# Kinetic model for fluorescence microscopy experiments in disordered media with binding sites and obstacles

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A model is proposed that describes the diffusion of molecules in a disordered medium with binding sites (traps) and obstacles (barriers). The equations of the model are obtained using the subordination method. As the parent process, random walks on a disordered lattice are taken, described by the random barrier model. As the leading process, the renewal process that corresponds to the multiple-trapping model is used. Theoretical expressions are derived for the curves obtained in the experiments using fluorescence microscopy (fluorescence recovery after photobleaching, fluorescence correlation spectroscopy, and single-particle tracking). Generalizations of the model are proposed to consider the correlations in the mutual arrangement of the traps and obstacles. This model can be used to determine parameters characterizing the diffusion and binding properties of molecules in crowded environments.

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## I. INTRODUCTION

Fluorescence recovery after photobleaching (FRAP), fluorescence correlation spectroscopy (FCS), and single-particle tracking (SPT) are experimental methods based on the use of fluorescence microscopy. They are widely used in the study of the diffusion and binding properties of biomolecules in crowded environments. An FRAP experiment involves photobleaching of fluorescing molecules in a small volume and the observation of the rate of fluorescence penetration into this volume. An FCS experiment consists of observing fluctuations in the intensity of the fluorescence in a small volume arising from the random movement of fluorescing molecules. An SPT experiment directly traces the trajectory of an individual molecule.

For a theoretical description of fluorescence microscopy experiments, the multiple-trapping model is often used [1–4]. The equations in this model have the following form:

$$\frac{\partial f(\mathbf{r},t)}{\partial t} = D\nabla^2 f(\mathbf{r},t) - \sum_{i=1}^{N} \omega_i f(\mathbf{r},t) + \sum_{i=1}^{N} \nu_i c_i(\mathbf{r},t), \tag{1}$$

$$\frac{\partial c_i(\mathbf{r},t)}{\partial t} = -\nu_i c_i(\mathbf{r},t) + \omega_i f(\mathbf{r},t), \quad i = 1,\ldots,N, \tag{2}$$

where $D$ is the diffusion constant. The symbol $\nabla^2$ is the Laplacian operator. The parameters $\omega_i$ and $\nu_i$ are the association and dissociation rates, respectively. The variables $f(\mathbf{r},t)$ and $c_i(\mathbf{r},t)$ have different meanings in different experiments. In FRAP experiments, $f(\mathbf{r},t)$ is the concentration of the unbound freely diffusing molecules and $c_i(\mathbf{r},t)$ is the concentration of the bound molecules at the binding sites of the $i$th type. In FCS experiments, $f(\mathbf{r},t)$ and $c_i(\mathbf{r},t)$ are the fluctuations of the concentrations of the unbound and bound molecules, respectively. In SPT experiments, $f(\mathbf{r},t)$ and $c_i(\mathbf{r},t)$ are the probabilities of finding the particle in the unbound and bound states, respectively. The first equation expresses the balance of the particles in the free state. The first term on the right-hand side describes diffusion, and the second and third terms describe the transition of the particles from the free state to the immobile binding sites and from the binding sites to the free state, respectively. The second equation expresses the balance of the particles in the binding sites of the $i$th type. The first term on the right describes the transition of the particles from the binding sites of the $i$th type to the free state, and the second term describes the reverse transition. Different binding sites contain different transition rates $\omega_i$ and $\nu_i$.

The multiple-trapping model is a generalization of the classical diffusion equation for the case when diffusing molecules can be delayed by stationary binding sites. However, in disordered media, particularly in living cells, diffusion is hindered by obstacles acting as potential barriers or as geometric constraints [1,5,6]. To describe the experimental data accurately, both of these factors should be considered. For example, if a FRAP experiment is described using the multiple-trapping model, unambiguous model parameters cannot be obtained from the experimental data. For different values of the radius of the bleached spot, different values of the model parameters are obtained [4].

In this study, a generalization of the multiple-trapping model that considers obstacles was proposed, and arguments were provided that indicated the proposed model extended the descriptive capabilities of the multiple-trapping model.

## II. GENERALIZATION OF THE MULTIPLE-TRAPPING MODEL

In this section, the process described by the multiple-trapping model is presented as a subordinated stochastic process, with usual diffusion as the parent process and the

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renewal process as the leading process. By replacing the usual diffusion in this subordinated process into a process described by a random barrier model, we can obtain a generalization of the multiple-trapping model. Then, the same result could be obtained within the framework of the lattice model. Some further generalizations and modifications are also considered.

In the Laplace space, the system of Eqs. (1) and (2) can be reduced to a single equation with respect to the total concentration $\rho = f + \sum_{i=1}^{N} c_i$ [in this study, the original functions $g(t)$ and their transforms $g(s) = \int_0^\infty dt \exp(-st) g(t)$ are distinguished by their arguments]:

$$s\rho(\mathbf{r}, s) - \rho^0(\mathbf{r}) = D\Phi(s)\nabla^2\left[\rho(\mathbf{r}, s) - \frac{1-\Omega(s)}{s}\rho^0(\mathbf{r})\right], \tag{3}$$

where

$$\Phi(s) = \left[1 + \sum_{i=1}^{N} \frac{\omega_i}{s+\nu_i}\right]^{-1}, \tag{4}$$

$$\Omega(s) = 1 - s\sum_{i=1}^{N} \frac{\theta_i^0}{s+\nu_i}, \tag{5}$$

$$\theta_i^0 = \frac{c_i^0(\mathbf{r})}{\rho_i^0(\mathbf{r})}, \tag{6}$$

and $c_i^0(\mathbf{r})$ and $\rho_i^0(\mathbf{r})$ are the initial conditions. The solution of this equation corresponding to the initial condition $\rho(\mathbf{r}, s) = \delta_d(\mathbf{r})$ (propagator) has the form

$$\rho(\mathbf{r}, s) = \frac{\Omega(s)}{s}\frac{\beta^d}{(2\pi)^{d/2}}(r\beta)^{1-d/2}K_{1-d/2}(r\beta) + \frac{1-\Omega(s)}{s}\delta_d(\mathbf{r}), \tag{7}$$

where $r = |\mathbf{r}|$, $K_{1-d/2}(r)$ is a modified Bessel function of the second kind. The parameter $\delta_d(\mathbf{r})$ is the $d$-dimensional delta function, and $\beta = \sqrt{\frac{s}{D\Phi(s)}}$.

