

# Application of Fractional Calculus to Reaction-Subdiffusion Processes and Morphogen Gradient Formation <sup>★</sup>

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**Abstract:** As is well known, subdiffusion equations in terms of fractional derivatives can be obtained from Continuous Time Random Walk (CTRW) models with long-tailed waiting time distributions. Over the last years various authors have shown that extensions of such CTRW models incorporating reactive processes to the mesoscopic transport equations may lead to non-intuitive reaction-subdiffusion equations. In particular, one such equation has been recently derived for a subdiffusive random walker subject to a linear (first-order) death process. We take this equation as a starting point to study a key problem in developmental biology, namely morphogen gradient formation. We consider both the uniform case where the morphogen degradation rate coefficient (reactivity) is constant and the non-uniform case (position-dependent reactivity). In the uniform case we obtain exponentially decreasing stationary concentration profiles and we study their robustness with respect to perturbations in the incoming morphogen flux. In the non-uniform case we find a rich phenomenology at the level of the stationary profiles. We conclude that the analytic form of the long-time morphogen concentration profiles is very sensitive to the spatial dependence of the reactivity and the specific values of the anomalous diffusion exponent and the anomalous diffusion coefficient.

*Keywords:* Riemann-Liouville fractional derivative, anomalous diffusion, reaction-subdiffusion equations, continuous-time random walks, morphogen profiles

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## 1. INTRODUCTION

Fractional diffusion equations are a powerful tool to study anomalous transport processes, i.e., processes in which the mean square displacement  $\langle x^2 \rangle$  of a randomly moving particle displays the long time-behavior  $\langle x^2 \rangle \sim K_\gamma t^\gamma$ , where  $\gamma$  is the anomalous diffusion exponent and  $K_\gamma$  is the so-called anomalous diffusion coefficient. When  $0 < \gamma < 1$ , one has sublinear growth of  $\langle x^2 \rangle$  (subdiffusion), while for  $\gamma > 1$  one speaks of superdiffusion. As it is well known, the classical diffusion equation corresponding to the  $\gamma = 1$  case can be obtained from an average over the trajectories of a Markovian random walk in the limit of large time scales and long displacements. In contrast, stochastic transport processes governed by anomalous diffusion equations reflect memory effects at the microscopic level. In particular, one can show that a suitably defined non-Markovian hopping process, namely a Continuous Time Random Walk (CTRW) with a long-tailed waiting time distribution, yields a subdiffu-

sion equation in terms of the Riemann-Liouville fractional derivative (1). This fractional subdiffusion equation can be taken as a starting point to deal with a number of biologically relevant problems, e.g. the localization of a target protein by a sea of subdiffusively moving ligands in the intracellular environment (2; 3). In this case, the complexity of the cell medium results in the ligands encountering a large number of obstacles, barriers, etc. in the course of their trajectories. In the framework of CTRW models, the effect of this crowded environment can be partly captured using waiting time distributions; subsequent averaging of the resulting equations over trajectories then leads to the associated fractional subdiffusion equations.

While anomalous diffusion and in particular subdiffusive processes play a central role in Nature as a manifestation of underlying memory effects at a microscopic level, the situation where the particles simultaneously undergo anomalous transport *and* reaction (understood as a particle creation, destruction or transformation process) is also very common and important from the point of view of biological applications. In the example of the target protein and the ligands given above, one could allow e.g. for the possibility of the ligands undergoing a degradation process as they sweep the cell medium. Degradation implies a change in

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chemical structure which results in the ligands losing their ability to interact with the target; for practical purposes this kind of transformation can therefore be regarded as a “death” or “evanescence” process.

In what follows, we shall focus on yet another biological process where degradation/death plays a central role, namely morphogen gradient formation. The location, differentiation and fate of many embryonic cells is governed by the spatial distribution of special signaling molecules called morphogens. Standard models of morphogen gradient formation assume that a specific part of the embryo secretes morphogens at a constant rate. The secreted morphogens then undergo degradation as they disseminate through the tissue and a concentration gradient builds up. Different target genes in the embryonic cells are activated above different morphogen concentration thresholds, implying that the cell response to the local environment will depend on how large the concentration is. Thanks to 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 the relevant genes.

