A microscopic approach to nonlinear Reaction-Diffusion: the case of morphogen gradient formation

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Abstract

We develop a microscopic theory for reaction-difusion (R-D) processes based on a generalization of Einstein's master equation with a reactive term and we show how the mean field formulation leads to a generalized R-D equation with non-classical solutions. For the n-th order annihilation reaction $A + A + A + ... + A \rightarrow 0$, we obtain a nonlinear reaction-diffusion equation for which we discuss scaling and non-scaling formulations. We find steady states with either solutions exhibiting long range power law behavior showing the relative dominance of sub-diffusion over reaction effects in constrained systems, or conversely solutions with finite support of the concentration distribution describing situations where diffusion is slow and extinction is fast. Theoretical results are compared with experimental data for morphogen gradient formation.

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I. INTRODUCTION

The random walk is the classical paradigm for the microscopic mechanism underlying diffusive processes as demonstrated in 1905 by Einstein who showed how the diffusion equation follows from the mean field formulation of the microscopic random walk. Here we generalize the formulation for situations where the diffusing particles are also subjected to a reactive process. From the phenomenological viewpoint, when diffusion and reaction are coupled, these processes are described by reaction-diffusion (R-D) equations. For instance, the evanescence process ($A \to 0$) of suspended particles diffusing in a non-reactive medium the concentration of species A, $c(r;t)$, is described by the classical R-D equation

$$\frac{\partial}{\partial t} c\,(r;t) = D\,\frac{\partial^2}{\partial r^2} c\,(r;t) \;-\; k\,c\,(r;t)\;, \tag{1}$$

where D denotes the diffusion coefficient and k the reaction (evanescence) rate. This classical equation yields a steady state solution showing spatial exponential decay of the concentration (but one can equally consider the distribution function): $c\,(r) \;=\; c(0)\,\exp\left(-\sqrt{k/D}\,|r|\right)$ when particles are injected with a constant flux at $r = 0$.

However there are many systems observed in nature where it seems logical to use the language of reaction-diffusion, but where non-classical distributions are found, i.e. the steady state spatial distributions are non-exponential e.g. when the particles encounter obstacles or are retarded in their diffusive motion, or because the reactive process is hindered or enhanced by concentration effects. Such situations are ubiquitous in chemical, rheological, biological, ... systems - a typical example being the diffusion and degradation of a morphogen in cells during the early developing stage [1] - and are certainly as commonly observed as those that can be described by the idealized R-D system of Eq.(1). This is why approaches to a more general description of R-D phenomena have been proposed, and recent developments in this direction [2, 3] are based (i) on a generalization of the diffusive mechanism accounting for time delay effects or obstacles hindrance using the continuous time random walk (CTRW) model and corresponding to a fractional Fokker-Planck equation (FFP) or the fractional Brownian motion (FBM), and (ii) on a space and time dependence of the reaction rate ($k \to k(r;t)$). However the resulting expressions for the steady state distribution have so far been subject to controversial comments expressing that "CTRW theory is compatible with available experiment" [4] and "that fractional Brownian motion is the underlying process" [5] or that "experimental results cannot be explained by a continuous time random walk"

[6] and "exclude fractional Brownian motion as a valid description" [7]. So the present state of the art certainly appears somewhat confusing while it seems nevertheless clear that a general R-D theory requires a generalization for both diffusion and reaction.

Here we present an alternative approach by developing a microscopic theory generalizing Einstein's master equation with a reactive term and we show how the mean field formulation leads to the nonlinear R-D equation with non-classical solutions. For the n-th order annihilation reaction $A + A + A + ... + A \to 0$, we obtain the nonlinear reaction-diffusion equation (with no drift)

$$\frac{\partial}{\partial t} c\,(r;t) = \frac{\partial}{\partial r}\, D\, \frac{\partial}{\partial r} c^{\alpha}\,(r;t) - k\, c^{n}\,(r;t)\ , \tag{2}$$

for which we discuss scaling and non-scaling formulations and the corresponding range of values of the nonlinear exponents. We obtain steady state solutions of the form $c(r) = c(0)\,(1 + C_{\alpha,n}(D,k)\,r/\nu)^{-\nu}$ where $\nu = \frac{2}{n-\alpha}$, giving long range power law behavior (for $n > \alpha$) showing the relative dominance of sub-diffusion over reaction effects in constrained systems, or conversely (for $n < \alpha < n{+}1$) leading to finite support of the concentration $c(r)$ describing the situation where diffusion is slow and extinction is fast. An experimental example of morphogen gradient formation is discussed.

