

Chapter 4

Reactions in Subdiffusive Media and Associated Fractional Equations

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We construct and solve fractional equations for the description of reactions in subdiffusive media starting from a mesoscopic continuous time random walk model. Our goal is to understand the spatial and temporal evolution of the reactant concentrations. Our discussion is presented in two parts. In the first part, the reactions occur at fixed locations such as immobile traps or hyper-surfaces enclosing a volume. Here the reactions appear as boundary conditions. Since the boundary conditions are identical for diffusive and subdiffusive reactants, there is a close connection between the solutions in both environments. In the second part we deal with the more complex problem of reactions that occur at random locations, either because all reactants are mobile or because the reaction is a degradation process that may occur anywhere in space. Now in general the reaction has to be built into the equations themselves, and each situation demands a particular derivation. In one case in this class it is possible to find asymptotic solutions using a bounding procedure that requires only the solution of boundary value problems, but this fortuitous solution is applicable only to this particular case. More generally, this chapter serves to point to the difficulties inherent in the reaction-subdiffusion problem.

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1. Introduction

Diffusive motion of particles in dense media is usually understood to be random motion characterized by a mean square displacement that grows linearly with time, $\langle r^2 \rangle \sim Dt$ (D is the diffusion coefficient). Reactions among particles that undergo diffusive motion are traditionally described by well-established reaction-diffusion equations in which a diffusion equation for the concentrations is simply augmented by a local reaction term typically constructed as a local version of the laws of mass action [1, 2]. However, in recent years it has become clear that motion in complex environments [3], especially in biological environments [4], is often hindered by the presence of traps or obstacles or other impediments, leading to subdiffusive motion, that is, motion characterized by a mean square displacement that grows sublinearly with time, $\langle r^2 \rangle \sim D_\gamma t^\gamma$ with $0 < \gamma < 1$ (D_γ is a generalized subdiffusion coefficient). The equations describing the spatio-temporal evolution of reactions among subdiffusive species are considerably more complicated than the familiar reaction-diffusion equations. Approaches based on heuristic macroscopic equations are often insufficient and can lead to incorrect conclusions. The derivation of these equations requires the formulation of a microscopic or mesoscopic model as a starting point. In this chapter we start from a particular mesoscopic point of view, namely, a continuous time random walk (CTRW) description of the motion in which the waiting time distributions between successive steps have a long or heavy tail. Starting from such a model, in Sec. 2 we discuss the derivation of a well-known

generic fractional subdiffusion equation for the concentrations of a subdiffusive species as it evolves in space and time. The resulting equation has to be appropriately modified when the species in question can undergo reactions. There is no universal way to do this, contrary to the case of ordinary diffusion where reaction terms are simply added. In subsequent sections we deal with this problem in a variety of scenarios.

Next we discuss a variety of ways to include reactive processes for our subdiffusive particles. We separate our discussion into two parts, one presented in Sec. 3 and the other in Sec. 4. First, in Sec. 3 we focus on systems in which reactions occur at fixed locations. Starting from a CTRW model, we arrive at a pure fractional diffusion equation in which the reactions are manifest as spatially fixed boundary conditions (we do not consider systems subject to external potentials). These systems adhere to a description parallel to that of the corresponding normally diffusive system except for the fact that the time evolution for long times is slower. Typically many of the results for the subdiffusive system can be found from those associated with the diffusive system if in the results for the latter we make the substitution $t \rightarrow \alpha t^\gamma$, where α is a parameter that depends on γ and on D_γ (see pp. 375 in Ref. 3). In Sec. 3.1 we focus on the survival probability of a fixed target that reacts with a subdiffusive particle. Section 3.2 extends the calculation of the target survival probability to the case where the target is surrounded by a sea of subdiffusive particles rather than by a single particle. In Sec. 3.3 we present the survival probability of particles that subdiffuse in a finite region surrounded by a boundary with which the particles can react and consequently vanish.

The second part of our discussion, in Sec. 4, deals with reactions that occur at random locations either because all reactants are mobile, or because the reaction is a degradation process that may occur anywhere in space. The reactions can thus no longer be handled as boundary value problems but are instead far more complex many-body problems. The results for subdiffusive particles are in general very different from those found for particles that undergo normal diffusion. Furthermore, the solution of these problems is typically far more complicated than the corresponding solution for the diffusive problem. In Sec. 4.1 we deal with a generalization of the problem of Sec. 3.2 in which all reactants are mobile. The reaction is of the form $A + B \rightarrow B$, where a particle (A) survives only if it does not touch any traps (B). The calculation of the survival probability of a particle even when both particle and traps move according to the normal laws of diffusion

is complicated and has only been solved asymptotically relatively recently. The generalization to the situation where one or the other or both species are subdiffusive presents interesting challenges, especially when the particle is diffusive and the traps are subdiffusive. In Sec. 4.2 we discuss some of the difficulties that are encountered when the fractional subdiffusion equation is to be modified by reactive contributions. It is now no longer possible to generalize reaction-diffusion equations in any simple manner. In particular, it is in general no longer appropriate to simply add a reaction term to the subdiffusion equation, and it is no longer possible to devise a general scheme to include the effects of reactions. We derive a reaction-subdiffusion equation for a class of problems that serves to illustrate the complicated nature of the task. In Sec. 4.3 we use this equation to find the survival probability of a particle in the presence of a fixed target surrounded by a “reactivity field.” In Sec. 4.4 we again solve this equation, but now for a scenario that may be appropriate in the context of the formation of morphogen gradients in an embryonic environment.

We conclude this chapter with a few final remarks in Sec. 5.

2. Subdiffusion and Fractional Calculus

A well-known model of anomalous diffusion is based on a CTRW in which the particles are described as random walkers whose step lengths \mathbf{r} and waiting times t are characterized by probability distributions $w(\mathbf{r})$ and $\psi(t)$, respectively. Let $\hat{w}(\mathbf{q})$ be the Fourier transform of $w(\mathbf{r})$ and $\tilde{\psi}(u)$ the Laplace transform of $\psi(t)$. We assume a (symmetric) walk with

$$\hat{w}(\mathbf{q}) \sim 1 - (\sigma q)^\mu \quad (1)$$

for small $q \equiv |\mathbf{q}|$, and

$$\tilde{\psi}(u) \sim 1 - (\tau u)^\gamma, \quad 0 < \alpha \leq 1 \quad (2)$$

for small u . The parameters σ^μ and τ^γ appear in combined form in the generalized diffusion coefficient $D_\gamma = \sigma^\mu / \tau^\gamma$. If $\mu = 2$, then σ^2 is half the variance of the jump length. If additionally $\gamma < 1$, then the mean square displacement of the walkers grows sublinearly with time, $\langle \mathbf{r}^2 \rangle \sim 2dD_\gamma t^\gamma / \Gamma(1 + \gamma)$ [5], where d denotes dimensionality. The limit of long time scales and large displacement scales yields the fractional diffusion equation [6, 7]

$$\frac{\partial c(\mathbf{r}, t)}{\partial t} = D_\gamma {}_0\mathcal{D}_t^{1-\gamma} \nabla^\mu c(\mathbf{r}, t), \quad 0 < \alpha < 1 \quad (3)$$

where $c(\mathbf{r}, t)$ is the concentration of walkers, ${}_0\mathcal{D}_t^{1-\gamma}$ is the operator whose Laplace transform \mathcal{L} is

$$\mathcal{L} \, {}_0\mathcal{D}_t^{1-\gamma} f(t) = u^{1-\gamma} \tilde{f}(u), \tag{4}$$

and ∇^μ is the operator whose Fourier transform \mathcal{F} is

$$\mathcal{F}\nabla^\mu g(\mathbf{r}) = -q^\mu \hat{g}(\mathbf{q}) \tag{5}$$

for sufficiently smooth functions f and g [8, 9]. Equation (3) is a particular case of the reaction-subdiffusion equation derived later in Sec. 4.2. The operator ${}_0\mathcal{D}_t^{1-\gamma}$ is the Grünwald–Letnikov fractional derivative [8]. When operating on well-behaved functions [functions $f(t)$ for which $\lim_{t \rightarrow 0} \int_0^t d\tau (t-\tau)^{\gamma-1} f(\tau) = 0$], this operator is equivalent to the Riemann–Liouville fractional derivative [8],

$${}_0\mathcal{D}_t^{1-\gamma} f(t) = \frac{1}{\Gamma(\gamma)} \frac{\partial}{\partial t} \int_0^t dt' \frac{f(t')}{(t-t')^{1-\gamma}}. \tag{6}$$

The fractional spatial derivative ∇^μ is the negative of the Riesz fractional derivative of order μ [9]. For $\mu = 2$ this operator is simply the Laplacian operator ∇^2 and Eq. (3) becomes the fractional subdiffusion equation

$$\frac{\partial c(\mathbf{r}, t)}{\partial t} = D_\gamma \, {}_0\mathcal{D}_t^{1-\gamma} \nabla^2 c(\mathbf{r}, t), \quad 0 < \alpha < 1. \tag{7}$$

From here on we focus on this case.

