Non-Markovian random walks and anomalous transport in biology: subdiffusion, Lévy walks and nonlinear fractional PDE's

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Plan de la présentation

1. INTRODUCTION to anomalous transport: subdiffusion and superdiffusion

2. NONLINEAR FRACTIONAL PDE's
   - Degradation and subdiffusion of morphogens, nonlinear fractional PDE
   - Subdiffusive transport in two-state systems

Anomalous transport: subdiffusion and superdiffusion

Spatial dispersal of Brownian particles: $\mathbb{E}B^2(t) = 2Dt$

Macroscopic transport: $\frac{\partial \rho}{\partial t} = D\frac{\partial^2 \rho}{\partial x^2}, \qquad x \in \mathbb{R}$

Subdiffusion:

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

What is the macroscopic equation for the concentration ρ?

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What is the macroscopic equation for the concentration ρ?

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

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

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

Superdiffusion (animals dispersal, cancer cells, intracellular transport along microtubule, etc.)

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

Anomalous transport: subdiffusion

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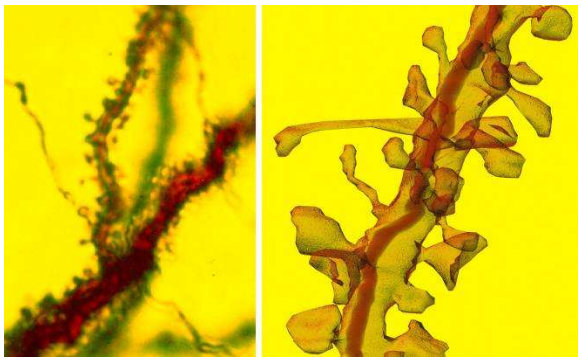
$$\mathbb{E}X^2(t) \sim t^\mu \qquad 0 < \mu < 1$$

Biology contains a wealth of subdiffusive phenomena:
1) transport of proteins and lipids on cell membranes (Saxton, Kusumi)
2) signaling molecules in spiny dendrites (Santamaria)



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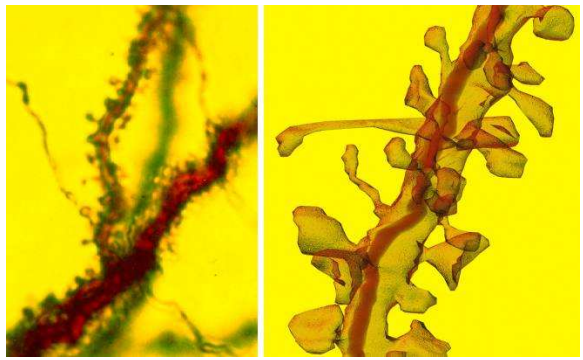


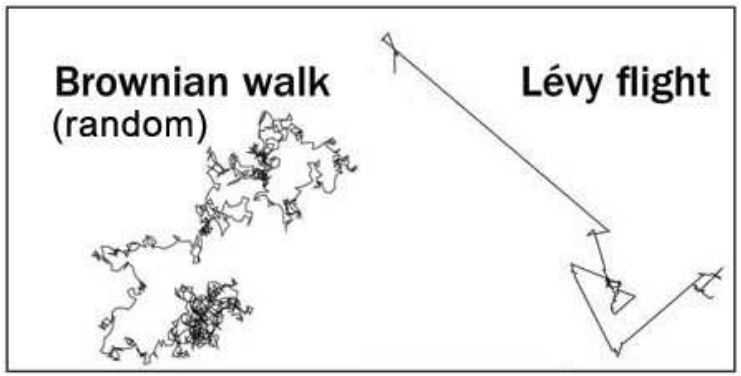
Apart from fractional Brownian motion, the *linear* fractional equations are the standard models for subdiffusive transport. In these models the diffusing particles do not interact. The question then arises as to how to extend these equations for the *nonlinear* case, involving particles interactions.

Superdiffusion: Lévy flight and Lévy walk

Lévy flight and Lévy walk are generalized random walk in which the step lengths during the walk are described by a "heavy-tailed" probability distribution: animal foraging patterns, the distribution of human travel, etc.

- Fractional equation for Lévy flights

$$\frac{\partial \rho}{\partial t} = -D_\alpha \left(-\Delta\right)^{\frac{\alpha}{2}} \rho, \qquad x \in \mathbb{R}^2$$



