A Model of Anomalous Enzyme-Catalyzed Gel Degradation Kinetics

Debarati Chatterjee and Binny J. Cherayil*

Department of Inorganic and Physical Chemistry, Indian Institute of Science, Bangalore-560012, India

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We show that a model of target location involving n noninteracting particles moving subdiffusively along a line segment (a generalization of a model introduced by Sokolov et al. [*Biophys. J.* **2005**, *89*, 895.]) provides a basis for understanding recent experiments by Pelta et al. [*Phys. Rev. Lett.* **2007**, *98*, 228302.] on the kinetics of diffusion-limited gel degradation. These experiments find that the time t_c taken by the enzyme thermolysin to completely hydrolyze a gel varies inversely as roughly the 3/2 power of the initial enzyme concentration $[E]$. In general, however, this time would be expected to vary either as $[E]^{-1}$ or as $[E]^{-2}$, depending on whether the Brownian diffusion of the enzyme to the site of cleavage took place along the network chains (1-d diffusion) or through the pore spaces (3-d diffusion). In our model, the unusual dependence of t_c on $[E]$ is explained in terms of a reaction−diffusion equation that is formulated in terms of fractional rather than ordinary time derivatives.

1. Introduction

Gels and related cross-linked macromolecular networks have recently emerged as versatile materials for the design and synthesis of nanoscale devices with tailored sensitivity to heat, light, and other external agents.[1] Susceptibility to site-specific bond cleavage is often one of the reasons for the stimuli-responsiveness of these materials and for their usefulness in such systems. A gel exposed to a degradative enzyme, for instance, tends to lose its structural and mechanical integrity over time in a manner that can be ideal for certain specialized functions, particularly those that require time-delayed or targeted release of encapsulated chemicals.[2] However, precise control over such behavior can usually only be achieved if the underlying molecular processes by which it is governed are well-understood. Experiments under controlled conditions are therefore especially valuable in identifying and characterizing these processes.

In this connection, an experiment by Pelta et al.[3] on the proteolytic activity of the enzyme thermolysin presents interesting new data on the kinetics of the transition of a gel phase of a cross-linked polymer to its sol phase. The experiment was carried out by first solidifying, in glass tubes, an initially liquid mixture of gelatin (having polymer volume fraction φ) and thermolysin (concentration $[E]$) containing a millimeter-sized polyacetal sphere, inverting the tubes following solidification, raising the temperature of the system from 4 to 14 °C (to initiate proteolysis), and finally measuring the time taken t_c for the solid gel to liquefy as a result of enzymatic action (t_c being identified with the time at which the sphere first begins to fall through the liquid under its own weight.) For different starting φ and $[E]$, it was found that t_c obeyed the following scaling relation: $t_c \approx \eta\varphi^{2.50\pm0.05}[E]^{-1.46\pm0.07}$, where η is the viscosity of the solvent.

It was also found that increasing the viscosity of the solution (by the addition of glycerol) led to an increase in t_c, independent of both $[E]$ and φ, which Pelta et al. argue is evidence that the degradation reaction is, in fact, diffusion-limited. (Had it been reaction-limited, there would have been a change in the character of the kinetics as η was increased and as the time scales of reaction and diffusion became comparable.) If it is indeed the case that the reaction is diffusion-limited, and if it is also assumed that the diffusion of the enzyme to the sites of bond scission proceeds predominantly by one-dimensional Brownian motion along the network chains, t_c would be expected to vary as $1/[E]^2$. On the other hand, t_c would be expected to vary as $1/[E]$ if the diffusion were predominantly three-dimensional and occurred through the pore spaces of the network. That the actual dependence of t_c on $[E]$ lies between these limits might indicate either a mechanism combining both modes of motion or, as Pelta et al. suggest, one involving anomalous diffusion. An earlier study by the same group[4] of the mean square displacements of the enzyme in the same reaction system provided independent evidence for the second of these possibilities.