3. Reactions Occurring at Spatially Fixed Locations

If a reaction occurs when a moving particle reaches a fixed target, the problem can be formulated as a boundary value problem. The boundary value formulation is essentially the same whether the moving particle undergoes normal diffusion or subdiffusion: the (sub)diffusion equation describes the motion of the particle in a region Ω in a region Ω external to the target, and this equation is augmented by the reactive boundary condition $F[c(\mathbf{r}, t), \nabla c(\mathbf{r}, t)] = 0$ at the reactive boundary $\mathbf{r} \in \partial\Omega$. Two types of boundary conditions are often considered in diffusion problems. One is the totally absorbing (or perfectly reactive) boundary, for which

$$c(\mathbf{r}, t) = 0, \quad \mathbf{r} \in \partial\Omega, \tag{8}$$

indicating immediate reaction (death) upon encounter with the boundary. The other is the radiation (or Robin, or partially absorbing) boundary condition

$$c(\mathbf{r}, t) = -\Lambda \frac{\partial}{\partial n} c(\mathbf{r}, t), \quad \mathbf{r} \in \partial\Omega. \quad (9)$$

Here $\partial c/\partial n$ is the component of the gradient of c perpendicular to the boundary and pointing away from the region Ω , and Λ is a reaction rate parameter. This latter condition describes partially reactive boundaries, that is, situations where it is possible for a particle to come in contact with the boundary and yet not react. That this is in fact the correct mathematical description of a partially reactive boundary is not immediately obvious [10–12].

Our starting point is the Laplace transform of Eq. (7),

$$u\tilde{c}(\mathbf{r}, u) - c(\mathbf{r}, 0) = u^{1-\gamma} D_\gamma \nabla^2 \tilde{c}(\mathbf{r}, u). \quad (10)$$

The Laplace transformed equation makes it clear that the subdiffusion equation can formally be obtained from the normal diffusion equation if in the latter we implement the change $D \rightarrow u^{1-\gamma} D_\gamma$. Since the boundary conditions (8) and (9) are the same for the diffusion and subdiffusion problem, it would seem reasonable to expect that the solution for the subdiffusive problem can be obtained from that of the diffusive problem with the simple replacement $D \rightarrow u^{1-\gamma} D_\gamma$. However, this must be implemented with care because there are exceptions to this assumption, as we will see in Sec. 3.3.

3.1. *Single-particle target problem*

In this section we consider a specific application of the boundary value problem described by Eq. (7) with (8) or (9), namely, the computation of the survival probability of a fixed target in the presence of a subdiffusive random walker (hereafter called the “particle”) in an unbounded d -dimensional domain. When the particle reaches the boundary $\partial\Omega$ of the target, reaction takes place with a given probability, as a result of which the target disappears. Since the ultimate fate of the particle after the reaction is irrelevant for the computation of the survival probability of the target, we can assume without loss of generality that both the targets *and* the particle vanish upon reaction. The survival probability of the target and the survival probability of the particle thus become the same. The latter can then be computed from

Eq. (7) complemented by the boundary condition (8) in the fully absorbing case (reaction with unit probability upon encounter) or Eq. (9) in the partially absorbing case (reaction with probability < 1 upon encounter). The fully absorbing boundary condition described by Eq. (8) (formally obtained from (9) in the limit $\Lambda \rightarrow 0$) corresponds to a so-called first passage problem since in this case the probability of first arrival of the particle at the target is precisely the probability of the target being absorbed by the particle. First passage statistics for the subdiffusive case are comprehensively dealt with in Sec. 5.1 of [13].

The target problem is relevant in a number of fields, including the optimization of target search strategies [14, 15], recombination kinetics [16], scavenging reactions [17], and photoluminescence quenching of excited states [18]. It is also the starting point for the case of many (sub)diffusing particles (see next subsection) and may be used as a reference to assess the effect of finite sized domains or confining boundaries [19, 20].

We begin by defining the survival probability $Q_1(\mathbf{r}, t)$ as the probability that the target and a particle that initially started at location \mathbf{r} have not reacted up to time t . The survival probability of the target (or of the particle) can be written as

$$Q_1(\mathbf{r}, t) = \int_{\Omega} d\mathbf{r}' c(\mathbf{r}', t; \mathbf{r}), \tag{11}$$

where $c(\mathbf{r}', t; \mathbf{r})$ is now interpreted as the probability density that the particle that initially started at \mathbf{r} is found at \mathbf{r}' at time t , that is, it is the solution of the boundary value problem (7) with (9) or with (8), with the initial condition $c(\mathbf{r}', 0; \mathbf{r}) = \delta(\mathbf{r}' - \mathbf{r})$ [21]. The survival probability $Q_1(r, t)$ of a hyperspherical target of radius R centered at the origin is especially simple to deal with. The calculation for the case of a subdiffusive particle can be straightforwardly derived from the corresponding calculation for a diffusive particle [17, 21, 22]. In the Laplace representation the boundary value problem becomes

$$u\tilde{Q}_1(r, u) - 1 = u^{1-\gamma} D_{\gamma} \nabla^2 \tilde{Q}_1(r, u), \tag{12}$$

$$\tilde{Q}_1(R, u) = -\Lambda \frac{\partial}{\partial n} \tilde{Q}_1(r, u)|_{r=R}, \tag{13}$$

$$\lim_{r \rightarrow \infty} \tilde{Q}_1(r, u) = \frac{1}{u}. \tag{14}$$

The equations for the subdiffusive case are obtained from the normal diffusive case with the replacement $D \rightarrow u^{1-\gamma}D_\gamma$. The subdiffusive solution can thus be found by performing the same replacement in the normal diffusion solution [21–23]. The result is

$$u\tilde{Q}_1(r, u) = 1 - \left(\frac{r}{R}\right)^{1-d/2} \frac{K_{d/2-1}(rz)}{K_{d/2-1}(Rz) + \Lambda z K_{d/2}(Rz)}, \quad (15)$$

where we have set $z = (u^\gamma/D_\gamma)^{1/2}$. In the above equation the K 's stand for modified spherical Bessel functions of the third kind [24]. In Laplace space, the solution for $d = 1$ and $d = 3$ in the fully absorbing case $\Lambda = 0$ takes a rather simple form, namely,

$$\tilde{Q}_1(r, u) = \frac{1}{u} - \left(\frac{R}{r}\right)^\alpha \frac{e^{(R-r)\sqrt{u^\gamma/D_\gamma}}}{u}. \quad (16)$$

Here $\alpha = 0$ for $d = 1$ and $\alpha = 1$ for $d = 3$. Its inverse Laplace transform can be expressed in terms of Fox's H function as [6, 25]

$$Q_1(r, t) = 1 - \left(\frac{R}{r}\right)^\alpha H_{11}^{10} \left[\frac{r - R}{\sqrt{D_\gamma t^\gamma}} \left| \begin{matrix} (1, \gamma/2) \\ (0, 1) \end{matrix} \right. \right]. \quad (17)$$

The Fox function reduces to a complementary error function when $\gamma = 1$, and in this limit we recover the correct result for classical diffusion, see, for example, [22].

The asymptotic long-time behavior of the survival probability depends strongly on dimension. In $d = 1$, one has a power-law decay, $Q_1(r, t) \sim (r - R)/t^{\gamma/2}$; in $d = 2$, one has a slower inverse logarithmic decay, $Q_1(r, t) \sim \ln(r/R)/\ln(D_\gamma t^\gamma)$. For $d = 3$, the target has a finite survival probability, $Q_1(r, t \rightarrow \infty) \sim 1 - R/r$. Asymptotically, the subdiffusive character of the particle is thus relevant only in the one-dimensional case and has only a marginal effect in $d = 2$.

