Random walk models and nonlinear fractional subdiffusive equations: applications in physics and biology".

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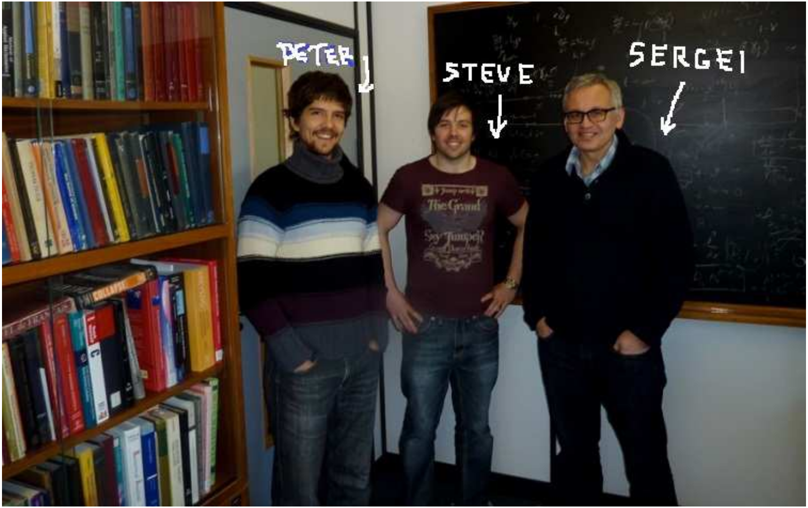
The standard models for the description of anomalous subdiffusive transport of particles are linear fractional equations. The question arises as to how to extend these equations for the nonlinear case involving particles interactions. The talk will be concerned with the structural instability of fractional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

Model reduction across disciplines. The conference is dedicated to the 60th birthday of Alexander Gorban

MANCHESTER "ANOMALOUS" TEAM

Collaboration with Steven Falconer and Peter Straka



Plan de la présentation

1. INTRODUCTION
2. NONLINEAR FRACTIONAL PDE's
   - Subdiffusive Fokker-Planck equation with space dependent anomalous exponent
   - Nonlinear fractional PDE's: nonlinear escape rate
   - Subdiffusive transport in two-state systems

Reaction-Advection-Diffusion Equation for Density ρ

Let $\rho(x,t)$ represent the density of particles at point x and time t.

- Reaction-advection-diffusion PDE:

$$\frac{\partial \rho}{\partial t} + v(x,t) \cdot \nabla \rho = D\Delta\rho + r(\rho)\rho, \qquad x \in \mathbb{R}^3$$

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• Fractional PDE with anomalous transport (Levy flights, subdiffusion, etc.):

$$\tau_\alpha D_t^\mu \rho = -D_\alpha (-\Delta)^{\frac{\alpha}{2}} \rho + r(\rho)\rho, \qquad x \in \mathbb{R}^3$$

where $D_t^\mu \rho$ is the Caputo derivative and the Laplacian Δ is replaced by a Riesz fractional operator: $-(-\Delta)^{\frac{\alpha}{2}}$.

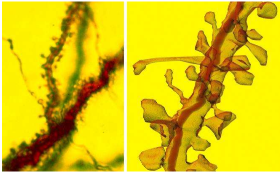
Anomalous transport: subdiffusion

Subdiffusion:

$$\mathbb{E}X^2(t) \sim t^\mu \qquad 0 < \mu < 1$$

Biology contains a wealth of subdiffusive phenomena:

1) transport of proteins and lipids on cell membranes (Saxton, Kusumi)
2) RNA molecules in the cells (Golding, Cox)
3) signaling molecules in spiny dendrites (Santamaria)



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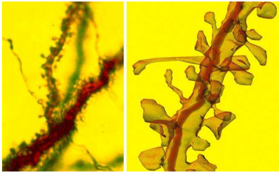

Apart from fractional Brownian motion, the *linear* fractional equations are the standard models for subdiffusive transport. In these models the diffusing particles do not interact. The question then arises as to how to extend these equations for the *nonlinear* case, involving particles interactions.

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

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

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

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

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

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

.

Gibbs-Boltzmann distribution

In the anomalous subdiffusive case the relaxation process is very slow and it is described by a Mittag-Leffler function with the power-law decay

$$t^{-\mu}$$

as $t \to \infty$ (R. Metzler and J. Klafter, 2000) .

If we put the reflecting barriers at $x = 0$ and $x = L$ and consider constant exponent μ and diffusion D_μ, then the fractional FP equation admits the stationary solution in the form of the Gibbs-Boltzmann distribution

$$p_{st}(x) = C \exp\left[-U(x)\right], \quad U(x) = \frac{1}{D_\mu} \int^x v_\mu(z) dz \tag{3}$$

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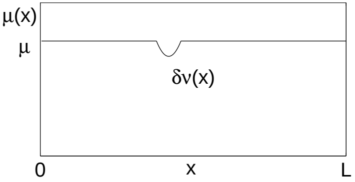
When the anomalous exponent μ depends on the space variable x, the Gibbs-Boltzmann distribution is not a long time limit of the fractional Fokker-Planck equation.

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.

$$\mu(x) = \mu + \delta\nu(x) \tag{4}$$



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

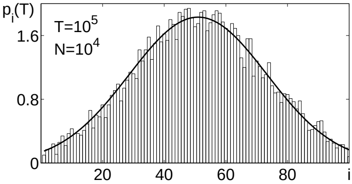


Figure : Long time limit of the solution to the system with $\mu_i = 0.5$ for all i. Gibbs-Boltzmann distribution is represented by the line.