Pelta et al. have analyzed the data from their most recent work in terms of two dimensionless scaling variables, one being the ratio of t_c to τ_0, where τ_0 is the time to diffuse the length ξ_0 between two junction points in the gel (a quantity that from scaling theory[5] varies as $\varphi^{-\nu_F/(3\nu_F-1)}$, ν_F being the Flory exponent) and the other being the product of $[E]$ and the elementary volume ξ_0^3. A plot of the data using these variables leads to their collapse onto a single universal curve when ν_F, the lone adjustable parameter, is set to 1/2. A model of gel degradation based on the growth of void spaces following the cleavage of junction points was found to recover the scaling structure of this universal curve but only when the enzyme's random walk through the gel was assumed to be self-attracting and characterized by an exponent lying between 1/5 and 1/4 (and not 1/2). While the model is suggestive and its results are indicative of a reaction mechanism based on diffusive anomalies, it does not provide a completely satisfactory microscopic picture of the events leading up to gel liquefaction.

In this paper, therefore, we explore the unusual $[E]$ dependence of t_c in terms of a model of chemical reaction that involves the notion of *fractional* diffusion[6] in one dimension. The model can be formulated quite generally in terms of the problem of target location under specified initial conditions. The target, in this instance, corresponds to a network junction that can be

* To whom correspondence should be addressed. E-mail: cherayil@ipc.iisc.ernet.in.

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proteolytically cleaved by an enzyme; the average time it takes for a collection of many enzymes to locate this target can be regarded as a measure of the liquefaction time t_c (provided, of course, that proteolysis is diffusion-limited, as seems to be the case in the experiments.) The time t_c is the quantity that we shall attempt to determine as a function of $[E]$.

The following section highlights the limitations of a purely Brownian model of reaction and diffusion in rationalizing the anomalies of ref 3. We then introduce, in section 3, a generalization of this model in which fractional time derivatives are incorporated into the formalism. This model is used to calculate the survival probability of the junction point that is targeted by the enzymes and, from it, the average survival time of the junction. A discussion of our results is presented in section 4, while three Appendices present further generalizations of our basic model and some technical details of our calculations.

2. Brownian Diffusion Models of Reaction Kinetics

To account for the scaling of t_c with $[E]$ in the data of ref 3, we seek an expression for the probability $S(t)$ that a bond in the gel survives up to a time t in the presence of many enzymes. If the degradation reaction is assumed to follow first-order kinetics, a possible starting point for the calculation of $S(t)$ is then the following phenomenological rate equation[7,8]

$$\frac{dS(t)}{dt} = -k(t)S(t) \tag{1}$$

where $k(t)$ is a rate constant that, in general, is time-dependent. In the absence of definite information about the functional form of $k(t)$, the simplest approximation that can be made at this stage is to set $k(t)$ to a constant, proportional to $[E]$. We can then write $k(t) = a[E]$, where a is some constant. After substitution of this approximation into eq 1, it immediately follows that

$$S(t) = \exp(-a[E]t) \tag{2}$$

The mean survival time of the bond, $\langle t \rangle$, can then be calculated from $S(t)$ using the relation

$$\langle t \rangle = \int_0^\infty dt S(t) \tag{3}$$

This leads to the result

$$\langle t \rangle \approx [E]^{-1} \tag{4}$$

which is expected to be generally true of reactions in three dimensions. If $\langle t \rangle$ is identified with t_c, we see that this simple model fails to account for the experimentally observed scaling of t_c with $[E]$.

An alternative model can be formulated in terms of the kind of targeting problem mentioned in the Introduction. Suppose that the cleavable bond is located at the origin $x = 0$ of a rectangular coordinate system and some density $\rho(x,t)$ of enzymes is found at the point $x > 0$ at time t. How long, on average, does it take for the bond to be found (and then cleaved at once) if the enzymes move along the x-axis by a simple random walk? If one identifies the flux of enzymes into $x = 0$ during this process with the rate $k(t)$ in eq 1, one can, in principle, calculate this flux and thereby $S(t)$, which then yields $\langle t \rangle \equiv t_c$.

