BIOLOGIJA. 2005. Nr. 4. P. 48–52

Anomalous diffusion in *Schizosaccharomyces pombe* cell cytoplasm and the fractional generalization of Fick's law

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Recent experimental data on an anomalous diffusion in living yeast cell are analyzed. A new mathematical model of passive transport by the concentration gradient is proposed. The macroscopic size of the diffusing molecules and the inhomogeneous character of the cytoplasmic medium offer a theoretical basis for modifying the available models of transport and thus for refining Fick's law.

Key words: passive transport, the first Fick's law, mathematical modeling

INTRODUCTION

Free diffusion is the simplest form of molecular transport in the cell. A usual picture of diffusion is based on the Brownian motion of free point particles. Such kind of random motion is characterized by the mean square displacement $\left\langle |\Delta\vec{r}(t)|^2 \right\rangle \sim 2Dt$ [1–3]. A recent experimental study of an anomalous diffusion in living yeast cells shows an explicit divergence from the classical diffusion. This phenomenon could be explained by the non-Brownian motion which is related to a new dependence of the mean square displacement on time and, as is shown below, allows a modification of Fick's law. The present work offers a mathematical model of passive transport determined by the concentration gradient. The macroscopic size of the diffusing molecules, on the one hand, and the inhomogeneous character of the cytoplasmic medium on the other serve as a theoretical basis for modifying the available models of transport. In author's opinion, these two important circumstances provide a sufficient reason for refining Fick's law. In this approach, as a consequence, also the mathematical model of the diffusion process undergoes changes.

EXPERIMENTAL DATA

In an experimental nanometric study of the living yeast *Schizosaccharomyces pombe* [4], which is characterized by a stiff cell wall responsible for the cell shape and resistance to deformation, diffusion was investigated as the motion of lipid granules naturally occurring in the cytoplasm. A large frequency range of the observation was obtained by a combination of video-based (optical tweezer (OT) experiments) and laser-based tracking methods (multiple particle tracking (MPT)).

Theoretically, the mean squared displacement of a diffusing particle varies with time as

$$\left\langle |\Delta\vec{r}(t)|^2 \right\rangle \infty t^{\alpha}, \qquad (1)$$

where the exponent α distinguishes the type of diffusion encountered; $\alpha = 1$ indicates normal Brow-

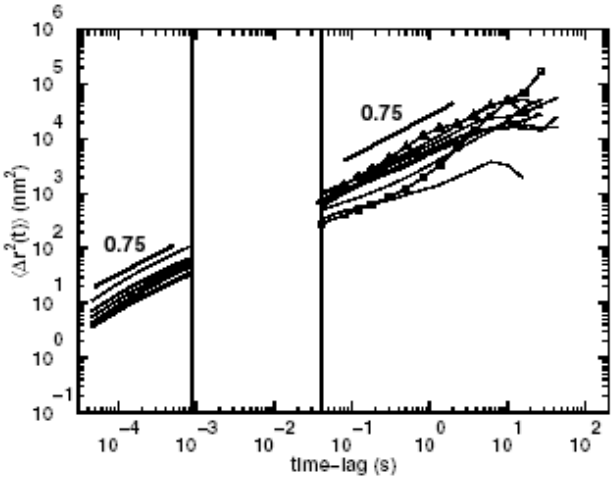

Fig. 1. Mean squared displacement, $\left\langle |\Delta\vec{r}(t)|^2 \right\rangle$, of granules as a function of time lag [4]

Table. **Distribution of the exponent in three different intervals of time lag [4]**

Method	Time interval (s)	Total count	α
OT	10^{-4}–10^{-3}	266	0.737 ± 0.003
MPT	0.1–1	52	0.68 ± 0.02
MPT	1–10	46	0.70 ± 0.03

nian diffusion, $\alpha < 1$ indicates subdiffusion, and $\alpha > 1$ indicates superdiffusion [5]. Experimental results of the exponent α are shown in Table.

The value α was derived by fitting the Gaussian law to the histogram of α. The 46 MPT granules are a subset of the 52 MPT granules, whereas the 266 OT granules are an independent set. The experimental plot of a mean squared displacement of granules as a function of time lag is shown in Fig. 1.

The short-time part of the data was obtained by OT (N = 10 randomly chosen granules), whereas the long-time part was obtained by MPT (another ten granules). Lines with a slope of 0.75 are drawn to guide the eye. Lines with symbols show examples of different types of motion: normal diffusion (Δ), subdiffusion with a plateau (•), and directed motion (□).

