The pair approach applied to kinetics in restricted geometries: strengths and weaknesses of the method

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In the rapidly emerging field of nanotechnology, as well as in biology where chemical reaction phenomena take place in systems with characteristic length scales ranging from micrometer to the nanometer range, understanding of chemical kinetics in restricted geometries is of increasing interest. In particular, there is a need to develop more accurate theoretical methods. We used many-particle-density-function formalism (originally developed to study infinite systems) in its simplest form (pair approach) to study two-species $A + B \rightarrow 0$ reaction-diffusion model in a finite volume. For simplicity reasons, it is assumed that geometry of the system is one-dimensional (1d) and closed into the ring to avoid boundary effects. The two types of initial conditions are studied with (i) equal initial number of A and B particles $N_{0,A} = N_{0,B}$ and (ii) initial number of particles is only equal in average $\langle N_{0,A} \rangle = \langle N_{0,B} \rangle$. In both cases it was assumed that in the initial state the particles are well mixed. It is found that particle concentration decays exponentially for both types of initial conditions. In the case of the type (ii) initial condition, the results of the pair-like analytical model agrees qualitatively with computer experiment (Monte Carlo simulation), while less agreement was obtained for the type (i) initial condition, and the reasons for such behavior are discussed.

I. INTRODUCTION

Classically, biochemical reaction kinetics is extrapolated from measurements in dilute solutions and fitted into the cellular reaction environment, and several flaws in this approach have been pointed out. The main motivation of our work is to improve the understanding of diffusion-controlled reactions in topologically complex nanoscale environments represented in biological cells. In this study attempt is made to develop better theoretical methods which could describe diffusion-controlled reactions with boundaries. To achieve this goal, a particular way of doing calculation, the many-particle-density-function (MPDF) approach,2–5 is modified to account for presence of boundaries.

The theoretical findings of this study are relevant for experimental work done in refs. 6–8. Even if we focus on biochemical reaction kinetics, the results should have an equal bearing on nanotechnological applications such as nanofluidics9 or molecular electronics10. Both are likely to be strongly dependent on reaction-diffusion behaviors of molecules (nanofluidics) or electrons and holes (molecular electronics) in restricted nanoscale geometries.

Most of the studies on diffusion-controlled reactions have been performed for infinite systems without boundaries and a variety of methods have been developed to do the analysis. The methods range from mean field treatments towards more exact approaches which employ quantum spin-chains11, field theory12,13, or MPDF formalism2–5. The references 3, 14 are an excellent review on the subject. The opposite case when reactions take place in restricted geometries with reactants confined into finite size, and eventually squeezed into very small volumes, is less understood. There is, however, some pioneering work in this area. In here, focus is on testing performance of MPDF on diffusion-controlled reactions in finite volumes.

The infinite diffusion-controlled systems posses quite

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remarkable properties. When dimensionality of the system \( d \) is lower than some critical dimension \( d_c \) (e.g. for \( A+\overline{A} \) reaction \( d_c = 2^{10} \), and for \( A + B \overline{d}_c = 4^{20} \)) a new non-trivial sort of kinetics sets in. Taking \( A + B \rightarrow \) 0 as an example: Classical chemical kinetic rate equation for this reaction, with initial densities equal and homogeneous, is given by \( \dot{n}(t) = -\lambda n(t) \) where dot over symbol denotes time derivative. For large time \( t \) this equation would predict density decay in the form of power law \( n(t) \approx A t^{-\alpha} \). The amplitude of decay equals \( A = 1/\lambda \) and decay exponent is given by \( \alpha = 1 \). In reality, \( \alpha = 1 \) holds only for a sufficiently high dimensionality of the system when \( d > 4 \), while for \( d < 4 \) one has \( \alpha = d/4 \) and \( A = \text{const.} \sqrt{\pi} D^{-d/4} \), and const is just a numerical factor. Please note that for \( d < 4 \) decay amplitude \( A \) does not depend on the reaction rate \( \lambda \) and exhibits lack of dependence on chemical details (universality).

The kinetics of the type described above is commonly referred to as anomalous or fluctuation-dominated. The term “anomalous” points to the fact that mean field (or classical rate equations) fail to describe such systems. The phrase “fluctuation-dominated” emphasizes importance of fluctuations in particle densities. Once the reaction creates a hole in the particle concentration, diffusion is very slow in restoring the homogeneous particle density. This has to do with recurrence of random walks. For \( d \leq 2 \) probability that the random walker will return to the same site after arbitrary number of steps is equal to one. Random walkers tend to wander around their initial position, and particles do not mix that well. Rule of thumb is that for lower dimensions the kinetics gets more anomalous. Role of dimensionality is well understood both for integer and fractal (non-integer) like dimensions.\(^{21} \) On the other hand, much less is known what happens when one shrinks the system size, which is studied here.

To impact some progress in understanding reactions in restricted geometry we analyze performance of MPDF approach and modify it to account for finite reaction volume. To test such method of calculation the \( A+B \) model approach and modify it to account for finite reaction volume. To test such method of calculation the \( A+B \) model serves as study case. The model used here is defined as follows. The two species, A and B, move on a 1d lattice performing random jumps with rates (diffusion constants) \( D_A \) and \( D_B \) respectively. It is assumed that \( D_A = D_B \). Position of lattice sites is given by \( x_i = ih \) with \( i = 0, 1, 2, 3, \ldots, M \) and \( h \) denotes lattice spacing. Sometimes, \( x \) and \( y \) will be used instead of \( x_i \). Periodic boundary conditions are assumed and sites \( i = 0 \) and \( i = M \) are defined to be equivalent. There are \( M \) lattice sites in total and \( L = M h \). By using periodic boundary conditions it is possible to work with a system of finite size and yet keep the spatial translational invariance. This greatly facilitates the analytical treatment of the problem.