As an aside, we note that the result (17) can also be obtained from the analogous result for normal diffusion via the relation $\tilde{Q}_1(u|\gamma) = u^{\gamma-1} \tilde{Q}_1(u^\gamma|1)$ between the Laplace transform of the survival probability $Q_1(t|\gamma)$ of the target when the particle is subdiffusive and of the corresponding quantity $Q_1(t|1)$ when it is diffusive [5, 13, 21]. This is a consequence of the integral transformation relating the propagators for fractional and normal diffusion [5, 6, 13, 26–28].

3.2. Many-particle target problem

The generalization of the one-particle problem treated in the previous subsection to the many-body case is of special interest in the framework of Smoluchowski's theory of diffusion-controlled reactions [1]. This theory has been applied to numerous problems such as electron trapping and recombination [29], free radical and ion-scavenging [17], geminate recombination [30], luminescence quenching [31], exciton trapping [32–34], and site location in DNA [35]. The theory deals with two-species binary reactions $A + B \rightarrow \text{products}$, where both species may undergo classical diffusion with different diffusion coefficients D_A and D_B until they meet and react at a rate which increases monotonically with increasing reaction rate parameter Λ . The theory allows one to compute the survival probability of the A particles as well as the associated decay of the concentration of A under the assumptions that the B species is in vast excess with respect to the A species, and that each A particle is surrounded by a sea of uncorrelated B particles. The Smoluchowski approach becomes exact in the limit $D_A \rightarrow 0$, a situation in which each A particle may be regarded as an immobile target immersed in a sea of diffusing B particles. This case is usually called the “target problem” in the literature. While extensive results for the survival probability and other related quantities (e.g., the distribution of reaction times) are available for the normal diffusive case, the subdiffusive version of the problem has remained unexplored until recently. Here we briefly outline the method and main findings for this problem in continuous space. Our results for $\Lambda = 0$ are the continuous counterparts to those of Section 13.3.1 of [3] for the case of anomalous diffusion on a discrete spatial support.

Our starting point is a setting similar to that of the previous subsection, the difference being that instead of a target and a single subdiffusive particle, we now consider a target surrounded by N independent subdiffusive point particles. The target is a hypersphere of radius R . Of interest here is the survival probability $Q(t)$ of the target. This survival probability is simply the probability that none of the N particles has been absorbed upon contact with the surface of the sphere. Under the assumption that the independently moving particles are randomly distributed in the volume V of Ω , one obtains the factorized form

$$Q(t) = \left[\frac{1}{V} \int_{r>R} d\mathbf{r} Q_1(r, t) \right]^N. \quad (18)$$

Equation (18) provides the connection between the solution for the many-body case and the one-particle problem treated in the previous subsection. In the thermodynamic limit $N \rightarrow \infty, V \rightarrow \infty$ at fixed density $\rho = N/V$, one finds

$$Q(t) = \exp\{-\rho R^d f(t)\}, \quad (19)$$

with

$$f(t) = \frac{1}{R^d} \int_{r>R} d\mathbf{r} [1 - Q_1(r, t)]. \quad (20)$$

The problem is readily solved in Laplace space. From Eq. (15), one obtains

$$\tilde{f}(u) = \frac{S_d}{Ru z} \frac{K_{d/2-1}(Rz)}{K_{d/2-1}(Rz) + \Lambda z K_{d/2}(Rz)}, \quad (21)$$

where $S_d = 2\pi^{d/2}/\Gamma(d/2)$ is the surface of a sphere of unit radius. The large- and small- u behavior of the above expression respectively provide the short and long time behaviors of $f(t)$ and the associated survival probability via the pertinent Tauberian theorems. In the special cases $d = 1$ and $d = 3$ the quantity $\tilde{f}(u)$ can be inverted exactly to obtain results valid for arbitrary t . For example, the one-dimensional case yields [23]

$$f(t) = \frac{\omega^{1/2}}{\Gamma(1 + \alpha/2)} - 2\frac{\Lambda}{R}[1 - E_{\gamma/2}(-\omega^{1/2}R/\Lambda)], \quad (22)$$

where $\omega = 4D_\gamma t^\gamma/R^2$, and

$$E_\gamma(z) = \sum_{n=0}^{\infty} \frac{z^n}{\Gamma(1 + n\gamma)} \quad (23)$$

stands for the Mittag-Leffler function [36, 37]. It is interesting to note that for long times t the partially reflecting nature of the surface is not relevant for $d \leq 2$ as $f(t) \sim \omega^{1/2}/\Gamma(1 + \gamma/2)$ for $d = 1$ and $f(t) \sim \pi\omega/[\Gamma(1 + \gamma)\ln(\omega)]$ for $d = 2$, both independent of Λ . However, for $d = 3$, the value of Λ appears explicitly in the characteristic decay function, i.e. $f(t) \sim \pi\omega/[\Gamma(1 + \gamma)(1 + \Lambda/R)]$. For later comparison, it is useful to exhibit

these asymptotic survival probability results explicitly [21, 23]:

$$Q(t) \sim \begin{cases} \exp \left[-\frac{2\rho}{\Gamma(1 + \gamma/2)} (D_\gamma t^\gamma)^{1/2} \right], & d = 1, \\ \exp \left[-\frac{4\pi\rho}{\Gamma(1 + \gamma)} \frac{D_\gamma t^\gamma}{\ln(4D_\gamma t^\gamma/R^2) + 2\Lambda/R} \right], & d = 2, \\ \exp \left[-\frac{2(d-2)\pi^{d/2}\rho R^{d-2}}{\Gamma(d/2)\Gamma(1 + \gamma)(1 + (d-2)\Lambda/R)} D_\gamma t^\gamma \right], & d \geq 3. \end{cases} \quad (24)$$

The above results show that the behavior of the survival probability changes drastically with respect to the one-particle case. Focusing on the fully absorbing case $\Lambda = 0$, one sees that the asymptotic long-time survival probability is given by a stretched negative exponential whose argument $f(t)$ grows more rapidly with time with increasing dimension d (the typical inverse logarithmic correction appears for $d = 2$). This implies that $Q(t)$ decays more rapidly with increasing dimension d , as opposed to the increase observed for $Q_1(r, t)$ with increasing d .

3.3. Escape problems

Escape problems are relevant for the study of processes that are triggered when a critical threshold value is attained. Numerous examples are found in physics, chemistry, biology, economics and social sciences [38]. One of the main goals in escape problems is to compute the distributions of the times (and the moments of these distributions) needed by one or more particles to irreversibly escape a given domain Ω . Familiar questions include those associated with first passage processes [38, 39], where one asks how long it takes the j th particle to reach an absorbing boundary $\partial\Omega$ (order statistics problems) [40–44]. Conversely, one can enquire about the number of particles that have escaped a domain Ω up to time t and the associated decay of the probability that a given particle has not escaped (survival probability) [6, 38, 39, 45].

In order to find the survival probability for this latter problem, Eq. (7) must be solved subject to the condition $c(\mathbf{r}, t) = 0$ at the boundary. In our route to the solution, we use the method of separation of variables [6, 13, 46] by making the superposition ansatz $c(\mathbf{r}, t) = \sum_{j=1}^\infty a_j T_j(t)\psi_j(\mathbf{r})$. We henceforth assume that the domain Ω that initially contains all the particles is a

hypersphere of radius R . Our ansatz leads to

$$\frac{T_j'(t)}{D_\gamma {}_0\mathcal{D}_t^{1-\gamma}T(t)} = \frac{\psi_j''(r) + (d-1)\psi_j'(r)/r}{\psi_j(r)} = \lambda_j, \tag{25}$$

where λ_j is the j th eigenvalue. The temporal part of the solution satisfies the equation $T_j'(t) = \lambda D_\gamma {}_0\mathcal{D}_t^{1-\gamma}T_j(t)$ [6, 36], i.e. $T_j(t) = E_\gamma(\lambda_j D_\gamma t^\gamma)$. This Mittag-Leffler function becomes equal to an exponential when $\gamma = 1$ (normal diffusion case), but displays rather different properties for *any* $\gamma < 1$. In contrast, the eigenfunctions $\psi_j(r)$ describing the spatial part of the solution and the set of acceptable eigenvalues λ_j which satisfy the equation $\psi_j''(r) + (d-1)\psi_j'(r)/r = \lambda_j\psi_j(r)$ are independent of γ and are thus *exactly* the same for the subdiffusion and normal diffusion problems [47–49]. The full solution has the form

$$c(r, t) = \sum_{j=1}^{\infty} a_j \psi_j(r) E_\gamma(-\lambda_j t^\gamma), \tag{26}$$

where the coefficients a_j are determined from the initial condition $c(r, 0)$ via the orthogonality properties of the eigenfunctions $\psi_j(r)$. The so-called propagator solution $c(r, t) \equiv G(r, t; r_0)$ corresponding to the initial condition $c(r, 0) = \delta(r - r_0)$ (representing a single particle initially located at r_0) has a special relevance, since it can be used to construct other types of more complex solutions involving, for example, localized particle sources. Recently, Grebenkov [39] has studied subdiffusive propagator solutions for other confining domains and boundary conditions.