The flux of enzymes into $x = 0$ is given formally by

$$k(t) = D\frac{\partial \rho(x,t)}{\partial x}\bigg|_{x=0} \tag{5}$$

where D is a one-dimensional diffusion coefficient. The evaluation of $S(t)$ (and thence $\langle t \rangle$) therefore reduces to the calculation of $\rho(x,t)$ for the case of ordinary Brownian diffusion in one dimension. This calculation has actually been carried out by Sokolov et al.,[7] who solved the equation

$$\frac{\partial \rho(x,t)}{\partial t} = D\frac{\partial^2 \rho(x,t)}{\partial x^2} \tag{6}$$

under the following conditions: (i) $\rho(x,0) = [E]\Theta(x)$, where $[E]$, as before, is the initial enzyme concentration and $\Theta(x)$ is the Heaviside step function, (ii) $\rho(x \to \infty,t) < \infty$, and (iii) $\rho(x = 0,t) = 0$ (the last condition representing the absorption of enzymes at the target site and the simultaneous loss of the network junction). In Laplace space [where the Laplace transform $\hat{g}(s)$ of a time-dependent function $g(t)$ is defined as $\hat{g}(s) = \int_0^\infty dt\, g(t)e^{-st}$], they showed that

$$\hat{\rho}(x,s) = \frac{[E]}{s}\left[1 - \exp\left(-x\sqrt{\frac{s}{D}}\right)\right] \tag{7}$$

This expression yields the s-dependent flux

$$\hat{k}(s) \equiv D\frac{\partial \hat{\rho}(x,s)}{\partial x}\bigg|_{x=0} = \frac{[E]\sqrt{D}}{\sqrt{s}} \tag{8}$$

which, after Laplace inversion, leads to

$$k(t) = \frac{\sqrt{D}[E]}{\sqrt{\pi}}t^{-1/2} \tag{9}$$

When eq 9 is combined with eqs 1 and 3, we find that the survival probability of the bond is given by

$$S(t) = \exp\left[-2[E]\sqrt{\frac{Dt}{\pi}}\right] \tag{10}$$

from which we then find that the mean survival time $\langle t \rangle$ (which we are identifying with the critical liquefaction time t_c) scales as

$$\langle t \rangle = t_c \approx [E]^{-2} \tag{11}$$

This result (applicable to diffusion in one dimension) also fails to reproduce the experimental observations.

3. Fractional Diffusion Model of Reaction Kinetics

These results suggest that to formulate a model of anomalous gel degradation kinetics that leads to the observed fractional concentration dependence of the liquefaction time, one should consider generalizing the Brownian diffusion model of enzyme dynamics defined by eq 6 to a model in which the dynamics is

subdiffusive (or at least non-Brownian). One way to do this is to replace eq 6 by its fractional analogue[6]

$$\frac{\partial \rho(x,t)}{\partial t} = {}_0D_t^{1-\alpha} D_\alpha \frac{\partial^2 \rho(x,t)}{\partial x^2} \tag{12}$$

Here, ${}_0D_t^{1-\alpha}$ is a fractional time derivative operator; its action on any function of the time, $f(t)$, is defined by

$${}_0D_t^{1-\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \frac{\partial}{\partial t} \int_0^t dt_1 (t - t_1)^{-(1-\alpha)} f(t_1) \tag{13}$$

where $\Gamma(\cdots)$ is the gamma function, α is a real number lying between 0 and 1 (with $\alpha = 1$ corresponding to simple Brownian motion), and D_α is a generalized diffusion coefficient whose dimensions are defined by the choice of α. Diffusion equations of the above form are obtained whenever the successive steps in an ordinary random walk are interrupted by a random waiting time whose distribution follows a power law decay $t^{-1-\alpha}$.