Traditional models of morphogen gradient formation are based on classical diffusion equations with a linear degradation term (4; 5). Here, we aim to go one step further and allow for the possibility of anomalous transport, as memory effects are likely to strongly influence the stochastic motion of morphogens in the complex embryonic environment. Some recent works indeed suggest that a strong dispersion of the waiting times between consecutive jumps may arise as a result of entrapment events arising from the interaction between morphogens and proteins of the heparan sulfate proteoglycans family (6).

If one accepts the idea that morphogens perform subdiffusive motion induced by a long tailed waiting time distribution, great caution must be exercised when incorporating the effect of a simultaneous degradation process to the transport equations because of the non-Markovian character of the latter. Several recent works indeed illustrate that heuristic equations where one has separate terms for the reaction and the transport process may lead to unphysical results, e.g. negative particle concentrations (see e.g. (7)). Therefore, the derivation of physically correct (but not necessarily intuitive) reaction-subdiffusion equations calls for the use of an extended CTRW formalism where the effect of reaction is incorporated at a *mesoscopic* level of description. In a recent work (8) the authors have shown by means of Fourier-Laplace techniques that CTRW models extended in such a way yield equations which (in addition to a standard, purely reactive term) display a mixed reaction-transport term containing both the reaction rate coefficient (reactivity) and a Riemann-Liouville fractional derivative with respect to time.

A remarkable property of morphogen gradients is their robustness against changes or fluctuations in the rate of morphogen production or degradation. An interesting question which we also aim to study in what follows is the interplay between subdiffusion and robustness with respect to such perturbations.

The remainder of the paper is organized as follows. We first give a brief reminder of classical reaction diffusion

equations used for modeling of morphogen gradients and subsequently discuss how to extend such equations to account for anomalous transport via fractional derivatives. We subsequently focus on the specific case of uniform reactivity and assess the robustness of the resulting stationary concentration profiles with respect to perturbations of the incoming morphogen flux. Next, we turn to the non-uniform case and discuss the long-time behaviour of the profiles for several specific situations, namely the case of a piecewise constant reactivity (which not always leads to a stationary profile) and the case of a decaying reactivity respectively given by an exponential and a power law. In some cases, we also provide numerical simulation results based on a CTRW model for evanescent particles and find excellent agreement with the analytic results obtained from the fractional diffusion equation approach. Finally, a summary of results and possible avenues for future research in this area are given in the conclusions section.

## 2. CLASSICAL REACTION-DIFFUSION EQUATION WITH LINEAR DEGRADATION

The cornerstone of many studies concerning morphogen gradients is the classical one-dimensional reaction-diffusion equation

$$\frac{\partial c(x,t)}{\partial t} = K_1 \frac{\partial^2 c(x,t)}{\partial x^2} - k(x,t) c(x,t), \quad (1)$$

where the evolution of the concentration  $c(x,t)$  is described by a Fickian term (characterized by a classical diffusion coefficient  $K_1$ ) and a linear degradation term (characterized by the reactivity  $k(x,t)$ ). Eq. (1) is then solved subject to the radiation-type boundary condition

$$-K_1 \left. \frac{\partial c(x,t)}{\partial x} \right|_{x=0+} + K_1 \left. \frac{\partial c(x,t)}{\partial x} \right|_{x=0-} = j_0. \quad (2)$$

This boundary condition simply states that a constant flux of morphogens  $j_0$  is injected at the origin  $x = 0$ . The simplest case is given by a constant degradation rate  $k(x,t) = k$ , which yields the exponentially decaying stationary profiles:

$$c(x, \infty) = \frac{j_0}{2\sqrt{kK_1}} e^{-\sqrt{\frac{k}{K_1}}|x|}. \quad (3)$$

Despite its simplicity, the exponential dependence of Eq. (3) captures surprisingly well the rapid concentration decay displayed by real profiles. However, the separate determination of  $K_1$  and  $k$  poses significant experimental difficulties and in most cases only the characteristic length  $\sqrt{K_1/k}$  can be unambiguously determined. This opens the door to the possibility of considering non-Markovian generalizations of Eq. (1) which are also compatible with the experimental results for the characteristic length.