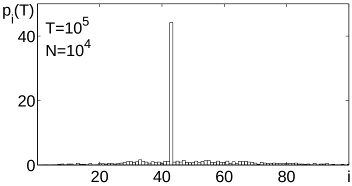


Figure : The parameters are $\mu_i = 0.5$ for all i except $i = 42$ for which $\mu_{42} = 0.3$.

Anomalous chemotaxis and aggregation

Mean field density:

$$\rho(x,t) \to \delta(x - x_M) \qquad as \qquad t \to \infty. \tag{5}$$

Here x_M is the point in space where the anomalous exponent $\mu(x)$ has a minimum. It means that all cells aggregate 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 (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 .
Therefore it is an important problem to find the way how to regularize subdiffusive fractional equations (Fedotov, Straka, unpublished work).

Self-enhanced degradation and subdiffusion of morphogens

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.

Our assumptions lead to the following nonlinear reaction-subdiffusion equation for the mean density of morphogen molecules

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

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

Linear degradation has been considered in the pioneering works by Igor Sokolov, Bruce Henry, et. al.

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.

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

where the diffusion coefficient D_θ is

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

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

Sergei Fedotov and Steven Falconer, Phys. Rev. E 89, 012107 (2014).

Nonlinear Escape Rate

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

$$\alpha(\rho(x,t))\Delta t + o(\Delta t), \tag{9}$$

where $\alpha(\rho)$ is the transition rate which is an increasing function of the particles density ρ.

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

$$\gamma(x,\tau) + \alpha(\rho(x,t)), \tag{10}$$

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

$$\gamma(x,\tau) = \frac{\psi(x,\tau)}{\Psi(x,\tau)}. \tag{11}$$

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

Nonlinear Subdiffusive Fractional PDE

Nonlinear fractional Fokker-Planck equation

$$\frac{\partial \rho}{\partial t} = -\beta a^2 \frac{\partial}{\partial x}\left[\frac{\partial U}{\partial x}\left(\frac{e^{-\Phi}}{{\tau_0}^{\mu(x)}}\mathcal{D}_t^{1-\mu(x)}[e^{\Phi}\rho] + \alpha(\rho)\rho\right)\right]$$
$$+ a^2 \frac{\partial^2}{\partial x^2}\left[\frac{e^{-\Phi}}{2{\tau_0}^{\mu(x)}}\mathcal{D}_t^{1-\mu(x)}[e^{\Phi}\rho] + \alpha(\rho)\rho\right], \qquad (12)$$

where

$$\Phi(x,t) = \int_0^t \alpha(\rho(x,s))\, ds. \qquad (13)$$

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

$$\frac{\partial}{\partial x}\left[2\beta\frac{\partial U}{\partial x}D(\rho_{st})\,\rho_{st}(x)\right]=\frac{\partial^2}{\partial x^2}\left[D(\rho_{st})\,\rho_{st}(x)\right], \qquad (14)$$

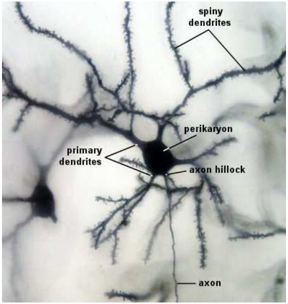
where $D(\rho_{st}(x))$ is the nonlinear diffusion coefficient defined as

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

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

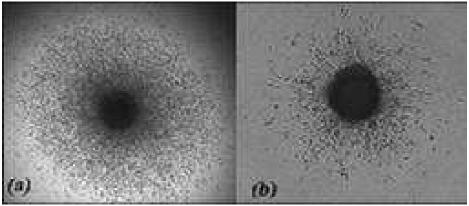
Transport in a Two-State System

• 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):



Migration and proliferation dichotomy in the tumor invasion

Proliferation and migration of tumor cells are mutually exclusive: the spreading suppresses cell proliferation and visa versa (Giese et al.)



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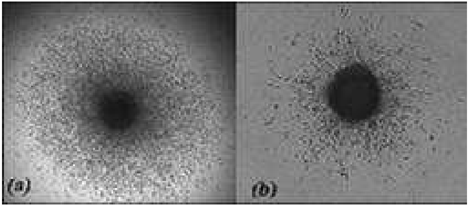

Two-state model: S. Fedotov and A. Iomin, Phys. Rev. Lett. **98**, 118101 (2007)

$\rho_1(x,t)$ - the density for the cells of migratory phenotype

$\rho_2(x,t)$ - the density for the cells of proliferating phenotype.

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

$$\frac{\partial \rho_1}{\partial t} = L_x \rho_1 - \gamma_1 \rho_1 + \gamma_2 \rho_2, \tag{15}$$

$$\frac{\partial \rho_2}{\partial t} = -r_2(\rho_2)\,\rho_2 - \gamma_2 \rho_2 + \gamma_1 \rho_1, \tag{16}$$

where the reaction rate $r_2(\rho_2)$ 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:

$$\frac{\partial \rho_1}{\partial t} = L_x \rho_1 - i_1(x,t) + i_2(x,t), \tag{17}$$

$$\frac{\partial \rho_2}{\partial t} = -r_2\left(\rho_2\right)\rho_2 - i_2(x,t) + i_1(x,t), \tag{18}$$

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

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$$i_1(x,t) = \int_0^t \int_{\mathbb{R}} K_1(t-t')p(x-z,t-t')\rho_1(z,t')dzdt', \tag{19}$$

$$i_2(x,t) = \int_0^t K_2(t-t')\rho_2(x,t')e^{-\int_{t'}^t r_2(\rho_2(x,s))ds}dt', \tag{20}$$

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