for an ungated system), *or* a gated Green's function $G(\mathbf{x},t|\mathbf{x}_0)$ (for a gated system). In this section, to differentiate positional Green's functions $G(\mathbf{r},t|\mathbf{r}_0)$ from gated Green's functions $G(\mathbf{x},t|\mathbf{x}_0)$, $G(\mathbf{x},t|\mathbf{x}_0)$ is subscripted as $G_g(\mathbf{x},t|\mathbf{x}_0)$.

Let $Q(\mathbf{q},t|\mathbf{q}_0)$ be the Green's function for the gating state, i.e., $Q(\mathbf{q},t|\mathbf{q}_0)$ is the probability that if the gating state is initially $\mathbf{q}_0$, it will be **q** at time t later. When the changes of the gating state **q** and the changes of the particle position **r** are independent, the gated Green's function $G_g(\mathbf{x},t|\mathbf{x}_0)$ for $\mathbf{x}=(\mathbf{q},\mathbf{r})$ is a product

$$G_g(\mathbf{x},t|\mathbf{x}_0)=Q(\mathbf{q},t|\mathbf{q}_0)G(\mathbf{r},t|\mathbf{r}_0). \tag{23}$$

In analogy to gating and gated states, **q** and $\mathbf{x}=(\mathbf{q},\mathbf{r})$, we refer to the "gating" and "gated" Green's functions $Q(\mathbf{q},t|\mathbf{q}_0)$ and $G_g(\mathbf{x},t|\mathbf{x}_0)$. As stated above, Eq. (23) gives $G_g(\mathbf{x},t|\mathbf{x}_0)$ a subscript "g" to distinguish it from the positional Green's function $G(\mathbf{r},t|\mathbf{r}_0)$. The following gives some examples that derive gated Green's functions $G_g(\mathbf{x},t|\mathbf{x}0)$ from the corresponding gating Green's functions $Q(\mathbf{q},t|\mathbf{q}_0)$.

A. Poisson gating

Let us revisit Poisson gating $(-)\underset{\beta_0}{\overset{\alpha_0}{\rightleftharpoons}}(+)$, this time as a possible model describing a ligand binding to a protein. For ease of linguistic reference, the gating of the ligand-protein system will be ascribed to the protein. Biologically, such gating might be caused by fluctuations in the protein's conformation, or by the binding of reversible blockers. Whatever the cause, the "active" protein state $(+)$ permits ligand binding, whereas the "blocked" protein state $(-)$ prevents it.

The protein's gating at time t is completely specified by four gating Green's functions $Q_{pg}(\pm,t|\pm)$. Let $Q_{pg}(+,t|+)$ be the probability that the protein is active at time t, given that it was active at time $t=0$. Define the other three Green's functions analogously. Since $Q_{pg}(-,t|+)=1-Q_{pg}(+,t|+)$, the Green's function $Q_{pg}(+,t|+)$ satisfies

$$\frac{dQ_{pg}(+,t|+)}{dt}=-\beta_0Q_{pg}(+,t|+)+\alpha_0[1-Q_{pg}(+,t|+)] \tag{24}$$

with the initial condition $Q_{pg}(+,t|+)=1$.

Recall the equilibrium probabilities $\rho_{pg}(+)=\alpha_0(\alpha_0+\beta_0)^{-1}$ and $\rho_{pg}(-)=\beta_0(\alpha_0+\beta_0)^{-1}$. The solution to Eq. (24) is

$$Q_{pg}(+,t|+)=\rho_{pg}(+)+\rho_{pg}(-)e^{-(\alpha_0+\beta_0)t}. \tag{25}$$

Thus $Q_{pg}(-,t|+)=1-Q_{pg}(+,t|+)=\rho_{pg}(-)[1-e^{-(\alpha_0+\beta_0)t}]$. Interchanging the roles of $(+)$ and $(-)$ in the solution gives $Q_{pg}(-,t|-)=\rho_{pg}(-)+\rho_{pg}(+)e^{-(\alpha_0+\beta_0)t}$ and $Q_{pg}(+,t|-)=\rho_{pg}(+)[1-e^{-(\alpha_0+\beta_0)t}]$.

Because of Eqs. (6) and (23), $Q(+,t|+)$ is the most important gating Green's function in trapping problems with a single active state $(+)$. All four Green's functions $Q_{pg}(\pm,t|\pm)$ were given here just for completeness.