Under the same initial and boundary conditions that were applied to treat eq 6, it proves quite straightforward to solve eq 12 using Laplace transform methods. The result is

$$\hat{\rho}(x,s) = \frac{[E]}{s}\left[1 - \exp\left(-x\sqrt{\frac{s^\alpha}{D_\alpha}}\right)\right] \tag{14}$$

Using the definition of the enzyme flux into $x = 0$, this expression yields the rate

$$k(t) = \frac{[E]\sqrt{D_\alpha}}{\Gamma(1 - \alpha/2)} t^{-\alpha/2} \tag{15}$$

from which the survival probability is found to be

$$S(t) = \exp\left[-[E]\frac{\sqrt{D_\alpha}}{\Gamma(2 - \alpha/2)} t^{1-\alpha/2}\right] \tag{16}$$

Calculating the mean survival time of the bond from this expression, we find the scaling relation

$$\langle t \rangle = t_c \approx [E]^{-1/(1-\alpha/2)} \tag{17}$$

This recovers the result in eq 11 when α is set to 1, while if α is set to any number between 0 and 1 (thereby implying subdiffusive motion of the enzyme), we find that the exponent of $[E]$ now lies between -1 and -2, consistent with the data of ref 1. The actual experimental result can be more or less exactly reproduced by the specific choice $\alpha = 2/3$, which leads to the relation $t_c \approx [E]^{-3/2}$. Thus, a model of subdiffusive target location involving many sliding enzymes provides a possible (zeroth-order) scenario for anomalous gel degradation kinetics when the reaction is diffusion-limited.

However, this still leaves open the possibility that ordinary one-dimensional Brownian diffusion of the enzymes could account for these kinetics if the enzymes were also allowed to adsorb onto or desorb from the network strand at some given rate. Such processes could, conceivably, alter the effective dimensionality of the random motion and thereby alter the scaling of t_c with $[E]$. When they are included in our model of target location, the equation satisfied by $\rho(x,t)$ is now given by[7]

$$\frac{\partial \rho(x,t)}{\partial t} = \left[D\frac{\partial^2 \rho(x,t)}{\partial x^2} - k_1 \rho(x,t) + k_2\right] \tag{18}$$

where k_1 and k_2 are the rate constants for adsorption and desorption, respectively. As Sokolov et al.[7] have shown, a closed form expression for $S(t)$ can be derived from this equation as well; their result is

$$S(t) = \exp\left[-\sqrt{D}\left\{\frac{k_2}{k_1}\sqrt{\frac{t}{\pi}}\exp(-k_1 t) + \frac{\mathrm{erf}(\sqrt{k_1 t})}{k_1^{3/2}}\left(k_1 k_2 t - \frac{k_2}{2} + [E]k_1\right)\right\}\right] \tag{19}$$

where $\mathrm{erf}(\cdots)$ is the error function. Unfortunately, it now no longer seems possible to similarly obtain a closed form expression for $\langle t \rangle \equiv \int_0^\infty dt\, S(t)$. In the following section, we shall suggest, however, that the dependence of $\langle t \rangle$ on $[E]$ is not anomalous and does not differ from eq 11.

4. Discussion and Conclusions

Equation 17 is the key finding of the present calculations. It shows that the anomalous kinetics of gel degradation by enzyme action, as reflected in the nonclassical scaling between the degradation time and the starting enzyme concentration, can be obtained from a model formulated in terms of a target searching problem involving many particles diffusing anomalously along a line.

As just stated, however, this does not entirely rule out a mechanism based on ordinary 1-d Brownian motion if adsorption or desorption of the enzymes is permitted, as in eq 18. But to make the case for this possibility, however, one would have to show that the integral $\int_0^\infty dt\, S(t)$, for some k_1 and k_2 not equal to 0, leads to the same or similar dependence on $[E]$ as seen experimentally. Although this integral cannot be evaluated analytically for arbitrary k_1 and k_2, it can be evaluated analytically in certain special limits of these parameters (see Appendix A). For none of these limits, however, does $\langle t \rangle$ scale with the experimental power of $[E]$. However, even if it did, the result would be difficult to reconcile with the earlier experimental observation[4] that the mean square displacement of the enzyme scales sublinearly with time, which is clearly not the behavior one sees in ordinary Brownian diffusion. It would seem to be the case then that ordinary Brownian diffusion, with or without enzyme adsorption or desorption, does not adequately account for anomalous degradation kinetics.