It is assumed that the reaction probability (per unit time) for particle \( A \) at \( x \) and \( B \) at \( y \) is given by \( \sigma(x-y) \). For \( \sigma(x-y) \) simplest possible form is used

\[
\sigma(x-y) = \sigma_0 \theta(|x-y| - a).
\]

where \( \theta(x) = 0 \) for \( x < 0 \) and \( \theta(x) = 1 \) for \( x \geq 0 \). In this way two important aspects of chemical reactions are

The \( A+B \) model in restricted geometry has been studied before with the assumption that one type of reactant is attached at the center of a small volume, and it was further assumed that one type of particle is in large excess.\(^{15-17} \) The more realistic problem where all particles are allowed to move is much harder to solve, and the goal of our study is to describe such a situation. Also, in here, the focus is on the case when the initial number of reactants is the same, or roughly the same. Naturally, the shape of the reaction container might be important but this issue is not addressed at the moment. To avoid boundaries completely, our 1d system will be closed into the ring.

The paper is organized as follows. In section II the model is developed, \( i.e. \) detailed account is given of how particles move and react. Lattice model is used due to its conceptual simplicity. In section III equations of motion are derived using MPDF formalism in its simplest form (pair approach). In section IV equations of motion are solved analytically and it is shown how multi-exponential decay emerges. The results of computer experiments (Monte Carlo Simulations) are given in section V followed by a comparison between theory and Monte Carlo simulations in section VI. We conclude by analysis of strengths and weaknesses of the pair-approach applied to a reactions in restricted geometry in section VII. In appendix A details are given how to calculate effective reaction rate \( k(t) \) which determines density decay. In appendix B the algorithm used to do Monte Carlo simulations is discussed in detail.

II. THE LATTICE MODEL

To test any theory one inevitably needs a model which serves as study case. The model used here is defined as follows. The two species, A and B, move on a 1d lattice performing random jumps with rates (diffusion constants) \( D_A \) and \( D_B \) respectively. It is assumed that \( D_A = D_B \). Position of lattice sites is given by \( x_i = ih \) with \( i = 0, 1, 2, 3, \ldots, M \) and \( h \) denotes lattice spacing. Sometimes, \( x \) and \( y \) will be used instead of \( x_i \). Periodic boundary conditions are assumed and sites \( i = 0 \) and \( i = M \) are defined to be equivalent. There are \( M \) lattice sites in total and \( L = M h \). By using periodic boundary conditions it is possible to work with a system of finite size and yet keep the spatial translational invariance. This greatly facilitates the analytical treatment of the problem.

It is assumed that the reaction probability (per unit time) for particle \( A \) at \( x \) and \( B \) at \( y \) is given by \( \sigma(x-y) \). For \( \sigma(x-y) \) simplest possible form is used

\[
\sigma(x-y) = \sigma_0 \theta(a - |x-y|).
\]
embedded, $a$ corresponds to the effective range of reaction and $\sigma_0$ is its strength. One could also say that each particle carries a ring of radius $a/2$ and when two rings overlap the particles can react. In this sense $a/2$ could be thought of as the size (radius) of particles. For simplicity reasons it is assumed that the reaction products do neither influence reactants, nor the A+B reaction. Also, exclusion or steric effects are not taken into account, i.e. particles are allowed to “enter” into each other (please see Fig. 1) and react with same probability independently from which direction they approach each other.

The model has the useful property that if $a$ is thought of as the size of reactants, then by varying $a$ several interesting situations can be studied. For example, when $a$ is on the order of the system size $L$, one can think of situations of extreme crowding. On the other hand when $a \ll L$ reactants appear as point-like objects. In Fig. 1 we offer a schematic way how to think about these situations. The model presented above is solved analytically and numerically by a Monte Carlo simulation in the following sections.

III. EQUATIONS OF MOTION IN PAIR APPROXIMATION

To solve the A+B reaction-diffusion model in a restricted geometry we use a many-particle-density-function formalism (MPDF), since it was already used to describe asymptotics of the same reaction in an infinite volume. We modify the formalism and apply it to the case of a restricted geometry. In the following the formulation presented in ref 2 will be closely followed. On the way, the changes made to the original formalism will be discussed.

The dynamics of the system, as defined in previous section, is stochastic and governed by Master Equation which describes time evolution of configurational probabilities of the system $P(c, t)$,

$$\dot{P}(c, t) = \sum_{c'} [W_{c' \to c} P(c', t) - W_{c \to c'} P(c, t)] \quad (2)$$

where $c$ is short notation for occupancy of lattice sites and $W_{c \to c'}$ are transition probabilities which can easily be deduced from the previous description of the model. Here and throughout the paper dot over symbol denotes time derivative.

The quantities of interest are particle densities $\rho_A(x, t)$ and $\rho_B(x, t)$ and they can be calculated from $P(c, t)$ (at least in principle). Since system is closed into a ring translational invariance holds and concentrations cease to be position dependent which leads to $\rho_A(x, t) = n_A(t)$ and $\rho_B(x, t) = n_B(t)$. Following recipe in ref. 2 gives following equations for $n_A$ and $n_B$,

$$\dot{n}_A(t) = -n_A(t)n_B(t) \int_{-L/2}^{L/2} dx \sigma(x) Y(x, t) \quad (3)$$

$$\dot{n}_B(t) = -n_A(t)n_B(t) \int_{-L/2}^{L/2} dx \sigma(x) Y(x, t) \quad (4)$$

The $Y(x, t)$ denotes correlation function for AB pairs. Absence of correlations is signaled by $Y(x, t) = 1$. Please note that in this work system size is finite which enters through finite integration domain in the integrals above (it might appear as minor technical detail but this fact is very important). Also, it is assumed that reversal symmetry holds, i.e. $Y(x, t) = Y(-x, t)$.

