Biophysical Journal Volume 106 June 2014 2541–2543

Comments to the Editor

Comment on “Anomalous versus Slowed-Down Brownian Diffusion in the Ligand-Binding Equilibrium”

In this article (1), the authors investigated the effect of transient subdiffusion and the heterogeneity of the medium on ligand-binding equilibrium. One of the main results of this investigation is that transient subdiffusion caused by power-law-distributed residence times strongly impairs the equilibrium fraction of bound receptors in a spatially homogeneous reaction. Herein, we argue that this result does not follow from the data presented in Soula et al. (1). Moreover, we show that the opposite conclusion is reached based on theoretical consideration: i.e., transient subdiffusion caused by power-law-distributed residence times can only increase the equilibrium fraction of bound receptors.

The basis of the results presented by Soula et al. (1) is the statement that “equilibrium configurations should in principle be independent of dynamics, i.e., values of transport coefficients, such as diffusion coefficients.” This statement is correct when equilibrium is determined by thermodynamics. However, in the case considered by Soula et al. (1), this condition has not been satisfied. If we look at Fig. 2 *A*, we see that equilibrium is not dependent on the diffusion coefficient only, at $D \geq 0.05$. At $D = 0.02$, the rate of diffusion starts to influence equilibrium. One may assume that at the further reduction of the diffusion coefficient, the equilibrium fraction of bound receptors will decrease as in Fig. 2 *C*. Such an assumption is dictated by the Smoluchowski theory, which suggests that the dependence of the rate constant of bimolecular reactions on the diffusion coefficient can be expressed as (2,3)

$$k_{\text{on}} = \frac{AD}{1+BD}, \tag{1}$$

where D is sum of the diffusion coefficients of the reacting molecules, and A and B are constants. From here, we see that the rate constant of the forward reaction significantly depends on the diffusion coefficients when they are small. Consequently, for small D, the equilibrium fraction of bound receptors, i.e.,

$$C_{\text{eq}}/R_T = L_T/\left(k_{\text{off}}/k_{\text{on}} + L_T\right),$$

should depend on the diffusion coefficient. Here, C_{eq} is the equilibrium amount of bound ligands, R_T is the total amount of the receptors, L_T is the total amount of ligand molecules, and k_{off} is the rate constant of the backward reaction.

Based on the aforementioned information, it follows that the authors’ conclusion (i.e., subdiffusion caused by power-law-distributed residence times strongly impairs the equilibrium fraction of bound receptors) is not justified. Additional calculations are needed to determine whether this conclusion is correct. Results obtained in a continuous-time random walk (CTRW) model with a diffusion coefficient D_M (see Fig. 1 *B*) should be compared with the results obtained in a model of Brownian motion with the same diffusion coefficient D_M (but not with $D \geq 0.05$). This coefficient is expressed as

$$D_M = \frac{(\Delta x)^2}{4\tau_M}, \tag{2}$$

where

$$\tau_M = \int_0^\infty \tau\varphi(\tau)d\tau$$

is the mean residence time; $\varphi(\tau)$ is the distribution of residence times; and Δx is the lattice spacing.

To theoretically consider the question studied by the authors, we must consider subdiffusion-reaction equations. Such equations were derived in a number of articles in the framework of the CTRW model and in an equivalent model of random trap. To describe the reversible bimolecular reaction considered here, equations proposed in Yadav and Horsthemke (4), Fedotov (5), and Seki et al. (6) can be used in principle. The equation derived in Yadav and Horsthemke (4) and Fedotov (5) corresponds to the case of activation-limited reaction. Diffusion-limited type of reaction has been considered in the framework of the CTRW model only in the case when one of the reactants is immobile (6). If both reactants are mobile then it is not clear how should one formulate the boundary conditions for reactions. Yuste et al. (7) have proposed a formal generalization of the equation derived in Seki et al. (6) to this case. But the physical meaning of the obtained equation is not clear.

The problem of describing a bimolecular reaction has been more fully considered in the framework of the random-trap model. Because, in this model, the problem of the boundary conditions does not arise, equations have been derived for the case of activation-limited reactions

---

Submitted January 2, 2014, and accepted for publication April 25, 2014.

*Correspondence: shkilevv@ukr.net

Editor: Anne Kenworthy.

0006-3495/14/06/2541/3 $2.00

http://dx.doi.org/10.1016/j.bpj.2014.04.035

and diffusion-limited reactions with two mobile reactants (8,9). Note that all the known subdiffusion-reaction equations are mean field equations, so they need to be confirmed by numerical simulation. In one study (10), the authors showed that the results obtained with the mean field equations in a random-trap model are consistent with the results of three-dimensional numerical simulations for the case of irreversible annihilation and coagulation reactions. Furthermore, the author of (8) showed that the mean field equations in a random-trap model qualitatively described the effect of medium inhomogeneity on the diffusion-reaction front velocity.