## 3. FRACTIONAL REACTION-SUBDIFFUSION EQUATION WITH UNIFORM REACTIVITY

### 3.1 Derivation from a mesoscopic CTRW model with reaction

The starting point to derive the reaction-subdiffusion equation is the fundamental equation of a particle performing a continuous time random walk in the presence of

a first order evanescence reaction (degradation). Consider the stochastic motion of an evanescent particle performing nearest-neighbor jumps on an infinite one-dimensional lattice. We shall hereafter denote the distribution of its waiting time between consecutive jumps by  $\psi(t)$ . The probability that a particle starting at site 0 arrives at site  $i$  in the time interval between  $t$  and  $t + dt$  can be written as  $q(i, t) dt$ , where the arrival density  $q$  obeys the following integral difference equation:

$$q(i, t) = \frac{1}{2} \sum_{j=0}^1 \int_0^t dt' \psi_{RW}(t - t') q(i + (-1)^j, t') + \delta_{i,0}. \quad (4)$$

In this equation,  $\psi_{RW}(t) = \psi(t)e^{-kt}$  is the probability per unit time that a particle found at a given site at time  $t = 0$  has performed a jump up to time  $t$  in the presence of a uniform evanescence reaction (since evanescence and jump are independent processes, the probability of jump is simply multiplied by the survival probability  $e^{-kt}$ ). Note that we assume reaction and hopping events to be independent processes, as opposed to the model in ref. (6), where they are mutually exclusive processes. Taking the diffusive limit of Eq. (4) one can show via suitable Fourier-Laplace techniques (7) that the probability  $w(x, t|0, 0)$  to find the particle at position  $x$  after a time  $t$  given that it was initially at  $x = 0$  obeys the following equation:

$$\frac{\partial w(x, t|0, 0)}{\partial t} = K_\gamma e^{-kt} {}_0D_t^{1-\gamma} e^{kt} \frac{\partial^2}{\partial x^2} w(x, t|0, 0) - kw(x, t|0, 0). \quad (5)$$

The operator  ${}_0D_t^{1-\gamma}$  is defined via the equation

$$\mathcal{L}_{u \rightarrow t}^{-1} \{u^{1-\gamma} \tilde{y}(u)\} = {}_0D_t^{1-\gamma} y(t), \quad (6)$$

where  $\tilde{y}(u)$  is the Laplace transform of the function  $y(t)$  and  $\mathcal{L}_{u \rightarrow t}^{-1} \{\cdot\}$  denotes the inverse Laplace transform. The operator  ${}_0D_t^{1-\gamma}$  is closely related to the Riemann-Liouville fractional derivative

$${}_0D_t^{1-\gamma} f(x, t) = \frac{1}{\Gamma(\gamma)} \frac{\partial}{\partial t} \int_0^t dt' \frac{f(x, t')}{(t - t')^{1-\gamma}}. \quad (7)$$

In fact,  ${}_0D_t^{1-\gamma}$  and  ${}_0D_t^{1-\gamma}$  are the same when applied to sufficiently regular functions  $f(t)$ , as determined by the condition  $\lim_{t \rightarrow 0} \int_0^t dt' (t - t')^{\gamma-1} f(t') = 0$ . This condition is actually fulfilled by all functions of  $t$  relevant to the morphogen problem, hence we shall use  ${}_0D_t^{1-\gamma}$  in place of  ${}_0D_t^{1-\gamma}$  in what follows.

If one is dealing with more than one particle, the concentration  $c(x, t)$  follows the same kinetics as above, i.e. (9; 7)

$$\frac{\partial c(x, t)}{\partial t} = K_\gamma e^{-kt} {}_0D_t^{1-\gamma} e^{kt} \frac{\partial^2}{\partial x^2} c(x, t) - kc(x, t). \quad (8)$$

As one can see, this equation is a non-trivial extension of Eq. (1) for the case of anomalous subdiffusion with constant reactivity  $k$ . In the normal diffusion limit  $\gamma \rightarrow 1$  the Riemann-Liouville operator reduces to unit and one recovers Eq. (1) with a constant  $k$ . On the other hand, in the absence of reaction ( $k \rightarrow 0$ ) Eq. (8) reduces to

the standard fractional diffusion equation, which yields sublinear growth of  $\langle x^2 \rangle$ .