Again, following ref. 2 one can derive equation for $Y(x, t)$ which is given by

$$\dot{Y}(x, t) = (D_A + D_B)Y''(x, t) - \sigma(x)Y(x, t)$$

$$-n_B Y(x, t) \int_{-L/2}^{L/2} dy \sigma(y) Y(y, t) [X_B(x-y, t) - 1]$$

$$-n_A Y(x, t) \int_{-L/2}^{L/2} dy \sigma(y) Y(y, t) [X_A(x-y, t) - 1] \quad (5)$$

where prime denotes spatial derivative, and $X_A(x, t)$ and $X_B(x, t)$ correlation functions for AA and BB pairs respectively. The $X_A(x, t)$ and $X_B(x, t)$ obey similar equations which are not given here to save the space.

The equations (3)-(5) are derived under assumption of Kirkwood superposition approximation, which is a technical way of saying that dynamics is governed by pair effects. Naturally, assumption of the dominance of pairs effects is an approximation. It might or might not work, and the goal of present study is to test this. In the following, to make analytic treatment possible, equations will be simplified further by setting $X_A(x, t)$ and $X_B(x, t)$ equal to one. This amounts to ignoring correlations among AA and BB pairs. In ref. 2 it was shown that (for infinite reaction volume) such approximation is too severe and does not lead to correct decay exponent $\alpha = d/4$ (it gives $\alpha = d/2$). Nevertheless, in here we consider such simplification. The validity of such an approximation, together with the fact that we are using Kirkwood approximation, is tested via computer experiment later on.

The form of boundary conditions for $Y(x, t)$ differs from the one used in ref. 2. In the case of infinite system one takes

$$Y(x, t) \to 1 \quad , \quad x \to \infty \quad (6)$$

while for finite system with periodic boundary conditions another form has to be used

$$Y(x + L, t) = Y(x, t) \quad (7)$$

It will be shown later that the change from (6) to (7) leads to a qualitative change from power law to (multi)
exponential behavior for correlation dynamics. The rest of the boundary conditions are standard, and are taken as in the case of an infinite system size,

\begin{align*}
n_A(0) &= n_0 \\
n_B(0) &= n_0 \\
Y(x,0) &= 1
\end{align*}

Also, taking \( L \rightarrow \infty \) should reproduce findings of ref. 2, within set of approximations employed here.

IV. EMERGENCE OF MULTI-EXPONENTIAL DENSITY DECAY

With assumptions \( X_A = X_B = 1 \) Eq. (5) reduces to

\[ Y(x,t) = (D_A + D_B)Y''(x,t) - \sigma(x)Y(x,t) \] (11)

Eq. (11) is solved by using a Laplace transform as shown in the appendix A. To simplify the algebra, it is assumed that \( \sigma_0 \) is arbitrary large. The exponential behavior emerges due to the fact that the spectrum of Eq. (11) is discrete due to particular nature of the boundary conditions. The final expression for \( k(t) \) reads

\[ k(t) = k_{reg}(t) + 2a\delta(t) \] (12)

and details of calculation are given in the appendix A. The regular part of \( k(t) \) is given by

\[ k_{reg}(t) = \frac{8D}{L - 2a} \sum_{m=1}^{\infty} e^{-\kappa_mDt} \] (13)

and \( \kappa_m \) are constants of multi-exponential decay (eigenvalues),

\[ \kappa_m = \pi^2 \left( \frac{2m - 1}{L - 2a} \right)^2 \] (14)

The \( \delta \)-function term in (12) arises from the second term on the right hand side of Eq. (A5) when \( \sigma_0 \rightarrow \infty \) (please see the appendix A).

Once \( k(t) \) is available one can calculate \( n(t) \) as

\[ n(t) = \frac{n_0}{1 + I(t)n_0 + 2an_0} \] (15)

where \( I(t) = \int_0^t dt'k_{reg}(t') \) and

\[ I(t) = \frac{8}{L - 2a} \sum_{m=1}^{\infty} \frac{1}{\kappa_m} (1 - e^{-\kappa_mD t}) \] (16)

The \( 2an_0 \) term in the denominator of (15) comes from the \( \delta(t) \) term in Eq. (12). It describes the immediate annihilation of particles which are within reaction range. When \( \sigma_0 \rightarrow \infty \), this happens instantaneously. Thus there is a sudden jump in particle concentration. For finite \( \sigma_0 \) this jump becomes a smooth transition (exponential decay with decay exponent proportional to large number \( \sigma_0 \)).

The question is whether one can obtain results for an infinite system from the Eq. (15) above. This can be done using Poisson resummation formula when \( Dt/(\frac{L}{2} - a)^2 \ll 1 \). The Poisson resummation procedure gives \( I(t) \sim t^{1/2} \) which results in the wrong exponent for the density decay; \( n(t) \sim t^{-1/2} \) instead of correct \( n(t) \sim t^{-1/4} \). Thus we just reconfirm the well known fact that for infinite systems, the pair approach predicts too fast decay of particles. However, for finite systems, the situation is not that clear, it appears to depend on the type of initial conditions the real system is subject to.

