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On the Relevance of Diffusion-Controlled Reactions for Understanding Living Cell Biochemistry

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Abstract In recent years, a considerable portion of the computer science community has focused its attention on studying the living cell biochemistry. Efforts to understand such complicated reaction environments have stimulated a range of activities, from the ones focusing on the systems biology techniques, through network analysis (motif identification), towards developing languages and simulations for low-level biochemical processes. The approaches that do not use computer simulation techniques, frequently employ mean field equations or, equivalently, classical chemical kinetics. The central quantity of interest is the concentration of reactants, and (mean field) equations describe the time evolution of this quantity. Such equations are used to address various issues among which stability, robustness, or sensitivity analysis. Rarely is the validity of mean field equations questioned. This paper will discuss various situations when mean field equations fail and should not be used. These equations can be derived from the more general theory of diffusion-controlled reactions by assuming that reactants mix well.
Key words: diffusion-limited reactions; fluctuation-dominated kinetics; living cell biochemistry; role of dimensionality

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1 Introduction

The emphasis of this paper is on discussing the use of the framework of diffusion controlled reactions to model the living cell biochemistry. The field is rather broad and no attempt is made to provide a comprehensive list of references. Instead, selected topics have been carefully chosen to help non-experts understand the most relevant issues. The first aim is to introduce a general framework for describing the living cell biochemistry, and to give a few examples of models and mathematics needed to solve such models. The second goal is to illustrate that mean field equations are the lowest order approximation of a more general (and complicated) set of equations that describe these models. The final aim is to discuss these equations, the way they are solved, and the typical behavior of their solutions.

Chemical reaction kinetics in vivo differs significantly from the one in a test tube[1]. The geometry of the living cell interior can be quite complicated. There is experimental evidence that the cell is structured in many ways. The cytoplasm is a

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typical example. For a single cell, the total amount of the protein content can be as high as 17-30% by weight. This results in an extremely structured and crowded space. In addition, the cell interior (roughly $10\mu m$ in diameter) is further partitioned into smaller regions, e.g. by using organelles. Organelles, such as mitochondria with $50nm$ in diameter, occupy roughly 50% of the intracellular volume. For typical physiological concentrations of proteins, about $1nM$, one can easily estimate that the number of the protein molecules is $N_{prot} \sim 1nM(10\mu m)^3 \sim 1000$. The number can be even lower. The low copy numbers of certain proteins lead to large temporal and spatial fluctuations in the protein numbers, and the delivery of proteins can become an issue.

There are two ways to theoretically study such complicated reaction environments, either by performing stochastic simulations or by constructing the equations of motion that describe the time evolution of quantities of interest. In here, the focus will be on discussing the equations of motion approach.

Thus systems of interest are stochastic. For a stochastic reaction system, useful variables that can describe the behavior of the system are various forms of ensemble averages (observables) that reveal information about the system. Typical examples would be the average number of particles, the concentration of particles. In that respect, it is crucial to construct the equations that can be used to predict how such variables change in time. It will be argued that any attempt to describe intracellular chemical reactions in terms of mean field equations (that assume perfect mixing) might fail spectacularly: Intracellular dynamics is intrinsically stochastic due to the low number of chemicals, exclusion effects are important and, ultimately, many scales interact with a large degree of spatio-temporal organization. Presence of exclusion effects implies that due to the Pauli principle the two molecules cannot occupy the same space. In such a case they are not allowed to overlap. Naturally, this is always true in reality but the question is whether one accounts for it in modeling. To develop a theoretical framework that can be used to describe such a situation is far from trivial.

The theory of diffusion-controlled reactions naturally suggests itself in this context and, in the following, some generic features of diffusion-controlled reactions will be discussed. The particular emphasis will be on describing mathematical and physical models that can be used to describe diffusion-controlled reactions. A very general approach of setting up equations of motion will be presented. Equations of motion will be discussed that describe relatively simple reaction systems. These equations will be simplified by truncating them. The validity of the truncated equation set will be critically reviewed, with a particular emphasis on understanding the approximations involved. The equations, in their simplest (trivial) form, result in the mean field equations for the problem, and are normally referred to as the equations of classical chemical kinetics.

2 Diffusion-Controlled Reactions: Simplification of Reality

Try to imagine the interior of the living cell, and a picture that comes to mind is one of a complete chaos where molecules collide and eventually react, and it is impossible to predict who will react with whom. The way we think about the problem is central to our understanding of it. Unfortunately, it is not at all clear what the best way to describe such an environment is, and which concepts one should focus on. The issue of choosing the right model is central, and the framework of diffusion-controlled

reactions appears as an useful candidate.

There are many processes in nature that can be naturally described using the diffusion-controlled framework. Such processes are ubiquitous in nature and occur on all scales, ranging from the matter-antimatter annihilation in the early universe to the epidemics spreading and, finally, occur frequently at small scales in the living cell. References on the topic can be found in Refs. [2,3,4,5]. Reviews[2,3] provide a gentle introduction to the field. The field of diffusion-controlled reactions is rather technical, and a paper that presents the technical side of the problem can be found in Ref. [4] and contains a tutorial of basic techniques. Furthermore, diffusion-controlled models in one dimension are special since some specific techniques can be used that are fine-tuned to study one dimensional kinetics. However, these techniques will not be discussed in here due to their intrinsically technical flavor. Instead we direct the reader to the review[5] which provides a rather lengthy account of the experimental and theoretical approaches used to describe one dimensional diffusion-controlled reactions.