The behavior of (26) at long times may be very different from that describing normal diffusion. For instance, if one takes a homogeneous initial concentration c_0 in the above example of a d -dimensional absorbing hyperspherical surface, one gets

$$c(r, t)/c_0 = 2(r/R)^{1-d/2} \sum_{j=1}^{\infty} \frac{J_{d/2-1}(z_j r/R)}{z_j J_{d/2}(z_j)} E_\gamma[-(z_j/R)^2 D_\gamma t^\gamma], \tag{27}$$

where z_j denotes the j th zero of the Bessel function $J_{d/2}$. For long times, one can use the asymptotic expansion

$$E_\gamma(z) \approx \sum_{m=1}^{\infty} \frac{(-z)^{m+1}}{\Gamma(1-m\gamma)} z^{-m}, \quad z \rightarrow \infty \tag{28}$$

and one can rearrange terms to get

$$c(r, t)/c_0 = \sum_{m=1}^{\infty} \frac{(-1)^{m+1}}{\Gamma(1 - m\gamma)} \left(\frac{R^2}{D_\gamma t^\gamma} \right)^m \Psi_m(r/R). \quad (29)$$

It can be proved that the $\Psi_m(x)$'s are *polynomials* of degree $2m$ with a zero at $x = 1$ [50, 51]. Neglecting subdominant terms with $m > 1$ in the above long-time solution, one finds $c(r, t)/\varphi(t) \propto \Psi_1(r/R)$ where $\varphi(t) = 1/(D_\gamma t^\gamma/R^2)$ and $\Psi_1(r/R) \propto 1 - r^2/R^2$. In contrast, a similar analysis for the normal diffusion case not only leads to a faster (exponential) time decay $\varphi(t) = \exp(-z_1 D_\gamma t^\gamma/R^2)$, but also to a different radial concentration profile at late times. One finds $c(r, t)/\varphi(t) \propto (r/R)^{1-d/2} J_{d/2-1}(z_1 r/R)$, which depends on dimensionality. In the subdiffusive case, the spatial dependence is universal in the sense that it depends *neither* on the dimension d *nor* on the anomalous diffusion exponent γ or the diffusion coefficient D_γ .

In conclusion, a minute amount of subdiffusivity in the particle motion is seen to destroy the form $(r/R)^{1-d/2} J_{d/2-1}(z_1 r/R)$ of the long-time normal diffusion mode and leads to the subdiffusive form $1 - r^2/R^2$ which holds for *any* $\gamma < 1$. The aforementioned singular long-time behavior of the solution with respect to γ is not an exclusive feature of the escape problem. A similar singular behavior is seen in the survival probability of a diffusing particle in a sea of subdiffusive traps, treated later in Sec. 4.1.

4. Reactions Occurring at Random Locations

In this section we address reactions that occur at random locations as well as random times. When all the reactants in a subdiffusive medium are mobile, the problem of describing any quantity used as an indicator of the progression of the kinetics is much more complex than it is in a diffusive medium, and also much more complex than it is if one of the reactants is immobile. These indicators include the quantities that we have introduced already: survival probabilities, escape probabilities, and local concentrations.

Reactions may occur at random locations for two reasons: either reactants that are all mobile must meet for a reaction to take place, or the reaction is a degradation process that is not restricted to a fixed boundary as in the previous section. Such reactions can in general no longer be treated as boundary value problems but instead become much more complicated many-body problems that require the introduction of new ideas. Furthermore, the subdiffusive character of the reactant motion leads to memory effects that introduce yet another level of complexity.

In Sec. 4.1 we deal with a problem similar to that of Sec. 3.2, but substantially complicated by the fact that the previously immobile target is now also mobile (diffusive or subdiffusive). As we did there, we focus on the survival probability of the target. Then, in Sec. 4.2 we derive a reaction-subdiffusion equation starting from a CTRW model. We subsequently use this equation in Sec. 4.3 to study the reaction between a set of mobile particles and a fixed target surrounded by a “reactivity field” $k(\mathbf{r})$. This reactivity field allows the reaction to take place at random distances between a mobile particle and the target with a probability determined by the field. Finally, in Sec. 4.4 we use the reaction-subdiffusion equation to study the reaction of a constant flux of particles that emerge from a given location (source), move subdiffusively, and disappear with a probability that in general depends on their location. This scenario is particularly interesting for the study of the timely problem of morphogen gradients. In these last two sections our indicator of the reaction is the concentration of surviving reactant.

4.1. *Mobile particles and traps*

We begin by considering the survival probability of a mobile particle in a sea of mobile traps. The characteristic exponent for the particle is μ . The exponent for the traps is γ . In earlier sections we called the exponent γ in all cases because only one of the species was mobile, but here it is important to differentiate between them and so we introduce a distinct notation for them. This problem has in fact not been solved for any of the indicators listed above. However, it has been possible to establish the asymptotic behavior of the survival probability of the particle in most if not all situations, as we will now see. Note that these results do not include an estimate of how long it takes the system to arrive at asymptotia (a numerical study of this can be found in Ref. [53]).

We suppose that a particle A moves diffusively ($\mu = 1$) or subdiffusively ($0 < \mu < 1$) in a sea of traps B that move diffusively ($\gamma = 1$) or subdiffusively ($0 < \gamma < 1$), with γ and μ not necessarily equal. One can imagine, for instance, a large difference in the sizes or in the interactions of A s and B s with the surrounding medium that may lead to large differences in the way they move. In chemical kinetics parlance we are looking at the reaction $A + B \rightarrow B$ when all components are mobile. Our goal is to calculate the survival probability $Q(t)$ of the A particle.

At the end of Sec. 3.3 we mentioned the fact that it makes a major difference in the asymptotic behavior of the survival probability of A whether it moves diffusively or subdiffusively. In addition, it makes an essential difference whether either of the species move at all or do not. The collection of results is thus somewhat confusing and perhaps best captured by writing the asymptotic survival probability in the form

$$Q(t) \sim \begin{cases} \exp(-\theta t^z), & d \neq 2, \\ \exp(-\theta t^z / \ln t), & d = 2, \end{cases} \tag{30}$$

where the constants θ and z depend on the nature of the motion of the particles of each species. Until quite recently, results (some exact, some approximate) were only available for situations where mobility necessarily implied diffusion. The entry of subdiffusion into the discussion is a rather modern event [53–56].

First, we differentiate the cases of mobile and immobile B particles (traps). When the traps are immobile, the survival probability of a diffusive particle A is given by the stretched exponential form [57]

$$Q(t) \sim \exp\left(-k_d \rho^{2/(d+2)} (D_A t)^{d/(d+2)}\right), \tag{31}$$

where ρ is the mean density of traps, D_A is the particle diffusion coefficient, and k_d is the d -dependent constant

$$k_d = \left(\frac{d+2}{2d}\right) (d\nu_d)^{2/(d+2)} (2\nu_d^2)^{d/(d+2)}. \tag{32}$$

Here ν_d is the first zero of the Bessel function $J_{(d-2)/2}(z)$ and $v_d = 2\pi^{d/2}/[d\Gamma(d/2)]$ denotes the volume of a d -dimensional sphere of unit radius. Note that there is no logarithmic correction for $d = 2$ in (31). The constants θ and z can immediately be read from these equations; specifically, $z = d/(d+2)$.