In here we consider two types of initial conditions. (i) When initially there is an equal number of A and B particles, one has \( n \rightarrow 0 \) as \( t \rightarrow \infty \); and at the end all particles have to annihilate. (ii) One can look at an ensemble of similar systems with equal number of A and B particles at \( t = 0 \) on average, \( \langle N_{0,A} \rangle = \langle N_{0,B} \rangle \). In such a case, one has different asymptotics, \( \langle N(t) \rangle \rightarrow N(\infty) \) as \( t \rightarrow \infty \).

Theoretical prediction is that, as time goes to infinity, the particle density exponentially approaches the value \( n_{th}(\infty) \);

\[ n_{th}(\infty) = \frac{n_0}{1 + n_0L} \] (17)

The value for \( n_{th}(\infty) \) above can be obtained by sending \( t \rightarrow \infty \) in Eqs. (15) and (16). From (17) one sees that asymptotically number of particles is given by

\[ N_{th}(\infty) = N_0/(1 + N_0) \] (18)

where \( N_{th}(\infty) = Ln_{th}(\infty) \). Please note that \( N_{th}(\infty) \) never approaches zero and settles at a number between zero and one. In the case of type (i) initial conditions, all particles annihilate and \( N(\infty) = 0 \). This is clearly in contradiction with Eq. (17). However, situation is not that hopeless, as will be discussed later. For the type (ii) initial condition, for each member in ensemble there is a chance that more than one particle will be left, since one start dynamics with (random) excess of A or B particles at \( t = 0 \). Thus, in average, \( \langle N(\infty) \rangle \) will be larger than 0. Clearly, pair approach has more chance to describe this situation correctly.

In summary, we find an exponential decay in the long time limit which is a pure artifact of the finites of the system. There is a clear indication that the quality of prediction depends on the type of initial conditions used in experiment. Also, the approximations made in deriving Eq. (15) are rather severe and in order to check the applicability of such a pair-approach Monte Carlo simulation is used.
V. RESULTS OF MONTE CARLO SIMULATIONS
OF A+B REACTION IN RESTRICTED
GEOMETRY

Figures 2, 3, and 4 summarize the results of the Monte Carlo simulations in $d = 1$. The Monte Carlo algorithm is described in detail in appendix B. Figure 2 shows a simulation for a system with a large initial number of particles with a varying reaction range from a nearest-neighbor interaction with $a/L = 0.0001$ towards a longer range with $a/L = 0.02$. Figure 3 shows the case when there are initially very few (exactly $10=5A+5B$) particles present in the reaction volume, also with varying reaction ranges from $a/L = 0.001$ to $a/L = 0.2$. Thus figures 2 and 3 give simulation results for type (i) initial condition. Figure 4 deals with type (ii) initial condition, when the initial number of particles in an ensemble varies with the constrain that the sum of A and B particles equals 10. (For example, one run could be done with 7A and 3B, the other run with 5A and 5B, and a third run with 4A and 6B particles, etc.) Figure 1 is a sketch of how to think of various situations when $a$ changes from small to large values.

From figure 2 it can be seen that in the case of the nearest neighbor reaction range ($a = 1$) four distinct regimes appear and the log-log plot is used to reveal them: (a) mean field decay, (b) the plateau region (c) power law decay and (d) exponential decay at the end. These regimes disappear as the reaction range is increased, and eventually, for very large $a$, one only has the exponential regime.

The mean field regime corresponds to annihilation of particles with all reactants being well mixed. This leads to depletion of lattice to concentration of the order $n \sim 1/a$, thus one particle per reaction range. Then diffusion starts to operate and mixes particles. What is interesting is that for very large values of $a$, the plateau region starts earlier and lasts longer. Apparently, it takes some time before the particles find each other by diffusion and start reacting again.

The power law decay starts after the plateau region. There is universality in the power-law regime since all curves with different values of $a$ merge into one. This is somewhat surprising since a larger $a$ should mean faster annihilation, which indeed happens in the mean field regime, but yet in the power law stage all curves share the same power-law behavior. We speculate that this has to do with self organization and build up of correlation.

The exponential regime is entered after the power law regime, when the number of particles in the system becomes small. With the present computer hardware it was not possible to resolve this exponential regime better. This is indeed done in figure 3 with a smaller lattice size and lower particle number.

To illuminate this exponential decay at later stages of annihilation, we performed simulations with a smaller number of particles ($10=5A+5B$) on a smaller lattice with $10^3$ sites. Thus we used type (i) initial condition. To obtain each curve we followed 1000-3000 realizations of dynamics and averaged over such an ensemble. The result is shown in figure 3. The upper figure is in log-$t$ scale to resolve the small and large $t$ region, respectively. The lower figure is in normal-$t$ scale and we use it to detect exponential decay (where a straight line indicates exponential decay).

The crossover from mean-field to plateau-like dynamics can be seen in the upper graph where all curves drop down to a plateau value which is $a$-dependent. The theoretical prediction for this plateau is $n(0^+) = n_0/(1 + 2a n_0)$. The initial drop in concentration is large for large $a$-values. In the upper figure, it is hard to say when the plateau behavior turns into exponential decay.

The lower graph shows that decay is indeed exponential since density curves at late times are straight lines in the log$_{10}(n)$-$t$ plot. Thus at the late times $n \sim \exp(-\kappa_1 t)$. Also, the decay constant $\kappa_1$ is $a$-dependent since slopes are different for various values of $a$, and $\kappa_1$ becomes larger with larger $a$. Also, it appears that there is an upper limit for $a$ at which decay becomes infinitely fast. Naturally, this happens when $a = L/2$ since none of the particles can escape from each other. The qualitative dependence of $\kappa_1$ on $a$ just discussed is in agreement with theoretical prediction in Eq. (14) with $m = 1$.