Subordination is a mathematical method that broadens the applicability of classical transport models [7–11]. In this method, the clock time of a stochastic process $X(t)$ is randomized by introducing a new time $\sigma = S(t)$. The resulting process $Y(t) = X[S(t)]$ is subordinated to the parent process $X(\sigma)$, and $\sigma$ is commonly referred to as the leading process or the operational time. If the processes $X(\sigma)$ and $S(t)$ are independent, then the propagator (one-point distribution function) of the resulting process is [12,11]

$$P^Y(\mathbf{r}, t) = \int_0^\infty d\sigma\, P^X(\mathbf{r}, \sigma) P^S(\sigma, t). \tag{8}$$

Here, $P^X(\mathbf{r}, \sigma)$ is a one-point distribution function of the process $X(\sigma)$, and $P^S(t, \sigma)$ is a one-point distribution function of the process $S(t)$. If the renewal process is taken as the leading process, the propagator of the resulting process in the Laplace space ($t \to s$) will be equal to [11]

$$P^Y(\mathbf{r}, s) = \frac{\phi(s, t_0)[1-\psi(s)]}{s\psi^2} P^X\left(\mathbf{r}, u = \frac{1-\psi(s)}{\psi(s)}\right) + \frac{\psi(s) - \phi(s, t_0)}{s\psi(s)}\delta(\mathbf{r}). \tag{9}$$

Here, $P^X(\mathbf{r}, u)$ is the Laplace image ($\sigma \to u$) of the propagator of the parent process, and $\psi(s)$ is the Laplace image of the waiting time distribution function. The parameter $\phi(s, t_0)$ is the recurrence time, and $t_0$ is the delay time. In the Laplace space ($t_0 \to \lambda$), the function $\phi(s, t_0)$ is written as

$$\phi(s, \lambda) = \frac{\psi(\lambda) - \psi(s)}{[1-\psi(\lambda)][s-\lambda]}. \tag{10}$$

The delay time is the time elapsed between the start of the renewal process and the beginning of the process monitoring.

To obtain the propagator (7) by the subordination method, the usual diffusion process (the Wiener process) should be used as the parent process. The propagator of this process in the Laplace space ($\sigma \to u$) is given by the formula

$$P^X(\mathbf{r}, u) = \frac{\beta^d}{u(2\pi)^{d/2}}(r\beta)^{1-d/2}K_{1-d/2}(r\beta), \tag{11}$$

where $\beta = \sqrt{\frac{u}{D}}$. The distribution function $\psi(s)$ should be given in the form

$$\psi(s) = \frac{W}{W + s + \sum_{i=1}^{N} \frac{s\omega_i}{s+\nu_i}} \tag{12}$$

with the parameter $W$ equal to 1 and the recurrence time in the form $\phi(s, \lambda) = \Omega(s)\psi(s)$. The last relation will be consistent with Eqs. (10) and (12) if the initial values $\theta_i^0$, which appear in expression (5), are given in the form

$$\theta_i^0(\lambda) = \frac{\Phi(\lambda)}{\lambda}\frac{\omega_i}{\lambda+\nu_i}. \tag{13}$$

From this formula, with the delay time equal to zero, all $\theta_i^0$ [$\theta_i^0(t_0 = 0) = \lim_{\lambda\to\infty} \lambda\theta_i^0(\lambda)$] are equal to zero. Therefore, the renewal process starts when the particle is in the transport state. With a delay time equal to infinity, all $\theta_i^0$ [$\theta_i^0(t_0 = \infty) = \lim_{\lambda\to 0} \lambda\theta_i^0(\lambda)$] are equal to the equilibrium values:

$$\theta_i^0(t_0 = \infty) = \frac{\omega_i}{\nu_i}\left[1 + \sum_{k=1}^{N}\frac{\omega_k}{\nu_k}\right]^{-1}. \tag{14}$$

[Integrating Eqs. (1) and (2) over the whole space and solving them in the Laplace space $t \to \lambda$ under the initial conditions $f^0 = 1$, $\theta_i^0 = 0$, the dependence of the probabilities $\theta_i$ on the delay time is described by Eq. (13) in the multiple-trapping model.]

Thus, the multiple-trapping model describes a subordinated stochastic process, in which the role of the parent process is represented by ordinary diffusion and the role of the leading process is represented by the renewal process with the waiting time distribution function (12). This interpretation of the model allows us to generalize it for the case in which there are obstacles other than traps in a disordered medium. Thus,

ordinary diffusion was not used as the parent process; instead, random walks in the random barrier model were used [13]. This model describes the motion along a random potential relief, in which all local minima are on the same level. For the properties, this model is similar to the Lorentz model [14]. (In review [14], the random barrier model was referred to as the random-resistor network.) The propagator of this model averaged over the ensemble of configurations satisfies the non-Markovian equation

$$\frac{\partial f(\mathbf{r},t)}{\partial t} = \int_0^t D(t-\tau)\nabla^2 f(\mathbf{r},\tau)d\tau. \tag{15}$$

In the Laplace space it differs from the usual diffusion propagator (11) in that the diffusion coefficient is a function of the Laplace variable: $D = D(u)$ [15]. Therefore, the propagator of the resulting process has the same form as propagator (7):

$$\rho(\mathbf{r},s) = \frac{\Omega(s)}{s}\frac{\beta^d}{(2\pi)^{d/2}}(r\beta)^{1-d/2}K_{1-d/2}(r\beta) + \frac{1-\Omega(s)}{s}\delta_d(\mathbf{r}), \tag{16}$$

with parameter $\beta$ equal to $\sqrt{\frac{s}{\Psi(s)\Phi(s)}}$, where $\Psi(s) = D(\frac{s}{\Phi(s)})$. This propagator satisfies the equation

$$s\rho(\mathbf{r},s) - \rho^0(\mathbf{r}) = \Psi(s)\Phi(s)\nabla^2\rho(\mathbf{r},s) - \frac{1-\Omega(s)}{s}\nabla^2\rho^0(\mathbf{r}) \tag{17}$$

with the initial condition $\rho^0(\mathbf{r}) = \delta_d(\mathbf{r})$. The analog of the system of Eqs. (1) and (2) in this case is the system

$$\frac{\partial f(\mathbf{r},t)}{\partial t} = \int_0^t \Psi(t-\tau)\nabla^2 f(\mathbf{r},\tau)d\tau - \sum_{i=1}^N \omega_i f(\mathbf{r},t) + \sum_{i=1}^N \nu_i c_i(\mathbf{r},t), \tag{18}$$

$$\frac{\partial c_i(\mathbf{r},t)}{\partial t} = -\nu_i c_i(\mathbf{r},t) + \omega_i f(\mathbf{r},t), \quad i = 1,\ldots,N. \tag{19}$$

The equations of this system have the same meaning as Eqs. (1) and (2). The difference between them is in the transport term, which in this case is non-Markovian because of the random barriers. System (18) and (19) cannot be obtained from the equation for the propagator of the model of the random barrier (15) by adding in this equation of the source terms and writing the equations for the traps. This could be accomplished if Eq. (15) were Markovian. In the non-Markovian case, the memory function $D(t)$ does not remain unchanged; however, it can be modified, i.e., replaced by a function $\Psi(t)$.

