Fractional Calculus and Morphogen Gradient Formation

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Abstract. Some microscopic models for reactive systems where the reaction kinetics is limited by *sub*diffusion are described by means of reaction-*sub*diffusion equations where fractional derivatives play a key role. In particular, we consider subdiffusive particles described by means of a Continuous Time Random Walk (CTRW) model subject to a linear (first-order) death process. The resulting fractional equation is employed to study the developmental biology key problem of morphogen gradient formation for the case in which the morphogens are subdiffusive. If the morphogen degradation rate (reactivity) is constant, we find exponentially decreasing stationary concentration profiles, which are similar to the profiles found when the morphogens diffuse normally. However, for the case in which the degradation rate decays exponentially with the distance to the morphogen source, we find that the morphogen profiles are qualitatively different from the profiles obtained when the morphogens diffuse normally.

INTRODUCTION

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 γ is the diffusion exponent and K_γ is the diffusion coefficient, are surprisingly frequent in Nature and, in particular, in biological systems. When $\gamma = 1$, we speak of normal diffusion, if $0 < \gamma < 1$, one has subdiffusion, while for $\gamma > 1$ there is superdiffusion. A well-known model of subdiffusion is the so-called Continuous Time Random Walk (CTRW) model where particles move with jumps of finite variance but with time intervals between jumps that follow a long-tailed (or power-law) waiting time distribution. Interestingly, this microscopic model gives rise to a *sub*diffusion equation in terms of fractional derivatives [1]. This fractional subdiffusion equation can be used to tackle some reaction-diffusion problems, some of them of biological interest, such as the time of localization of a target protein by a sea of subdiffusively moving ligands in the intracellular environment [2, 3].

In this communication, we shall focus on a reaction-subdiffusion model of morphogen gradient formation. This process is very important in developmental biology because the location, differentiation and fate of many embryonic cells is governed by the spatial distribution of special signaling molecules called morphogens [4, 5, 6]. Standard models of morphogen gradient formation assume that a specific part of the embryo secrets morphogens at a constant rate. These morphogens then undergo degradation as they disperse through the tissue and a concentration gradient develops. 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.

A traditional model of morphogen gradient formation is based on normal diffusion equations with a linear degradation term. Here, we aim to study how the anomalous subdiffusive character of the morphogenes affects the transient morphogen gradients and the stationary gradient (if the latter exists).

The paper is organized as follows. We first introduce the classical and fractional reaction diffusion model used for describing the development of morphogen gradients. Then we study two important cases: in the first one, the degradation rate (or reactivity) of the morphogens is constant, whereas in the second case the reactivity decays exponentially with the distance to the morphogen source. In both cases we compare our analytical results with numerical simulation and find an excellent agreement. We close with some conclusions and remarks.

THE REACTION-DIFFUSION MODEL WITH LINEAR DEGRADATION

The classical reaction-diffusion equation traditionally used to describe the development of morphogen gradients is

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

where $c(x,t)$ is the concentration of the morphogens, K_1 is the normal diffusion coefficient and $k(x,t)$ is the linear degradation term. Despite its simplicity, Eq. (1) together with the boundary condition of a constant flux j_0 of morphogens injected at the origin describe surprisingly well the *form* of morphogen profiles in real systems [6].

The reaction-subdiffusion equation to be considered here can be rigorously derived from a microscopic model in which the particles evanesce at a given rate $k(x,t)$ while performing a CTRW. The probability distribution $\psi(t)$ for the waiting time between consecutive jumps is assumed to go as $t^{-1-\gamma}$ for long times. In this case [7, 8, 9, 10, 11, 12, 13]

$$\frac{\partial c(x,t)}{\partial t} = K_\gamma \frac{\partial^2}{\partial x^2} \left\{ e^{-\int_0^t k(x,\tau)d\tau} \,_0\mathscr{D}_t^{1-\gamma} \left[e^{\int_0^t k(x,\tau)d\tau} c(x,t) \right] \right\} - k(x,t)c(x,t) \tag{2}$$

with $_0\mathscr{D}_t^{1-\gamma}$ being the fractional derivative operator defined by

$$\mathscr{L}_{u\to t}^{-1}\left\{ u^{1-\gamma}\tilde{y}(u) \right\} = \,_0\mathscr{D}_t^{1-\gamma}y(t), \tag{3}$$

and where $\tilde{y}(u)$ is the Laplace transform of the function $y(t)$ and $\mathscr{L}_{u\to t}^{-1}\{\cdot\}$ denotes the inverse Laplace transform. The operator $_0\mathscr{D}_t^{1-\gamma}$ is very close to the Riemann-Liouville fractional derivative

$$_0D_t^{1-\gamma}f(x,t) = \frac{1}{\Gamma(\gamma)}\frac{\partial}{\partial t}\int_0^t dt' \frac{f(x,t')}{(t-t')^{1-\gamma}}. \tag{4}$$

as $_0\mathscr{D}_t^{1-\gamma}$ and $_0D_t^{1-\gamma}$ lead to the same result when applied to functions $f(t)$ where $\lim_{t\to 0}\int_0^t dt'(t-t')^{\gamma-1}f(t') = 0$.