Figure 4 is obtained in a similar way as figure 2. The only difference is that figure 4 deals with the type (ii) initial condition. For the particular run, when $N_{0,A} \neq N_{0,B}$, the final number of particles in the system is not zero. For example, when starting from 7A and 3B particles, the system will end up in the state of 4A particles. This comes from that fact that the A+B reaction conserves the particle difference $N_A(t) - N_B(t) = const$. Curves for different values of $a$ saturate at one single value which is, independent of $a$. Clearly, the value of the plateau is solely controlled by the excess of particles at $t = 0$, and can be calculated from theory if needed, but result of Monte Carlo simulation is equally informative.

VI. COMPARISON OF COMPUTER EXPERIMENT AND THEORY

Figure 5 shows a comparison of the analytical treatment with computer experiment (simulation parameters as in figure 3). It can be seen that the pair (Smoluchowskiii) approach does not predict that the number of particles in the system should approach zero. The reasons for this are discussed later but have to do with the fact that we are looking at highly symmetric situation with equal number of A and B particles all the time. To enforce such zero asymptotics by hand we use interpola-
tion formula
\[ n_{\text{int}}(t) = n(t) - n(\infty)(1 - e^{-\kappa_1 t}) \] (19)
where \( \kappa_1 \) is the first dominant large time exponent in expression for \( k(t) \) (see Eqs. 15 and 16). It can be easily seen that the equation above holds exactly for \( t = 0 \) and \( t = \infty \). If Eq. (19) is used instead of (15) the agreement with simulation improves in the sense that the decay is exponential and the qualitatively theoretical exponent is roughly the same as the one obtained from simulations. More work is in progress to develop improved interpolation formulas.

Figure 6 deals with the same type of comparison, but with a simulation setup as in figure 4 when the initial number of particles is not fixed, just the total number (type (ii) initial condition). One can see that the agreement between theory and simulation is much better. Clearly, Smoluchowskii theory deals better with the type (ii) initial condition represented by the figure 4 than by the type (i) represented by the figure 3. Also, in figure 6, one can see that theory predicts too fast particle annihilation. This is no surprise since this is what one would expect form such pair approach which does not take into account formation of domains. (In that respect there is similarity with infinite systems, but only for the type (ii) initial condition).

VII. DISCUSSION

The goal of present work was to impact some understanding of diffusion-controlled reactions in restricted geometries, with aim to describe some aspects of chemical reactions in biological cells. Two issues have been dealt with:

(1) The particular way of doing calculation was tested, the MPDF formalism developed by Kuzovkov and Kotomin (see ref. 2 for details). To be able to solve equations analytically the hierarchy of many-particle-densities was truncated at the level of three-particle-density using shortened Kirkwood superposition approximation. This approximation amounts to assuming that pair effects dominate correlations, and present calculation can be viewed as a variant of pair approach.

(2) A two species reaction-diffusion model \( A + B \to 0 \) in a restricted geometry was taken as a study case. Two types of initial conditions were considered, type (i) where the initial number of A and B particles is strictly equal, and type (ii) initial conditions where the initial number of particles is equal only approximatively.

Thus the paper is best viewed as a method paper since the main goal is to test the strengths and weaknesses of the pair approach. To test quality of approximations involved all results have been compared with the results of computer experiment (Monte Carlo simulation).

From a theoretical point of view, it seems that the pair method, being widely used in calculation of bulk properties, works with mixed success for the restricted reaction diffusion systems, at least the one studied in here. The agreement between theoretical calculation and computer experiment is qualitative in the case of type (ii) initial conditions. In the case of type (i) initial conditions there is less agreement, however, situation is not that hopeless.

In the case of type (i) initial conditions pair approach makes error of the order of one particle (please see Eq. 18), since it predicts that, in the average, after very long time, there will be between zero and one particle in the system (though all particles should vanish). When initial number of particles is relatively large, the pair approach can describe evolution of system for rather long time, before the regime is reached where only one particle is left in the reaction volume. However, in the case of small initial number of particles, there is no such time interval, and the mismatch between pair approach and simulation has to be addressed more seriously.

The weakness of pair approach in dealing with type (i) initial condition rests on the fact that the truncated set of equations for many-particle-densities do not recognize any effects which go beyond pair correlations. For example, in the present case, all information related to the fact that initially there were 5A and 5B particles in the system, and that all particles have to vanish eventually, is missing. Work is in progress to pass such type of information from higher order particle-density-functions to lower order ones. For example, we already have better interpolation scheme than the one given in Eq. (19) for the case when there are initially three particles in the system, but we are trying to understand how to extend such analysis to higher numbers.

Interestingly enough, it seems that, contrary to the systems with infinite sizes, setting \( X_A(x,t) = X_B(x,t) = 1 \) is reasonable approximation for a finite system, but we have to perform more tests. This could have to do with the fact that if the system is too small, there will be no time to develop clusters of A and B particles, and setting \( X_A(x,t) = 1 \) and \( X_B(x,t) = 1 \) might turn to be a good approximation after all. Thus, one does not have to turn to more complicated methods of calculation if qualitative results are needed. Nevertheless, it is highly desirable to see what happens as one includes correlations among AA and BB pairs.

To be able to solve equations analytically, we had to simplify MPDF considerably down to the level of a pair like approach and various calculation schemes contain pair approach as possible approximation. Perhaps the most common form of pair approach is the one suggested by Smoluchowskii (see e.g. ref. 3 for interesting review). The Smoluchowskii approach boils down to solution of Poisson equation with different boundary conditions. (Many readers will be familiar with this in the
context of heat transfer or quantum mechanical problems.)