Nevertheless, eq 18 and generalizations of it that incorporate fractional operators are of considerable interest in their own right because the general phenomenon of search and location is paradigmatic of a number of stochastic processes in biology.[9] For many of these processes, it is survival — interpreted broadly — that regulates their dynamics. Therefore, the calculation of survival probabilities, $S(t)$, can be important in predicting the course of their evolution. In Appendix B, therefore, we show how *exact* expressions for $S(t)$ may be derived from two possible fractional generalizations of eq 18.

In the context of biology, the bond cleavage reaction that underlies enzymatic gel degradation is itself an elementary

reaction of considerable significance. It is often exploited (as mentioned earlier) to fabricate drug delivery systems, and it can also be used to generate autonomous motion in nanoparticle systems.[10] Similar chemical reactions are believed to power the movement of pathogens through the network of entangled polymer chains in cell membranes that typically form the first line of defense against their entry into the interior of the cell.[11] Such reactions may also be responsible for the growth and spread of tumors, which in at least some instances is driven by the enzymatic proteolysis of the extracellular matrix that surrounds cancerous tissue.[12] Understanding the details of gel degradation at the molecular level should therefore aid in devising methods to combat or control bacterial, viral, or cancerous infections. The present model, being a heuristic representation of the reactivity of large particles that move through viscoelastic media, is a highly coarse-grained depiction of such a process. Although it cannot predict the dependence of $\langle t \rangle$ on φ (since it considers just a single fixed junction point), it is successful in describing an important aspect of gel degradation, viz. the dependence of $\langle t \rangle$ on $[E]$.

It also makes one other interesting scaling prediction. Recall that the reaction time t_c was found from experiment to vary linearly with the solvent viscosity η. The only parameter in the model that depends explicitly on the viscosity is the generalized diffusion coefficient D_α, which ordinarily (i.e., for the case $\alpha = 1$) scales as η^{-1} by the Stokes−Einstein relation. If this relation were to hold even for $\alpha \neq 1$, it is clear from eqs 16 and 17 that t_c would no longer scale as η. To ensure that $t_c \approx \eta$, therefore, D_α must scale as $\eta^{-(2-\alpha)}$ (specifically as $\eta^{-4/3}$ if α is assigned the value 2/3 that produces agreement between the predicted and observed scaling of t_c with $[E]$). This fractional generalization of the Stokes−Einstein relation (variants of which have been introduced as useful empiricisms in the fitting of experimental and simulation data[13]) is potentially open to experimental verification.

In conclusion, the model presented here must be seen as the first step in the development of a more comprehensive theory of enzymatic degradation reactions and of others like it. For such a theory to describe the kinds of real-world problems mentioned above, one must clearly work with more realistic models of the gel itself, account for at least some of the characteristic properties that define its mechanical and rheological behavior, and tie these elements up with a model of anomalous diffusion and reaction.

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Appendix A: Mean Reaction Time in Special Limits

Equation 19 can be used to calculate the mean reaction time $\langle t \rangle$ in closed form in certain special limits of k_1 and k_2. These include (i) $k_2 \neq 0$ and $k_1 = 0$ and (ii) $k_2 \neq 0$ and $k_1 \gg 1$, which we now consider in turn.

(i) The case $k_2 \neq 0$, $k_1 = 0$:

Using the series representations of the exponential and the error function in eq 19 and then passing to the limit $k_1 = 0$, $S(t)$ becomes

$$S(t) = \exp[-at^{1/2} - bt^{3/2}] \tag{A.1}$$

where $a = 2[E](D/\pi)^{1/2}$ and $b = (4/3)k_2(D/\pi)^{1/2}$. The reaction time is therefore given by

$$\langle t \rangle = 2\int_0^\infty \mathrm{d}x\, x \exp(-ax - bx^3) \tag{A.2a}$$

$$\equiv 2I_1 \tag{A.2b}$$

The integral I_1 turns out to have a closed form expression (as determined by Mathematica); it is