The solution of Eq. (2) with a space dependent rate $k(x)$ and constant flux j_0 at the origin can conveniently be written in Laplace space in terms of the Green function or propagator $G(x,t)$ of the problem as $\tilde{c}(x,u) = j_0\tilde{G}(x,u)/u$. It is convenient to introduce a new function $v(x,t)$ defined via the transformation $\tilde{v}(x,u) = [u+k(x)]^{1-\gamma}\tilde{G}(x,u)$. It satisfies the ordinary differential equation

$$[u+k(x)]^\gamma \tilde{v}(x,u) - \delta(x) = K_\gamma \frac{\partial^2}{\partial x^2}\tilde{v}(x,u). \tag{5}$$

In what follows, Eq. (5) is used to investigate the effect of a number of representative reactivity profiles.

SOME EXAMPLES

For the fundamental case of constant reactivity, $k(x,t) = k$, the solution of Eq. (5) leads to

$$\tilde{c}(x,u) = \frac{j_0}{2}\frac{(u+k)^{\gamma/2-1}}{u\sqrt{K_\gamma}}\exp\left[-(u+k)^{\gamma/2}/\sqrt{K_\gamma}|x|\right], \tag{6}$$

so that

$$c_s(x) = \frac{j_0}{2}\frac{k^{\gamma/2-1}}{\sqrt{K_\gamma}}\exp\left[-|x|k^{\gamma/2}/\sqrt{K_\gamma}\right] \tag{7}$$

is the stationary solution. Therefore, we see that steady state profiles exist even in the presence of anomalous diffusion. This is in contrast to the result found by Hornung et al. [14], albeit for a different anomalous diffusion model. In Fig. 1 we compare these theoretical results with numerical simulations. The agreement is excellent.

An interesting property of the morphogens gradients is their robustness with respect to changes in the incoming flux j_0. Proceeding as usual, we characterize the robustness of the stationary profile quantifying its shift when the secreted flux changes. More specifically, let $c_\times$ be the concentration at the position $x_\times$:

$$x_\times = \sqrt{\frac{K_\gamma}{k^\gamma}}\ln\left(\frac{k^{\gamma/2-1}j_0}{2c_\times\sqrt{K_\gamma}}\right) \tag{8}$$
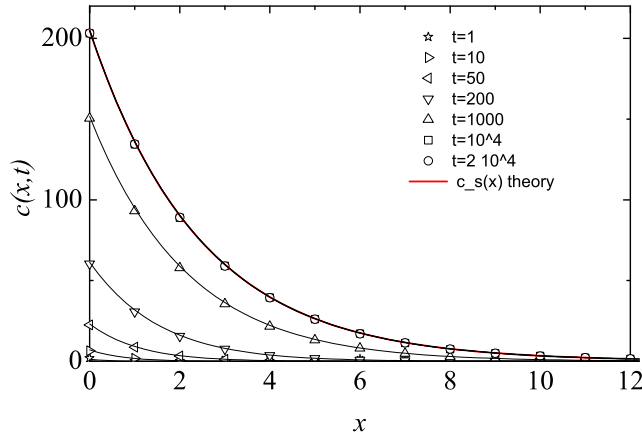
FIGURE 1. Concentration profiles for $j_0 = 1$, $\gamma = 0.5$, $K_\gamma = 1/\sqrt{9\pi}$, $k(x) = 1/1000$ and increasing times. Symbols: CTRW simulation results; lines: theoretical predictions [c.f., Eq. (6)]. The thick line corresponds to the stationary profile given by Eq. (7). There are no free parameters.

Then, the robustness of the profile with respect to changes in j_0 is defined by

$$\mathcal{R}_{j_0} = a \left(j_0 \frac{\partial x_\times}{\partial j_0} \right)^{-1} \tag{9}$$

with a being a characteristic length of the problem (e.g. the linear size of a cell). Inserting Eq. (8) into this definition we find that the robustness of the morphogen gradient depends on the anomalous diffusion exponent γ as

$$\mathcal{R}_{j_0} \propto \sqrt{\frac{k^\gamma}{K_\gamma}}. \tag{10}$$

Another interesting case occurs when the reactivity decays exponentially: $k(x) = k_0 e^{-\beta|x|}$. Then, it is possible to prove that the stationary morphogen gradient is given by

$$c_s(x) = j_0 \frac{k_0^{\gamma/2-1}}{2K_\gamma^{1/2}} \frac{I_0 \left(\alpha k_0^{\gamma/2} e^{-\beta\gamma|x|/2} \right)}{I_1 \left(\alpha k_0^{\gamma/2} \right)} e^{-(\gamma-1)\beta|x|}, \tag{11}$$

where the I_n's are modified Bessel functions and $\alpha = 2/(\beta\gamma\sqrt{K_\gamma})$. This expression predicts quite different behaviors for normal and anomalous diffusion. For normal diffusion ($\gamma = 1$), one gets a monotonically decreasing profile that goes from the maximum concentration value at the origin to a finite final value. In contrast, for subdiffusion ($\gamma < 1$) we find that the concentration decreases until it reaches a minimum and then it increases without bound (see Fig. 2).

