Nonlinear Fractional PDE's and Their Applications in Biology

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The standard models for the description of anomalous subdiffusive transport of particles are linear fractional equations. The question arises as to how to extend these equations for the nonlinear case involving particles interactions. The talk will be concerned with the structural instability of fractional subdiffusive equations and nonlinear aggregation phenomenon.

Workshop on Future Directions in Fractional Calculus Research and Applications

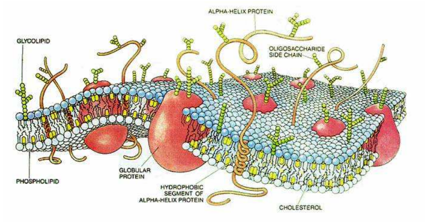
Plan de la présentation

1. INTRODUCTION
2. NONLINEAR FRACTIONAL PDE's
   - Subdiffusive Fokker-Planck equation with space dependent anomalous exponent
   - Subdiffusion of morphogens, degradation enhanced diffusion
   - Self-organized anomaly (SOA)
   - Nonlinear subdiffusive fractional PDE's
   - Subdiffusive and superdiffusive transport in two-state systems

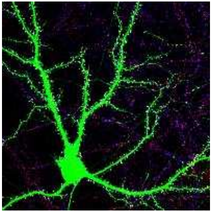
Anomalous subdiffusion: $< X^2(t) > \sim t^{\mu} \qquad 0 < \mu < 1$

Biology contains a wealth of subdiffusive phenomena:

- Transport of proteins and lipids on cell membranes (Saxton, Kusumi)



- Transport of signaling molecules in a neuron with spiny dendrites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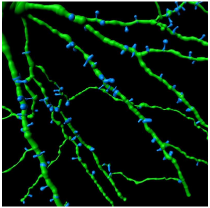

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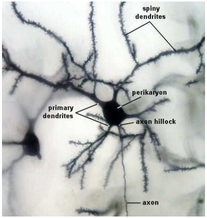
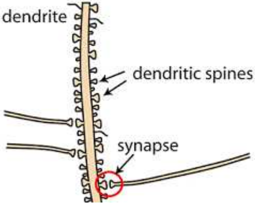
- Subdiffusion is due to trapping inside dendritic spines





Non-Markovian behavior of particles performing random walk occurs when particles are trapped during the random time with non-exponential distribution.

Power law waiting time distribution

$$\phi(t) \sim \frac{1}{t^{1+\mu}}$$

with $0 < \mu < 1$ as $t \to \infty$.

The mean waiting time is infinite.

Subdiffusive Fractional Fokker-Planck (FFP) Equation

Let $p(x,t)$ be the PDF for finding the particle in the interval $(x, x+dx)$ at time t, then

$$\frac{\partial p}{\partial t} = -\frac{\partial \left(v_\mu(x) \mathcal{D}_t^{1-\mu} p \right)}{\partial x} + \frac{\partial^2 \left(D_\mu(x) \mathcal{D}_t^{1-\mu} p \right)}{\partial x^2} \quad (1)$$

with the fractional diffusion $D_\mu(x)$ and drift $v_\mu(x)$; $\mu < 1$.

The Riemann-Liouville derivative $\mathcal{D}_t^{1-\mu}$ is defined as

$$\mathcal{D}_t^{1-\mu} p\,(x,t) = \frac{1}{\Gamma(\mu)} \frac{\partial}{\partial t} \int_0^t \frac{p\,(x,u)\,du}{(t-u)^{1-\mu}} \quad (2)$$

The difference between standard Fokker-Planck equation and FFP equation is the rate of relaxation of

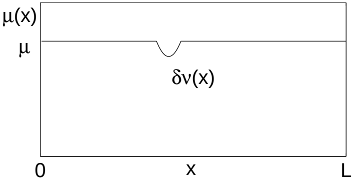
$$p\,(x,t) \to p_{st}(x)$$

.

Fractional Fokker-Planck (FFP) equation

Subdiffusive fractional equations with constant μ in a bounded domain $[0, L]$ are not structurally stable with respect to the non-homogeneous variations of parameter μ.

$$\mu(x) = \mu + \delta\nu(x) \tag{3}$$



The space variations of the anomalous exponent lead to a drastic change in asymptotic behavior of $p(x, t)$ for large t.
S. Fedotov and S. Falconer, Phys. Rev. E, 85, 031132, 2012

Monte Carlo simulations

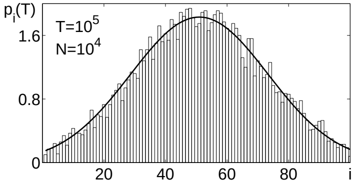


Figure : Long time limit of the solution to the system with $\mu_i = 0.5$ for all i. Gibbs-Boltzmann distribution is represented by the line.