However, one has to keep in mind that pair approach is an approximation, and it has to be tested to see whether it works. (For example, the pair approach can not describe A+B reaction-diffusion model when system size is very large. This has been discussed in ref. 4.) The advantage of pair approach, in the form used here, is that it is possible to go beyond it in a systematic way.

Also, from the particular way we have approached pair problem, one can see that the difficulties associated with Eq. (18) are likely to be much deeper than just the fact that we are using pair approach. (This problem clearly vanishes when system size is infinite, as \(n_{th}(\infty)\) goes to zero.) Any scheme which focuses on low rank particle-density-function will suffer in a similar way, in the case of the highly symmetric, e.g. type (i), initial condition. One really has to find a way how to incorporate information of higher order correlation functions into lower order ones, without calculating higher order correlations functions explicitly. This is a pressing issue.

A few words about the model used. The goal of present work is to develop calculation method rather than to describe specific chemical system. We used the model which we could solve, within reasonable level of approximation. Nevertheless, the question whether present model has any relevance for real biological and chemical systems needs to be addressed.

The reaction diffusion model studied here appears to be too simple, for two reasons. First, it does not account for chemical details which enter only through two parameters, diffusion constant \(D\) and reaction rate \(\lambda\). For example, the exclusion effects and steric effects are not contained in it. Also, the influence of product molecule is completely ignored. Second, 1d character of the model might be too restrictive.

Despite its simplicity, the model used here contains basic characteristics of diffusion-controlled reactions (reaction times \(t_R\) are much smaller than the corresponding diffusion times \(t_D\)); particles are moving on the on the lattice and react when within reaction range with no memory of initially velocity. Previous research reviewed in refs. 2, 3 has shown that diffusion-controlled models, similar to the one used here, can be used to describe real chemical reactions. In particular, the A+B model have been used to study two reactions in capillary tube quite successfully, bromine + cyclohexene \(\rightarrow\) adduct, and Cu\(^{2+}\) + disodium ethyl bis(5-tertazolylazo)acetate trihydrate \(\rightarrow\) 1:1 complex in water.\(^{30}\)

Why can one be sloppy and ignore chemical details to some extent? The reason for this is universality. Most often, predictions of the reaction-diffusion models (on lattice) are insensitive to the details of the chemistry involved. (For example, the decay amplitude for A+B reaction does not depend on the reaction rate \(\lambda\).) This statement is valid provided one deals with very large system sizes. Naturally, this view is not the only one. There are other ways to approach diffusion-controlled reactions. For more chemical or biological approach to diffusion-controlled reactions see refs. 14, 31 and 32 respectively.

The simplicity of the model is not necessarily such a big handicap, until one reaches extremely small sizes. For small system sizes, density decay will start depending on details. However, there is a large window in system sizes between extremely large and extremely small where such kind of universality could survive. In here we push the model over its borders by studying situation of extreme crowding and not accounting for exclusion effects.

Furthermore, we would like to notify the reader that we do refer to the model here as a “toy” model, it relatively simple to formulate it. However, this does not mean that the model is easy to solve, quite the contrary. In the case of infinite system size it has taken a lot of research effort to clarify that the decay exponent indeed is \(d/4\). This issue was finally settled in ref. 27 which provides a strict mathematical proof.

The model has a potential to describe experiments in refs. 6–8 where, for example, the average diameter of the reaction container (liposome) is \(L \sim 1 – 25\mu m\). The reactants A (enzyme) and B (substrate) are of the size of \(a_E, a_S \sim 1nm\) and the typical number of reactants inserted is on the order of \(N \sim 1000\). Thus, \(a \ll L\) holds to a very good approximation. In these experiments reactants appear as point-like objects and there is no need to give structure to reactants. Also, problems associated with Eq. (18) will likely not to case any damage due to large number of particles at \(t = 0\).

From the data above, the concentration of particles \(n_{A,B} \sim N/L^3\), is easily estimated to be \(n \sim 1\mu m^{-3}\), and the typical distance between particles is \(d_{AB} \approx 1/c^{1/3} \approx L/N^{1/3} \approx 0.1\mu m\). Thus, in average, \(a_E, a_S \ll d_{AB}\), and particles are very well separated. Therefore, it is reasonable to assume that pair effects are the dominant ones. This in turn simplifies the theoretical description considerably. Clearly, there are other scales in the problem and the criteria on applicability of the pair approach are more subtle in reality.\(^3,^4\)

To summarize, it would be extremely interesting to have a general method of calculation which could describe diffusion-controlled reactions in finite volumes, perhaps something on the level of the pair approach. Pair approach is attractive since inclusion of chemical details such as exclusion or steric effects is possible (see e.g. work in ref. 33) which certainly opens a new route towards more quantitative results. However, pair approach is an approximation, and before burdening pair approach with increasing amount of chemical details, one has to test its ultimate reach. Present work is an attempt in this direction.
APPENDIX A: DERIVATION OF THE REACTION RATE $k(t)$