In the subordination method, it is assumed that the parent and leading processes are independent. For the application of this model, the traps and barriers are chaotically distributed. Near a barrier of any height, there can be a trap of any depth with equal probability. This is a limitation of this approach, as in real environments the distributions of traps and barriers can be correlated. To obtain more general models, the Markov representation of the random barrier model can be used instead of the non-Markovian equation for the propagator (15). In this approach, it is assumed that at each position in space, the particle can be in $M$ different transport states, and that the probabilities of being in these states satisfy the equations [16,17]

$$\frac{\partial f_i(\mathbf{r},t)}{\partial t} = -\kappa_i f_i(\mathbf{r},t) + \kappa_i\alpha_i F(\mathbf{r},t), \quad i = 1,\ldots,M, \tag{20}$$

where $f_i$ is the probability of a particle in the state of the $i$th type. The parameter $\kappa_i$ is the escape rate from the state of the $i$th type, and $\alpha_i$ is the fraction of states of the $i$th type. The function $F(\mathbf{r},t)$ is equal to $f(\mathbf{r},t) + a^2\nabla^2 f(\mathbf{r},t)]$, $f = \sum_{i=1}^M f_i$ is the total probability, and $a^2$ is a constant. Different states are treated as particle locations surrounded by barriers of different heights. From these equations, with an equiprobable initial state distribution $f_i^0 = \alpha_i f^0$, the total probability satisfies Eq. (15) with the memory function, which in the Laplace space has the form

$$D(u) = a^2\frac{u\chi(u)}{1-\chi(u)}, \tag{21}$$

where $\chi(u) = \sum_{i=1}^M \frac{\alpha_i\kappa_i}{u+\kappa_i}$. The equiprobable distribution $f_i^0 = \alpha_i f^0$ is also an equilibrium distribution for Eqs. (20). Hence, Eq. (15) is also valid for an equilibrium initial distribution [Eqs. (20) preserve the characteristic properties of the random barrier model].

Because Eqs. (20) are Markovian, source terms can be added without additional modifications. Correlations can be taken into account, i.e., in different equations, different source terms can be added, and different equations can be written for the traps corresponding to these equations. To obtain the model considered above (17), (18), and (19), the same source terms should be added to Eqs. (20) and the same set of equations for the traps corresponding to these equations should be used:

$$\frac{\partial f_i(\mathbf{r},t)}{\partial t} = -\kappa_i f_i(\mathbf{r},t) + \kappa_i\alpha_i F(\mathbf{r},t) - \sum_{j=1}^N \omega_j f_i(\mathbf{r},t) + \sum_{j=1}^N \nu_j c_{ij}(\mathbf{r},t), \quad i = 1,\ldots,M, \tag{22}$$

$$\frac{\partial c_{ij}(\mathbf{r},t)}{\partial t} = -\nu_j c_{ij}(\mathbf{r},t) + \omega_j f_i(\mathbf{r},t), \quad i = 1,\ldots,M, \quad j = 1,\ldots,N. \tag{23}$$

The concentrations of the particles in the traps have two indexes. One of them ($j$) corresponds to the trap type, and the other ($i$) corresponds to the type of transport state associated with the trap. A particle is assumed to fall into a trap only from a transport state of one type and move from a trap to a transport state of the same type, i.e., a certain type of transport state corresponds to each trap. If this condition is abandoned, and the transitions are assumed to occur in different states with the same probability, the model considered in [18] is

obtained:

$$\frac{\partial f_i(\mathbf{r},t)}{\partial t} = -\kappa_i f_i(\mathbf{r},t) + \kappa_i \alpha_i F(\mathbf{r},t) - \sum_{j=1}^{N} \omega_j f_i(\mathbf{r},t) + \alpha_i \sum_{j=1}^{N} \nu_j c_j(\mathbf{r},t), \quad i = 1,\ldots,M, \tag{24}$$

$$\frac{\partial c_j(\mathbf{r},t)}{\partial t} = -\nu_j c_j(\mathbf{r},t) + \omega_j f(\mathbf{r},t), \quad j = 1,\ldots,N. \tag{25}$$

Both of these systems of equations are brought to the same equation for the total concentration (17) (see Appendix A). In the first case, the memory function has the same form as that in the method of subordination:

$$\Psi(s) = D\left(\frac{s}{\Phi(s)}\right), \tag{26}$$

and in the second,

$$\Psi(s) = D\left(s + \sum_{i=1}^{N} \omega_i\right). \tag{27}$$

Here, the memory function $D(u)$ is given by Eq. (21). Both of these memory functions behave qualitatively, as does the function $D(u)$. They are positive monotonically increasing functions with a negative second derivative [in the lattice model, which is the random barrier model, $D(u)$ satisfies these properties [19,15]].

The simplest model with correlations has the form

$$\frac{\partial f_i(\mathbf{r},t)}{\partial t} = -\kappa_i f_i(\mathbf{r},t) + \kappa_i \alpha_i F(\mathbf{r},t) - \omega_i f_i(\mathbf{r},t) + \nu_i c_i(\mathbf{r},t), \quad i = 1,\ldots,M, \tag{28}$$

$$\frac{\partial c_i(\mathbf{r},t)}{\partial t} = -\nu_i c_i(\mathbf{r},t) + \omega_i f_i(\mathbf{r},t), \quad i = 1,\ldots,M. \tag{29}$$

Here, each transport state is connected with its own type of traps, and different states have different types of traps. In this model, the propagator has the same form as that in the models without correlations (17). However, there are other factors in front of the Bessel function and the $\delta$ function, as well as another expression for the parameter $\beta$ (see Appendix B).

In the following sections, the expression for the propagator (16) and Eq. (17) are used to determine theoretical expressions corresponding to the curves obtained in the experiments using fluorescence spectroscopy.