Turning now to the morphogen problem, Eq. (8) is to be solved subject to the boundary condition (2). The solution  $c(x, t)$  for the case of a particle source can be obtained from the propagator solution  $c_P(x, t) \equiv G(x, t)$  (corresponding the initial condition  $G(x, 0) = \delta(x)$ ) via the relation  $\tilde{c}(x, u) = j_0 \tilde{G}(x, u)/u$  between the Laplace transforms. The solution in Laplace space is found to be

$$\tilde{c}(x, u) = \frac{j_0}{2} \frac{(u + k)^{\gamma/2-1}}{u \sqrt{K_\gamma}} \exp \left[ -(u + k)^{\gamma/2} / \sqrt{K_\gamma} |x| \right]. \quad (9)$$

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

$$c_s(x) = \lim_{u \rightarrow 0} u \tilde{c}(x, u) = \frac{j_0}{2} \frac{k^{\gamma/2-1}}{\sqrt{K_\gamma}} \exp \left[ -|x| k^{\gamma/2} / \sqrt{K_\gamma} \right]. \quad (10)$$

Eq. (10) generalizes the exponential profile described by Eq. (3). Steady state profiles are thus seen to also exist in the presence of anomalous diffusion, as opposed to what had been suggested in some previous works for the case of uniform reactivity (6).

### 3.2 Robustness of stationary profiles

Using Eq. (10) it is possible to study the robustness of the concentration profiles with respect to a perturbation in the incoming flux  $j_0$ . To this end, we take a reference value  $c_x$  of the concentration and assess how large the shift of the associated position

$$x = \sqrt{\frac{K_\gamma}{k^\gamma}} \ln \left( \frac{k^{\gamma/2-1} j_0}{2c_x \sqrt{K_\gamma}} \right) \quad (11)$$

becomes when  $j_0$  is perturbed; the larger the shift, the smaller the robustness of the profile. The latter can thus be characterized by the inverse of the relative change of  $x$  with respect to a characteristic length  $a$  of the problem (e.g. the linear size of a cell), i.e.

$$\mathcal{R}_{j_0} = a \left( j_0 \frac{\partial x}{\partial j_0} \right)^{-1} \quad (12)$$

Inserting Eq. (11) into this definition we find

$$\mathcal{R}_{j_0} \propto \sqrt{\frac{k^\gamma}{K_\gamma}}. \quad (13)$$

## 4. FRACTIONAL REACTION-SUBDIFFUSION EQUATION WITH NON-UNIFORM REACTIVITY

Seki et al. (10) have shown that a CTRW process described by a generalization of Eq. (4), namely

$$q(i, t) = \frac{1}{2} \sum_{j=0}^1 \int_0^t dt' \psi_{RW}(i + (-1)^j, t - t') q(i + (-1)^j, t') + \delta_{i,0} \quad (14)$$

with  $\psi_{RW}(i, t) = \psi(t)e^{-k(i)t}$  yields the following reaction-subdiffusion equation:

$$\frac{\partial c(x,t)}{\partial t} = K_\gamma \frac{\partial^2}{\partial x^2} \left[ e^{-k(x)t} {}_0D_t^{1-\gamma} \left( e^{k(x)t} c(x,t) \right) \right] - k(x)c(x,t). \quad (15)$$

In order to tackle the corresponding morphogen problem, it is first necessary to find the propagator solution of Eq. (15). To this end it is convenient to introduce a new function  $v(x,t)$  defined via the transformation

$$\tilde{v}(x,u) = [u + k(x)]^{1-\gamma} \tilde{c}(x,u) \quad (16)$$

in Laplace space. This function is readily found to fulfil the equation

$$[u + k(x)]^\gamma \tilde{v}(x,u) - \delta(x) = K_\gamma \frac{\partial^2}{\partial x^2} \tilde{v}(x,u). \quad (17)$$

In what follows, Eq. (17) will be used to investigate the effect of a non-uniform reactivity for several special cases.