With initial condition $Y(x, 0) = 1$, the Laplace transform of (11) becomes

$$sY(x, s) - 1 = (D_A + D_B)Y''(x, s) - \sigma(x)Y(x, s) \quad (A1)$$

The correlation functions are symmetric around origin, i.e. $Y(x, t) = Y(-x, t)$. They are also periodic in $L$. This implies that it is sufficient to focus on positive $x$ axis and impose boundary conditions $\frac{D}{\partial x}Y(x, s) = 0$ for $x = 0$ and $x = L/2$. Equation (A1) is an ordinary second order differential equation, which is easily solved by solving it in regions $0 < x < a$ and $a < x < L/2$ separately and then matching solutions at the end. After some algebra one obtains

$$Y_1(x, s) = \frac{1}{D} \left( \frac{1}{\nu} - \frac{1}{\mu} \right) \times
\frac{\cosh(x\sqrt{\mu})}{\cosh(a\sqrt{\mu}) + \frac{1}{\nu} \cosh(a\sqrt{\mu})\cosh[\sqrt{\nu}(\frac{L}{2} - a) + \frac{1}{D\nu}]} \quad (A2)$$

and

$$Y_2(x, s) = \frac{1}{D} \left( \frac{1}{\mu} - \frac{1}{\nu} \right) \times
\frac{\cosh(\nu x)}{\cosh(\nu (\frac{L}{2} - a)\sqrt{\nu}) + \frac{1}{\mu} \cosh(\nu (\frac{L}{2} - a)\sqrt{\nu})\cosh(a\sqrt{\mu})} + \frac{1}{D\nu} \quad (A3)$$

where $Y(x, s) = Y_1(x, s)$ for $0 \leq x \leq a$ and $Y(x, s) = Y_2(x, s)$ for $a \leq x \leq L/2$ with $\mu = (s + \sigma_0)/D$ and $\nu = s/D$. The reaction rate $k(s)$ is given by $k(s) = 2\sigma_0 \int_0^a dx Y_1(x, s)$ and equals

$$k(s) = \frac{2\sigma_0}{D} \left( \frac{1}{\nu} - \frac{1}{\mu} \right) \times
\frac{\cosh(\nu x)}{\cosh(\nu (\frac{L}{2} - a)\sqrt{\nu}) + \frac{1}{\mu} \cosh(\nu (\frac{L}{2} - a)\sqrt{\nu})\cosh(a\sqrt{\mu})} + \frac{2\sigma_0}{D\mu} \quad (A4)$$

We could not find the inverse Laplace transform of the expression above in closed analytic form. However, this is possible when $\sigma_0 \to \infty$. In such a case one has

$$k(s) \approx 2\sqrt{\frac{D}{s}} \frac{1}{\nu \cosh[(\frac{L}{2} - a)\sqrt{s}]} + \frac{2\sigma_0 a}{\sigma_0 + s} + O(1/\sigma_0) \quad (A5)$$

The inverse Laplace transform of the approximate expression for $k(s)$ can be found by a residuum method. The $s = 0$ is not a branching point nor pole. The only poles come from $\cosh$ term in denominator which has poles at $s_m = -\pi^2 (m - 1/2)^2 D/(L/2 - a)^2$. This fully fixes form of $k(t)$ in Eq. (12).

APPENDIX B: COMPUTER EXPERIMENT VIA MONTE CARLO SIMULATIONS

We have chosen the minimal process algorithm for the simulations for two reasons. The first reason is that the algorithm reproduces the master equation (2). Second, our goal is to study a whole range of particle sizes and relatively large numbers of particles at the same time. Clearly, there are another possibilities to carry out Monte Carlo simulation, but the main advantage of the minimal process algorithm is that it can be applied for systems containing relatively large number of particles. An original algorithm was devised for the situation where $a \sim h$, i.e. particles react at the same lattice site or when nearest neighbors. We had to modify the original version of the algorithm to account for finite reaction range when $a \gg h$. A detailed description of the algorithm is given below.

Algorithm:

(1) Site $i$ is chosen at random.

(2) If the site is empty go to step (5).

(3) For a chosen site $i$, one has to calculate the rate $W_i$ for a certain process to occur (diffusion or reaction). Also, one needs a null rate $N_i$ where nothing happens (the so called “null process”). The null rate is defined from $W_i + N_i = Q$, where $Q$ is arbitrary but known at each simulation step. $Q$ is chosen in such a way that none of the $N_i$ is negative. In practise, the case when $Q$ is taken as the largest of $W_i$ works best since this leads to the smallest possible values for $N_i$, i.e. chance that nothing is done in course of simulation is reduced. (Please note that this requires that $Q$ is updated as simulation proceeds, but can be done in a straight forward manner as explained in ref. 34)

$$W_i = D_i + R_i \quad (3)$$

accounts for possibilities that a particle at the site diffuses to the neighboring site with rate $D_i$, or reacts with a particle in some other site with rate $R_i = \sum_{j \in \Omega_i} \sigma(ij)$. $\Omega_i$ denotes set of sites which are within reaction range of the site $i$. The calculation of $R_i$ is by far the most costly step when $a$ is large. In that case, a large region has to be searched in order to find all particles within $\Omega_i$. This step costs $M_{search} \sim (a/h)^d$ computational steps if the sites are checked one by one. The cost can be reduced further by introducing a list which specifies which sites that contain particles within the reaction range of the particle at site $i$. In that case one has to update the list for each diffusion step made. The best algorithm we have so far updates the list in roughly $M_{search} \sim (a/h)^{d-1}$ steps.

$W_i = D_i + R_i$
(4) Once the rates for the site $i$ have been calculated one can use them to evaluate probabilities for specific process $p^{(D)} = D_i/Q$, $p^{(R)} = R_i/Q$ and $p^{(null)} = N/Q$. Once the probabilities are calculated a certain process is chosen by linear selection algorithm. First one decides if diffusion, reaction or nothing is going to happen. If diffusion is to happen then the particle is moved to one of the randomly chosen $2 \times d$ nearest neighbors. If reaction was chosen, then one of the sites containing particles in reaction range is chosen at random, e.g. at site $j$, and pair of particles from site $i$ and $j$ are annihilated.