II. GENERALIZED MASTER EQUATION

We consider a diffusive process where particles are subject to annihilation using the microscopic approach of Einstein's original random walk model. For simplicity we consider a one-dimensional lattice where the particle hops to the nearest neighboring site (left or right) in one time step, and can then also be annihilated by a some reactive process as described by the discrete equation

$$n^{*}(r;t+1) = \xi_{-}\, n^{*}(r+1;t_{\,-}) + \xi_{+}\, n^{*}(r-1;t_{\,-}) - \xi_{R}\, n^{*}(r;t_{\,+})\,, \tag{3}$$

where the Boolean variable $n^{*}(r;t) = \{0,1\}$ denotes the occupation at time t of the site located at position r and $\xi_{\pm}$ is a Boolean random variable controlling the particle jump between neighboring sites ($\xi_{+} + \xi_{-} \leq 1$), while ξ_R is the reactive Boolean operator controling particle annihilation. The mean field description follows by ensemble averaging Eq.(3) with $\langle n^{*}(r;t)\rangle = n(r;t)$, $\langle \xi_{\pm}\rangle = P_i$, and $\langle \xi_R\rangle = R_i$, where i is an index for the position; using statistical independence of the ξ's and n^*, and extending the possible jump steps over the whole lattice, we obtain

$$n(r;t+\delta t) \;=\; \sum_{j=-\infty}^{+\infty} P_j(r-j\delta r;t)n(r-j\delta r;t) \;-\; R\,(r;t)\,n(r;t)\;, \tag{4}$$

where $P_j(r-j\delta r)$ denotes the probability of a jump of j sites from site $r-j\delta r$, and $R\,(r)$ the annihilation probability at site r; the number density is $n\,(r;t)$ so that $n\,(r;t)\,dr$ is the expected number of particles to find in the interval $[r-dr/2, r+dr/2]$. Note that in a closed system, i.e. without the second term on the right, the total number of particles, N, is constant so that one can divide through by this number to express the master equation in terms of $f(r,t) = n(r,t)/N$, the probability density. Alternatively, if the system contains multiple components, then a more useful concept is the concentration. For example, if there are two components, one of which is the solvent and the other the solute, then the solute concentration would be $c(r,t) = n(r,t)/(n(r,t)+n_s(r,t))$, where $n_s(r,t)$ is the local number density for the solute. In the common case that the solvent is uniform and stationary, $n_s(r,t) = n_s$, and that the solute is relatively dilute, $n_s >> n(r,t)$, one has, to first approximation, $c(r,t) = n(r,t)/n_s$, which is what we will use in the following.

In the classical case, the jump probabilities are constants, $P_j(r-j\delta r;t) = p_j \geq 0$ with $\sum_{j=-\infty}^{\infty} p_j = 1$, as is the reaction probability, $R\,(r;t) = p_R$ with $1 \geq p_R \geq 0$. We take into account the configurational complexity of the reactive medium by allowing for the possibility that both the jump probabilities and the reaction probability are modified by interaction between the particles. This is modeled by writing $P_j\,(r-j\delta r;t) = p_j\,F\,[c\,(r-j\delta r;t)]$, with $j \neq 0$ and $R\,(r;t) = p_R\,G\,[c\,(r;t)]$ giving the Generalized Master Equation

$$c\,(r;t+\delta t) - c\,(r;t) = \sum_{j=-\infty}^{+\infty} \left(p_j F\,[c\,(r-j\delta r;t)]\,(c\,(r-j\delta r;t) \;- c\,(r;t)\right)) - p_R\,G\,[c\,(r;t)]\;c(r;t)\,. \tag{5}$$

Notice that in order to retain their nature as probabilities, the functions $F\,[c]$ and $G\,[c]$ must both be greater than zero and less than one for all values of their arguments.

III. DIFFUSION AND REACTION

A. Generalized diffusion equation

Considering the diffusive process alone, it was shown [8] that the generalized diffusion equation that follows from Eq.(5) (without the second term on the $r.h.s$) is

$$\frac{\partial c}{\partial t}+C\frac{\partial}{\partial r}\left(xF\left(x,x\right)\right)_{c}=D\frac{\partial}{\partial r}\left(\frac{\partial xF\left(x,y\right)}{\partial x}-\frac{\partial xF\left(x,y\right)}{\partial y}\right)_{c}\frac{\partial c}{\partial r}$$
$$+\frac{C^{2}\delta t}{2}\frac{\partial}{\partial r}\left(\frac{\partial xF\left(x,y\right)}{\partial x}-\frac{\partial xF\left(x,y\right)}{\partial y}-\left(\frac{\partial xF\left(x,x\right)}{\partial x}\right)^{2}\right)_{c}\frac{\partial c}{\partial r}, \quad (6)$$

with the compact notation $(...)_c = (...)_{x=c(r,t),y=c(r,t)}$. Here $C = \left(\sum_j j\, p_j\right) \frac{\delta r}{\delta t}$ is the advection speed and $D = \left(\sum_j j^2 p_j\right) \frac{(\delta r)^2}{2\delta t}$ is the diffusion coefficient. In [8] it was also shown that the existence of a scaling solution $c\left(r;t\right) = t^{-\gamma/2}\phi\left(r/t^{\gamma/2}\right)$ demands that $F[c] \sim c^{\eta}$ in which case the scaling exponent is $\gamma = \frac{2}{2+\eta}$; since the jump probabilities $P_j = p_j F\left[c\right]$ must be ≤ 1, one must have $\eta > 0$, that is $\gamma < 1$, which is the signature of sub-diffusion [1]. We now combine the description of sub-diffusion (with no drift, i.e. $C = 0$ in (6)) with reactive processes.