## III. FLUORESCENCE RECOVERY AFTER PHOTOBLEACHING

In the FRAP experiment, the recovery of fluorescence after photobleaching in a small volume is measured. The fluorescence recovery originates from fluorescently tagged particles that move randomly in the volume and cause replacement of the bleached particles. Before photobleaching, the system is in equilibrium.

Together with the authors of a previous study [2], a model that accounts for a finite nucleus and an arbitrary initial bleach profile is considered. A circular nucleus of radius $R_N$ that is photobleached at its center with an arbitrary, radially symmetric bleach profile $I(r)$ was assumed. The intensity was measured within a centered circle of radius $R_M$.

The authors of [2] used a standard multiple-trapping model (1) and (2) with one type of trap ($N = 1$). In this study, a more general model was considered, with the presence of barriers with an arbitrary number of types of traps (18) and (19). The problem was solved in the Laplace space.

Equation (17) should be solved in the two-dimensional region $r \leqslant R_N$ with the initial condition $\rho^0(r) = I(r)$ and the boundary condition $\frac{\partial \rho}{\partial r}|_{R_N} = 0$. The solution should be finite at $r = 0$. Because the initial state of the system (before the flash) was in equilibrium, the values of $\theta_i^0$ were expressed by formula (14). Thus, the function $\Omega(s)$ equals $\frac{\Phi(0)}{\Phi(s)}$ [from relations (13) and (14)]. To obtain a curve corresponding to the experiment, the obtained solution $\rho(\mathbf{r},s)$ was integrated over the circle $r \leqslant R_M$.

The solution of Eq. (17) is represented in the form

$$\rho(\mathbf{r},s) = Q(\mathbf{r},s) + \frac{1-\Omega(s)}{s}\rho^0(\mathbf{r}), \tag{30}$$

where the function $Q(\mathbf{r},s)$ is a solution of the equation

$$sQ(\mathbf{r},s) - \Omega(s)\rho^0(\mathbf{r}) = \Psi(s)\Phi(s)\nabla^2 Q(\mathbf{r},s). \tag{31}$$

The solution of this equation was expressed in terms of the Green's function. The Green's function can be defined as a bounded solution of the one-dimensional equation

$$sG(r,r^0,s) - \delta(r-r^0) = \Psi(s)\Phi(s)\left(\frac{\partial^2}{\partial r^2} + \frac{1}{r}\frac{\partial}{\partial r}\right)G(r,r^0,s) \tag{32}$$

satisfying the boundary condition $\frac{\partial G(r,r^0,s)}{\partial r}|_{R_N} = 0$. The function $Q(r,s)$ was expressed as follows:

$$Q(r,s) = 2\pi\Omega(s)\int_0^{R_N} dr^0 r^0 I(r^0) G(r,r^0,s). \tag{33}$$

Integrating $\rho(r,s)$ (30) over the circle $r \leqslant R_M$, the following relation was obtained:

$$\mathrm{frap}(s) = 2\pi\Omega(s)\int_0^{R_N} dr\, r I(r) P(r,s) + \frac{1-\Omega(s)}{s} 2\pi \int_0^{R_M} dr\, r I(r), \tag{34}$$

where

$$P(r^0,s) = 2\pi\int_0^{R_M} dr\, r G(r,r^0,s) \tag{35}$$

is the probability that the particle starting from the point $r^0$ is in circle $r \leqslant R_M$. This probability satisfies the equation analogous to (32), with a different initial condition [20]:

$$sP(r,s) - \Theta_M(r) = \Psi(s)\Phi(s)\left(\frac{\partial^2}{\partial r^2} + \frac{1}{r}\frac{\partial}{\partial r}\right)P(r,s). \tag{36}$$

The parameter $\Theta_M(r)$ is the characteristic function of the interval $0 \leqslant r \leqslant R_M$. The boundary condition remains the same: $\frac{\partial P(r,s)}{\partial r}|_{R_N} = 0$.

The bounded solution of Eq. (36) has the form

$$P(r,s) = \begin{cases} \frac{1}{s} + AI_0(\beta r), & 0 < r < R_M, \\ BK_0(\beta r) + CI_0(\beta r), & R_M < r < R_N. \end{cases} \tag{37}$$

Here, $I_0$ and $K_0$ are the modified Bessel functions of the first and second kind, respectively, $\beta = \sqrt{\frac{s}{\Psi(s)\Phi(s)}}$. The coefficients $A$, $B$, and $C$ were determined from the boundary condition and the requirement of continuity of the function $P(r,s)$ and its first derivative at the point $r = R_M$. The final expression for the function $P(r,s)$ can be written as

$$P(r,s) = \begin{cases} \frac{1}{s} - \frac{\beta R_M}{s} I_0(\beta r)\left[K_1(\beta R_M) - I_1(\beta R_M)\frac{K_1(\beta R_N)}{I_1(\beta R_N)}\right], & 0 < r < R_M, \\ \frac{\beta R_M}{s} I_1(\beta R_M)\left[K_0(\beta r) + I_0(\beta r)\frac{K_1(\beta R_N)}{I_1(\beta R_N)}\right], & R_M < r < R_N. \end{cases} \tag{38}$$

[In the course of calculation, the following relations between the modified Bessel functions were used: $\frac{dI_0(x)}{dx} = I_1(x)$, $\frac{dK_0(x)}{dx} = -K_1(x)$, $I_1(x)K_0(x) + I_0(x)K_1(x) = x^{-1}$.] Substituting this expression into Eq. (34), the final expression was obtained for frap$(s)$:

$$\text{frap}(s) = 2\pi \int_0^{R_N} dr\, r I(r) S(r,s), \tag{39}$$

where the function $S(r,s)$ has the form

$$S(r,s) = \begin{cases} \frac{1}{s} - \Omega(s)\frac{\beta R_M}{s} I_0(\beta r)\left[K_1(\beta R_M) - I_1(\beta R_M)\frac{K_1(\beta R_N)}{I_1(\beta R_N)}\right], & 0 < r < R_M, \\ \Omega(s)\frac{\beta R_M}{s} I_1(\beta R_M)\left[K_0(\beta r) + I_0(\beta r)\frac{K_1(\beta R_N)}{I_1(\beta R_N)}\right], & R_M < r < R_N. \end{cases} \tag{40}$$