The mean field equations of a random-trap model without reactions are (11)

$$\frac{\partial \rho_i}{\partial \tau} = -\nu_i \rho_i + \alpha_i F, \quad (i = 1, 2, \ldots, N), \tag{3}$$

$$\frac{\partial \rho}{\partial \tau} = a^2 \sum_{j=1}^{N} \nu_j \Delta \rho_j, \tag{4}$$

where ρ_i represents partial concentrations;

$$\rho = \sum_{j=1}^{N} \rho_j$$

is the total concentration; the values ν_i and α_i are sets of positive parameters in terms of the residence times' distribution function,

$$\varphi(\tau) = \sum_{j=1}^{N} \alpha_j \nu_j \exp(-\nu_j \tau); \tag{5}$$

Δ is the Laplace operator; and

$$F = \sum_{j=1}^{N} \nu_j \{\rho_j + a^2 \Delta \rho_j\} \tag{6}$$

is the number of jumps of molecules per unit time per unit volume. Parameter α_i satisfies the condition

$$\sum_{j=1}^{N} \alpha_j = 1.$$

This model describes transient subdiffusion (11) with

$$D_M = \frac{a^2}{\tau_M}. \tag{7}$$

Mean residence time is expressed as

$$\tau_M = \sum_{j=1}^{N} \frac{\alpha_j}{\nu_j}. \tag{8}$$

The random-trap model with a bimolecular diffusion-controlled reaction was considered in (9). In the case of a reversible ligand-binding reaction, $L + R = C$, the mean field equations are

$$\begin{aligned} \frac{\partial \rho_i^L}{\partial \tau} = &-\nu_i \rho_i^L + \alpha_i F^L - K \rho_i^L F^R - \alpha_i K \rho^R F^L \\ &+ \alpha_i k_{\mathrm{off}} \rho^C, \ (i = 1, 2, \ldots, N), \end{aligned} \tag{9}$$

$$\frac{\partial \rho^L}{\partial \tau} = a^2 \sum_{j=1}^{N} \nu_j \Delta \rho_j^L - K \rho^L F^R - K \rho^R F^L + k_{\mathrm{off}} \rho^C, \tag{10}$$

$$\begin{aligned} \frac{\partial \rho_i^R}{\partial \tau} = &-\nu_i \rho_i^R + \alpha_i F^R - K \rho_i^R F^L - \alpha_i K \rho^L F^R \\ &+ \alpha_i k_{\mathrm{off}} \rho^C, \ (i = 1, 2, \ldots, N), \end{aligned} \tag{11}$$

$$\frac{\partial \rho^R}{\partial \tau} = a^2 \sum_{j=1}^{N} \nu_j \Delta \rho_j^R - K \rho^R F^L - K \rho^L F^R + k_{\mathrm{off}} \rho^C, \tag{12}$$

where ${\rho_i}^R$ and ρ^L are ligand concentrations; ${\rho_i}^R$ and ρ^R are receptor concentrations; ρ^C is the bond complex concentration; F^L and F^R are the numbers of jumps of ligand and receptor molecules per unit time per unit volume; and K is a constant.

In equilibrium, this system of equations is reduced to

$$k_{\mathrm{on}} \rho^L \rho^R = k_{\mathrm{off}} \rho^C \tag{13}$$

with

$$k_{\mathrm{on}} = K(\mu^L + \mu^R), \tag{14}$$

where mobility values μ^L and μ^R are expressed as

$$\begin{aligned} \mu^L &\overset{\mathrm{def}}{=} \frac{F^L}{\rho^L} = \Theta(K F^R), \\ \mu^R &\overset{\mathrm{def}}{=} \frac{F^R}{\rho^R} = \Theta(K F^L) \end{aligned} \tag{15}$$

with

$$\begin{aligned} \Theta(x) &= \frac{\psi(x)}{\Psi(x)}, \\ \psi(x) &= \sum_{j=1}^{N} \frac{\alpha_j \nu_j}{\nu_j + x}, \\ \Psi(x) &= \sum_{j=1}^{N} \frac{\alpha_j}{\nu_j + x}. \end{aligned} \tag{16}$$

Note that Eq. 14 is an analog of the Smoluchowski formula

$$k_{\mathrm{on}} = 4\pi R_0 (D^L + D^R).$$

Brownian diffusion is a special case of the considered model, i.e., when all the frequencies ν_i are the same: $\nu_i = \nu_0$. From Eqs. 7, 8, and 16, it follows that we have to put

$$\nu_0 = \left(\sum_{j=1}^{N} \frac{\alpha_j}{\nu_j} \right)^{-1} = \Theta(0). \tag{17}$$

In this case, we have

$$k_{\mathrm{on}} = K\left(\mu^L + \mu^R\right) \tag{18}$$

with

$$\mu^L = \Theta(0),\ \mu^R = \Theta(0). \tag{19}$$

Because the function $\Theta(x)$ is increasing, we use Eqs. 14, 15, 18, and 19 to show that the constant k_{on} corresponding to transient subdiffusion is greater than the constant k_{on} corresponding to Brownian diffusion. The reason for this is that in the model of transient subdiffusion, the molecule mobility is higher than that in the model of Brownian diffusion.