CONCLUSIONS AND OUTLOOK

Although subdiffusion is widely present in biological media, subdiffusion processes are rarely taken into account when the formation of morphogen profiles is considered. We address this issue modeling the formation of a gradient of subdiffusive morphogens by means of a CTRW model with a superimposed linear death process and a localized source of particles. This way, the classical reaction-diffusion equations of the morphogen gradient formation are generalized in the form of *fractional* reaction-diffusion equations. The formulation of the problem in terms of fractional diffusion equations is very convenient as this allows us to employ in their solution and analysis some well-studied analytical techniques of fractional calculus.
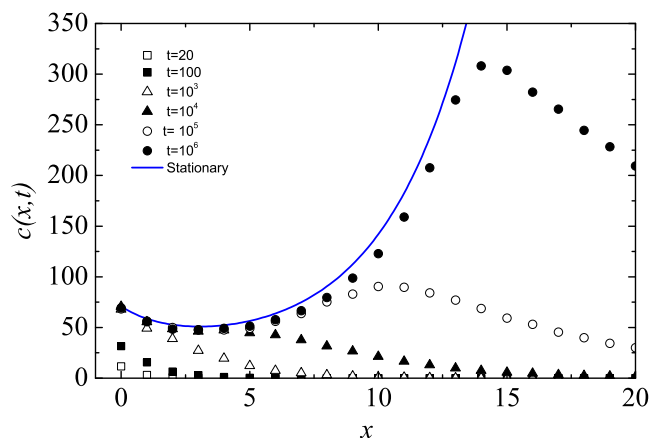
FIGURE 2. Convergence of CTRW simulation results (symbols) to the stationary profile predicted by the formula (11) for $j_0 = 1$, $\gamma = 0.5$, $K_\gamma = 1/\sqrt{9\pi}$ and $k(x) = k_0 \exp(-\beta|x|)$ with $k_0 = 1/200$ and $\beta = 0.6$ (solid line). The simulation results go towards the stationary solution as time increases, although the convergence for large x is slow. There are no free parameters.

We have considered two particular cases: the case in which the degradation rate is constant and the case where the degradation rate changes exponentially with the distance to the morphogen source. For the first case, we find exponentially decaying stationary concentration profiles that are qualitatively similar to the profiles obtained by means of the normal diffusive model. However, for the second case, we find that the profiles obtained when the morphogens are subdiffusive are *qualitatively* different from the profiles obtained when the morphogens diffuse normally. In this case, the concentration grows without bound for $\gamma < 1$ (anomalous diffusion) when $|x| \to \infty$ whereas it goes to a constant limiting value for $\gamma = 1$ (normal diffusion). We have carried out numerical simulations and found and excellent agreement between numerical and analytical results.

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REFERENCES

1. R. Metzler and J. Klafter, *Phys. Rep.* **339** 1 (2000).
2. S. B. Yuste and K. Lindenberg, *Phys. Rev. E* **76**, 051114 (2007).
3. R. Borrego, S. B. Yuste, and E. Abad, *Phys. Rev. E* **80**, 061121 (2009).
4. M. Ibáñes and J. C. Izpisúa, *Molecular Systems Biology* **4**, 176 (2008).
5. O. Wartlick, A. Kicheva and M. González-Gaitán, *Cold Spring Harb. Perspect. Biol.* **1**, a001255 (2009).
6. SR. Yu, M. Burkhardt, M. Nowak, J. Ries, Z. Petrášěk, S. Scholpp, P. Schwille, and M. Brand, *Nature* **461**, pp. 533 (2009).
7. V. Mendez, S. Fedotov, and W. Horsthemke, *Reaction-Transport Systems: Mesoscopic Foundation, Fronts, and Spatial Instabilities*, Springer-Verlag, Berlin, 2010.
8. A. Yadav and W. Horsthemke, *Phys. Rev. E* **74**, 066118 (2006).
9. K. Seki, A. I. Shushin, M. Wojcik, and M. Tachiya, *J. Phys.: Condens. Matter* **19**, 065117 (2007).
10. A. Yadav, S. M. Milu, and W. Horsthemke, *Phys. Rev. E* **78**, 026116 (2008).
11. I. M. Sokolov, M. G. W. Schmidt, and F. Sagués, *Phys. Rev. E* **73**, 031102 (2006).
12. B. I. Henry, T. A. M. Langlands, and S. L. Wearne, *Phys. Rev. E* **74**, 031116 (2006).
13. E. Abad, S. B. Yuste, and K. Lindenberg, *Phys. Rev. E* (2010).
14. G. Hornung, B. Berkowitz, and N. Barkai, *Phys. Rev. E* **72**, 041916 (2005).