On the other hand, when all the reactants move diffusively, we immediately enter more complex territory. Standard chemical kinetics based on a reaction-diffusion equation leads to [58]

$$Q(t) \sim \begin{cases} \exp[-\rho(4Dt/\pi)^{1/2}], & d = 1, \\ \exp[-4\pi\rho Dt / \ln(Dt/(a+b)^2)], & d = 2, \\ \exp(-d(d-2)v_d(a+b)^{d-2}\rho Dt), & d \geq 3, \end{cases} \tag{33}$$

where D is the sum of the diffusion coefficients of the particle and the traps, and a and b are the radii of the A and B particles, respectively. This is a two-body approximation to a many-body problem and is in general not exact. The result is in fact exact only in the limit of an immobile A particle. Note that these decays are entirely different from the stretched exponential of Eq. (31).

It was only many years after these results were established that Bramson and Lebowitz [59] were able to show that the time dependences ($z = 1/2$ when $d = 1$, $z = 1$ for $d \geq 2$) in Eq. (33) are in fact asymptotically correct even when A does move, but with different constant prefactors than given above. They were not able to determine these prefactors. Here the field stood for many years, until Bray and Blythe [60, 61] managed to determine the prefactors for $d = 1$ and 2. Their methodology consisted in constructing upper and lower bounds to the survival probability that meet asymptotically. These bounds could be calculated exactly because they only involve boundary value problems. The great insight of their solution was this: the prefactors were found to be independent of the diffusion coefficient D_A of the particle! This immediately points to a startling conclusion: the asymptotic survival probability of the diffusing A is the same as it would be if the A remained immobile. In other words, the many-body problem is reduced to the boundary value problem discussed in Sec. 3.2, with the asymptotic results of Eq. (24) with $\gamma = 1$.

Of interest here is what happens when the particle and/or the traps move subdiffusively. If both move subdiffusively, then a fairly straightforward extension of the diffusive approach is possible and one finds once again that the survival probability of the subdiffusive A is the same as that of an immobile A particle in a sea of subdiffusive traps [52], that is, as given in (24). We immediately see that the exponent z can be read off of those earlier results: $z = \gamma/2$ in one dimension and $z = \gamma$ in two and three dimensions and above. The prefactors θ can also be read off of the earlier results. In summary so far, we see that if A is subdiffusive, no matter how the B s move, the asymptotic survival probability of A is the same as it would be if A stood still.

The case that presents the most serious difficulties occurs when the traps move subdiffusively and the A particle is diffusive. To solve this problem, the upper and lower bound approach can again be invoked, but it turns out that additional bounds to those used in the earlier Bray–Blythe construction are needed because these earlier bounds do not always meet.

A lower bound is constructed as originally devised for diffusive particles and traps and later extended to the case of (sub)diffusive particles and traps. This bound involves only boundary value problems. An upper bound is also constructed as originally devised for the diffusive case, based on the (proven) assertion that the A particle lives at least as long as it does in the original problem if the A stands still. This bound has been called the ‘‘Pascal principle’’ [56, 62]. However, this upper bound is not always the tightest bound, and another upper bound was devised on the (proven) basis that the worst possible strategy for traps in their search for a target is to remain immobile. The associated survival probability is again the solution to a boundary value problem and is precisely as given in Eq. (31). This bound has been called the ‘‘anti-Pascal principle’’ [56]. The interesting point is that depending on the value of the subdiffusive exponent γ of the traps, one or the other of these bounds is tighter. In other words, depending on how fast the traps move in the face of a diffusive A , the better upper bound is provided by the problem where the A stands still or by the problem where the B s stand still. Fortunately, in most cases (albeit not in all, see below) the tighter upper bound asymptotically approaches the lower bound, thus providing a solution to our problem. The outcome depends on γ and also on dimensionality.

Table 1 collects the results for the exponents z in Eq. (30) for the survival probability. A number of points are of special note. First, *when the particle is diffusive* ($\mu = 1$), there is a singular change in behavior of the exponent z as the exponent γ of the traps sweeps the range from immobile to diffusive. When the traps move very slowly, the survival probability of the particle is the same as it would be if the traps simply stood still,

Table 1. Collected results for the asymptotic survival probability exponent z .

Dimension	Trap exponent	Particle exponent	Survival probability exponent z
$d = 1$	$0 \leq \gamma \leq 2/3$	$\mu = 1$	$1/3$
	$2/3 \leq \gamma \leq 1$	$\mu = 1$	$\gamma/2$
	$0 < \gamma \leq 1$	$0 \leq \mu < 1$	$\gamma/2$
$d = 2$	$0 \leq \gamma \leq 1/2$	$\mu = 1$	$1/2$
	$1/2 < \gamma \leq 1$	$\mu = 1$	γ
	$0 < \gamma \leq 1$	$0 \leq \mu < 1$	γ
$d = 3$	$0 \leq \gamma \leq 2/5$	$\mu = 1$	$3/5$
	$2/5 \leq \gamma \leq 3/5$	$\mu = 1$	$3/5 \leq z \leq 1/3 + 2\gamma/3$
	$3/5 \leq \gamma \leq 1$	$\mu = 1$	$\gamma \leq z \leq 1/3 + 2\gamma/3$
	$0 < \gamma \leq 1$	$0 \leq \mu < 1$	γ

that is, $z = d/(d + 2)$ as in the Donsker–Varadhan formula (31). If, on the other hand, the traps move sufficiently quickly, the survival probability in $d = 1$ and $d = 2$ is that of the Bramson–Lebowitz–Bray–Blythe problem associated with an immobile particle, that is, $z = d\gamma/2$. In three or more dimensions we also see the Donsker–Varadhan behavior if the traps move sufficiently slowly, but we are not able to determine the exponent z if the traps move too quickly. In this case we can only determine that there is, again, a singular change in behavior and we can also determine a range for the value of the exponent, but the precise determination is still an open problem. Second, *when the particle is subdiffusive* ($0 \leq \mu < 1$), then $z = \gamma/2$ for $d = 1$ and $z = \gamma$ for $d \geq 2$. These results are all given in the table. The values of the prefactor θ are also available for most of these cases [52, 56] but have not been collected here.

4.2. Fractional diffusion-reaction equations

When normal diffusive particles react, the standard reaction-diffusion equation that describes the spacetime evolution of their concentrations $c(\mathbf{r}, t)$ is given by the normal diffusion equation plus a reaction term, say $F(c)$, that takes into account the rate of change of $c(\mathbf{r}, t)$ due to reactions,

$$\frac{\partial}{\partial t} c(\mathbf{r}, t) = D\nabla^2 c(\mathbf{r}, t) + F(c). \quad (34)$$

However, when particles that diffuse anomalously react, the deduction of the corresponding subdiffusion-reaction equation for $c(\mathbf{r}, t)$ is more elusive [10, 16, 63–69]. An extensive and recent discussion of this topic can be found in [70]. Here we focus on the deduction of the subdiffusion-reaction equation starting from the CTRW model for the case in which the *loss* of particles at location \mathbf{r} due exclusively to reactions is given by

$$\left. \frac{\partial}{\partial t} c(\mathbf{r}, t) \right|_{\text{reaction}} = -k(\mathbf{r}, t)c(\mathbf{r}, t), \quad (35)$$

where $k(\mathbf{r}, t)$ is the reaction rate coefficient (also hereafter called the reactivity). Integrating this equation leads to $c(\mathbf{r}, t')/c(\mathbf{r}, t) = A(\mathbf{r}, t, t')$, with

$$A(\mathbf{r}, t, t') = \exp\left(-\int_{t'}^t k(\mathbf{r}, t'')dt''\right), \quad (36)$$

which describes the time evolution of the ratio of the concentration of the particles at \mathbf{r} at time t and the concentration at \mathbf{r} at the initial time t' when

the number of particles at \mathbf{r} changes due *exclusively* to reactions, that is, when the changes in concentration at \mathbf{r} caused by particle jumps into or out of a small volume element centered at \mathbf{r} are not considered.