If the bimolecular reaction rate is not influenced by diffusion, then the mean field equations describing the reaction $L + R = C$ are (8)

$$\frac{\partial \rho_i^L}{\partial \tau} = -\nu_i \rho_i^L + \alpha_i F^L - k_{\mathrm{on}} \rho_i^L \rho^R + \alpha_i k_{\mathrm{off}} \rho^C,\ (i = 1, 2, \ldots, N), \tag{20}$$

$$\frac{\partial \rho^L}{\partial \tau} = a^2 \sum_{j=1}^{N} \nu_j \Delta \rho_j^L - k_{\mathrm{on}} \rho^R \rho^L + k_{\mathrm{off}} \rho^C, \tag{21}$$

$$\frac{\partial \rho_i^R}{\partial \tau} = -\nu_i \rho_i^R + \alpha_i F^R - k_{\mathrm{on}} \rho_i^R \rho^L + \alpha_i k_{\mathrm{off}} \rho^C,\ (i = 1, 2, \ldots, N), \tag{22}$$

$$\frac{\partial \rho^R}{\partial \tau} = a^2 \sum_{j=1}^{N} \nu_j \Delta \rho_j^R - k_{\mathrm{on}} \rho^R \rho^L + k_{\mathrm{off}} \rho^C. \tag{23}$$

In this case, the rates of a bimolecular reaction in the model of transient subdiffusion and in the model of Brownian diffusion are identical. However, the mobility of molecules in the model of transient subdiffusion, i.e.,

$$\begin{aligned} \mu^L &= \Theta\left(k_{\mathrm{on}} \rho^R\right), \\ \mu^R &= \Theta\left(k_{\mathrm{on}} \rho^L\right), \end{aligned} \tag{24}$$

is higher than that in the model of Brownian diffusion (Eq. 19).

Thus, in the model of transient subdiffusion, the bimolecular reaction always increases the mobility of the molecules. A detailed discussion of this phenomenon is given in (8). Therefore, if the reaction rate is influenced by diffusion, it will be higher in the model of transient subdiffusion than in the model of Brownian diffusion. If diffusion is not an influential factor, the reaction rates in the two models are the same. Hence, in the mean field theory, transient subdiffusion caused by power-law-distributed residence times can only increase the rate of the forward reaction. Accordingly, it can only increase the equilibrium fraction of the bound receptors. Interestingly, this prediction, based on the aforementioned reasoning, is consistent with the simulation results.

We considered the case where the term describing the backward reaction is written in the form

$$\alpha_i k_{\mathrm{off}} \rho^C.$$

This form corresponds to the assumption in the CTRW model that every new molecule resulting from a reaction has a new residence time (8,9). Other possible reaction mechanisms (8,12) are too complex for theoretical consideration.

V. P. Shkilev*
Chuiko Institute of Surface Chemistry, National Academy of Sciences of Ukraine, Kiev, Ukraine

REFERENCES

1. Soula, H. A., B. Caré, …, H. Berry. 2013. Anomalous versus slowed-down Brownian diffusion in the ligand-binding equilibrium. *Biophys. J.* 105:2064–2073.
2. Rice, S. A. 1985. Comprehensive chemical kinetics. *In* Diffusion-Limited Reactions Elsevier, Amsterdam, The Netherlands.
3. Szabo, A. 1989. Theory of diffusion-influenced fluorescence quenching. *J. Phys. Chem.* 93:6929–6939.
4. Yadav, A., and W. Horsthemke. 2006. Kinetic equations for reaction-subdiffusion systems: derivation and stability analysis. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* 74:066118.
5. Fedotov, S. 2010. Non-Markovian random walks and nonlinear reactions: subdiffusion and propagating fronts. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* 81:011117.
6. Seki, K., M. Wojcik, and M. Tachiya. 2003. Fractional reaction-diffusion equation. *J. Chem. Phys.* 119:2165.
7. Yuste, S. B., L. Acedo, and K. Lindenberg. 2004. Reaction front in an $A + B \rightarrow C$ reaction-subdiffusion process. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* 69:036126.
8. Shkilev, V. P. 2009. Effect of microscopic inhomogeneity of the medium on reaction-diffusion front velocity. *J. Exp. Theor. Phys.* 108:356–363.
9. Shkilev, V. P. 2009. Macroscopic description of subdiffusion-controlled bimolecular reaction. *J. Exp. Theor. Phys.* 109:852–858.
10. Sokolov, I. M., S. B. Yuste, …, K. Lindenberg. 2009. Mean field model of coagulation and annihilation reactions in a medium of quenched traps: subdiffusion. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* 79:051113.
11. Shkilev, V. P. 2005. A model of anomalous transport. *J. Exp. Theor. Phys.* 101:526–567.
12. Shkilev, V. P. 2011. Propagation of a subdiffusion reaction front and the “aging” of particles. *J. Exp. Theor. Phys.* 112:711–716.