#### 4.1 Piecewise constant reactivity

Here, we assume that the reactivity is given by a superposition of Heaviside functions, i.e.  $k(x) = k_0 H(R - |x|) + k_1 H(|x| - R)$ . This can be regarded as a schematic model of morphogenesis across the interface of two media with different degradation properties. In region 0 ( $0 \leq |x| < R$ ) we take  $k(x) = k_0 > 0$ , whereas in region 1 ( $|x| \geq R$ ) we assume  $k(x) = k_1 \geq 0$ . Let us respectively denote by  $\tilde{v}_0(x,u)$  and  $\tilde{v}_1(x,u)$  the solutions of Eq. (17) in the regions 0 and 1. These functions must fulfil the continuity conditions

$$\tilde{v}_0(R,u) = \tilde{v}_1(R,u) \quad (18)$$

and

$$\left. \frac{\partial \tilde{v}_0(x,u)}{\partial x} \right|_{|x|=R} = \left. \frac{\partial \tilde{v}_1(x,u)}{\partial x} \right|_{|x|=R}. \quad (19)$$

In contrast, an integration of Eq. (17) across the origin shows that the solution must be discontinuous there:

$$\left. \frac{\partial \tilde{v}_0(x,u)}{\partial x} \right|_{x=0+} - \left. \frac{\partial \tilde{v}_0(x,u)}{\partial x} \right|_{x=0-} = -\frac{1}{K_\gamma}. \quad (20)$$

Using Eqs. (18)-(20) one can find explicit expressions for the Laplace transforms  $\tilde{v}(x,u)$ ,  $\tilde{G}(x,u)$  and  $\tilde{c}(x,u) = j_0 \tilde{G}(x,u)/u$ . For  $|x| < R$  one gets the stationary biexponential solution

$$c_s(x) = j_0 k_0^{\gamma-1} \tilde{v}_0(x, u \rightarrow 0) \quad (21)$$

with

$$\tilde{v}_0(x,u) = A_0 e^{-\alpha_0 x} + B_0 e^{\alpha_0 x}, \quad \alpha_0^2 = \frac{(u + k_0)^\gamma}{K_\gamma} \quad (22)$$

The characteristic constants are

$$A_0 = \frac{(2\alpha_0 K_\gamma)^{-1}}{\left( \frac{2}{-1 - (k_1 + u)^{\gamma/2} \alpha_0^{-1} K_\gamma^{-1/2}} + 1 \right) e^{-2\alpha_0 R} + 1}$$

$$B_0 = \frac{(2\alpha_0 K_\gamma)^{-1}}{\left( \frac{2}{1 - (k_1 + u)^{\gamma/2} \alpha_0^{-1} K_\gamma^{-1/2}} - 1 \right) e^{2\alpha_0 R} - 1}$$

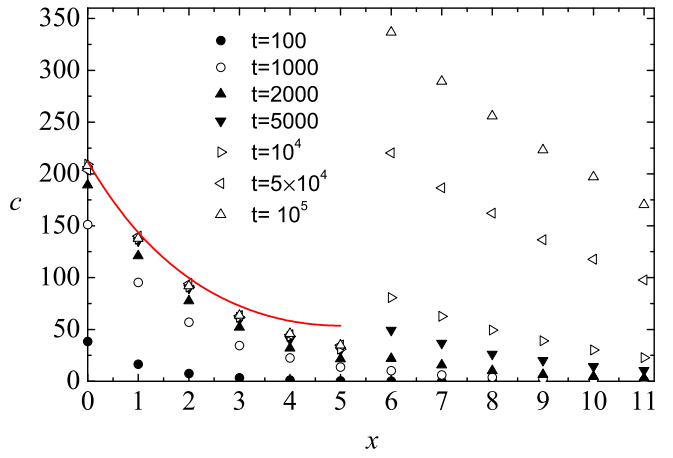


Fig. 1. Simulation results (symbols) of  $c(x,t)$  for a step reactivity [ $k(x) = k_0 H(R - x)$ ] with  $k_0 = 1/1000$  and  $R = 5$  for  $\gamma = 1/2$  (only values for  $x \leq 0$  are shown). The particles are simulated by means of a CTRW model with the Pareto waiting time distribution  $\psi(t) = \gamma/(1+t)^{1+\gamma}$  and equiprobable jumps  $\{-1, 0, 1\}$ . These parameters lead to the  $K_\gamma$ -value  $1/\sqrt{9\pi}$ . The solid line corresponds to the theoretical prediction for the steady-state profile when  $x < R$ . For  $x > R$  no stationary profile is developed. 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.