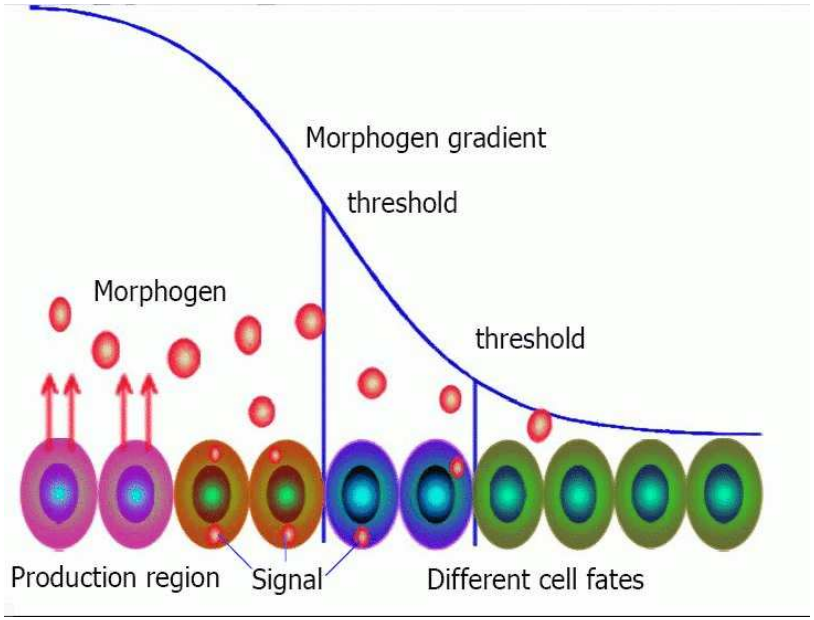
Animals take lots of short steps in a localized area before making long jumps to new areas: the Lévy pattern for tuna, cod, turtles and penguins.

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.

$$\frac{\partial \rho}{\partial t} = D\frac{\partial^2 \rho}{\partial x^2} - \theta(\rho)\rho, \tag{3}$$

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:

$$\frac{\partial \rho}{\partial t} = D_\mu \frac{\partial^2}{\partial x^2} \left[e^{-\int_0^t \theta(\rho) ds} \mathcal{D}_t^{1-\mu} \left[e^{\int_0^t \theta(\rho) ds} \rho(x,t) \right] \right] - \theta(\rho)\rho, \qquad (4)$$

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

LINEAR CASE: Yuste, Abad, Lindenberg Phys. Rev. E (2010)
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.

$$\frac{d^2}{dx^2}\left(D_\theta(\rho_{st})\rho_{st}\right) = \theta(\rho_{st})\rho_{st}. \tag{5}$$

where the diffusion coefficient D_θ is

$$D_\theta(\rho_{st}) = \frac{a^2\left[\theta(\rho_{st})\right]^{1-\mu}}{2{\tau_0}^\mu}. \tag{6}$$

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

Non-linear effects

Typical nonlinear effects:

1) quorum sensing phenomenon: biophysical processes in microorganisms depend on the their local population density.

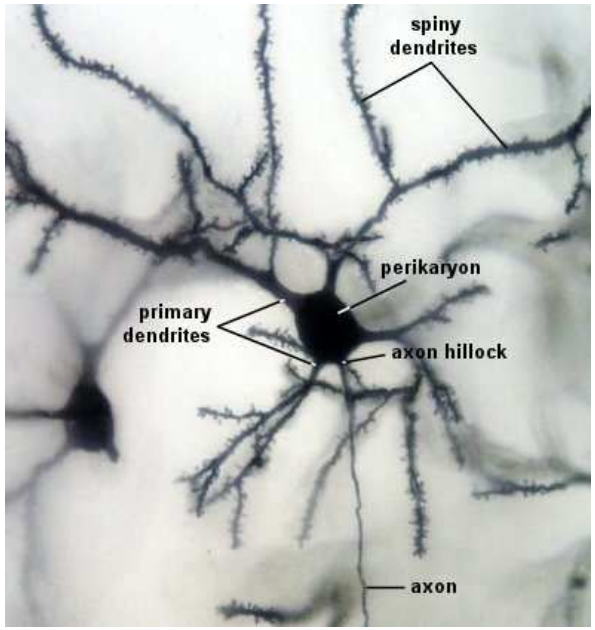
2) cellular adhesion which involves the interaction between neighboring cells

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 interaction, J. Theor. Biology 366, 71-83

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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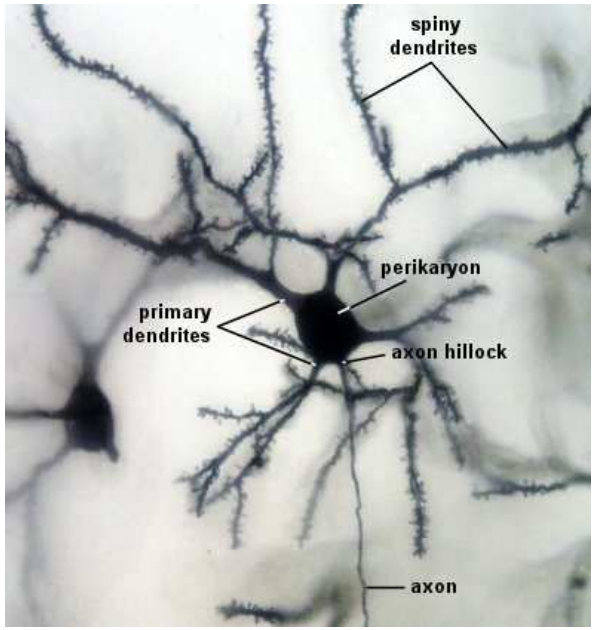
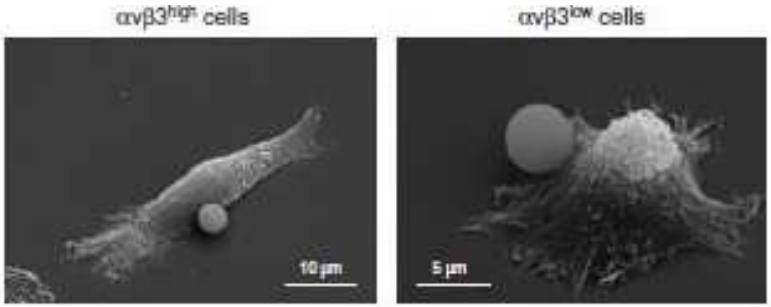


