Non-Markovian Models of Intracellular Transport

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Plan de la présentation

1. INTRODUCTION to non-Markovian models of intracellular transport
2. FRACTIONAL PDE's
   - Subdiffusive Fokker-Planck equation with space dependent anomalous exponent
   - Superdiffusive transport (Lévy walk) in two-state systems

Non-Markovian transport: subdiffusion and superdiffusion

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

Subdiffusion:

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

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

• Transport of signaling molecules in a neuron with spiny dendrites (Santamaria)

Macroscopic equation for the concentration ρ involves the memory

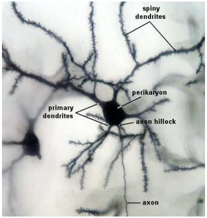
$$\frac{\partial \rho}{\partial t} = D_{\mu} \frac{\partial^2}{\partial x^2} \left(\mathcal{D}_t^{1-\mu} \rho \right), \qquad (1)$$

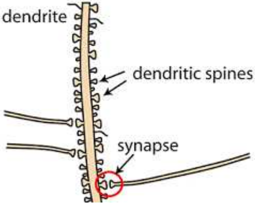
where the Riemann-Liouville (fractional) derivative $\mathcal{D}_t^{1-\mu}$ is defined as

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

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

- 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

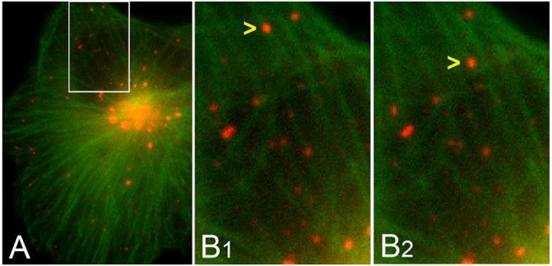
$$\phi(t) \sim \frac{1}{t^{1+\mu}}$$

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

The mean waiting time is infinite.

Transport in a Two-State System, Lévy walk

- Switching between passive subdiffusion and active intracellular transport



Experiment by Viki Allan: Endosome (red) movement along microtubules (green) visualized in a living HeLa cell (panel A).

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

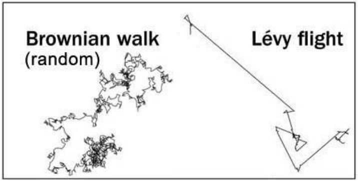
- Virus trafficking (Holcman): slow diffusion and ballistic movement along microtubules.

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.

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

$$\frac{\partial p}{\partial t} = -\frac{\partial \left(v_\mu(x) \mathcal{D}_t^{1-\mu} p \right)}{\partial x} + \frac{\partial^2 \left(D_\mu(x) \mathcal{D}_t^{1-\mu} p \right)}{\partial x^2} \tag{3}$$

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

$$\mathcal{D}_t^{1-\mu} p\,(x,t) = \frac{1}{\Gamma(\mu)} \frac{\partial}{\partial t} \int_0^t \frac{p\,(x,u)\,du}{(t-u)^{1-\mu}} \tag{4}$$

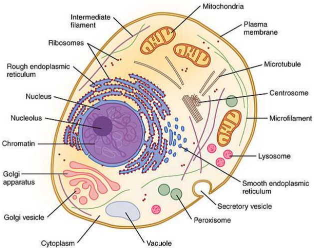
The difference between standard Fokker-Planck equation and FFP equation is the rate of relaxation of

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

.

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) .
The fractional FP equation admits the stationary solution in the form of the Gibbs-Boltzmann distribution

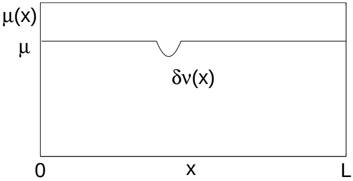


When the anomalous exponent μ depends on the space variable x, the Gibbs-Boltzmann distribution is not a long time limit of the fractional Fokker-Planck equation.

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.

$$\mu(x) = \mu + \delta\nu(x) \tag{5}$$



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

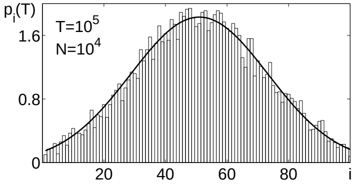


Figure : Long time limit of the solution to the system with $\mu_i = 0.5$ for all i. Gibbs-Boltzmann distribution is represented by the line.

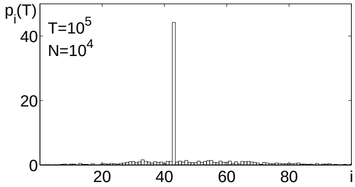
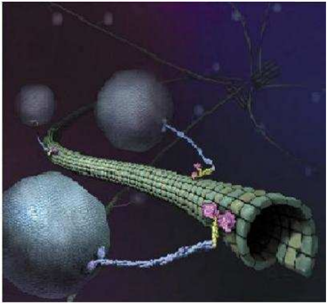


Figure : The parameters are $\mu_i = 0.5$ for all i except $i = 42$ for which $\mu_{42} = 0.3$.

Lévy motility of vesicles

The main challenge is to develop the quantitative analysis of non-Markovian Lévy motility of vesicles along the microtubules.



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

Stochastic model for superdiffusion

We consider the vesicles moving with two velocities v and $-v$ alternating randomly in time.

We define the densities $n_{\pm}(x, t, \tau)$ for the vesicles at point x and time t moving in the right $(+)$ and the left $(-)$ direction during time τ since the last switching. The balance equations are

$$\frac{\partial n_{\pm}}{\partial t} \pm v \frac{\partial n_{\pm}}{\partial x} + \frac{\partial n_{\pm}}{\partial \tau} = -\gamma(\tau) n_{\pm} \quad (6)$$

for $\tau < t$ with the boundary conditions at $\tau = 0$

$$n_{\pm}(x, t, 0) = \int_0^t \gamma(\tau) n_{\mp}(x, t, \tau) d\tau, \quad (7)$$

Stochastic model for superdiffusion

The balance equations for the unstructured density

$$\rho_{\pm}(x,t) = \int_0^t n_{\pm}(x,t,\tau)d\tau$$

can be written as

$$\frac{\partial \rho_+}{\partial t} + v\frac{\partial \rho_+}{\partial x} = -i_+(x,t) + i_-(x,t), \tag{8}$$

$$\frac{\partial \rho_-}{\partial t} - v\frac{\partial \rho_-}{\partial x} = i_+(x,t) - i_-(x,t), \tag{9}$$

where

$$i_{\pm}(x,t) = \int_0^t K(t-\tau)\rho_{\pm}(x \mp v(t-\tau),\tau)d\tau, \tag{10}$$

where $K(t)$ is the memory kernel.

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:

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

$$p(x - u\tau, t - \tau)\, du d\tau = 0, \quad (11)$$

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

$$\varphi(u) = \frac{1}{2}\delta(u - v) + \frac{1}{2}\delta(u + v) \quad (12)$$

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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$$\varphi(u) = \frac{1}{2}\delta(u - v) + \frac{1}{2}\delta(u + v) \qquad (14)$$

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