For an infinite nucleus and special profile $I(r) = 0$ for $0 < r < R_M$ and $I(r) = \frac{1}{\pi R_M^2}$ for $r > R_M$, the following was obtained from (39):

$$\text{frap}(s) = \frac{2\Omega(s)}{s} I_1(\beta R_M) K_1(\beta R_M). \tag{41}$$

[For the calculations, the following properties of the modified Bessel functions were used: the quotient $\frac{K_1(\beta R_N)}{I_1(\beta R_N)}$ was equal to zero for an infinite $R_N$; the integral $\int_{R_M}^{\infty} dr\, r K_0(\beta r)$ was equal to $\frac{R_M}{\beta} K_1(\beta R_M)$.] This formula was obtained in previous studies [3,4] for $N = 1$. In these studies, $\Phi(s)$ was equal to $[1 + \frac{k_{\text{on}}^*}{s + k_{\text{off}}}]^{-1}$, and the function $\Omega(s)$ was equal to $[1 + \frac{k_{\text{on}}^*}{s + k_{\text{off}}}][1 + \frac{k_{\text{on}}^*}{k_{\text{off}}}]^{-1}$. The function $\Psi(s)$ in study [3] was equal to $D_\gamma (s + k_{\text{on}}^*)^{1-\gamma}$, and in study [4] it was equal to the constant $D_f$.

The transition to real time in Eq. (39) should be carried out numerically. In some cases, an analytical expression can be obtained in the form of an infinite series. To accomplish this, function (40) is expanded in a Fourier series with respect to the Bessel functions $J_0(\alpha_i r)$ on the interval $(0, R_N)$, and term-by-term integration in (39) is performed. The result is an expression

$$\text{frap}(s) = 2\pi R_M \sum_0^{\infty} \left( \frac{\Omega(s)}{s + \alpha_i^2 \Psi(s)\Phi(s)} + \frac{1 - \Omega(s)}{s} \right) \times \frac{f_i}{\alpha_i} J_1(\alpha_i R_M). \tag{42}$$

Here, $\alpha_i = \frac{\kappa_i}{R_N}$, $\kappa_i$ are the zeros of the function $J_1(r)$,

$$f_i = \frac{2}{R_N^2 J_0^2(\kappa_i)} \int_0^{R_N} dr\, r I(r) J_0(\alpha_i r). \tag{43}$$

(This result can also be obtained by solving the initial problem using the method of separation of variables.) For the simple functions $\Phi(s)$ and $\Psi(s)$, each term of this series can be inverted analytically. In particular, when $\Phi(s) = [1 + \frac{k_{\text{on}}^*}{s + k_{\text{off}}}]^{-1}$ and $\Psi(s) = D_f$, the result from a previous study is obtained [2].

## IV. FLUORESCENCE CORRELATION SPECTROSCOPY

In the FCS experiment, the time correlation function of the fluorescence fluctuations is measured. The fluorescence stems from fluorescently tagged particles that move randomly in the volume. The random movement creates spontaneous local concentration changes, which cause fluorescence fluctuations. The measurements are carried out in an equilibrium system.

The FCS curve is represented as an integral from the product of the propagator to the apparatus function that determines the laser intensity distribution [21]:

$$G(t) = \int d\mathbf{r}\, \rho(\mathbf{r}, t) F(\mathbf{r}). \tag{44}$$

If the laser intensity distribution is Gaussian, then the apparatus function can be written as

$$F(\mathbf{r}) = \exp\left( -\frac{x^2 + y^2}{a} - \frac{z^2}{b} \right), \tag{45}$$

where $a$ and $b$ are positive parameters. For normal diffusion, the integral (44) is calculated explicitly:

$$G_{\text{norm}}(t) = \left(1 + \frac{4Dt}{a}\right)^{-1} \left(1 + \frac{4Dt}{b}\right)^{-0.5}. \tag{46}$$

Using this result, the Laplace image of the FCS curve for the model under consideration was determined. In the Laplace space, formula (44) can be written in the form

$$G(s) = \int d\mathbf{r}\, \rho(\mathbf{r}, s) F(\mathbf{r}). \tag{47}$$

In the model under consideration, the propagator $\rho(\mathbf{r}, s)$ is given by Eq. (16). The dependence on $\mathbf{r}$ of the first term on the right-hand side of this formula does not differ from the dependence on $\mathbf{r}$ of the diffusion propagator (11). Consequently, the integral of this term has the same functional form as the integral of the diffusion propagator. The difference is the appearance of a factor $\Omega(s)$ and the replacement of the diffusion constant $D$ with the product $\Psi(s)\Phi(s)$. The second term is integrated. Taking into account that for normal diffusion the Laplace image of the FCS curve has the form

$$G_{\text{norm}}(s) = \int_0^\infty dt \exp(-st)\left(1+\frac{4Dt}{a}\right)^{-1}\left(1+\frac{4Dt}{b}\right)^{-0.5}, \tag{48}$$

the Laplace image of the FCS curve can be obtained for the model under consideration:

$$G(s) = \Omega(s)\int_0^\infty dz \exp(-sz)\left(1+\frac{4\Psi(s)\Phi(s)z}{a}\right)^{-1} \times \left(1+\frac{4\Psi(s)\Phi(s)z}{b}\right)^{-0.5} + \frac{1-\Omega(s)}{s}. \tag{49}$$

Because the FCS experiment was performed under equilibrium conditions, the function $\Omega(s)$ in this formula is equal to $\frac{\Phi(0)}{\Phi(s)}$. For clarity, the integration variable $t$ is renamed ($t \to z$) because it does not refer to time.

## V. SINGLE-PARTICLE TRACKING

The SPT experiment included tracing the trajectory of an individual particle. A labeled particle is introduced into the test sample and monitored with a video microscope. The trajectory of the particle $r(t)$ is recorded for a time sufficient to have a complete statistics of spatial displacements. The information thus obtained allows, in principle, to find all the correlation functions. In particular, the propagator (16) and all the quantities calculated with it can be found. The expression for the mean-square displacement is given as [$\langle \mathbf{r}^2\rangle(s) = \int d\mathbf{r}\, \mathbf{r}^2 \rho(\mathbf{r}, s)$]:

$$\langle \mathbf{r}^2\rangle(s) = 2d\Psi(s)\Phi(s)\frac{\Omega(s,\lambda)}{s^2}. \tag{50}$$

Here, the dependence of the initial probabilities (13) on $\lambda$ is considered, which allows for the calculation of a widely used quantity, the mean-square displacement averaged over the ensemble and in time (delay time). For a fully equilibrated system [when $\Omega(s) = \frac{\Phi(0)}{\Phi(s)}$], expression (50) reduces to

$$\langle \mathbf{r}^2\rangle(s) = 2d\Psi(s)\frac{1}{\bar{\tau}s^2}, \tag{51}$$

where $\bar{\tau} = \frac{1}{W}[1 + \sum_{k=1}^{N} \frac{\omega_k}{\nu_k}]$. The characteristic feature of this expression is that it does not depend on the function $\Phi(s)$; therefore, if there are no barriers, i.e., if $\Psi(s)$ does not depend on $s$, the mean-square displacement is a linear function of time.