Anomalous superdiffusion in the tumor invasion

Experiments by C. T. Mierke et al, (J. Cell Science 124 (2010) 369; New J. Physics 15 (2013) 015003) and V Peschetola et al, (Cytoskeleton 70 (2013), 201) reveal that the migration process of cancer cells is not a Brownian motion but is superdiffusive due to directional persistence



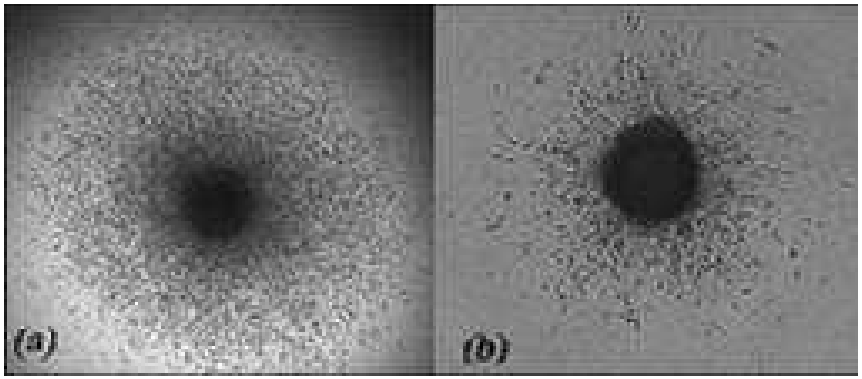
Spatial dispersal of Brownian particles: $\mathbb{E}B^2(t) = 2Dt$

Lévy walk of cancer cells: $\mathbb{E}X^2(t) \sim t^{3-\mu} \qquad 1 < \mu < 2$
where $X(t)$ is the cells position, $\mathbb{E}$ is the expectation (mean value).

The importance of Mierke's experiments is that the Lévy walks represent an optimal search strategy that is often employed by human T cells, microorganisms, insects, fish, birds, etc.

Migration and proliferation dichotomy

Proliferation and migration of tumor cells are mutually exclusive: the spreading suppresses cell proliferation and visa versa (Giese, Khain, Fedotov, Iomin). "Go or Grow" (Hatzikirou, Deutsch, Chauviere)



Cancer cells can migrate in a two fundamentally different ways: diffusive random walks or Lévy walk with random running time drawn from the probability density function with heavy power-law tails.

Lévy walk takes the cancer cell much further from the tumor core than a Brownian motion.

Lévy motility of cancer cells

The main feature of Lévy walk is the distribution of step lengths, l, with a heavy power-law tails described by the formula $p(l) \sim l^{-\gamma}$, where γ is the anomalous exponent from the interval $1 < \gamma < 3$.

The main challenge is to develop the quantitative analysis of Lévy motility of cancer cells together with inhibition of cell proliferation by anticancer therapeutic agents, Fedotov, Tan, Zubarev, Phys. Rev. E (2015).

What is the macroscopic equation for the density of cancer cells ρ?

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What is the macroscopic equation for the density of cancer cells ρ?

We introduce a non-Markovian switching mechanism for cell velocity which leads to Lévy motility of cells. Power-law running time distribution is dynamically generated by internal switching involving the age dependent switching rate.

We find the fractional equations for the density ρ and superdiffusive subbullistic motion of cancer cells:

$$\mathbb{E}X^2(t) \sim t^{3-\mu} \qquad 1 < \mu < 2$$

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

$$\frac{\partial \rho_1}{\partial t} = L_x \rho_1 - \gamma_1 \rho_1 + \gamma_2 \rho_2, \tag{7}$$

$$\frac{\partial \rho_2}{\partial t} = -r_2\left(\rho_2\right)\rho_2 - \gamma_2 \rho_2 + \gamma_1 \rho_1, \tag{8}$$

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:

$$\frac{\partial \rho_1}{\partial t} = L_x \rho_1 - i_1(x,t) + i_2(x,t), \tag{9}$$

$$\frac{\partial \rho_2}{\partial t} = -r_2(\rho_2)\,\rho_2 - i_2(x,t) + i_1(x,t), \tag{10}$$

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

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$$i_1(x,t) = \int_0^t \int_{\mathbb{R}} K_1(t-t') p(x-z, t-t') \rho_1(z,t') dz dt', \tag{11}$$

$$i_2(x,t) = \int_0^t K_2(t-t') \rho_2(x,t') e^{-\int_{t'}^t r_2(\rho_2(x,s))ds} dt', \tag{12}$$

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