Next we introduce $j(\mathbf{r}, t)$ and $i(\mathbf{r}, t)$, the incoming and outgoing fluxes of particles at location \mathbf{r} at time t , which are related by the equation

$$j(\mathbf{r}, t) = \int i(\mathbf{r} - \mathbf{r}', t)w(\mathbf{r}')d\mathbf{r}', \tag{37}$$

where $w(\mathbf{r})$ is the probability distribution introduced just before Eq. (1).

The above equation simply states that the incoming flux at \mathbf{r} at time t arises from outgoing fluxes at all other locations $\mathbf{r}-\mathbf{r}'$ at that time. Including all of the contributions to the change in the concentration then yields

$$\frac{\partial}{\partial t}c(\mathbf{r}, t) = j(\mathbf{r}, t) - i(\mathbf{r}, t) - k(\mathbf{r}, t)c(\mathbf{r}, t) \tag{38}$$

because the changes in the concentration at \mathbf{r} are due to the incoming and outgoing fluxes and to the reaction process at that location. An additional relation connecting the fluxes and concentration is

$$i(\mathbf{r}, t) = \psi(t)A(\mathbf{r}, t, 0)c(\mathbf{r}, 0) + \int_0^t \psi(t - \tau)A(\mathbf{r}, t, \tau)j(\mathbf{r}, \tau)d\tau, \tag{39}$$

which states that the outgoing flux from \mathbf{r} at time t arises from two sources. One is the contribution of the particles that started out at \mathbf{r} at time $t = 0$, did not react or move anywhere up to time t , and then took a step away from \mathbf{r} at time t . The other is from those particles that arrived at \mathbf{r} at some earlier time τ , waited there up to time t without degradation, and then stepped away.

Defining $c^*(\mathbf{r}, t) \equiv c(\mathbf{r}, t)A(\mathbf{r}, 0, t)$, we can write Eq. (38) as

$$A(\mathbf{r}, t, 0)\frac{\partial}{\partial t}c^*(\mathbf{r}, t) = j(\mathbf{r}, t) - i(\mathbf{r}, t). \tag{40}$$

Equivalently, from Eq. (37),

$$A(\mathbf{r}, t, 0)\frac{\partial}{\partial t}c^*(\mathbf{r}, t) = \mathcal{F}^{-1} \left\{ [\hat{w}(\mathbf{q}) - 1] \hat{i}(\mathbf{q}, t) \right\} \tag{41}$$

or, equivalently, from Eq. (5),

$$A(\mathbf{r}, t, 0)\frac{\partial}{\partial t}c^*(\mathbf{r}, t) = \sigma^\mu \nabla^\mu i(\mathbf{r}, t). \tag{42}$$

Upon Laplace transforming Eq. (39) with respect to time one gets

$$\mathcal{L}[A(\mathbf{r}, 0, t)i(\mathbf{r}, t)] = \tilde{\psi}(u)c^*(\mathbf{r}, 0) + \tilde{\psi}(u)\mathcal{L}[A(\mathbf{r}, 0, t)j(\mathbf{r}, t)]. \quad (43)$$

Taking into account that, from Eq. (38),

$$\mathcal{L}[A(\mathbf{r}, 0, t)j(\mathbf{r}, t)] = \mathcal{L}\left[\frac{dc^*}{dt}\right] + \mathcal{L}[A(\mathbf{r}, 0, t)i(\mathbf{r}, t)], \quad (44)$$

Eq. (43) can be rewritten as

$$i(\mathbf{r}, t) = A(\mathbf{r}, t, 0)\mathcal{L}^{-1}\left\{\frac{u\tilde{\psi}(u)}{1-\tilde{\psi}(u)}\tilde{c}^*(\mathbf{r}, u)\right\}. \quad (45)$$

Using the Laplace transform expression (4) of the fractional derivative operator along with the explicit form Eq. (2), this expression can be rewritten as

$$i(\mathbf{r}, t) = A(\mathbf{r}, t, 0)\tau^{-\gamma}{}_0\mathcal{D}_t^{1-\gamma}c^*(\mathbf{r}, t). \quad (46)$$

Finally, inserting Eq. (46) into Eq. (42) and expanding the abbreviated notation, we arrive at the general reaction-subdiffusion equation that is the starting point of our analysis in the next two sections:

$$\begin{aligned} \frac{\partial}{\partial t}c(\mathbf{r}, t) &= D_\gamma\nabla^\mu\left\{e^{-\int_0^t k(\mathbf{r}, t')dt'}{}_0\mathcal{D}_t^{1-\gamma}\left[e^{\int_0^t k(\mathbf{r}, t')dt'}c(\mathbf{r}, t)\right]\right\} \\ &\quad - k(\mathbf{r}, t)c(\mathbf{r}, t). \end{aligned} \quad (47)$$

Note that in the absence of reactions, $k(\mathbf{r}, t) = 0$, Eq. (3) is recovered. More specifically, we focus on the case $\mu = 2$ so that the spatial operator is the Laplacian, as mentioned earlier, and we also do not consider a time-dependent reactivity here. Our starting equation therefore is

$$\frac{\partial}{\partial t}c(\mathbf{r}, t) = D_\gamma\nabla^2\left\{e^{-k(\mathbf{r})t}{}_0\mathcal{D}_t^{1-\gamma}\left[e^{k(\mathbf{r})t}c(\mathbf{r}, t)\right]\right\} - k(\mathbf{r})c(\mathbf{r}, t). \quad (48)$$

In order to solve (48), it is convenient to work with a new function $v(\mathbf{r}, t)$:

$$\tilde{v}(\mathbf{r}, u) = [u + k(\mathbf{r})]^{1-\gamma}\tilde{c}(\mathbf{r}, u). \quad (49)$$

Taking into account that

$$\mathcal{L}\left[e^{-k(\mathbf{r})t}{}_0\mathcal{D}_t^{1-\gamma}\left(e^{k(\mathbf{r})t}c(\mathbf{r}, t)\right)\right] = [u + k(\mathbf{r})]^{1-\gamma}\tilde{c}(\mathbf{r}, u), \quad (50)$$

Eq. (48) becomes

$$u\tilde{c}(\mathbf{r}, u) - c(\mathbf{r}, 0) = D_\gamma\nabla^2\left\{[u + k(\mathbf{r})]^{1-\gamma}\tilde{c}(\mathbf{r}, u)\right\} - k(\mathbf{r})\tilde{c}(\mathbf{r}, u) \quad (51)$$

or, equivalently,

$$[u + k(\mathbf{r})]^\gamma \tilde{v}(\mathbf{r}, u) - c(\mathbf{r}, 0) = D_\gamma \nabla^2 \tilde{v}(\mathbf{r}, u). \tag{52}$$

This is then a variant of our starting equation (48).

One final remark is in order. It should be noted that Eq. (35) does not necessarily imply a first-order reaction, since the reaction rate $k(\mathbf{r}, t)$ is quite arbitrary and might itself depend on $c(\mathbf{r}, t)$ or on the concentration of some other species. For example, suppose that we have two species with concentrations $c_1(\mathbf{r}, t)$ and $c_2(\mathbf{r}, t)$ that disappear due to bimolecular reactions at the rate $\dot{c}_1 = \dot{c}_2 = -k_0 c_1 c_2$. The fractional diffusion equation for the species i is then Eq. (47) with a reaction rate given by $k(\mathbf{r}, t) = k_0 c_j(\mathbf{r}, t)$.

4.3. Single-particle target problem with a reactivity field

The problem we consider here is that of Sec. 3.1, i.e. the single-particle target problem, but now when the reaction between the target and the particle does not necessarily take place only at one fixed distance R between them. Specifically, we now assume that the probability that a reaction can take place at the distance r is determined by an isotropic and time-independent reactivity $k(r)$, that is, $k(\mathbf{r}, t) = k(r)$. In this case, with $c(\mathbf{r}, 0) = \delta(\mathbf{r} - \mathbf{r}_0)$, the equation for $\mathbf{r} \neq \mathbf{r}_0$ is

$$[u + k(\mathbf{r})]^\gamma \tilde{v}(\mathbf{r}, u) = D_\gamma \nabla^2 \tilde{v}(\mathbf{r}, u). \tag{53}$$

This problem has been studied by Seki *et al.* in [63] in their analysis of the kinetics of geminate reactions in three-dimensional systems. They considered three different spatial dependences for $k(r)$ (square box or step function, exponential, and inverse power), paying special attention to the escape probability $Q_1(r_0, t \rightarrow \infty)$. For the Heaviside step function reactivity $k(r) = k_0 \Theta(R - r)$, the reaction occurs with rate coefficient k_0 at any distance between particle and target centers that is smaller than R . This problem can be solved exactly. For $r_0 < R$, the survival probability is

$$Q_1(r, u) = \frac{1}{u + k_0} \left[1 + \frac{k_0}{u} \frac{(1 + Rq) \sinh(rp)}{r_0 p \cosh(Rp) + r_0 q \sinh(Rp)} \right], \tag{54}$$

with $q = \sqrt{u^\gamma/D_\gamma}$ and $p = \sqrt{(u + k_0)^\gamma/D_\gamma}$. No exact solutions are known for the exponential and inverse power reactivity cases. For these unsolved cases one can try to apply the approximate method, proposed by Seki *et al.* [63], in which the term $[u + k(\mathbf{r})]^\gamma$ in Eq. (53) is replaced by $u^\gamma + k^\gamma(x)$.