The mean squared displacement of a diffusing particle embedded in a semi-flexible polymer network $\left\langle |\Delta\vec{r}(t)|^2 \right\rangle$ at long-time lags is expected to display a plateau at which the particle is elastically trapped. Also, the confinement of a granule between larger cell organelles would result in a plateau in $\left\langle |\Delta\vec{r}(t)|^2 \right\rangle$. For N = 8 granules (~15%), a flattening of the mean squared displacement curve consistent with the onset of a plateau was observed at times of 1–10 s. There was a large variation between individual granules with respect to whether they showed or not a mean squared displacement plateau at the time scale of the experiments, and a 10-fold variation in the plateau value among those that did. This variation could be due to a variation in granule size and in the local properties of the cytoplasm, *i.e.* filament length and density, as well as the density of cross-linkers. The references are in the original paper [4].

The crucial role of the anomalous character of the diffusion in the cytoplasm belongs to the skeleton [4] and inhomogeneous properties of the medium. The theoretical substantiation of the experimental observation (1) requires a revision of the first Fick's law.

THE FIRST FRACTIONAL FICK'S LAW

We shall stress, and it is very important for the further exposition, that the classical equation of diffusion in general and in the case of passive transport in particular requires a series of conditions to be imposed (see, *e.g.*, [6, 7]):

- the particle size of a diffusing substance is negligibly small and is not a characteristic scale of the model;
- the medium of diffusion is homogeneous and isotropic;
- T = const, *i.e.* thermodiffusion is absent;
- p = const, *i.e.* barodiffusion is absent;
- there are no chemical reactions, *i.e.* sources and outlets of the substance are absent;
- external fields are absent (*e.g.*, there is no electrical diffusion);
- D = const, *i.e.* at the existing concentration gradients the coefficient of diffusion can be regarded as a constant value;
- the system under study is a two-component one, otherwise changes in the concentration of one of the components at the expense of transport of the other components should be accounted for.

In the cases when at least one of the above conditions is not observed, the mathematical model needs to be adjusted.

Considering inhomogeneity and numerous bordering effects, let us regard the intrinsic cytoplasmic layer as a manifold M^D with a non-integer dimension D, where $1 < D < 3$. In this case, since the direction x is no more a smooth one-dimensional manifold, the definition of the concentration gradient dc / dx should be specified.

To formulate the modified Fick's law, we shall use the definition of the fractional derivative ${}_aD_x^\alpha f(x)$ [8]:

$$ {}_aD_x^\alpha f(x) = \frac{1}{\Gamma(1-\alpha)} \int_a^x \frac{f'(t)dt}{(x-t)^\alpha}, \quad 0<\alpha<1, \qquad (2) $$

where Ã(x) is the Euler gamma function [9], and α is the parameter of nonlocality. From the mathema-

tical point of view, ${}_a D_x^{\alpha}$ is a linear singular integro-differential operator.

Then the first fractional Fick's law in the simplest one-dimensional case can be expessed in the from

$$J = -D\left(l_0^{\alpha-1}\,{}_a D_x^{\alpha}\right)c\,, \qquad (3)$$

where J is the flow, D is the diffusion coefficient, and $c = c(x, t)$ is the concentration.

Like in the case of the conventional Fick's law, the process of matter transport (3) implies the length parameter l_0(cm). This peculiarity holds also for the dimensionless fractional Fick's law when the relative dimensionless flow $\overline{J} = J / J_{\max}$ and the concentration $c = c/c_{\max}$:

$$\overline{J} = \overline{D}\cdot \overline{D}_x^{\alpha} c\,, \qquad (4)$$

where l_0 is part of the definition of the dimensionless coefficient of diffusion and fractional derivative:

$$\overline{D} = D\frac{c_{\max}}{J_{\max} l_0}\,, \quad {}_a\overline{D}_x^{\alpha} = l_0^{\alpha}\,{}_a D_x^{\alpha}\,. \qquad (5)$$