(5) Time is updated according to the formula $t \rightarrow t + \Delta t$ where $\Delta t = 1/LQ$ where $L$ was specified before and $Q$ is the maximum rate at the present step.

(6) Move back to (1) unless some criteria to stop is invoked.

Applying the same type of reasoning as in ref. 34 one can see that the algorithm proposed here reproduces the behavior described by the master equation (2). As time of the simulation progresses we monitor the number of particles and calculate all the statistics.

As the original minimal process algorithm, the present simulation method is not that efficient at the later stages of dynamics when the lattice becomes sparse. The quantity that governs computational cost of this method is the number of Monte Carlo steps needed to see some change in the number of particles. We describe it by the number of Monte Carlo steps needed to annihilate the last pair of particles. To make such estimate, it is best to move to the reference frame of one of these particles. Then one particle is fixed and another one is trying to find it. The number of diffusion steps that the moving particle needs to find the one who sits still is roughly given by $M^{(diff)} \sim L^d/a$ (here and in the following it is implicitly assumed that every length variable is measured in units of lattice spacing $h$). Each diffusion step bears $M^{(step/diff)}$ computational steps which gives the total number of steps to annihilate the pair of particles equal to $M^{(tot)} = M^{(diff)}M^{(step/diff)}$. The number of Monte Carlo steps per one diffusion step is roughly 1, $M^{(step/diff)} \sim 1$. However, calculation of $R_i$ requires updating the internal list which costs $M_{search} \sim a^{d-1}$ search steps whenever the particle is moved. Thus, the true number of computational steps per diffusion step is given by $M^{(step/diff)} \sim M_{search} \sim a^{d-1}$. Finally, one gets an estimate for the number of computational steps needed to annihilate the last pair of particles as $M^{(tot)} \sim L^d a^{d-2}$.

The algorithm has an interesting property that for $d = 1$ there is a reduction in the computational cost when comparing large and small $a$ cases. For larger $a$ the algorithm works more efficiently. For $d = 2$ the computational cost does not depend on $a$. Simulating a large $a$ situation for $d = 3$ is more costly. One could avoid this growing cost problem at $d = 3$ by browsing through particles instead of searching for sites when calculating $R_i$. This is clearly the preferred option when the number of particles in the system is not that large.

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FIG. 1. Various situations which are simulated are shown. The three figures schematically depict various types of initial conditions from which simulation is started. (a) The upper most graph shows a situation where particles react when nearest-neighbors only. The reaction range is very short and particles come rarely in contact. (c) The lowest figure shows a situation of dense packing with a large reaction range. It corresponds to situation of high packing which occurs in a cell environment. It is unrealistic that particles can penetrate into each other but we consider this case nevertheless since it is simpler to model. (b) The middle graph is midway between two extremes.

FIG. 2. Result of Monte Carlo simulations in 1d for type (i) initial condition. A very large system is simulated on a lattice with $L = 10^4$ sites. Also, the initial number of particles $N_{0,A} = N_{0,B} = 5000$ is very large. Simulation starts from the largest possible density $n_{tot}(0) = 1$ particle/site. A and B particles have the same diffusion constant $D_A = D_B = 1s^{-1}$. Asymptotically, the number of particles approaches zero. There are three distinct regimes present; (a) of the mean field decay ($\log_{10}(t) < -2$), (b) plateau where particle concentration does not change much ($-2 < \log_{10}(t) < 2$), (c) power law decay ($2 < \log_{10}(t) < 5$), and (d) exponential decay at the end $5 < \log_{10}(t) < \infty$. The indicated ranges are given roughly just to guide the eye. They also depend on which $a$ is used in simulation.

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FIG. 3. Study of the exponential regime where small number of particles is present on the lattice for type (i) initial condition with $N_{0,A} = N_{0,B} = 5$. The number of lattice sites is $L = 1000$. All other parameters are same as in figure 1. Each curve is obtained as average over 1000-3000 runs. Asymptotically, the number of particles approaches zero. Panel (a) shows log-n versus log-t plot to trace down power law decay (should appear as a straight line). There is no power law decay. Also, small and large $t$ region are resolved better. Panel (b) shows log-n versus $t$ plot to indicate exponential decay (corresponds to straight lines). The particle density vanishes exponentially $n \sim \exp(-\kappa t)$ where $\kappa$ depends on $a$ since the slopes for all curves are different. There is a value $a = L/2$ when $\kappa$ becomes infinite (particles can not escape each other).

FIG. 4. Simulation for type (ii) initial condition. All parameters as in the figure 2. The only difference from figure 2 is in the initial condition. $N_{0,A}$ and $N_{0,B}$ vary randomly with constraint that $N_{0,A} + N_{0,B}$ is fixed and equals 10. Asymptotically, number of particles does not approach zero.

FIG. 5. Comparison of theory and experiment (Monte Carlo simulation) for type (i) initial condition. Simulation data are taken from figure 2. Panel (a): theory (dotted line, Eq. 15) predicts $\lim_{t \to \infty} n(t) \neq 0$ while in reality $n(t = \infty) = 0$. Reasons for this discrepancy are given in the text. Panel (b): by using interpolation formula (19) one obtains dashed curve. Agreement with simulation gets better.
FIG. 6. Comparison of theory and experiment (Monte Carlo simulation) for type (ii) initial condition. Both theory and simulation give $n(\infty) \neq 0$. Theory (dotted line, calculated with Eq. 15) predicts faster annihilation of particles.