B. Scaling reaction-diffusion

Starting from the generalized master equation (5), we proceed along the lines of derivation of the generalized diffusion equation given in [8]. Performing a multiple scale expansion up to second order, we obtain the general form of the reaction-diffusion (R-D) equation (with no drift and with reaction rate $k = p_R \frac{1}{\delta t}$):

$$\frac{\partial}{\partial t}c\left(r;t\right)=D\frac{\partial^{2}}{\partial r^{2}}\left(F[c\left(r;t\right)]c\left(r;t\right)\right)-\,k\,G[c\left(r;t\right)]\,c\left(r;t\right)\,. \quad (7)$$

As for the generalized diffusion equation [8], we ask under which conditions there is a scaling solution to equation (7) of the form $c\left(r;t\right) = t^{-\gamma/2}\phi\left(r/t^{\gamma/2}\right) = t^{-\gamma/2}\phi\left(x\right)$. Expressing the time and space derivatives in terms of x, Eq.(7) can be written as

$$-\gamma\frac{d}{dx}x\phi\left(x\right)=2\,Dt^{1-\gamma}\frac{d^{2}}{dx^{2}}F\left(t^{-\gamma/2}\phi\left(x\right)\right)\phi\left(x\right)-\,k\,t\,G\left(t^{-\gamma/2}\phi\left(x\right)\right)\phi\left(x\right)\,. \quad (8)$$

[1] The case of super-diffusion will be presented elsewhere.

The time-dependence on the right can only be eliminated if $F(c)$ and $G(c)$ have a functional power law form: $F(c) = c^{\alpha-1} = t^{(1-\alpha)\gamma/2}\,\phi^{\alpha-1}$ and $G(c) = c^{n-1} = t^{(1-n)\gamma/2}\,\phi^{n-1}$, for some numbers $\alpha \geq 1$ and $n \geq 1$; hence we must have $1 = t^{1-\gamma} t^{(1-\alpha)\,\gamma/2}$, and $1 = t\; t^{(1-n)\,\gamma/2}$, that is

$$\gamma = \frac{2}{\alpha+1}\ ; \quad n-1 = \frac{2}{\gamma}\ . \tag{9}$$

Thus, according to scaling consistency the exponents should be such that $n = \alpha + 2$. When $\alpha \neq 1$, we have anomalous diffusion: $\langle r^2 \rangle \sim t^{\frac{2}{\alpha+1}}$ (and more generally $\langle r^m \rangle \sim t^{\frac{m}{\alpha+1}}$), and the reaction term goes like $\sim -k\,\phi^n$. More explicitly, using in (8) the reduced variable

$$\zeta = x k^{-\gamma/2}\sqrt{\frac{k}{D}}\ , \tag{10}$$

we obtain the scaled equation

$$\frac{d^2}{d\zeta^2}\,\phi^{\alpha}(\zeta)\ +\ \frac{1}{\alpha+1}\frac{d}{d\zeta}(\zeta\,\phi(\zeta))\ -\ \phi^{n}(\zeta) = 0\,, \tag{11}$$

which can be rewritten in terms of the original variables (r and t) to give

$$\frac{\partial}{\partial t}c\,(r;t) = \frac{\partial}{\partial r}\ D\,\frac{\partial}{\partial r}c^{\alpha}\,(r;t) -\ kc^{n}\,(r;t)\ . \tag{12}$$

Without the reactive term, i.e. with $k = 0$, this reduces to our previous generalized diffusion equation in the absence of drift. Equation(12) is the generalized reaction-diffusion equation.

IV. STEADY-STATE DISTRIBUTIONS

In this Section we explore Eq.(12) as a natural extension of our previous description of generalized diffusion to include extinction. Because we are not solely interested in scaling solutions in this case, we will allow for arbitrary exponents α and n.