Most of the gating solutions in Sec. II require the Laplace transform of $G_g(\mathbf{a}_+,t|\mathbf{a}_+)$. Accordingly, Eqs. (23) and (25), along with the shift property $\hat{f}(s+\alpha)=\int_0^{\infty}e^{-st}[e^{-\alpha t}f(t)]dt$ of Laplace transforms, give the Poisson gated Green's function

$$\hat{G}_{pg}(\mathbf{r}_+,s|\mathbf{r}_{0+})=\rho_{pg}(+)\hat{G}(\mathbf{r},s|\mathbf{r}_0)+\rho_{pg}(-)\times\hat{G}(\mathbf{r},s+\alpha+\beta|\mathbf{r}_0). \tag{26}$$

The Laplace transforms of the other gated Green's functions $\hat{G}_{pg}(\mathbf{r}_{\pm},s|\mathbf{r}_{0\pm})$ can be similarly derived from the gating Green's functions $Q_{pg}(\pm,t|\pm)$ listed above. Note, however, that only $\hat{G}_{pg}(\mathbf{r}_+,s|\mathbf{r}_{0+})$ is required in Eq. (13).

For any initial gating state $\mathbf{q}_0$, $\lim_{t\to\infty}Q_{pg}(+,t|\mathbf{q}_0)=\rho_{pg}(+)$, by letting $t\to\infty$ in $Q_{pg}(+,t|+)=\rho_{pg}(+)+\rho_{pg}(-)e^{-(\alpha_0+\beta_0)t}$ [Eq. (25)] and the equation $Q_{pg}(+,t|-)=\rho_{pg}(+)[1-e^{-(\alpha_0+\beta_0)t}]$. Thus regardless of initial gating state(s), the independence of gating and particle movement imply that $\rho_{pg}(\mathbf{a}_+)=\rho_{pg}(+)\rho(\mathbf{a})$ for an initial unit particle density. For a gated trap at $\mathbf{r}=\mathbf{a}$, the trapping strength is

$c(\mathbf{r}_+)=\kappa\delta(\mathbf{r}-\mathbf{a})$ in the active gating state $(+)$, and $c(\mathbf{r}_-)=0$ otherwise. Since $\rho_{pg}(-)/\rho_{pg}(+)=\beta_0/\alpha_0$, Eq. (26) substituted in Eq. (13) gives

$$\begin{aligned}\hat{\lambda}_{pg}(s) &= \frac{1+\kappa\rho_{pg}(+)\hat{G}(\mathbf{a},s|\mathbf{a})+\kappa\rho_{pg}(-)\hat{G}(\mathbf{a},s+\alpha_0+\beta_0|\mathbf{a})}{\kappa\rho_{pg}(+)\rho(\mathbf{a})}\\ &=\hat{\lambda}(s)+\frac{\beta_0}{\alpha_0}\hat{\lambda}(s+\alpha_0+\beta_0),\end{aligned} \tag{27}$$

where $\hat{\lambda}(s)$ for the ungated problem is given by substituting the spatial Green's function $G(\mathbf{r},t|\mathbf{r}_0)$ and the ungated equilibrium density $\rho(\mathbf{a})$ into Eq. (13). Because of the definition $\hat{\lambda}(s):=[s\hat{k}(s)]^{-1}$, Eq. (27) implicitly relates the transformed rates of gated and ungated trapping $\hat{k}(s)$, in agreement with previous, more specialized results about diffusive particle movements [1,13].

When the asymptotic rate of trapping $k_\infty=\lim_{t\to\infty}k(t)=\lim_{s\to 0}s\hat{k}(s)$ exists, setting $s=0$ in Eq. (27) gives the gated characteristic time $k_{pg\infty}^{-1}=\hat{\lambda}_{pg}(0)$ in terms of the ungated characteristic time $k_\infty^{-1}=\hat{\lambda}(0)$ and $\hat{\lambda}(s)$ for the ungated problem

$$k_{pg\infty}^{-1}=k_\infty^{-1}+\frac{\beta_0}{\alpha_0}\hat{\lambda}(\alpha_0+\beta_0). \tag{28}$$

Again, the above derivation shows that Eq. (28) is valid not only for diffusion, but also other types of particle movement.