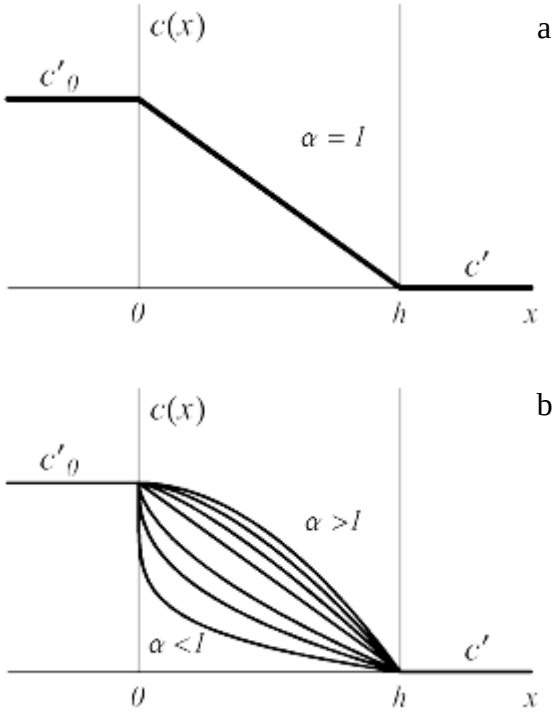

Fig. 2. Dependence of the substance concentration $c(x)$ on the diffusion depth x, corresponding to the constant substance flow $J = kD$ in the cases of the common (a) and the first fractional (b) Fick's laws; h is layer thickness; c_0' and c' are the concentrations of surrounding solutions at the inlet and outlet of the cytoplasm layer

Let us also note that employment of the value l_0 in expression (3) allows not to change the dimension of the coefficient of diffusion D.

Since, for $\alpha \to 1$, from expression (3) we obtain the expression of classical flow, it is more reasonable to call the first fractional Fick's law the generalized Fick's law. However, the term "generalized Fick's law" is already in use for multicomponent systems [2]. If a system contains more than two components, the concentration dynamics of one of the components at the expense of transport of the other components should be accounted for.

In the case of a stationary flow across the cytoplasm layer of the width h, the concentration dependence $c(x)$ is already not linear but power:

$$c(x) = \begin{cases} c'_0\,, & x \le 0 \\ \dfrac{k}{a}x^{\alpha}, & a = \dfrac{\Gamma(1+\alpha)}{l_0^{1-\alpha}}, \quad 0 < x < h\,. \\ c'\,, & x \ge h \end{cases} \qquad (6)$$

The graphical representation of this dependence is shown in Fig. 2.

Thus, if the change of concentration within the thickness of the cytoplasmic layer observes the power law, it can serve as a feature of the fractional Fick's law. The coefficient of proportionality k

$$k = \frac{c'_0 - c'}{h^{\alpha}} \xrightarrow[\alpha\to 1]{} \frac{c'_0 - c'}{h}. \qquad (7)$$

Using the bordering values c_0 and c, we obtain the expression for the flow value J through the concentrations of the surrounding solutions:

$$J = kD = P\left[c_0 - \Gamma(1+\alpha)\left(\frac{h}{l_0}\right)^{1-\alpha} c\right], \qquad (8)$$

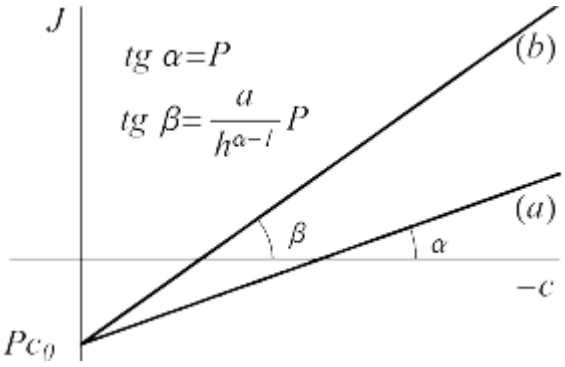

Fig. 3. Dependence of the flow value J on solution concentration c in the cases of common (a) and fractional (b) Fick's laws. P is layer permeability, c_0 and c are concentrations of surrounding solutions; $tg\alpha = P$, $tg\beta = aP/h^{\alpha-1}$, where a = Ã(1 + α) / $l_0^{1-\alpha}$, l_0 is the characteristic parameter of length, and h is cytoplasm layer thickness

where $P = \gamma D/h$ is the layer permeability $c' = \gamma c$ and $c'_0 = \gamma c_0$. An essential difference of expression (7) from the corresponding linear expression is the presence of the coefficient

$$\frac{a}{h^{\alpha-1}} = \Gamma(1+\alpha)\left(\frac{h}{l_0}\right)^{1-\alpha} = \begin{cases} 1, & \alpha = 1 \\ \neq 1, & \alpha \neq 1 \end{cases}, \qquad (9)$$

which can considerably differ from unity (see Fig. 3).