For  $|x| > R$  we shall distinguish two subcases with different physical behaviour. For  $k_1 > 0$  one asymptotically gets the exponential decay law

$$c_s(x) = c(x, t \rightarrow \infty) \propto e^{-k_1^{\gamma/2}(x-R)/\sqrt{K_\gamma}}. \quad (23)$$

In contrast, for  $k_1 = 0$  the behaviour is different. For normal diffusion the profile becomes constant for large  $|x|$ , i.e.,

$$c_s(x) \propto j_0 \quad (k_1 = 0, \gamma = 1, |x| \geq R). \quad (24)$$

However, when the diffusion is anomalous one has

$$c(x, t \rightarrow \infty) \propto j_0 t^{1-\gamma} \quad (k_1 = 0, \gamma < 1, |x| \geq R), \quad (25)$$

i.e., there is no steady state! In view of Eq. (21) and (25), we conclude that the profile is discontinuous at  $x = R$ . This behaviour is confirmed by numerical simulations (see Fig. 1). The lack of steady state in this case is induced by an increased escape rate of the particles from the central region with enhanced reactivity. Most probably the large escape rate arises from the fat tails of the subdiffusion propagator, as opposed to the rapid decrease of the sojourn probability associated with the Gaussian solution for normal diffusion.

#### 4.2 Exponentially decaying reactivity

Here, we assume the decay law  $k(x) = k_0 e^{-\beta|x|}$ . While in this case Eq. (17) does not seem exactly solvable for finite  $u$ , it is possible to find an exact expression of the steady

state profile by techniques similar to the ones used above. The final result is

$$c_s(x) = j_0 \frac{k_0^{\gamma/2-1} I_0(\alpha k_0^{\gamma/2} e^{-\beta\gamma|x|/2})}{2K_\gamma^{1/2} I_1(\alpha k_0^{\gamma/2})} e^{-(\gamma-1)\beta|x|}, \quad (26)$$

where the  $I_n$ 's are modified Bessel functions and  $\alpha = 2/(\beta\gamma\sqrt{K_\gamma})$ . As in the case of piecewise reactivity with  $k_1 = 0$ , this expression displays a different behaviour for normal and anomalous diffusion. In the normal diffusion case ( $\gamma = 1$ ) one gets a monotonically decreasing profile from the concentration value

$$c_s(x=0) = \frac{j_0}{\sqrt{4k_0K_\gamma}} \frac{I_0(\alpha k_0^{1/2})}{I_1(\alpha k_0^{1/2})} \quad (27)$$

at the origin to the limiting value

$$c_s(x \rightarrow \pm\infty) = \frac{j_0}{\sqrt{4k_0K_\gamma}} \frac{1}{I_1(\alpha k_0^{1/2})}. \quad (28)$$

(see Fig. 2). In contrast, for  $\gamma < 1$  we find a qualitatively different behaviour. As one moves away from the source, first the concentration decreases until it reaches a minimum and then it increases (see Fig. 3). From a biological point of view, one is tempted to hypothesize that the combined action of anomalous transport and a sufficiently fast decreasing reactivity induces complex tissue patterning where certain cells far apart from each other follow a similar developmental pathway by virtue of the non-monotonicity of the morphogen profiles.

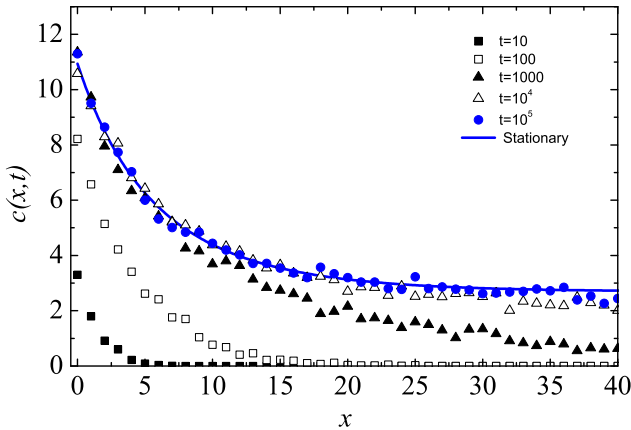


Fig. 2. Convergence of CTRW simulation results (symbols) to the stationary profile predicted by formula (26) for  $j_0 = 1, \gamma = 1$ , the corresponding value of the diffusion coefficient  $K_\gamma = 1/3$  and exponentially decaying reactivity  $k(x) = k_0 \exp(-\beta|x|)$  with  $k_0 = 1/100$  and  $\beta = 1/8$  (solid line). CTRW jump characteristics as in fig. 1