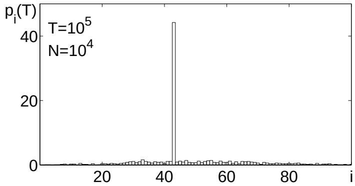


Figure : The parameters are $\mu_i = 0.5$ for all i except $i = 42$ for which $\mu_{42} = 0.3$.

Anomalous chemotaxis and aggregation

Mean field density:

$$\rho\,(x,t) \to \delta(x - x_M) \qquad as \qquad t \to \infty. \tag{4}$$

It means that all cells aggregate (very slow) into a tiny region of space forming high density system at the point $x = x_{M.}$ This phenomenon can be referred to as anomalous aggregation (S Fedotov, PRE 83, 021110 (2011)).

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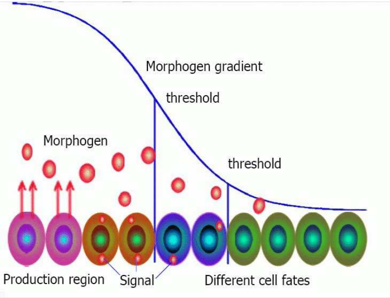
Typical nonlinear effects:
1) quorum sensing phenomenon: biophysical processes in microorganisms depend on the their local population density.
2) cellular adhesion which involves the interaction between neighbouring cells
3) volume-filling effect which describes the dependence of cell motility on the availability of space in a crowded environment .
P. Straka and S. Fedotov (2015), Transport equations for subdiffusion with nonlinear particle interation, J. Theor. Biology 366, 71-83

Kinetics of morphogen gradient formation

Random morphogen molecules movement. Molecules are produced at the boundary $x = 0$ of infinite domain $[0, \infty)$ at the given constant rate g and perform the classical random walk involving the symmetrical random jumps of length a and the random residence time T_x between jumps.

$$\frac{\partial \rho}{\partial t} = D \frac{\partial^2 \rho}{\partial x^2} - \theta(\rho)\rho, \tag{5}$$

where $\theta(\rho)$ is the non-linear degradation rate.



Self-enhanced degradation and subdiffusion of morphogens

Nonlinear reaction-subdiffusion equation for the mean density of morphogen molecules:

$$\frac{\partial \rho}{\partial t} = D_\mu \frac{\partial^2}{\partial x^2}\left[e^{-\int_0^t \theta(\rho)ds}\mathcal{D}_t^{1-\mu}\left[e^{\int_0^t \theta(\rho)ds}\rho(x,t)\right]\right] - \theta(\rho)\rho, \qquad (6)$$

where $\theta(\rho)$ is the "self-enhanced degradation" rate.

NON-LINEAR CASE: Fedotov, Falconer, Phys. Rev. E (2014)

The degradation rate leads to the natural non-linear tempering of the subdiffusion and, as a result, to the transition to a seemingly normal diffusion regime. However, this may lead to a wrong conclusion in analyses of experimental results on transient subdiffusion that the process is normal for large times.

Degradation enhanced diffusion

We find that in the subdiffusive case, a self-enhanced degradation of morphogen leads directly to a degradation enhanced diffusion.

• The main result is that in the long time limit the gradient profile can be found from the nonlinear stationary equation for which the diffusion coefficient is a nonlinear function of the nonlinear reaction rate.

$$\frac{d^2}{dx^2}\left(D_\theta(\rho_{st})\rho_{st}\right) = \theta(\rho_{st})\rho_{st}. \tag{7}$$

where the diffusion coefficient D_θ is

$$D_\theta(\rho_{st}) = \frac{a^2\left[\theta(\rho_{st})\right]^{1-\mu}}{2\tau_0{}^{\mu}}. \tag{8}$$

This unusual form of nonlinear diffusion coefficient is a result of the interaction between subdiffusion and nonlinearity.

Fedotov, Korabel, Phys. Rev. E (2015)

Self-organized anomaly (aggregation) of particles performing nonlinear and non-Markovian random walk

We model the escape rate $\mathbb{T}$ as a decreasing function of the density $\rho(x, t)$

$$\mathbb{T}(\tau, \rho) = \frac{\mu(\tau)}{1 + A\rho(x, t)}, \tag{9}$$

This nonlinear function describes the phenomenon of conspecific attraction: the rate at which individuals emigrate from the point x is reduced due to the presence of many conspecifics.