Note that the equation resulting from this replacement can also be obtained from the corresponding normal diffusion equation (the equation with $\gamma = 1$) by the replacements $D \rightarrow u^{1-\gamma} D_\gamma$ and $k(\mathbf{r}) \rightarrow u^{1-\gamma} k(\mathbf{r})$, so that one can then arrive at the approximate solution from the solution of the normal diffusion problem. Since the approximation $[u + k(\mathbf{r})]^\gamma \rightarrow u^\gamma + k(\mathbf{r})^\gamma$ improves as $u \gg k(\mathbf{r})$ and $u \ll k(\mathbf{r})$, it is in fact quite accurate for short and long times [63].

4.4. *Reaction-subdiffusion equations and morphogen gradient formation*

In Sec. 4.3, Eq. (48) was taken as a starting point to study the escape problem of a single subdiffusive particle subject to a degradation process. Beyond this specific application, there are many other classical reaction-transport problems of interest whose solution can be extended to the anomalous diffusion case via Eq. (48). In certain cases the interplay between the reaction kinetics and memory effects associated with anomalous diffusion may drastically change the phenomenology of the system at hand. One such case concerns a problem of utmost importance in developmental biology, namely, the formation of morphogen gradients leading to patterning in embryonic tissues [72].

The location, differentiation and fate of many embryonic cells is governed by the spatial distribution of special signaling molecules called morphogens. These molecules are secreted at localized sites of the embryo at a fairly constant rate. The secreted morphogens then undergo degradation as they disseminate through the tissue, and a concentration gradient forms as a result of the balance between the secretion and degradation processes. Different target genes in embryonic cells are activated when the morphogen gradient exceeds appropriate concentration thresholds, implying that the cell response to the local environment depends on the local concentration. As a result of this differential response, cells are able to interpret the morphogen gradient and translate it into specific “code” for their further development via the expression of relevant genes.

Traditional models of morphogen gradient formation are based on classical diffusion equations with an added linear degradation term. The typical decay profile of the gradient is modulated by both the value of the diffusion constant and the degradation rate [72]. Recently there has been a recognition that subdiffusive rather than diffusive transport might more appropriately describe temporary morphogen trapping upon binding to proteins. Such trapping events may be mimicked in the framework of a CTRW model

by considering the morphogens as random walkers subject to a long-tailed waiting time distribution [73]. Degradation may occur either as a death process caused by enzymes inside the cell, or as irreversible escape from the surface of the cell.

Neglecting finite size effects, the concentration profile for the morphogen problem may be obtained by solving Eq. (48) in a one-dimensional infinite domain (a one-dimensional description is typically appropriate because the secretion geometry renders the problem effectively one-dimensional) subject to a radiation-type boundary condition (constant morphogen influx j_0 at the origin $x = 0$) [7]. Proceeding as in Sec. 4.3, we arrive at a particular case of Eq. (52), namely,

$$[u + k(x)]^\gamma \tilde{v}(x, u) - \delta(x) = D_\gamma \nabla^2 \tilde{v}(x, u). \tag{55}$$

4.4.1. *Constant reactivity*

Let us first address the case of homogeneous reactivity, i.e., $k(x) = k$. The solution in Laplace space is

$$\tilde{c}(x, u) = \frac{j_0}{2} \frac{(u + k)^{\gamma/2-1}}{u\sqrt{D_\gamma}} \exp \left[-|x|(u + k)^{\gamma/2}/\sqrt{D_\gamma} \right]. \tag{56}$$

The stationary solution is obtained from the final value theorem for the Laplace transform:

$$c_s(x) = \lim_{u \rightarrow 0} u\tilde{c}(x, u) = \frac{j_0}{2} \frac{k^{\gamma/2-1}}{\sqrt{D_\gamma}} \exp \left[-|x|k^{\gamma/2}/\sqrt{D_\gamma} \right]. \tag{57}$$

4.4.2. *Piecewise constant reactivity*

Here we assume that the reactivity is given by a superposition of Heaviside functions, i.e., $k(x) = k_0H(R - |x|) + k_1H(|x| - R)$. This profile provides a simple way to model a change in the degradation mechanism across an interface or beyond a certain distance from the source. In region 0 ($0 \leq |x| < R$) one has $k(x) = k_0 > 0$, whereas in region 1 ($|x| \geq R$) one has $k(x) = k_1 \geq 0$. Let us respectively denote by $\tilde{v}_0(x, u)$ and $\tilde{v}_1(x, u)$ the solutions of Eq. (55) in the regions 0 and 1. These functions and their spatial derivatives must fulfill the continuity conditions

$$\tilde{v}_0(R, u) = \tilde{v}_1(R, u) \tag{58}$$

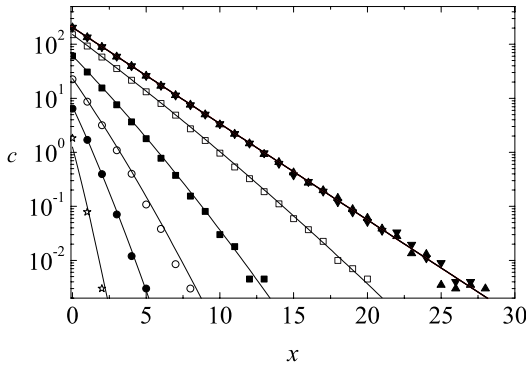


Fig. 1. Simulation results over 1000 realizations (symbols) for $c(x, t)$ with $k = 1/1000$, $\gamma = 1/2$, and $j_0 = 1$ for (from bottom to top) $t = 1, 10, 50, 200, 10^3, 10^4, 2 \times 10^4$. The particles are simulated by means of the CTRW model where the waiting time distribution is a Pareto law, $\psi(t) = \gamma/(1+t)^{1+\gamma}$, and the jumps $\{-1, 0, 1\}$ are equiprobable. These parameters lead to the D_γ -value $1/\sqrt{9\pi}$. The thin lines are the profiles obtained from the inverse numerical transformation of Eq. (56). The thick line is the theoretical prediction for the steady-state profile, Eq. (56). There are no adjustable parameters.

and

$$\left. \frac{\partial \tilde{v}_0(x, u)}{\partial x} \right|_{|x|=R} = \left. \frac{\partial \tilde{v}_1(x, u)}{\partial x} \right|_{|x|=R}. \tag{59}$$

In contrast, an integration of Eq. (55) across the origin shows that the solution must be discontinuous there,

$$\left. \frac{\partial \tilde{v}_0(x, u)}{\partial x} \right|_{x=0+} - \left. \frac{\partial \tilde{v}_0(x, u)}{\partial x} \right|_{x=0-} = -\frac{1}{D_\gamma}. \tag{60}$$

Using Eqs. (58)–(60) one gets for $|x| < R$ the stationary biexponential solution

$$c_s(x) = j_0 k_0^{\gamma-1} \tilde{v}_0(x, u = 0) \tag{61}$$

with

$$\tilde{v}_0(x, u) = A_0(u)e^{-\alpha_0 x} + B_0(u)e^{\alpha_0 x}, \quad \alpha_0^2 = \frac{(u + k_0)^\gamma}{D_\gamma}. \tag{62}$$

The characteristic coefficients $A_0(u)$ and $B_0(u)$ are determined from the conditions imposed on $\tilde{v}(x, u)$ at $|x| = 0$ and $|x| = R$. For $|x| > R$, we shall distinguish two subcases with different physical behavior. For $k_1 > 0$, one

asymptotically gets the exponential decay law

$$c_s(x) = c(x, t \rightarrow \infty) \propto e^{-k_1^{\gamma/2}(x-R)/\sqrt{D}^\gamma}. \tag{63}$$

The behavior is radically different for $k_1 = 0$. For normal diffusion the profile becomes constant for large $|x|$, i.e.,

$$c_s(x) \propto j_0, \quad k_1 = 0, \gamma = 1, |x| \geq R. \tag{64}$$

However, when the diffusion is anomalous, degradation is globally too slow and one has

$$c(x, t \rightarrow \infty) \propto j_0 t^{1-\gamma}, \quad k_1 = 0, \gamma < 1, |x| \geq R, \tag{65}$$

i.e., the profile at $x = |R|$ becomes discontinuous and there is no steady state. This behavior is confirmed by numerical CTRW simulations (see Fig. 2), indicating that secreted morphogens which escape region 0 are not as efficiently dispersed back into the reactive region as they are in the case of normal diffusion, and they thus accumulate in region 1.