#### 4.3 Power law reactivity

Next, we take  $k(x) = \kappa_0(x_0 + |x|)^{-\frac{\mu}{\gamma}}$  with  $\mu > 0$ . Since a steady state was already attained for an exponentially decaying reactivity, this will also be the case under

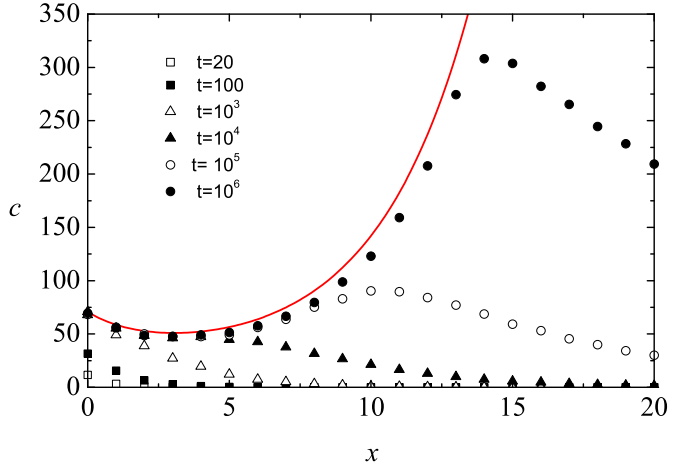


Fig. 3. Convergence of CTRW simulation results (symbols) to the stationary profile predicted by the formula (26) for  $j_0 = 1, \gamma = 0.5$ , the corresponding value  $K_\gamma = 1/\sqrt{9\pi}$  and exponentially decaying reactivity  $k(x) = k_0 \exp(-\beta|x|)$  with  $k_0 = 1/200$  and  $\beta = 0.6$  (solid line). CTRW jump characteristics as in fig. 1. The simulation results clearly go towards the stationary solution (solid line) as time increases, although the convergence for large  $x$  is slow.

the present situation, which describes enhanced particle evanescence. The general solution of Eq. (17) for  $\mu \neq 2$  is given by the modified Bessel functions  $I_{|\nu|}$  and  $K_{|\nu|}$  with  $\nu = (\mu - 2)^{-1}$ . In order to single out the Bessel function corresponding to the physical solution, we use the fact that the incoming flux must be equal to the amount of particles per unit time that disappear due to degradation, i.e.,

$$j_0 = \int_{-\infty}^{\infty} k(x)c_s(x)dx. \quad (29)$$

This condition leads to different solutions depending on the value of  $\mu$ . For  $\mu < 2$  one gets

$$c_s(x) \propto (x_0 + |x|)^{\frac{\mu}{\gamma} - \mu + \frac{1}{2}} K_{|\nu|}(\Phi(x_0 + |x|)^{-\frac{1}{2\nu}}), \quad (30)$$

where  $\Phi = 2|\nu|\sqrt{\kappa_0^\gamma/K_\gamma}$ . For large  $|x|$ , the above stationary solution can be shown to go to zero as  $x^{\frac{\mu}{\gamma} - \frac{3\mu}{4}} \exp(-\Phi|x|^{1-\frac{\mu}{2}})$ . In contrast, for  $\mu > 2$  one has

$$c_s(x) \propto (x_0 + |x|)^{\frac{\mu}{\gamma} - \mu + \frac{1}{2}} I_{|\nu|}(\Phi(x_0 + |x|)^{-\frac{1}{2\nu}}). \quad (31)$$

As  $|x| \rightarrow \infty$ , this expression tends to a constant limiting value in the normal diffusion case and grows as  $x^{\frac{\mu}{\gamma} - \mu}$  for  $\gamma < 1$ .

When  $\mu = 2$  the solution is not given by a power law rather than by Bessel functions. One has

$$c_s(x) \propto (x_0 + x)^{\frac{2}{\gamma} - 2 + \lambda_-} \quad (32)$$

with  $\lambda_- = 1 \pm \sqrt{1 + 4(\kappa_0^\gamma/K_\gamma)}/2$ . For  $|x| \rightarrow \infty$  this solution goes to infinity, a constant value or zero depending on whether  $\frac{2}{\gamma} - 2 + \lambda_-$  is positive, zero or negative.