A. Boundary conditions

One frequently studied problem is that of a semi-infinite sytem with constant injection of particles at the boundary. To be specific, we use the interval $[0,\infty]$ and note that the rate of change of the total number of particles in is simply

$$\begin{aligned}\frac{dN\,(t)}{dt} &= n_s \int_0^{\infty} \frac{\partial c\,(r;t)}{\partial t} dr \\ &= Dn_s\,\left.\frac{\partial c^{\alpha}\,(r;t)}{\partial r}\right|_{r\to\infty} - Dn_s\,\left.\frac{\partial c^{\alpha}\,(r;t)}{\partial r}\right|_{r=0} - kn_s \int_0^{\infty} \frac{\partial c^{n}\,(r;t)}{\partial t} dr\,.\end{aligned} \tag{13}$$

The first term on the right is the rate at which matter leaves the system via the boundary at infinity: we will assume that the concentration goes to zero sufficiently fast at infinity so that this term is zero - an assumption that will have to be checked a posteriori. The second term on the right is the rate at which particles are injected at the left boundary and the last term is the rate at which particles are removed by the extinction process. Our boundary condition will be to control the rate at which particles are injected so we set

$$\left(\frac{dN(t)}{dt}\right)_{in} \equiv j_0 = -Dn_s \left.\frac{\partial c^\alpha(r;t)}{\partial r}\right|_{r=0} \tag{14}$$

as the boundary condition of interest.

B. Steady-state solution

We now seek a steady state solution with this boundary condition,

$$0 = D\frac{\partial^2}{\partial r^2}c^\alpha(r) - kc^n(r) \qquad \text{with} \qquad -Dn_s \left.\frac{\partial c^\alpha(r)}{\partial r}\right|_{r=0} = j_0. \tag{15}$$

It is convenient to rewrite the problem with the change of variables

$$r \to z = \sqrt{\frac{k}{D}}r \quad ; \quad j_0 \to j_0^* = \frac{j_0}{n_s\sqrt{kD}}, \quad ; \quad c \to g = c^\alpha \tag{16}$$

so that the steady state equation has the simple form

$$\frac{\partial^2}{\partial z^2}g(z) = g^{\frac{n}{\alpha}}(z) \qquad \text{with} \qquad \left.\frac{\partial g(z)}{\partial z}\right|_{z=0} = -j_0^*. \tag{17}$$

This is integrated to get

$$\frac{dg(z)}{dz} = \pm\sqrt{A + \frac{2\,\alpha}{\alpha+n}g^{\frac{\alpha+n}{\alpha}}(z)}. \tag{18}$$

Recall that we assumed that the flux at infinity goes to zero. This means that either $A = 0$ and $\lim_{z\to\infty} g(z) = 0$ or that $A < 0$ and $\lim_{z\to\infty} g(z)$ is finite . We rule out the latter case on the ground that without extinction we should get purely diffusive behavior and that adding extinction should not cause an increase in particles far from the source.

A second integration then gives the implicit solution

$$\pm z = \int_0^z \frac{dg}{\sqrt{\frac{2\alpha}{\alpha+n}g^{\frac{\alpha+n}{\alpha}}}} = \sqrt{\frac{\alpha+n}{2\alpha}}\frac{2\alpha}{\alpha-n}\left(g^{\frac{\alpha-n}{2\alpha}}(z) - g^{\frac{\alpha-n}{2\alpha}}(0)\right), \tag{19}$$

or, upon rearrangement,

$$g(z) = g(0)\left(1 \pm g^{-\frac{\alpha-n}{2\alpha}}(0)\,\frac{\alpha-n}{2\alpha}\sqrt{\frac{2\alpha}{\alpha+n}}z\right)^{\frac{2\alpha}{\alpha-n}} . \tag{20}$$

The boundary condition is

$$j_0^* = -\left.\frac{dg}{dz}\right|_{z=0} = \mp\sqrt{\frac{2\,\alpha}{\alpha+n}}\,g^{\frac{\alpha+n}{2\alpha}}(0)\,. \tag{21}$$

Since we are interested in the circumstance that the injection rate is positive we must take the lower sign so

$$g(z) = \left(j_0^*\sqrt{\frac{\alpha+n}{2\alpha}}\right)^{\frac{2\alpha}{\alpha+n}}\left(1-\frac{\alpha-n}{2}\frac{z}{z_0}\right)^{\frac{2\alpha}{\alpha-n}} , \quad z_0 = \alpha {j_0^*}^{\frac{\alpha-n}{\alpha+n}}\left(\frac{\alpha+n}{2\alpha}\right)^{\frac{\alpha}{n+\alpha}} , \tag{22}$$

or, rewriting the result in terms of the physical variables,

$$c(r) = \left(j_0^*\sqrt{\frac{\alpha+n}{2\alpha}}\right)^{\frac{2}{\alpha+n}}\left(1-\frac{\alpha-n}{2}\frac{r}{r_0}\right)^{\frac{2}{\alpha-n}} , \quad r_0 = \alpha {j_0^*}^{\frac{\alpha-n}{\alpha+n}}\left(\frac{\alpha+n}{2\alpha}\right)^{\frac{\alpha}{n+\alpha}}\sqrt{\frac{D}{k}}\,. \tag{23}$$