Similarly, when the gated system has an equilibrium probability distribution, taking the limit as $s\to 0$ in Eq. (20) shows that the mean survival times also obey Eq. (28) with the gated survival time $\tau_{pg}=\lim_{s\to 0}[\hat{\lambda}_{pg}(s)-s^{-1}]$ and the ungated survival time $\tau=\lim_{s\to 0}[\hat{\lambda}(s)-s^{-1}]$ replacing $k_{pg\infty}^{-1}$ and k_∞^{-1}.

Equations (16) and (22) can be used to provide specific solutions for Poisson gating (and for double and multiple Poisson gating, below). The result for Poisson gating is known [1,5,6,13].

B. Double Poisson gating

Equation (25) is easily extended to double Poisson gating, where both the protein and the ligand are Poisson gated. In double Poisson gating, the active state $(+)$ requires that both the protein and that the ligand be active. In an obvious extension of notation, with subscripts "1" and "2" referring to protein and ligand, Eq. (25) gives

$$\begin{aligned}Q_{dg}(+,t|+)=&[\rho_1(+)+\rho_1(-)e^{-(\alpha_1+\beta_1)t}]\\ &\times[\rho_2(+)+\rho_2(-)e^{-(\alpha_2+\beta_2)t}].\end{aligned} \tag{29}$$

When either the protein ($\beta_1=0$) or the ligand ($\beta_2=0$) does not gate, Eq. (29) reduces to Eq. (25), as indeed it should.

Equations (23) and (29) therefore yield the double gated Green's function

$$\begin{aligned}\hat{G}_{dg}(\mathbf{r}_+,s|\mathbf{r}_{0+})&\\ =\rho_1(+)\rho_2(+)&\hat{G}(\mathbf{r},s|\mathbf{r}_0)\\ &+\rho_1(+)\rho_2(-)\hat{G}(\mathbf{r},s+\alpha_2+\beta_2|\mathbf{r}_0)\\ &+\rho_1(-)\rho_2(+)\hat{G}(\mathbf{r},s+\alpha_1+\beta_2|\mathbf{r}_0)\\ &+\rho_1(-)\rho_2(-)\hat{G}(\mathbf{r},s+\alpha_1+\beta_2+\alpha_2+\beta_2|\mathbf{r}_0).\end{aligned} \tag{30}$$

In double Poisson gating, $\mathbf{r}_+$ (or $\mathbf{r}_{0+}$) denotes the gated system state with the particle at position $\mathbf{r}$ (or $\mathbf{r}_0$), with *both* the protein *and* the ligand active. Although other double gated Green's functions could be derived, only Eq. (30) is required in Eq. (13).

Proceeding by analogy to Poisson gating shows that regardless of the initial gating state $\mathbf{q}_0$, $\lim_{t\to\infty}Q_{dg}(+,t|\mathbf{q}_0)=\rho_1(+)\rho_2(+)$, so $\rho_{dg}(\mathbf{a}_+)=\rho_1(+)\rho_2(+)\rho(\mathbf{a})$. For a gated trap at $\mathbf{r}=\mathbf{a}$, the trapping strength is $c(\mathbf{r}_+)=\kappa\delta(\mathbf{r}-\mathbf{a})$ in the active gating state $(+)$, and $c(\mathbf{r}_-)=0$ otherwise. With double Poisson gating, Eq. (30) substituted in Eq. (13) gives

$$\begin{aligned}\hat{\lambda}_{dg}(s)=\hat{\lambda}(s)&+\frac{\beta_1}{\alpha_1}\hat{\lambda}(s+\alpha_1+\beta_1)+\frac{\beta_2}{\alpha_2}\hat{\lambda}(s+\alpha_2+\beta_2)\\ &+\frac{\beta_1\beta_2}{\alpha_1\alpha_2}\hat{\lambda}(s+\alpha_1+\beta_1+\alpha_2+\beta_2).\end{aligned} \tag{31}$$

Again, Eq. (31) relates the transformed rates of trapping $\hat{k}(s)$ for the double gated and ungated problems.