The expression (50) can be rewritten as

$$\langle \mathbf{r}^2\rangle(s,\lambda) = 2d\frac{\Psi(s)}{s(\lambda - s)}\left(\frac{\Phi(s)}{s} - \frac{\Phi(\lambda)}{\lambda}\right). \tag{52}$$

Performing inverse Laplace transforms with respect to $s$ and $\lambda$, the expression for the mean-square displacement of the particles as a function of time $t$ and delay time $t_0$ is obtained:

$$\langle \mathbf{r}^2\rangle(t, t_0) = \int_0^t d\tau\ f_1(t-\tau) f_2(t_0+\tau). \tag{53}$$

The parameter $f_1(t)$ is the original of the function $\frac{2d\Psi(s)}{s}$, and $f_2(t_0)$ is the original of the function $\frac{\Phi(\lambda)}{\lambda}$. After averaging this expression with respect to $t_0$, the expression for the mean-square displacement of the particles averaged over both time and ensemble is obtained [the notation for the variable $t$ ($t \to \Delta$) is changed]:

$$\langle \bar{\mathbf{r}^2}\rangle(\Delta, T) = \frac{1}{T-\Delta}\int_0^{T-\Delta} dt_0 \times \int_0^{\Delta} d\tau\ f_1(\Delta-\tau) f_2(t_0+\tau). \tag{54}$$

Here, $T - \Delta$ is the period of time over which the averaging is carried out. If the condition $\Delta \ll T$ is fulfilled, then by substituting $T - \Delta \to T$ and $t_0 + \tau \to t_0$, the last expression can be reduced to the form

$$\langle \bar{\mathbf{r}^2}\rangle(\Delta, T) = \frac{1}{T}\int_0^{T} dt_0 f_2(t_0)\int_0^{\Delta} d\tau\ f_1(\tau). \tag{55}$$

## VI. DISCUSSION AND CONCLUSION

The subordination method has been used in numerous studies to model diffusion processes in disordered media. The approach proposed in this study differs from the others in two aspects. First, using this approach, it is possible to obtain an analytic propagator expression (as well as the corresponding equation) for a disordered medium that contains traps and obstacles. Second, this propagator (and corresponding equation) can be applied to nonequilibrium and equilibrium systems. In previous studies, the subordination method was applied only to nonequilibrium systems. In addition, if a medium with traps and obstacles was considered, the expression for the propagator remained unknown. For example, in previous studies [5,22], the continuous-time random walk (CTRW) on fractals was considered. This model described diffusion in a medium with traps and obstacles; however, there was no analytic expression for the propagator in this model. An equation describing the diffusion process was also absent. In previous studies [23,24], the CTRW model was used to describe FRAP and FCS experiments. The equation describing the diffusion process in the Laplace space was as follows:

$$s\rho(\mathbf{r}, s) - \rho^0(\mathbf{r}) = \Phi(s)\nabla^2\rho(\mathbf{r}, s) \tag{56}$$

with $\Phi(s) = K_\alpha s^{1-\alpha}$. Comparing this equation with Eq. (17), the function $\Psi(s)$ and inhomogeneous term $\frac{1-\Omega(s)}{s}\nabla^2\rho^0(\mathbf{r})$ are absent. The absence of the function $\Psi(s)$ shows that this approach neglected the presence of obstacles in disordered

media, and the absence of the inhomogeneous term showed that the experiment was carried out in a nonequilibrium system. However, obstacles can be present in a disordered medium, and the experiment is usually carried out in an equilibrium system.

The multiple-trapping model is a form of the CTRW model [13]. In this form, the waiting time distribution, $\psi(s)$, is definite: $\psi(s) = \frac{W}{W+s+\sum_{i=1}^{N} \frac{s\omega_i}{s+\nu_i}}$. This form of the CTRW model was used because its parameters have a certain physical meaning, and it is used in practice to describe the experimental data. However, all the expressions obtained here are also valid for the general CTRW model. In this case, the functions $\Phi(s)$ and $\Omega(s,\lambda)$ have the forms $\Phi(s) = \frac{s\psi(s)}{1-\psi(s)}$ and $\Omega(s,\lambda) = \frac{\phi(s.\lambda)}{\psi(s)} = \frac{\psi(\lambda)-\psi(s)}{\psi(s)[1-\psi(\lambda)][s-\lambda]}$.

The model considered in this study has two functions as parameters: $\Phi(s)$ and $\Psi(s)$. The form of the function $\Phi(s)$ is given by Eq. (4). For an unambiguous determination, the parameters $N$ and $2N$ of the parameters $\nu_i$ and $\omega_i$ should be specified. The function $\Psi(s)$ is expressed in terms of the indeterminate function $D(s)$; therefore, its form can be set arbitrarily. It should be a positive monotonically increasing function with a negative second derivative. For the simplest functions satisfying these conditions, a power function $\Psi(s) = A(s+k)^n$, where $A > 0$, $k > 0$, $1 > n > 0$, or a fractional rational function $\Psi(s) = A\frac{1+as}{1+bs}$, where $A > 0$, $b > 0$, $a > b$, can be used. If one type of binding site is assumed, $N = 1$, then the model would contain five parameters: $\nu_1$, $\omega_1$, $A$, $k$, and $n$ in the first case and $\nu_1$, $\omega_1$, $A$, $a$, and $b$ in the second case. The numerical values of these parameters can be determined by the method of least squares. The input data can be the FRAP curve, FCS curve, propagator, or mean-square displacement. The corresponding theoretical expressions are (39) and (40) for the FRAP curve, (49) for the FCS curve, (16) for the propagator, and (53) and (54) for the mean-square displacement. For the functions $\Phi(s)$ and $\Psi(s)$, the parameters $\nu_i$ and $\omega_i$ are known, which characterize the binding properties of the molecules. To establish the diffusion properties, one of the functionals Eq. (26) or (27) with respect to the function $D(s)$ should be solved. The equations to be solved are dependent on which of the two systems of Eqs. (22) and (23) or Eqs. (24) and (25) is more adequate for the case under consideration. However, the structure of the disordered medium under consideration should be known.