$$I_1 = \frac{1}{27b}[2\sqrt{3}\pi a\{J_{-2/3}(\sqrt{4a^3/27b}) + J_{2/3}(\sqrt{4a^3/27b})\} - 9a_1F_2(1;2/3,4/3;-a^3/27b)] \tag{A.3}$$

where $J_\nu(z)$ is the Bessel function of index ν and ${}_1F_2(\alpha;\beta,\gamma;z)$ is the generalized hypergeometric function. In order to probe the dependence of $\langle t \rangle$ on $[E]$ in a regime distinct from the limit $k_1 = k_2 = 0$ (which we have already considered), we shall only examine eq A.3 in the limit $k_2 \gg 1$, where analytical results are easily obtained using the series representations of the special functions. These results demonstrate that $\langle t \rangle$ does not reproduce the experimentally observed concentration scaling.

(ii) The case $k_2 \neq 0$, $k_1 \gg 1$:

The asymptotic expansion of the error function is now used in eq 19, after which $S(t)$ can be approximated as

$$S(t) \approx \exp\left[-\sqrt{\frac{D}{k_1}}\{k_2 t + [E] + O(k_1^{-3/2})\}\right] \tag{A.4}$$

Hence

$$\langle t \rangle = \frac{1}{k_2}\sqrt{\frac{k_1}{D}}\exp\left(-[E]\sqrt{\frac{D}{k_1}}\right) \tag{A.5}$$

This expression clearly does not match the experimental result either.

Appendix B: Derivation of $S(t)$ for $\alpha \neq 1$ and Nonzero Adsorption and Desorption Rates

The inclusion of reaction terms in the fractional diffusion equation of eq 12 is not entirely straightforward since the existence of a distribution of waiting times between steps in the random walk may now cause the exit time from the encounter radius to interfere with the reaction and thereby affect its overall time course. Given this possibility, there are at least two ways in which the effects of subdiffusive motion may be treated in models of reaction and diffusion (more incisive studies of this issue may be found in the articles listed in ref 14); these are defined by the equations

$$\frac{\partial \rho(x,t)}{\partial t} = {}_0D_t^{1-\alpha}\left[D_\alpha \frac{\partial^2 \rho(x,t)}{\partial x^2} - k_1\rho(x,t) + k_2\right] \tag{B.1}$$

and

$$\frac{\partial \rho(x,t)}{\partial t} = {}_0D_t^{1-\alpha} D_\alpha \frac{\partial^2 \rho(x,t)}{\partial x^2} - k_1\rho(x,t) + k_2 \tag{B.2}$$

The first generally applies to processes (such as geminate recombination) in which the memory effects arising from encounter

distance interference are expected to show up in the reaction terms, while the second generally applies to processes in which such effects are expected to be unimportant.

Expressions for $S(t)$ can be derived in closed form for both of these equations (which we shall denote $S_1(t)$ and $S_2(t)$, respectively, to distinguish between them), but details of the derivation will be provided only for the first.

The calculation of $S_1(t)$ begins by using Laplace transforms to solve eq B.1 under the same initial and boundary conditions as those used earlier to treat eq 6. The result is

$$\hat{\rho}(x,s) = \frac{(k_2 + s^\alpha[E])}{s(k_1 + s^\alpha)}\left[1 - \exp\left(-x\sqrt{\frac{k_1 + s^\alpha}{D_\alpha}}\right)\right] \tag{B.3}$$

from which the flux $\hat{k}(s)$ into the target is found to be

$$\hat{k}(s) = \sqrt{D_\alpha}\frac{(k_2 + [E]s^\alpha)}{s\sqrt{k_1 + s^\alpha}} \tag{B.4}$$