4.4.3. Exponentially decaying reactivity

Here, we assume the decay law $k(x) = k_0 e^{-\beta|x|}$ ($\beta > 0$). While in this case Eq. (55) does not appear exactly solvable for finite u , in the limit $u \rightarrow 0$ it is

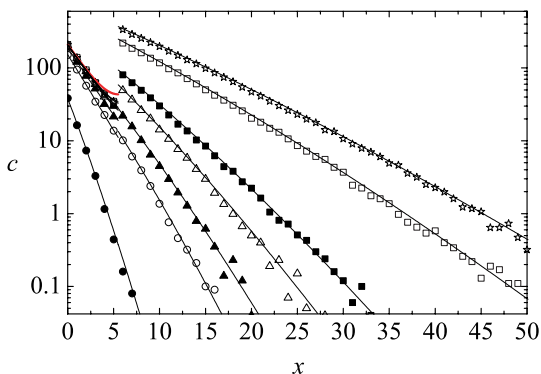


Fig. 2. Simulation results (symbols) of $c(x, t)$ for a step reactivity [$k(x) = k_0 H(R - x)$] with $k_0 = 1/1000$ and $R = 5.5$ for $\gamma = 1/2$ and (from bottom to top) $t = 100, 10^3, 2 \times 10^3, 5 \times 10^3, 10^4, 5 \times 10^4, 10^5$ (only values for $x > 0$ are shown). The particles are simulated as in Fig. 1. The solid line corresponds to the theoretical prediction for the steady-state profile when $x < R$. For $x > R$ no stationary profile develops. The convergence of the simulation results to the stationary profile for $x < R$ is very slow for values of x close to the discontinuity at $x = R$. No adjustable parameters were used.

possible to find an exact expression for the steady state profile by techniques similar to those used above. The final result is

$$c_s(x) = j_0 \frac{k_0^{\gamma/2-1} I_0(\alpha k_0^{\gamma/2} e^{-\beta\gamma|x|/2})}{2D_\gamma^{1/2} I_1(\alpha k_0^{\gamma/2})} e^{-(\gamma-1)\beta|x|}, \tag{66}$$

where the I_n 's are modified Bessel functions and $\alpha = 2/(\beta\gamma\sqrt{D_\gamma})$. As in the previous case of piecewise reactivity with $k_1 = 0$, the right-hand side of Eq. (66) displays different qualitative behaviors for normal and anomalous diffusion. In the normal diffusion case ($\gamma = 1$) one gets a monotonically decreasing profile from the concentration value at the origin to the limiting value $c_s(x \rightarrow \pm\infty) = j_0 / [\sqrt{4k_0 D_\gamma} I_1(\alpha k_0^{1/2})]$. Instead, for $\gamma < 1$ the concentration first decreases as one moves away from the source until it reaches a minimum and then it increases as $\exp[(1-\gamma)\beta|x|]$, a vestige of the divergence found for piecewise constant reactivity with $k_1 = 0$. This result is again confirmed by CTRW simulations (cf. Fig. 3). The nonmonotonicity of the profile may have interesting biological consequences: the combined action of subdiffusive transport and a rapid spatial decrease of the reactivity may induce complex tissue patterning where spatially distant cells follow a similar developmental pathway.

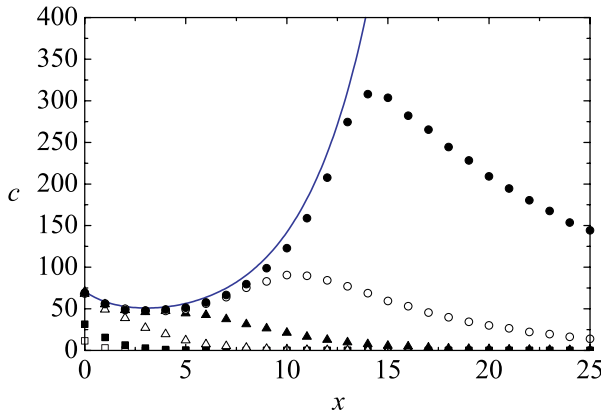


Fig. 3. Convergence of CTRW simulation results for (from bottom to top) $t = 20, 100, 10^3, 10^4, 10^5, 10^6$ (symbols) to the stationary profile predicted by the formula (66) for $j_0 = 1, \gamma = 0.5$, the corresponding value $D_\gamma = 1/\sqrt{9\pi}$ and exponentially decaying reactivity $k(x) = k_0 \exp(-\beta|x|)$ with $k_0 = 1/200$ and $\beta = 0.6$ (solid line). The particles are simulated as in Fig. 1. The simulation results clearly tend to the stationary solution as time increases, although the convergence is slow for large x .

5. Final Remarks

Anomalous diffusion such as the subdiffusive processes that we have discussed in this chapter is found everywhere in nature. It is perhaps not surprising that anomalous diffusion in the form of subdiffusion is actually a normal state of affairs in biological environments [4]. Although a great deal of effort has been invested in understanding how reactant and product concentrations evolve in space and time in subdiffusive media [70, 71, 74], the subject is still in its infancy. One of the great difficulties is that a broad macroscopic phenomenology such as the one we are used to in the case of normal diffusion (in the form of reaction-diffusion equations) is simply not applicable in the presence of subdiffusion. This seems to signify that every mesoscopic model needs to be dealt with separately, and that the associated macroscopic reaction-subdiffusion models are neither particularly intuitive nor broadly applicable to many mesoscopic models.

In this chapter we have chosen a particular mesoscopic starting point, namely, a continuous time random walk, and have derived and solved the associated fractional reaction-subdiffusion equations. These equations have been obtained for a few very specific models and cannot be translated to even other CTRW models without going back to the proverbial drawing board. Parenthetically, we might note that it is not yet known how to include reactions in other mesoscopic subdiffusion models, e.g., the fractional Brownian motion model.

More specifically, in this chapter we have constructed and solved a number of reaction-subdiffusion equations using the tools of fractional calculus. We have separated our discussion into two parts. In one, we have studied reactions that take place at spatially fixed locations such as the surface of an immobile particle (trap) or the hypersurface of a volume that encloses the particle whose fate we are following. In these problems the equation to be dealt with is a pure fractional subdiffusion equation, and the reactions are entirely built into boundary conditions. In the second part we have dealt with reactions that take place at random locations. Now in general the reaction has to be built into the fractional equation. We have applied the resultant equation to two examples for which we have obtained explicit solutions. In this section we have also studied a third problem, the classic $A+B \rightarrow B$ problem where the particle A and the traps B are all mobile and thus reactions occur at random locations. For this problem we have not constructed a reaction-subdiffusion equation. Instead, we have discussed a way to obtain asymptotic results using bounds that involve only pure fractional subdiffusion equations plus boundary conditions. These three examples, in

addition to their inherent interest, serve to make the point that in the world of subdiffusion every single scenario seems to require an analysis that is suitable only for that particular scenario. Every reaction in a subdiffusive medium requires its own full analysis starting from a mesoscopic description. Whether it will always be this way, or whether some future insight will help pull together many mesoscopic cases into a macroscopic description as broad and useful as a reaction-diffusion equation in the case of normal diffusion, remains to be seen.

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