There are two cases that must be distinguished depending on whether $n > \alpha$ or $\alpha > n$. In the first case the solution has *infinite support* and is a simple algebraic decay

$$c(r) = \left(j_0^*\sqrt{\frac{\alpha+n}{2\alpha}}\right)^{\frac{2}{\alpha+n}}\left(1+\frac{n-\alpha}{2}\frac{r}{r_0}\right)^{-\frac{2}{n-\alpha}} , \quad n > \alpha\,. \tag{24}$$

The second, more complicated case occurs when $\alpha > n$. Then it is clear from Eq.(23) that the concentration will, in general become imaginary and in all cases its magnitude will increase without bound for sufficiently large r. The only way to avoid this unphysical behavior is if the solution has *finite support* so that

$$c(r) = \left(j_0^*\sqrt{\frac{\alpha+n}{2\alpha}}\right)^{\frac{2}{\alpha+n}}\left(1-\frac{\alpha-n}{2}\frac{r}{r_0}\right)^{\frac{2}{\alpha-n}}\Theta\left(\frac{2}{\alpha-n}r_0 - r\right) , \quad \alpha > n\,, \tag{25}$$

where the step function $\Theta(x) = 1$ for $x > 0$ and zero otherwise. Noting that

$$\begin{aligned} \frac{d}{dx}f(x)\,\Theta(x) &= f'(x)\,\Theta(x) + f(0)\,\delta(x)\,, \\ \frac{d^2}{dx^2}f(x)\,\Theta(x) &= f''(x)\,\Theta(x) + f'(0)\,\delta(x) + f(0)\,\delta'(x)\,, \end{aligned}$$

it is clear that (25) can only be an acceptable solution to the steady state equation (15) if the first two derivatives of the coefficient of the step function vanish at $r = \frac{2\,r_0}{\alpha-n}$. This simply imposes the requirement on the exponent that $\frac{2\alpha}{\alpha-n}-2>0$ which is always true provided that $n>0$, as was already required. Thus, the final, physically valid solution with finite support (25) is restricted to a narrow range of values of the coefficient $\alpha>n>0$.

We note that the solutions (24) and (25) can be expressed as q-exponentials, $e_q(x)=(1+(1-q)x)^{\frac{1}{1-q}}\ \Theta(1+(1-q)x)$ with the identification $q=\frac{n-\alpha}{2}+1$ and that $q>1$ gives the case of infinite support while $1>q$ gives the case of finite support. From the properties of the q-exponential we know that for $q=1$ the decay of the concentration will be expontial, $c(r)=(j_0^*)^{\frac{1}{\alpha}}\ e^{-r/r_0}$ with $r_0=\alpha\sqrt{\frac{D}{k}}$. This of course includes the steady state solution of the classical reaction-diffusion equation with $\alpha=n=1$.

The physical interpretation of these results can be understood as follows: increasing n decreases the extinction rate (since the reaction term goes like c^n and $c<1$) while increasing α decreases the rate of diffusion (this is easily seen from the scaling $r\sim t^{\gamma/2}$ or by writing the diffusion term as $\frac{\partial}{\partial r}D\frac{\partial c^\alpha}{\partial r}=\frac{\partial}{\partial r}\left(\alpha\, Dc^{\alpha-1}\right)\frac{\partial c}{\partial r}$, so the effective diffusion coefficient goes like $c^{\alpha-1}$). Hence, making n large or α small leads to infinite support: diffusion is fast, extinction is slow. The converse, making n small or α large leads to finite support because diffusion is slow and extinction is fast. The resulting steady state profiles are compared in Fig. 1.

C. Robustness of the steady state

The question of robustness is an important issue as discussed by Eldar et al. [9] and by Yuste et al. [3] in particular for morphogen gradient formation as precursor to cell differentiation. Robustness is a measure of the strength of the steady state profile versus changes in the variables controlling input flux and degradation, such as j_0 and k. The cited authors characterized it as the quantity $\mathcal{R}_b=d\,|\partial L/\partial\log b|^{-1}$ where d is a characteristic microscopic length (e.g. the cell size) and b denotes j_0 or k; L is the distance at which the steady state $c(r)$ takes a given value and is obtained by inversion of the steady state solution $c(r)_{r=L}$. A high value of $\mathcal{R}_b$ is an indication of the buffering capacity against changes in the input flux and degradation rate. Here, however, we prefer to consider directly the relative change in the concentration at point r due to a change in the value of quantity b, thereby defining the (position-dependent) *sensitivity* to parameter b as

$$\mathcal{S}_b(r)=\frac{\partial\log c(r)}{\partial\log b}\,. \tag{26}$$

For $n > \alpha$, the case of infinite support, a short calculation gives the sensitivity as