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The rate parameter $\mu(\tau)$ is a decreasing function of the residence time (negative aging):

$$\mu(\tau) = \frac{\mu_0}{\tau_0 + \tau}, \tag{10}$$

where μ_0 and τ_0 are positive parameters. This particular choice of the rate parameter $\mu(\tau)$ has been motivated by non-Markovian crowding: the longer the living organisms stay in a particular site, the smaller becomes the escape probability to another site.

Self-organized anomaly

Let me remind you that self-organized criticality (SOC) is a property of a dynamical system that has a critical point as an attractor. It displays the spatio-temporal scale-invariance characteristic of the critical point of a phase transition, but without the need to tune control parameters to precise values.

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What about self-organized anomaly ?

Can we set up the dynamical system for which the anomalous regime is self-organized and arises spontaneously without the need for a heavy tailed waiting time distribution with an infinite mean time from the inception?

We formulate a nonlinear and non-Markovian continuous time random walk model. Instead of the waiting time probability density function (PDF) we use the escape rate $\mathbb{T}(\tau, \rho)$ that depends on the residence time τ and the density of particles ρ.. Our intention is to take into account nonlinear social crowding effects and non-Markovian negative aging.

Nonlinear Escape Rate

We assume that the probability of escape due to the repulsive forces during a small time interval Δt is

$$\alpha(\rho(x,t))\Delta t + o(\Delta t), \tag{11}$$

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The effective transition rate is the sum of two escape rates:

$$\gamma(x, \tau) + \alpha(\rho(x, t)), \tag{12}$$

where the anomalous escape rate $\gamma(x, \tau)$ can be written in terms of the PDF of residence time $\psi(x, \tau)$ and the survival probability $\Psi(x, \tau) = \int_t^\infty \psi(x, u)du$ as follows

$$\gamma(x, \tau) = \frac{\psi(x, \tau)}{\Psi(x, \tau)}. \tag{13}$$

Note that $\alpha(\rho(x, t))$ can be considered as a death rate.

Nonlinear Subdiffusive Fractional PDE

Nonlinear fractional Fokker-Planck equation

$$\frac{\partial \rho}{\partial t} = -\beta a^2 \frac{\partial}{\partial x}\left[\frac{\partial U}{\partial x}\left(\frac{e^{-\Phi}}{\tau_0{}^{\mu(x)}}\mathcal{D}_t^{1-\mu(x)}[e^{\Phi}\rho] + \alpha(\rho)\rho\right)\right]$$
$$+ a^2 \frac{\partial^2}{\partial x^2}\left[\frac{e^{-\Phi}}{2\tau_0{}^{\mu(x)}}\mathcal{D}_t^{1-\mu(x)}[e^{\Phi}\rho] + \alpha(\rho)\rho\right], \quad (14)$$

where

$$\Phi(x,t) = \int_0^t \alpha(\rho(x,s))\, ds. \quad (15)$$

This equation describes the transition from subdiffusive transport to asymptotic normal advection-diffusion transport.

At lower values of $\Phi = \int_0^t \alpha(\rho(x,s))ds$, the early evolution is the development of a single peak at the point of the minimum of $\mu(x)$. (anomalous aggregation).

Nonlinear Fokker-Planck equation

Incorporating the escape rate $\alpha(\rho)$ and the nonlinear tempering factor $e^{-\Phi}$ provide a regularization of anomalous aggregation.
In the long-time limit for sufficiently large Φ the density profile $\rho(x,t)$ must converge to a stationary solution of a nonlinear Fokker-Planck equation

$$\frac{\partial}{\partial x}\left[2\beta\frac{\partial U}{\partial x}D(\rho_{st})\,\rho_{st}(x)\right]=\frac{\partial^2}{\partial x^2}\left[D(\rho_{st})\,\rho_{st}(x)\right], \tag{16}$$

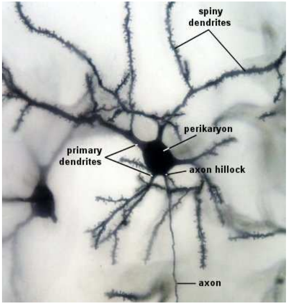
where $D(\rho_{st}(x))$ is the nonlinear diffusion coefficient defined as

$$D(\rho_{st}(x))=\frac{a^2\left[\alpha(\rho_{st}(x))\right]^{1-\mu(x)}}{2\tau_0^{\mu(x)}}.$$