ANOMALOUS DIFFUSION

Now we have to do the last step: to show a relation between the fractional Fick's law and anomalous diffusion. The derivative $\partial c / \partial t$ is related to the flow $J(x, t)$. This relation in the one-dimensional case could be expressed by the generalized continuity condition:

$$\frac{\partial c}{\partial t} = -\left(l_0^{\alpha-1}\, {}_a D_x^{\alpha}\right) J . \qquad (10)$$

After substituting the value of flow J from expression (3) in the case of the constant diffusion coefficient D we obtain

$$\frac{\partial c}{\partial t} = -D\left(l_0^{2\alpha-2}\, {}_a D_x^{2\alpha}\right) c , \qquad (11)$$

i.e. the equation of anomalous diffusion. As follows from equation (11), the mean square displacement of a diffusing particle varies with time as $\left\langle |\Delta\vec{r}(t)|^2 \right\rangle \infty t^{\alpha}$, which corresponds to equation (1) at $\alpha = 0.75 < 1$, *i.e.* to subdiffusion. Thus, we have modified the fractional Brownian motion of lipid granules in the cytoplasm.

Note here an important difference between the nonlinear and the nonlocal types of diffusion. In the case of nonlocal diffusion, the mean squared displacement of a diffusing particle varies with time as $\left\langle |\Delta\vec{r}(t)|^2 \right\rangle \infty t^{\alpha}$, whereas in the case of nonlinear diffusion, when the evolution equation looks like $\partial c / \partial t = D\,\partial(c^m \partial c / \partial t) / \partial t$, the same value changes as $t^{\frac{m+1}{2}}$ does. The main difference could be presented in the form of solutions of the corresponding equations. For the cases of linear, nonlinear and nonlocal diffusion the solutions have the corresponding forms:

$$c(x,t) = A(x^2 + 2at) + B \quad c(x,t) = (\pm kx + k\lambda t + A)^{1/m} ,$$

$$c(x,t) = \frac{\sin(\pi\alpha)}{2\pi}\Gamma(1+2\alpha)\frac{t}{|x|^{2\alpha+1}}, \text{ for } x \to \infty ,$$

where A, B, a, k and λ are arbitrary constants. Thus, the experimental data presented in [4] on diffusion in the yeast *Schizosaccharomyces pombe* cytoplasm demonstrate the nonlocal type of diffusion.

CONCLUSIONS

Thus, the finite size of the molecules that diffuse through the cytoplasm, and the inhomogeneous character of the latter provide a sufficient theoretical basis for changing the mathematical model of passive concentration transport. As a consequence, in the new model we obtain:

- a power change of the concentration in the thick of the cytoplasm layer instead of the conventional linear change;
- a changed dependence of the flow value on the concentration;
- a changed expression of the first Fick's law.

Passive transport through the homogeneous cytoplasm is modified by the concentration and transport rate of a substance, whereas in the case of inhomogeneous cytoplasm it depends on the pressure gradient. These two types of transport (diffusive and convective) may be regarded as two theoretical limit cases. In real cells they are superimposed. The proposed fractional Fick's law deals with exactly such intermediate properties. Therefore the proposed model of the fractional Fick's law is well applicable to real cells.

Received 24 May 2005
Accepted 15 December 2005

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ANOMALI DIFUZIJA *Schizosaccharomyces pombe* LÀSTELËS CITOPLAZMOJE IR TRUPMENINIS FIKO DËSNIO APIBENDRINIMAS

S a n t r a u k a

Eksperimento metu, analizuojant difuzijà gyvoje *Schizosaccharomyces pombe* làstelëje, pastebëtas nuokrypis nuo klasikinës difuzijos. Pasiûlytas naujas koncentracijos gradiento nulemtas matematinis transporto modelis. Makroskopinis iðsklaidomø molekuliø dydis ir nehomogeniðka làstelës vidinë terpë leidþia teoriðkai modeliuoti cheminiø medþiagø koncentracijos srautà kaip pasyvø transportà, vykstantá nehomogeniðkoje vidinëje làstelës terpëje. Tokia terpë gali bûti matematiðkai modeliuojama kaip terpë su trupmenine dimensija. Suformuluotas trupmeninis pirmojo Fiko dësnio apibendrinimas ir parodyti tokio bei klasikinio modelio skirtumai.