$$\mathcal{S}_{j_0}(r) = \frac{2}{\alpha + n}\frac{1}{1 + \frac{n-\alpha}{2}\frac{r}{r_0}} \quad ; \quad n \geq \alpha, \tag{27}$$

and for $n = \alpha = 1$, i.e in the classical case of exponential decay, this becomes

$$\mathcal{S}_{j_0}(r) = 1 \quad ; \quad n = \alpha = 1, \tag{28}$$

which we will take as a reference point. One also gets exponential decay for the more general condition $n = \alpha$ (see section IV B), but in this case we find

$$\mathcal{S}_{j_0}(r) = \frac{1}{n} \quad ; \quad n = \alpha, \tag{29}$$

so that even though the decay is exponential, it is nevertheless true that increasing the nonlinearity of the process decreases the sensitivity of the concentration to variations in the injection rate. Note that the general result for infinite support is bounded by

$$\mathcal{S}_{j_0}(r) \leq \frac{2}{\alpha + n} \quad ; \quad n \geq \alpha, \tag{30}$$

so that - independent of position - increasing nonlinearity in either the diffusion process or in the extinction process has the effect of buffering the concentration against changes in the rate at which material is injected.

The case of finite support, $\alpha < n$, is more complicated. A simple calculation gives

$$\mathcal{S}_{j_0}(r) = \frac{1}{1 - \frac{\alpha-n}{2}\frac{r}{r_0}}\frac{2}{\alpha + n} \quad ; \quad \alpha > n, \tag{31}$$

so that there are two effects at work: decreasing sensitivity with increasing nonlinearity, as above, and increasing sensitivity with increasing distance from the source. In fact, in this case we find

$$\mathcal{S}_{j_0}(r) > 1 \Longleftrightarrow r > r_* \equiv \frac{2}{\alpha - n}\left(1 - \frac{2}{\alpha + n}\right) r_0. \tag{32}$$

Clearly, this is only relevant if the right hand side is less than r_0. For $n < 1$, this is always the case: i.e., there is always a region of enhanced sensitivity in the range $r_* < r < r_0$. For $n > 1$, there is a region of enhanced sensitivity for

$$\alpha > \alpha_* \equiv 1 + \sqrt{(n-1)(n+3)} = n + 2 - \frac{2}{n} + ... \quad ; \quad \alpha > n > 1. \tag{33}$$

Only for the restricted range $\alpha_* > \alpha > n > 1$ is there no region of enhanced sensitivity for the case of finite support.

In summary, we find that (i) for infinite support, $n \geq \alpha$, increasing nonlinearity *always* decreases sensitivity of the concentration to the injection rate; (ii) the same holds true for the case of finite support when $\alpha_* > \alpha > n > 1$; (iii) the case of finite support will, for $n < 1$ or $\alpha > \alpha_*$ show enhanced sensitivity in the region $r_* < r < r_0$.

V. COMPARISON TO SIMULATION AND EXPERIMENT

A. Numerical solution of master equation

We have performed numerical computation of the master equation (5) in order to verify three aspects of this theory: first, that the non-linear dynamics eventually leads to a steady state; second, that the steady state is independent of the initial conditions and third, that our analytic, continuum result is a good representation of the steady state. Figure 2 shows the result of solving the master equation with an initial condition $c(r) = 0$ and with constant flux at the origin for two cases: one with finite support, $n < \alpha$, and one with infinite support, $n > \alpha$. In both cases, we do indeed find that at long times the system settles into a steady state that is well-described by the analytic results, (24) and (25). Note that, in the case of infinite support, one must go to somewhat longer times to reach the steady state. To test that the sensitivity of the steady state to the boundary conditions, the calculations were repeated with a boundary condition of fixed value of the concentration at $r = 0$. The result for the case of finite support is shown in Fig. 3 where it is again seen that the system reaches a steady state and that the steady state is that of the continuum theory. Similar results were found for the case of infinite support. This comparison of numerical and analytical results therefore shows good agreement between the continuum approximation and the discrete microscopic dynamics and furthermore provides evidence that the steady state is unique.

B. Comparison to experiment

As an application of the theory we compare our analytical solution for the steady state with experimental results obtained from measurements performed in the *Drosophila* wing disc where morphogens are produced by a subset of cells wherefrom they diffuse and are degraded thereby forming a concentration gradient whose profile shape appears crucial for subsequent cell specification [9]. This situation corresponds to the reaction-diffusion theory