When the asymptotic rate of trapping $k_\infty=\lim_{t\to\infty}k(t)=\lim_{s\to 0}s\hat{k}(s)$ exists, setting $s=0$ in Eq. (31) gives the double gated characteristic time $k_{dg\infty}^{-1}=\hat{\lambda}_{dg}(0)$ in terms of the ungated characteristic time $k_\infty^{-1}=\hat{\lambda}(0)$ and $\hat{\lambda}(s)$ for the ungated problem

$$\begin{aligned}k_{dg\infty}^{-1}=k_\infty^{-1}&+\frac{\beta_1}{\alpha_1}\hat{\lambda}(\alpha_1+\beta_1)+\frac{\beta_2}{\alpha_2}\hat{\lambda}(\alpha_2+\beta_2)\\ &+\frac{\beta_1\beta_2}{\alpha_1\alpha_2}\hat{\lambda}(\alpha_1+\beta_1+\alpha_2+\beta_2).\end{aligned} \tag{32}$$

When the particle movement has an equilibrium probability distribution, by analogy with single Poisson gating results, taking the limit as $s\to 0$ in Eq. (20) shows that the mean survival times also obey Eq. (32) with the double gated mean survival time $\tau_{dg}=\lim_{s\to 0}[\hat{\lambda}_{dg}(s)-s^{-1}]$ and the ungated mean survival time $\tau=\lim_{s\to 0}[\hat{\lambda}(s)-s^{-1}]$ replacing $k_{dg\infty}^{-1}$ and k_∞^{-1}.

C. Multiple Poisson gating

Similarly, in multiple Poisson gating, the active state $(+)$ requires J Poisson components to be active

$$Q_{mg}(+,t|+)=\prod_{j=1}^{J}[\rho_j(+)+\rho_j(-)e^{-(\alpha_j+\beta_j)t}]. \tag{33}$$

Just as in single or double Poisson gating, Eq. (33) permits $\hat{G}_{mg}(\mathbf{r}_+,s|\mathbf{r}_{0+})$ to be written down explicitly from Eq. (23).

By an easy extension of the above results, the multiple gating analogue of Eq. (30) can be written out, and again, regardless of the initial gating state(s), it can be shown that

$\lim_{t\to\infty} Q_{mg}(+,t|\mathbf{q}_0)=\rho_1(+)\rho_2(+)\cdots\rho_{\mathbf{J}}(+)$ and so $\rho_{mg}(\mathbf{a}_+)=\rho_1(+)\rho_2(+)\cdots\rho_{\mathbf{J}}(+)\rho(\mathbf{a})$.

Equation (31) generalizes to

$$\hat{\lambda}_{mg}(s)=\hat{\lambda}(s)+\sum_{j=1}^{J}\left[\frac{\beta_j}{\alpha_j}\,\hat{\lambda}(s+\alpha_j+\beta_j)\right] + \sum_{\substack{j,k=1\\ j\neq k}}^{J}\left[\frac{\beta_j}{\alpha_j}\,\frac{\beta_k}{\alpha_k}\,\hat{\lambda}(s+\alpha_j+\beta_j+\alpha_k+\beta_k)\right]\cdots + \left(\prod_{j=1}^{J}\frac{\beta_j}{\alpha_j}\right)\hat{\lambda}\left(s+\sum_{j=1}^{J}(\alpha_j+\beta_j)\right). \tag{34}$$

When the asymptotic rate of trapping $k_\infty=\lim_{t\to\infty}k(t)=\lim_{s\to 0} s\hat{k}(s)$ exists, setting $s=0$ in Eq. (34) relates the multiple gated and ungated characteristic times just as it did for single and double gated characteristic times. When the particle movement has an equilibrium probability distribution, taking the limit as $s\to 0$ in Eq. (20) similarly relates the multiple gated and ungated mean survival times.

D. Markovian gating with a single active state

Single, double, and multiple Poisson gating are all specializations of this model, which assumes a multistate random walk model for the gating state $\mathbf{q}$. Consider a gating state fluctuating between N different states $\mathbf{q}_1 \rightleftharpoons \mathbf{q}_2 \rightleftharpoons \ldots \rightleftharpoons \mathbf{q}_N$ according to a system of linear differential equations with constant coefficients

$$\left[\frac{dQ(\mathbf{q}_i,t|\mathbf{q})}{dt}\right]=\mathbf{L}[Q(\mathbf{q}_i,t|\mathbf{q})]. \tag{35}$$