S Fedotov, Phys. Rev. E 88, 032104 (2013)
Applications: (1) the problem of morphogen gradient formation, (2) chemical reactions with subdiffusion;

Transport in a Two-State System

• Switching between passive diffusion and active intracellular transport (Bressloff, Newby, 2013);
• Virus trafficking (Brandenburg and Zhuang, 2007; Holcman, 2007). Transport in crowded cytoplasm involves two states: slow diffusion and ballistic movement along microtubules;
• Protein search for DNA binding site (Berg et al 1981, Mirny et al., 2009). Transport involves 3-D diffusion and 1-D diffusion along DNA
• Transport in spiny dendrites(Santamaria, 2006):



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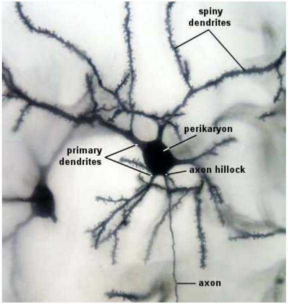

Anomalous Transport and Nonlinear Reactions in Two-State Systems

Two-state Markovian random process: we assume that the transition probabilities γ_1 and γ_2 are constants.

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Master equations for the mean density of particles in state 1 (mobile), $\rho_1(x,t)$, and the density of particles in state 2 (immobile), $\rho_2(x,t)$, are

$$\frac{\partial \rho_1}{\partial t} = L_x \rho_1 - \gamma_1 \rho_1 + \gamma_2 \rho_2, \tag{17}$$

$$\frac{\partial \rho_2}{\partial t} = -r_2\left(\rho_2\right)\rho_2 - \gamma_2 \rho_2 + \gamma_1 \rho_1, \tag{18}$$

where the reaction rate $r_2\left(\rho_2\right)$ depends on the local density of particles ρ_2. Here L_x is the transport operator acting on x-coordinate.

Non-Markovian model for the transport and reactions of particles in two-state systems

Nonlinear Master equations:

$$\frac{\partial \rho_1}{\partial t} = L_x \rho_1 - i_1(x,t) + i_2(x,t), \tag{19}$$

$$\frac{\partial \rho_2}{\partial t} = -r_2\left(\rho_2\right)\rho_2 - i_2(x,t) + i_1(x,t), \tag{20}$$

where the densities $i_1(x,t)$ and $i_2(x,t)$ describe the exchange flux of particles:

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where the densities $i_1(x,t)$ and $i_2(x,t)$ describe the exchange flux of particles:

$$i_1(x,t) = \int_0^t \int_{\mathbb{R}} K_1(t-t') p(x-z, t-t') \rho_1(z,t') dz dt', \tag{21}$$

$$i_2(x,t) = \int_0^t K_2(t-t') \rho_2(x,t') e^{-\int_{t'}^{t} r_2(\rho_2(x,s)) ds} dt', \tag{22}$$

where $K_i(t)$ is the memory kernel defined as $\tilde{K}_i(s) = \frac{\tilde{\psi}_i(s)}{\tilde{\Psi}_i(s)}$.

Single integro-differential wave equation for Lévy walk

We solved a long-standing problem of a derivation of the single integro-differential wave equation for the probability density function of the position of a classical one-dimensional Lévy walk:

$$\frac{\partial^2 p}{\partial t^2} - v^2 \frac{\partial^2 p}{\partial x^2} + \int_0^t \int_V K(\tau)\, \varphi(u) \left(\frac{\partial}{\partial t} - u \frac{\partial}{\partial x} \right) \times$$

$$p(x - u\tau, t - \tau)\, du d\tau = 0, \tag{23}$$

where v is a constant speed of walker, $\varphi(u)$ is the velocity jump density:

$$\varphi(u) = \frac{1}{2}\delta(u - v) + \frac{1}{2}\delta(u + v) \tag{24}$$

in the velocity space V. The standard memory kernel $K(\tau)$ is determined by its Laplace transform $\hat{K}(s) = \hat{\psi}(s)/\hat{\Psi}(s)$, where $\hat{\psi}(s)$ and $\hat{\Psi}(s)$ are the Laplace transforms of the running time density $\psi(\tau)$ and the survival function $\Psi(\tau)$.

MANCHESTER "ANOMALOUS" TEAM