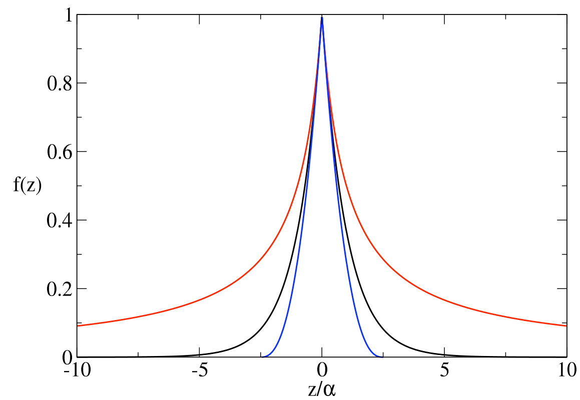

FIG. 1. Steady state: $c(r)/c(0) = \exp\left(-r/r_0\right)$ ($q = 1$; black); $c(r)/c(0) = \left(1 + \frac{n-\alpha}{2}\frac{r}{r_0}\right)^{-\frac{2}{n-\alpha}}$ for $n = \alpha + 2$ (infinite support, $q = 2$; red) and $\alpha = n + 0.8$ (finite support, $q = 0.6$; blue).

presented in the present article. Experimental results given in [10] present the intensity signal of the Wg morphogen as a function of distance from the source obtained by image processing showing the profile of the diffusing protein in selected regions of the *Drosophila* wing disc. In the absence of numerical data, we processed the signal images to obtain the data shown in Figs. 4 and 5 where they are compared to our analytical results. Clearly we find that the sub-diffusive nonlinear reactive steady state profile (24) with infinite support reproduces very well the experimental data indicating slow degradation combined with extended sub-diffusion. In all cases, we also show best-fits to an exponential of the form $f(z) = Ae^{(-B|z|)}$ and it is clear that the experimental data are very poorly fit by an exponential decay.

VI. COMMENTS

We derived the nonlinear reaction-diffusion equation starting from Einstein's microscopic model where the diffusing particles are also subject to an annihilation reactive process. The nonlinear reaction-diffusion equation was obtained under the demand that scaling be satisfied for diffusive motion wherefrom a relation follows between the scaling exponent and the nonlinear exponents whose range of possible values exhibit the signature of sub-diffusion. While full scaling should in principle be satisfied for the space-time dependent equation, this requirement can be relaxed between the reaction term exponent and the scaling exponent for the steady state equation. This observation is important for the analysis of the R-D

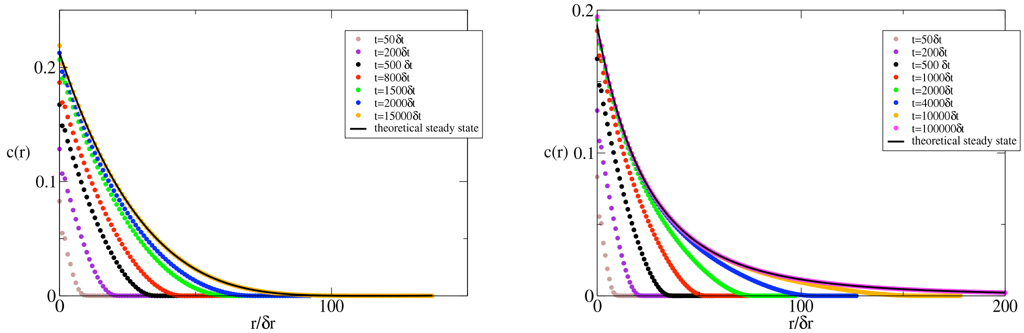

FIG. 2. Numerical and analytical solutions for the steady state profile. Left panel: Case of finite support. Numerical solution of the Master Equation (5) where $p_j\, F = p_j\, c_j^{\alpha-1}$ with $p_j = 0.2$ for $j \in [-2, +2]$ and $\alpha = 1.5$ and $G = p_R\, c^n$ with $n = 1$ and $p_R = 10^{-3}$, for $t = 50, 200, 500, 800, 1.5 \times 10^3, 2 \times 10^3, 1.5 \times 10^4$ time steps (symbols); the boundary condition is finite flux at $r = 0$ and the initial condition is zero concentration everywhere. Analytical steady state solution (25) (black curve). Right panel : Case of infinte support. Same as left panel except $n = 2$ and $p_R = 10^{-2}$, for $t = 50, 200, 500, 10^3, 2 \times 10^3, 4 \times 10^3, 10^4, 1 \times 10^5$ time steps (symbols) and steady state solution (24) (black curve). Note that there are no adjustable parameters in either case.