$\mathbf{q}$ is an arbitrary initial gating state, and the dimensions of the three matrices in Eq. (35) are $N\times 1$, $N\times N$, and $N\times 1$. The elements of the matrix $\mathbf{L}=[L_{ij}]_{N\times N}$ give the rate constants L_{ij} of the interconversions $\mathbf{q}_j\to\mathbf{q}_i$ $(i,j=1,2,\ldots,N)$. Single Poisson gating, e.g., is Markovian gating with $N=2$, $\mathbf{q}_1=(+)$, $\mathbf{q}_2=(-)$, and $L_{ij}=(-1)^{i+j-1}[\delta_{1j}\beta+\delta_{2j}\alpha]$, where again Kronecker's delta $\delta_{ij}=1$ if $i=j$ and 0 otherwise. Note that the $\{L_{ij}\}$ may be negative.

Using standard methods [21] to solve Eq. (35) subject to the initial conditions $Q(\mathbf{q}_i,0|\mathbf{q}_j)=\delta_{ij}$, yields

$$[Q(\mathbf{q}_i,t|\mathbf{q}_j)]=e^{\mathbf{L}t}. \tag{36}$$

so $Q(\mathbf{q}_i,t/\mathbf{q}_j)$ is the (i,j)th element of the matrix $e^{\mathbf{L}t}=\Sigma_{k=0}^{\infty}(\mathbf{L}t)^k/k!$. When the rate coefficients $\{L_{ij}\}$ and equilibrium distribution $\rho(\mathbf{q})$ satisfy the detailed balance condition $L_{ij}\rho(\mathbf{q}_j)=L_{ji}\rho(\mathbf{q}_i)$, the matrix $\mathbf{L}$ can be diagonalized to $\mathbf{\Lambda}=[\delta_{ij}\Lambda_{ii}]=\mathbf{S}^{-1}\mathbf{LS}$. Computing $e^{\mathbf{L}t}=\mathbf{S}e^{\mathbf{\Lambda}t}\mathbf{S}^{-1}$ is then particularly easy.

Let $\mathbf{x}=(\mathbf{q}_j,\mathbf{r})=\mathbf{r}_j$ (or $\mathbf{x}=\mathbf{r}_{0j}$) denote the system state where the particle is at position $\mathbf{r}$ (or $\mathbf{r}_0$) while the gating state is $\mathbf{q}_j$. Since the matrix of gated Green's functions is

$$[G_g(\mathbf{r}_i,t|\mathbf{r}_{0,j})]=[Q(\mathbf{q}_i,t|\mathbf{q}_j)]G(\mathbf{r},t|\mathbf{r}_0)=e^{\mathbf{L}t}G(\mathbf{r},t|\mathbf{r}_0), \tag{37}$$

the shift property of Laplace transforms and Eq. (35) yield $\hat{G}_g(\mathbf{r}_i,s|\mathbf{r}_{0,j})$ as a linear combination of $\hat{G}(\mathbf{r},s+\Lambda_{jj}|\mathbf{r}_0)$, $j=1,2,\ldots,N$ when $\mathbf{L}$ can be diagonalized.

The previous Poisson gated models are special cases of Markovian gating when the system state $\mathbf{q}_1=(+)$ is active, with the other states $\mathbf{q}_j$ all blocked $(j=2,\ldots,N)$. In this case, $G_g(\mathbf{r}_+,t|\mathbf{r}_{0+})=[e^{\mathbf{L}t}]_{11}G(\mathbf{r},t|\mathbf{r}_0)$. For a gated trap at $\mathbf{r}=\mathbf{a}$, the trapping strength is $c(\mathbf{r}_+)=\kappa\delta(\mathbf{r}-\mathbf{a})$ in the single active gating state $\mathbf{q}_1=(+)$, and $c(\mathbf{r}_j)=0$ for the other states $\mathbf{q}_j$ $(j=2,\ldots,N)$, Markovian gating has a similar solution to the previous Poisson gated models. Substitution of the Laplace transform of $G_g(\mathbf{a}_+,t|\mathbf{a}_+)=[e^{\mathbf{L}t}]_{11}G(\mathbf{a},t|\mathbf{a})$ into Eq. (13) produces formulas of sufficient complexity, however, that they need not appear in this paper.

IV. DISCUSSION

This paper provides a simple, unified formalism for solving problems with a single moving particle in the presence of gated static traps, when gating is independent of the particle movement. Smoluchowski mean-field rate constants [7–9] depend on solving single particle, single trap problems. Thus Eqs. (28), (32), and (34) implicitly give rate constants for single [5,6], double, and multiple Poisson gating.

