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.
INTRODUCTION

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: $< X^2(t) > \sim t^\mu \quad 0 < \mu < 1$

Biology contains a wealth of subdiffusive phenomena:

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

  ![Cell membrane diagram](image1)

- Transport of signaling molecules in a neuron with spiny dendrites

  ![Neuron image](image2)
Anomalous subdiffusion: $<X^2(t)> \sim t^\mu \quad 0 < \mu < 1$

- 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

\[
\frac{\partial p}{\partial t} = -\frac{\partial}{\partial x} \left( v_\mu(x) D_t^{1-\mu} p \right) + \frac{\partial^2}{\partial x^2} \left( D_\mu(x) D_t^{1-\mu} p \right)
\]

(1)

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

The Riemann-Liouville derivative \( D_t^{1-\mu} \) is defined as

\[
D_t^{1-\mu} p(x, t) = \frac{1}{\Gamma(\mu)} \frac{\partial}{\partial t} \int_0^t \frac{p(x, u) du}{(t - u)^{1-\mu}}
\]

(2)

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

\[ p(x, t) \rightarrow p_{st}(x) \]
Subdiffusive fractional equations with constant $\mu$ in a bounded domain $[0, L]$ are not structurally stable with respect to the non-homogeneous variations of parameter $\mu$.

$$\mu(x) = \mu + \delta \nu(x) \quad (3)$$

The space variations of the anomalous exponent lead to a drastic change in asymptotic behavior of $p(x, t)$ for large $t$.

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:

$$\rho(x, t) \to \delta(x - x_M) \quad as \quad t \to \infty.$$ (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)).
Anomalous chemotaxis and aggregation

Mean field density:

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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.

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.

\[
\frac{\partial \rho}{\partial t} = D \frac{\partial^2 \rho}{\partial x^2} - \theta(\rho)\rho,
\]

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:

\[
\frac{\partial \rho}{\partial t} = D^\mu \frac{\partial^2}{\partial x^2} \left[ e^{-\int_0^t \theta(\rho) ds} D_t^{1-\mu} \left[ e^{\int_0^t \theta(\rho) ds} \rho(x, t) \right] \right] - \theta(\rho)\rho, \quad (6)
\]

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


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 \( D_\theta \) 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.

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 \( \rho(x, t) \)

\[
\mathbb{T}(\tau, \rho) = \frac{\mu(\tau)}{1 + A\rho(x, t)},
\]

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

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

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

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.

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

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

where $\mu_0$ and $\tau_0$ 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.
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 $\tau(\tau, \rho)$ that depends on the residence time $\tau$ and the density of particles $\rho$. 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 $\Delta t$ is

$$\alpha(\rho(x, t))\Delta t + o(\Delta t),$$

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

Nonlinear Escape Rate

We assume that the probability of escape due to the repulsive forces during a small time interval $\Delta t$ is

$$\alpha(\rho(x, t)) \Delta t + o(\Delta t), \quad (11)$$

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

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

$$\gamma(x, \tau) + \alpha(\rho(x, t)), \quad (12)$$

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 $\Psi(x, \tau) = \int_0^\infty \psi(x, u) du$ as follows

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

Note that $\alpha(\rho(x, t))$ can be considered as a death rate.
Nonlinear fractional Fokker-Planck equation

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

where

\[
\Phi(x, t) = \int_0^t \alpha(\rho(x, s)) \, ds. \tag{15}
\]

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 $\Phi$ the density profile $\rho(x, t)$ must converge to a stationary solution of a nonlinear Fokker-Planck equation

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

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

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


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 (Santamaría, 2006):
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Two-state Markovian random process: we assume that the transition probabilities $\gamma_1$ and $\gamma_2$ 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

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

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

where the reaction rate $r_2(\rho_2)$ depends on the local density of particles $\rho_2$. 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:

\[ \frac{\partial \rho_1}{\partial t} = L_x \rho_1 - i_1(x, t) + i_2(x, t), \]  \hspace{1cm} (19)

\[ \frac{\partial \rho_2}{\partial t} = -r_2(\rho_2) \rho_2 - i_2(x, t) + i_1(x, t), \]  \hspace{1cm} (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:

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

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

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:

\[
\frac{\partial^2 p}{\partial t^2} - v^2 \frac{\partial^2 p}{\partial x^2} + \int_0^t \int_V K(\tau) \varphi(u) \left( \frac{\partial}{\partial t} - u \frac{\partial}{\partial x} \right) \times \\
p(x - u\tau, t - \tau) \, du \, d\tau = 0,
\]

(23)

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

\[
\varphi(u) = \frac{1}{2} \delta(u - v) + \frac{1}{2} \delta(u + v)
\]

(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 \( \Psi(\tau) \).
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