The number of parameters in the model under consideration is large; therefore, determining them from a single FRAP curve or a single FCS curve is not possible. The results of study [3] show that for two FRAP curves measured at different bleached spot radius values, the parameters cannot be determined reliably. In [6], the data from FRAP, FCS, and SPT experiments were simultaneously used to determine the parameters. Because the SPT experiment provides detailed information on diffusion and binding processes, the model parameters can be reliably determined based on data from this experiment. However, it is necessary to have an appropriate method for processing the experimental data. As a possible method, the model parameters can be determined when the mean-square displacement is known for delay times, $t_0$, of zero and infinity. A delay time of zero represents the start of the monitoring of the system at the time of its creation, i.e., at the moment when the particle that is being monitored is placed in the medium. In this case, all $\theta_i^0$ values are equal to zero; hence, $\Omega(s) = 1$. The expression for the MSD is in the form

$$\langle \mathbf{r}^2 \rangle(s) = 2d\frac{\Psi(s)\Phi(s)}{s^2}. \tag{57}$$

A delay time equal to infinity means that the system reaches an equilibrium state. In this case, the MSD has the form of Eq. (51). Because the function $\Phi(s)$ is not in Eq. (51), the parameters $\frac{A}{\bar{\tau}}$, $k$, and $n$ (or $\frac{A}{\bar{\tau}}$, $a$, and $b$) can be determined from the MSD measured in the equilibrium state. Subsequently, the two parameters $\omega_1$ and $\nu_1$ from the MSD measured in the nonequilibrium system, (57), should be determined. Figure 1 shows the qualitative behavior of the MSD for a nonequilibrium system, (57), and MSD for an equilibrium system, (51), in different models. The MSD for the nonequilibrium system behaves qualitatively the same in all models (curve 1); however, the MSD for the equilibrium system behaves differently in different models. In the random barrier model [i.e., when $\Phi(s) = 1$ and $\bar{\tau} = 1$], MSD (57) and MSD (51) coincided (curve 1). In the multiple-trapping model (i.e., when $\Psi(s) = \text{const}$), MSD (51) is a straight line (curve 2), and MSD (57) is a curve with an asymptote parallel to this straight line (curve 1). In the mixed model, MSD (51) (curve 3) is located between MSD (57) (curve 1) and the straight line, leaving the origin parallel to the asymptote of MSD (57) (curve 2).

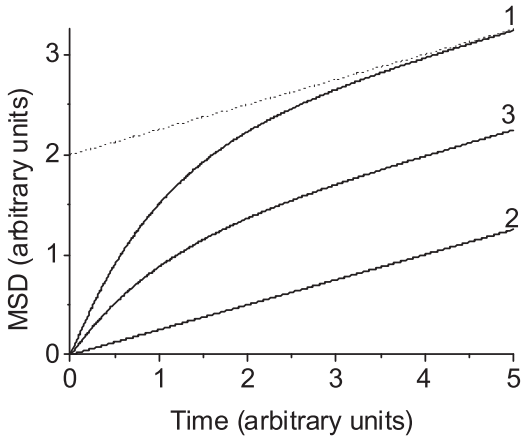


FIG. 1. MSD for equilibrium and nonequilibrium systems in different models. Curve 1, MSD for a nonequilibrium system in all models and for an equilibrium system in the random barrier model. Curve 2, MSD for an equilibrium system in the multiple-trapping model. Curve 3, MSD for an equilibrium system in a mixed model. Dots: the asymptote of curve 1.

These two examples confirm the accuracy of the proposed model. For the first example, the authors of study [3] used a special case of the model to describe the experimental data obtained in study [4]. A model with a function $\Psi(s)$ different from a constant is more adequate than the traditional model. The authors of [4] found that with the standard multiple-trapping model, it is impossible to determine unambiguous values of the model parameters. For different values of the radius of the bleached spot, different values of the model parameters are obtained. Concurrently, the authors of [3] established that with a generalized multiple-trapping model,

the data corresponding to different bleached spot radii by one set of parameters could be determined. Note that the authors of [3] interpreted their equations differently from those in this study. They believed that the appearance of the function $\Psi(s)$ was a result of the anomalous diffusion described by the continuous-time random-walk model. They have neglected the fact that in the framework of this model, Eq. (15) is valid only in the nonequilibrium case.

For the second example, the model under consideration provides the same result as the CTRW on fractals [22]. If the function $D(s)$ has the form

$$D(s) \sim s^{1-\beta} \tag{58}$$

(i.e., it describes the anomalous subdiffusion resulting from the barriers), and the function $\Phi(s)$ has the form

$$\Phi(s) \sim s^{1-\alpha} \tag{59}$$

(i.e., it describes the anomalous subdiffusion resulting from the traps), then the function $\Psi(s)$ [Eq. (26)] can be written as

$$\Psi(s) \sim s^{\alpha-\alpha\beta}, \tag{60}$$

and the time-averaged mean-square displacement (55) can be written in the form

$$\langle \bar{\mathbf{r}^2} \rangle(\Delta, T) \sim T^{\alpha-1}\Delta^{1+\alpha\beta-\alpha}. \tag{61}$$

The same dependence was obtained experimentally in study [5] with $\alpha = 0.9$ and $\beta = 0.77$. The standard multiple-trapping model corresponds to the value $\beta = 1$; therefore, it is not capable of reproducing this behavior.

In conclusion, in this study, a mathematical model was proposed to describe experiments using fluorescent microscopy in disordered media containing binding sites and obstacles. In the Laplace space, the expressions for the propagator, the mean-square displacement as a function of the observation and delay times, the FRAP curve, and the FCS curve were derived. The model can be used to determine the parameters characterizing the diffusion and binding properties of molecules in crowded environments.