This paper's formalism is general and simple, and helps indicate which gating problems are likely to have explicit solutions.

The gating solutions in Sec. II use the Laplace transform of the reflecting Green's function $\hat{G}(\mathbf{r},s|\mathbf{r}_0)$ with arbitrary arguments. Implicitly, if an equilibrium probability distribution exists, they also use $\hat{S}(s|\mathbf{r}_0)$ from Eq. (17), also with arbitrary arguments. This indicates that solving arbitrary gating problems requires knowledge (at least implicitly) of $\hat{G}(\mathbf{r},s|\mathbf{r}_0)$ or $\hat{S}(s|\mathbf{r}_0)$. Note, however, that Eqs. (14), (19), and (21) can be used to calculate rate constants and mean survival times numerically from the gating Green's functions $G_g(\mathbf{a}_+,t|\mathbf{x}_0)$ without recourse to analytic Laplace transformation. This is useful, because the gating Green's function $G_g(\mathbf{x},t|\mathbf{x}_0)=Q(\mathbf{q},t|\mathbf{q}_0)G(\mathbf{r},t|\mathbf{r}_0)$ in Eq. (23) may be accessible without its also having a simple Laplace transform.

This paper's formalism requires more than just knowledge of $Q(\mathbf{q},t|\mathbf{q}_0)$ and $G(\mathbf{r},t|\mathbf{r}_0)$, however. It is based on Eq. (2), which requires the system evolution as a whole to be Markovian. Thus, e.g., the formalism does not directly apply to coherent gating [5,6], a deterministic gating where the trap is active and blocked over predetermined time periods. Although the coherent gating Green's function $Q(\mathbf{q},t|\mathbf{q}_0)$ is simply a square switching function, when particle movement is considered, the memory in coherent gating leads to a continuum of trapping states in Eq. (2) and an integral equation. In other non-Markovian gating problems, i.e., other problems where the transition times are not described by a first-order kinetic scheme, Eq. (2) also yields integral equations. Similarly, problems with several diffusing particles can be transformed into problems with a single particle diffusing in a high dimensional space, and Eq. (2) is again an integral equation. Unfortunately, these integral equations appear to lack analytic solutions.

Other types of memory can be embedded into a Markovian description without significant complications, however. In double Poisson gating, e.g., Eq. (29) for the gating

Green's function $Q_{dg}(+,t|+)$ appears superficially non-Markovian. Indeed, e.g., knowing that binding is blocked does not determine whether it is the protein or the ligand that is blocked. Knowing that the binding is active defines a regenerative (Markovian) gating state; however, if trapping is active, both the protein and the ligand must be active. Thus double Poisson gating was solved by implicitly embedding it into a Markovian gating problem with one active gating state. This solution can also be developed explicitly with Eq. (5), which handles multiple discrete trapping states.

For simplicity, this paper focused on the case $M=1$ in Eq. (5), but solutions with $M=2$ are also practicable, since they involve inverting only 2×2 matrices. The case $M=2$ provides a solution for the following problems: (1) a single trap fluctuating between two positive strengths $c(\mathbf{r}_1)=\kappa_1\delta(\mathbf{r}-\mathbf{a})$ and $c(\mathbf{r}_2)=\kappa_2\delta(\mathbf{r}-\mathbf{a})$, with $c(\mathbf{r}_j)=0$ for other states $\mathbf{q}_j$; and (2) two separate traps, one gated, the other not. Two *independently* gated traps have at least four distinct gating states $++$, $+-$, $-+$, and $--$, of which the first three are active, in general requiring at least $M=3$ in Eq. (5).

In many physical situations, e.g., protein gating and blocking chemical reactions, gating is independent of particle movement. On the other hand, a related situation called ''dynamic trapping'' does couple particle movement and gating. Like the gating problems here, dynamic trapping problems can be solved [2,3] by extending ungated trapping formalisms [22]. Unlike the gating solutions here, however, those dynamic trapping solutions seem to require particle movement and gating to be coupled. On the other hand, although Eq. (23) assumes the independence of particle movement and gating, the assumption was not crucial when Sec. II extended its ungated formalism [14] to gated trapping. Thus it will be interesting to see if the present formalism can be applied to dynamic trapping as well.

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