## 5. CONCLUSIONS AND OUTLOOK

In the present work we investigate both analytically and numerically the behaviour of the long time concentration profiles arising from fractional reaction-subdiffusion equations derived from a CTRW model with a superimposed death process. These fractional equations are a natural extension of classical reaction-diffusion equations traditionally used to study the problem of morphogen gradient formation. We consider the case of linear degradation with both a uniform and non-uniform reactivity. The formulation of the problem in terms of fractional diffusion equations turns out to be a key ingredient in the analysis of the properties of morphogen gradients. This approach allows us to exploit a plethora of powerful analytical techniques available from fractional calculus to tackle the morphogen problem. In conclusion, we see that the form of the long time concentration profiles is very sensitive to the spatial dependence of the reactivity and the characteristic quantities of subdiffusive transport, i.e.,  $\gamma$  and  $K_\gamma$ . Anomalous diffusion leads to novel effects not seen for normal diffusion (absence of steady states, non-monotonic profiles, transitions between monotonic and non-monotonic profiles, etc.).

In the uniform case one obtains exponentially decaying stationary concentration profiles. Their robustness with respect to changes in the incoming flux increases with increasing  $k$ . Likewise, one can study the robustness of the profiles with respect to a perturbation in  $k$  by introducing the quantity

$$\mathcal{R}_k = a \left( k \frac{\partial x}{\partial k} \right)^{-1} \quad (33)$$

This issue will be the subject of future research.

In the non-uniform case the behaviour of the stationary profiles turns out to be very sensitive to the specific spatial dependence prescribed for  $k$  and to the value of  $\gamma$ . Moreover, for the case of a piecewise constant reactivity with  $k_1 = 0$  and anomalous diffusion, we see that a discontinuous profile arises and no steady state is reached in region 1. This is a novel effect not seen for normal diffusion. For exponentially decaying reactivity the concentration goes to a constant limiting value far away from the source ( $|x| \rightarrow \infty$ ) when  $\gamma = 1$ , but it grows without bound for  $\gamma < 1$ . Finally, when the connectivity decays as a power law, the stationary concentration may go to zero, to a constant or to infinity depending on the values of the characteristic decay exponent and  $\gamma$ .

In view of the strong inhomogeneities encountered by the diffusing morphogens in the embryonic environment, we believe that the sensitivity of the concentration gradients to the form of  $k(x)$  may be relevant for the modeling of morphogen gradient formation and interpretation. The case of a spatial-dependent degradation rate is motivated by the fact that there are several morphogen degradation pathways (e.g. intracellular degradation in lysosomes, extracellular degradation by proteases, release from tissue, etc.) which, for practical purposes, can be regarded as a “death” or “evanescence” process. The rates of each of these evanescence processes depend strongly on the local environment.

Up to the case of piecewise constant reactivity with  $k_1 = 0$ , in the present work we limit ourselves to study the behaviour of the stationary concentration profiles. However, analytic solutions for transient profiles are available for some of the cases studied, and others can be investigated via numerical techniques for the inversion of Laplace transforms. Besides, a reaction-subdiffusion equation was recently obtained that generalizes the above results to the general case  $k = k(x, t)$  (11; 12). As one could have guessed in view of Eqs. (8) and (15), this equation reads as

$$\frac{\partial c(x, t)}{\partial t} = K_\gamma \frac{\partial^2}{\partial x^2} \left\{ e^{-\int_0^t k(x, t') dt'} \right. \\ \left. {}_0 D_t^{1-\gamma} \left[ e^{\int_0^t k(x, t') dt'} c(x, t) \right] \right\} - k(x, t) c(x, t) \quad (34)$$

Our aim is to use the above equation to investigate further problems related to morphogen gradient formation in future. Beyond this goal, Eq. (34) can be applied to many other physical problems of interest characterized by different kinds of boundary conditions.

Finally, one of our major long term goals is to explore feedback effects in the degradation process. There is some evidence that morphogen signaling enhances to some extent degradation (4), leading to non-linear degradation terms and to even more complex equations. In such cases, it is questionable whether exact analytic solutions still exist; one may thus be led to use some kind of mean field approximation to tackle the underlying nonlinear problem.

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