Using the identity[15]

$$\frac{1}{A^a B^b} = \frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)}\int_0^1 \mathrm{d}x\, \frac{x^{a-1}(1-x)^{b-1}}{[Ax + (1-x)B]^{a+b}} \tag{B.5}$$

eq B.4 can be rewritten as

$$\hat{k}(s) = \frac{\sqrt{D_\alpha}}{\pi}[k_2\hat{I}_1(s) + [E]\hat{I}_2(s)]$$

where

$$\hat{I}_1(s) = \int_0^1 \mathrm{d}x\, \frac{x^{-1/2}(1-x)^{-1/2}s^{\alpha/2-1}}{(s^\alpha + k_1 x)} \tag{B.6}$$

and

$$\hat{I}_2(s) = \int_0^1 \mathrm{d}x\, \frac{x^{-1/2}(1-x)^{-1/2}s^{3\alpha/2-1}}{(s^\alpha + k_1 x)} \tag{B.7}$$

The inverse Laplace transforms of eqs B.6 and B.7 can now be obtained from results tabulated in, for instance, ref 16. Thus

$$I_1(t) = \int_0^1 \mathrm{d}x\, x^{-1/2}(1-x)^{-1/2}t^{\alpha/2}E_{\alpha,1+\alpha/2}(-k_1 x t^\alpha) \tag{B.8}$$

where $E_{a,b}(z) \equiv E^1_{a,b}(z)$ is a special case of the generalized Mittag−Leffler function,[17] which is defined as $E^\delta_{\beta,\gamma}(z) = \sum_{n=0}^\infty [(\delta)_n z^n/(\Gamma(\beta n + \gamma)n!]$, with $(\delta)_n \equiv \Gamma(n+\delta)/\Gamma(\delta)$ as the Pochammer symbol. Similarly

$$I_2(t) = \int_0^1 \mathrm{d}x\, x^{-1/2}(1-x)^{-1/2}t^{-\alpha/2}E_{\alpha,1-\alpha/2}(-k_1 x t^\alpha) \tag{B.9}$$

From other results given in ref 16, we can now determine the integrals $\int_0^t \mathrm{d}t'\, I_1(t')$ and $\int_0^t \mathrm{d}t'\, I_2(t')$, which are needed to obtain $S_1(t)$. These integrals are

$$\int_0^t \mathrm{d}t'\, I_1(t') \equiv J_1(t) = \int_0^1 \mathrm{d}x\, x^{-1/2}(1-x)^{-1/2}t^{1+\alpha/2}E_{\alpha,2+\alpha/2}(-k_1 x t^\alpha) \tag{B.10}$$

and

$$\int_0^t \mathrm{d}t'\, I_2(t') \equiv J_2(t) = \int_0^1 \mathrm{d}x\, x^{-1/2}(1-x)^{-1/2}t^{1-\alpha/2}E_{\alpha,2-\alpha/2}(-k_1 x t^\alpha) \tag{B.11}$$

The integrals over x in eqs B.10 and B.11 can be carried out as well. Referring once again to ref 16, we now have

$$J_1(t) = \sqrt{\pi}t^{1+\alpha/2}\,{}_2\psi_2\left(\begin{matrix}(1/2,1) & (1,1)\\ (2+\alpha/2,\alpha) & (1,1)\end{matrix}\middle| -k_1 t^\alpha\right) \tag{B.12}$$

and

$$J_2(t) = \sqrt{\pi}t^{1-\alpha/2}\,{}_2\psi_2\left(\begin{matrix}(1/2,1) & (1,1)\\ (2-\alpha/2,\alpha) & (1,1)\end{matrix}\middle| -k_1 t^\alpha\right) \tag{B.13}$$

where ${}_2\psi_2$ is the Wright function, defined in general by the expansion

$${}_p\psi_q\left(\begin{matrix}(a_1,A_1), & \cdots & (a_p,A_p)\\ (b_1,B_1), & \cdots & (b_q,B_q)\end{matrix}\middle| z\right) = \sum_{n=0}^\infty \frac{\prod_{j=1}^p \Gamma(a_j + nA_j)}{\prod_{j=1}^q \Gamma(b_j + nB_j)}\frac{z^n}{n!} \tag{B.14}$$