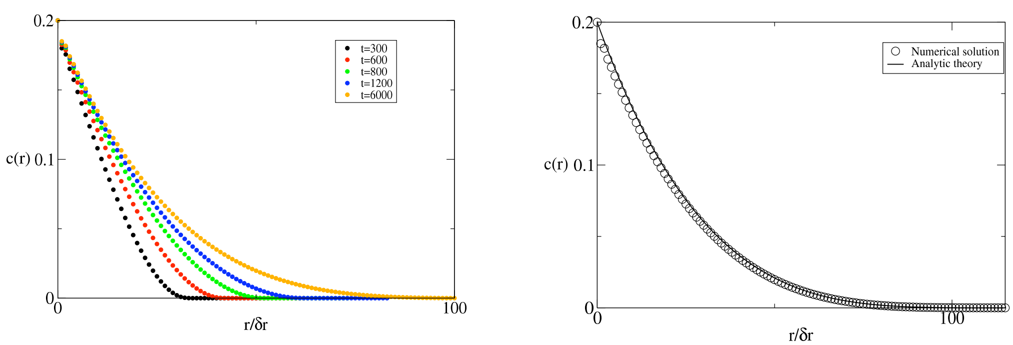

FIG. 3. Numerical and analytical solutions for finite support profile ($n < \alpha$) with boundary condition of fixed $c(0)$. Left panel: Numerical solution of the Master Equation (5) where $p_j\, F = p_j\, c_j^{\alpha-1}$ with $p_j = 0.2$ for $j = [-2, +2]$ and $\alpha = 1.5$ and $G = p_R\, c^n$ with $n = 1$ and $p_R = 10^{-3}$, for $t = 3\times10^2, 6\times10^2, 8\times10^2, 1.2\times10^3, 6\times10^3$ time steps. Right panel: Comparison between numerical solution of the Master Equation (5) for $t = 6 \times 10^3$ time steps (open circles) and analytical steady state solution (25) (black curve). Note that there are no adjustable parameters.

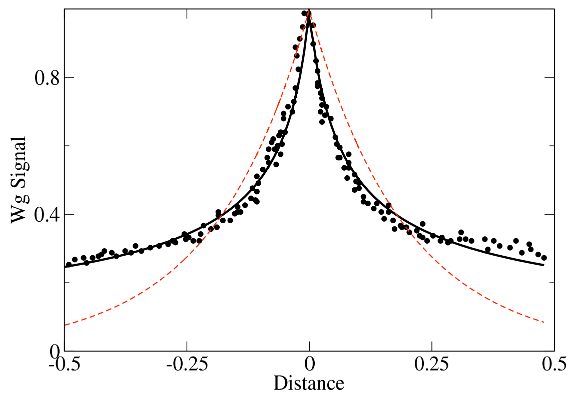

FIG. 4. Experimental data (black dots) from Han *et al*, Fig.6.A in [10] ; best-fit to the theoretical steady state (24) with $n - \alpha \simeq 4$ (black curve). The horizontal axis shows the distance (in a.u.) from the anterior-posterior axis along the dorsoventral direction in the anterior compartment of the wing disc [10]. For comparison the dashed curve shows the best-fit exponential profile.

steady state solutions which take the form of a power law with in one case infinite support and in the other case finite support.

We discussed the sensitivity of the steady state versus changes in the input flux and we found that profiles with infinite support show minimal sensitivity, and such profiles with infinite support were shown to correspond to experimental observations. On the other hand we showed that profiles with finite support should exhibit stronger sensitivity to input flux changes, and it seems that such profiles with finite support have not been observed in morphogen gradient formation. This observation may suggest that extreme sensitivity excludes this type of profile in natural morphogen gradient formation because degradation is too fast with respect to diffusion in order to establish the necessary gradient for subsequent cell differentiation.

ACKNOWLEDGMENTS

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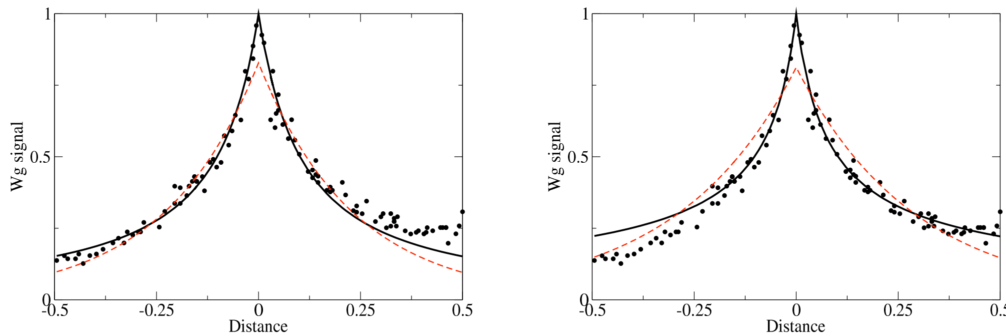

FIG. 5. Fit of theoretical steady state (24) to experimental data (black dots) from Han *et al*, Fig.6.B in [10]. Axes defined as in Fig.4. Because of the obvious asymetry of the data along the dorsoventral axis, the left panel shows a fit based only on the data for negative distances, giving $n - \alpha \simeq 3.3$, and the right panel shows a fit to data for positive distances, giving $n - \alpha \simeq 1.7$. In both cases, a best-fit to an exponential decay is shown as the dashed curves.

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