## APPENDIX A

In the Laplace space, Eqs. (22) and (23) have the form

$$sf_i(\mathbf{r}, s) - \alpha_i f^0(\mathbf{r}) = -\kappa_i f_i(\mathbf{r}, s) + \kappa_i\alpha_i F(\mathbf{r}, s) - \sum_{j=1}^{N} \omega_j f_i(\mathbf{r}, s) + \sum_{j=1}^{N} \nu_j c_{ij}(\mathbf{r}, s), \quad i = 1, \ldots, M, \tag{A1}$$

$$sc_{ij}(\mathbf{r}, s) - \alpha_i c_j^0(\mathbf{r}) = -\nu_j c_{ij}(\mathbf{r}, s) + \omega_j f_i(\mathbf{r}, s), \quad i = 1, \ldots, M, \quad j = 1, \ldots, N. \tag{A2}$$

The second equation $c_{ij}$ is expressed as

$$c_{ij} = \frac{\alpha_i c_j^0 + \omega_j f_i}{s + \nu_j}, \quad i = 1, \ldots, M, \quad j = 1, \ldots, N. \tag{A3}$$

This expression is substituted into the first equation:

$$\left(s + \kappa_i + \sum_{j=1}^{N} \frac{s\omega_j}{s + \nu_j}\right) f_i = \alpha_i \left(f^0 + \sum_{j=1}^{N} \frac{c_j^0 \nu_j}{s + \nu_j}\right) + \alpha_i\kappa_i F(r, s). \tag{A4}$$

We express from here $f_i$ and the sum over $i$:

$$f = \Sigma(s)\left(f^0 + \sum_{j=1}^{N} \frac{c_j^0 \nu_j}{s + \nu_j}\right) + \phi(s)F(r, s). \tag{A5}$$

Here,

$$\phi(s) = \sum_{i=1}^{M} \frac{\alpha_i\kappa_i}{s + \kappa_i + \sum_{j=1}^{N} \frac{s\omega_j}{s+\nu_j}}, \tag{A6}$$

$$\Sigma(s) = \frac{1 - \phi(s)}{s + \sum_{j=1}^{N} \frac{s\omega_j}{s+\nu_j}}. \tag{A7}$$

By dividing Eq. (A5) by $\Sigma(s)$ and transforming, the following is obtained:

$$sf(\mathbf{r}, s) - f^0(\mathbf{r}) = \frac{s\phi(s)}{1 - \phi(s)} a^2 \nabla^2 f(\mathbf{r}, s) - f(\mathbf{r}, s) \sum_{j=1}^{N} \frac{s\omega_j}{s + \nu_j} + \sum_{j=1}^{N} \frac{c_j^0 \nu_j}{s + \nu_j}. \tag{A8}$$

Further, summing Eqs. (A2) with respect to $i$ and $j$, and adding (A8), the following is obtained:

$$s\rho(\mathbf{r}, s) - \rho^0(\mathbf{r}) = \frac{s\phi(s)}{1 - \phi(s)} a^2 \nabla^2 f(\mathbf{r}, s), \tag{A9}$$

where $\rho = f + \sum_{i,j}^{M,N} c_{ij} = f(1 + \sum_{j=1}^{N} \frac{\omega_j}{s+\nu_j}) + \sum_{j=1}^{N} \frac{c_j^0}{s+\nu_j}$. Expressing $f$ in this equation in terms of $\rho$, Eq. (17) is obtained with function $\Psi(s)$ equal to (26).

In the Laplace space, Eqs. (24) and (25) have the form

$$s f_i(\mathbf{r}, s) - \alpha_i f^0(\mathbf{r}) = -\kappa_i f_i(\mathbf{r}, s) + \kappa_i \alpha_i F(\mathbf{r}, s) - \sum_{j=1}^{N} \omega_j f_i(\mathbf{r}, s) + \alpha_i \sum_{j=1}^{N} \nu_j c_j(\mathbf{r}, s), \quad i = 1, \ldots, M, \tag{A10}$$

$$s c_j(\mathbf{r}, s) - c_j^0(\mathbf{r}) = -\nu_j c_j(\mathbf{r}, s) + \omega_j f(\mathbf{r}, s), \quad j = 1, \ldots, N. \tag{A11}$$

From these equations, as a result of similar calculations, Eq. (17) is obtained with the function $\Psi(s)$ equal to (27).

## APPENDIX B

In the Fourier-Laplace space, Eqs. (28) and (29) have the form

$$s f_i(\mathbf{k}, s) - \alpha_i f^0(\mathbf{k}) = -\kappa_i f_i(\mathbf{k}, s) + \kappa_i \alpha_i (1 - a^2\mathbf{k}^2) f(\mathbf{k}, s) - \omega_i f_i(\mathbf{k}, s) + \nu_i c_i(\mathbf{k}, s), \quad i = 1, \ldots, M, \tag{B1}$$

$$s c_i(\mathbf{k}, s) - c_i^0(\mathbf{k}) = -\nu_i c_i(\mathbf{k}, s) + \omega_i f_i(\mathbf{k}, s), \quad i = 1, \ldots, M. \tag{B2}$$

At the initial instant of time, the whole probability is assumed to be concentrated at one point, $r = 0$; therefore, the initial values $f^0$ and $c_i^0$ do not depend on $k$. The second equation $c_i$ is expressed as

$$c_i = \frac{c_i^0 + \omega_i f_i}{s + \nu_i}, \quad i = 1, \ldots, M. \tag{B3}$$

This expression is substituted into the first equation and solved with respect to $f_i$:

$$f_i = \frac{\alpha_i [f^0 + \kappa_i (1 - a^2\mathbf{k}^2) f] + \frac{\nu_i c_i^0}{s+\nu_i}}{s + \kappa_i + \frac{s\omega_i}{s+\nu_i}}, \quad i = 1, \ldots, M. \tag{B4}$$

This relation is summarized with respect to $i$, and $f$ is expressed as

$$f = \frac{\Sigma(s)}{1 - \phi(s)(1 - a^2\mathbf{k}^2)}. \tag{B5}$$

Here,

$$\Sigma(s) = \sum_{i=1}^{M} \frac{\alpha_i f^0 + \frac{\nu_i c_i^0}{s+\nu_i}}{s + \kappa_i + \frac{s\omega_i}{s+\nu_i}}, \tag{B6}$$

$$\phi(s) = \sum_{i=1}^{M} \frac{\alpha_i \kappa_i}{s + \kappa_i + \frac{s\omega_i}{s+\nu_i}}. \tag{B7}$$

The expression $(1 - a^2\mathbf{k}^2) f$ can be transformed to the form $\frac{f - \Sigma(s)}{\phi(s)}$. Using the expressions obtained, propagator $\rho = \sum_{i=1}^{M} (f_i + c_i)$ is determined in the Fourier-Laplace space. Performing the inverse Fourier transform, an expression similar to (17) is obtained with other factors in front of the Bessel function and the delta function, as well as with another expression for the parameter $\beta$.


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