From the definition of the Wright function given in eq B.14, it is evident that eqs B.12 and B.13 can be reduced to

$$J_1(t) = \sqrt{\pi}t^{1+\alpha/2}\,{}_1\psi_1\left(\begin{matrix}(1/2,1)\\ (2+\alpha/2,\alpha)\end{matrix}\middle| -k_1 t^\alpha\right) \tag{B.15}$$

and

$$J_2(t) = \sqrt{\pi}t^{1-\alpha/2}\,{}_1\psi_1\left(\begin{matrix}(1/2,1)\\ (2-\alpha/2,\alpha)\end{matrix}\middle| -k_1 t^\alpha\right) \tag{B.16}$$

Equations B.15 and B.16 can be written in terms of the generalized Mittag−Leffler function, specifically, $J_1(t) = \pi t^{1+\alpha/2}E^{1/2}_{\alpha,2+\alpha/2}(-k_1 t^\alpha)$ and $J_2(t) = \pi t^{1-\alpha/2}E^{1/2}_{\alpha,2-\alpha/2}(-k_1 t^\alpha)$. These two expressions finally lead to the result

$$S_1(t) = \exp[-\sqrt{D_\alpha}\{k_2 t^{1+\alpha/2}E^{1/2}_{\alpha,2+\alpha/2}(-k_1 t^\alpha) + [E]t^{1-\alpha/2}E^{1/2}_{\alpha,2-\alpha/2}(-k_1 t^\alpha)\}] \tag{B.17}$$

By exactly the same sequence of steps, one can show that the survival probability, $S_2(t)$, for the reaction defined by eq B.2 is

$$S_2(t) = \exp[-\sqrt{D_\alpha}\{k_2 t^{2-\alpha/2} E^{1/2}_{1,3-\alpha/2}(-k_1 t) + [E] t^{1-\alpha/2} E^{1/2}_{1,2-\alpha/2}(-k_1 t)\}] \quad \text{(B.18)}$$

When $\alpha = 1$, corresponding to simple Brownian motion, both eqs B.17 and B.18 reduce to exactly the same expression, and this expression in turn reduces exactly to the result obtained by Sokolov et al.[7] in eq 19 (for a proof, see Appendix C).

Appendix C: Reduction of Equation B.17 or B.18 to Equation 19

When α is set to 1 in eq B.17, the generalized Mittag−Leffler functions that appear there can be reduced to simpler special functions. In particular, it is easy to show, based on the series expansion representations of the Mittag−Leffler function and the error function, that

$$E^{1/2}_{1,3/2}(-k_1 t) = \frac{1}{\sqrt{k_1 t}} \operatorname{erf}(\sqrt{k_1 t}) \quad \text{(C.1)}$$

The function $E^{1/2}_{1,5/2}(-k_1 t)$ is less readily reduced to a simpler form, but certain integral identities listed in ref 16 make simplification possible. In particular, the following general relation

$$z^\gamma E^\delta_{\beta,\gamma+1}(wz^\beta) = \int_0^z \mathrm{d}t\, t^{\gamma-1} E^\delta_{\beta,\gamma}(wt^\beta) \quad \text{(C.2)}$$

allows $E^{1/2}_{1,5/2}(-k_1 t)$ to be written as

$$E^{1/2}_{1,5/2}(-k_1 t) = \frac{1}{t\sqrt{k_1 t}} \int_0^t \mathrm{d}t' \operatorname{erf}(\sqrt{k_1 t'}) \quad \text{(C.3)}$$

While the integral in this relation does not appear to be tabulated, it can be carried out using Mathematica. The result, after simplification, is

$$E^{1/2}_{1,5/2}(-k_1 t) = \frac{1}{2\sqrt{\pi}(k_1 t)^2}[2k_1 t \exp(-k_1 t) + \sqrt{\pi k_1 t}(2k_1 t - 1) \operatorname{erf}(\sqrt{k_1 t})] \quad \text{(C.4)}$$

This result, combined with eq C.1, leads to the expression for $S(t)$ derived by Sokolov et al. (eq 19).

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