The assumption that makes the diffusion-controlled reactions paradigm useful is the hypothesis that the two most important scales in the problem, related to reactions and transport, can be clearly separated. In general, it is not possible to separate these two processes, at least not at atomic scales. The efficiency of the two processes is quantified by using the transport rate D and the reaction rate λ. To calculate these rates from the first principles is far from trivial, and the discussion of this topic will be silently omitted. The very fact that one is using the concept of a rate brings in the separation of scales automatically. The assumption that all processes are Poissonian, e.g. the probability $p(1r)$ for one process to happen in a time interval $[t, t + dt]$ is proportional to dt, automatically leads to the fact that only one such process can happen in a very small time interval. For example, the probability $p(2r)$ of two processes happening in a very small time interval would be proportional to dt^2, and $p(1r) \gg p(2r)$. This assumption luckily works in most cases, leading to the fact that the validity of the rate concept is always assumed, but easily forgotten. However, once in place, the assumption is of paramount importance in understanding workings of diffusion-controlled reactions, and, in turn, developing a critical mind about the validity of mean field equations.

Once the relevant scales are separated, there are two ways to describe a system, either by using off- or on-lattice models. In an on-lattice model particle positions are restricted to lattice sites, while in an off-lattice particles can be placed anywhere within the systems volume. Accordingly, an off-lattice model is normally referred to as a continuous model. In this work, on-lattice models will be used since they are easier to understand. However, as a rule of thumb, results obtained for lattice models hold for off-lattice models as well, and focusing on on-lattice models does not reduce the generality of the discussion that follows. Also, the continuous model can be obtained from a lattice model once the appropriate limits are taken: assuming that the spacing in the lattice is h, the continuous model can be obtained by taking the $h \to 0$ limit, and by re-scaling variables in the appropriate way. Reference [4] discusses rigorously how this is to be carried out and some elementary steps will be also discussed in this section.

Apart from deciding whether to use on- or off-latice model a modeler needs to choose either Fermionic or Bosonic representation of particles. If Fermionic

representation is used, particles cannot enter into each other. For Bosonic models particles are allowed to occupy same space. It is clear that the Bosonic representation is not realistic. Two particles can not share same space due to the already mentioned Pauli principle. This is a fundamental physical law. However, in many cases Bosonic representation can be very useful. For example, it naturally occurs for on-lattice models where each cell corresponds to a very small sub-volume. More than particle one is allowed to occupy such a volume.

To introduce the concepts discussed so far, two stochastic benchmark models will be discussed: the $A + A \leftrightarrow P$ and the $A + B \leftrightarrow P'$ reaction-diffusion models. For simplicity reasons, both reactions are assumed to result in the same product and $P \equiv P'$ and it will be assumed that only forward reactions are allowed. This naturally does not describe the biological reality faithfully but greatly simplifies the calculations and the discussion that follows. Furthermore, by assumption, particles A and B move on a lattice with jump rates $D_A \equiv D_0$ and D_B respectively. Further, it is assumed that a pair of particles X and Y, that are positioned at lattice sites r and r', reacts with rate $\sigma_{X,Y}(r - r')$ where $X, Y \in \{A, B\}$. The assumption of translational invariance has been implicitly used, as the rate is expressed as a function of $(r - r')$ instead of (r, r'). For simplicity reasons, we will assume that

$$\sigma_{A,A}(r - r') = \lambda_0 \Delta_{r,r'} \tag{1}$$

and

$$\sigma_{A,B}(r - r') = \delta_0 \Delta_{r,r'} \tag{2}$$

where $\Delta_{r,r'} = 1$ when $r = r'$, and 0 else. A more complicated model can be obtained by allowing for finite reaction range. However, in the context of this review, the more complicated reaction model would be much more technical, and it would not convey anything new. Please note that in the case of a lattice model, all rates have the dimension of inverse time. These rates need to be re-scaled when the limit $h \to 0$ is taken, leading to the parameters that can be directly related to experiments. For example, jump rates turn into diffusion constants $D = h^2 D_0$: when $h \to \infty$ the jump rate grows, $D_0 \to \infty$, in such a way that D stays constant. Likewise, the reaction rates need to re-scaled in a similar way. For example, in the $h \to 0$ limit one has

$$\sigma_{A,A}(r - r') = \lambda \delta(r - r') \tag{3}$$

where $\lambda = \lambda_0 h^d$ and $\delta(r - r') = \Delta_{r,r'}/h^d$. Here and in the following d denotes the dimensionality of the system. Furthermore, please note that in the $h \to 0$ limit $\lambda_0 \to \infty$ and $\Delta_{r,r'}$ becomes the Dirac delta function. Also, exactly the same consideration applies to $\sigma_{A,B}(r - r')$.

An additional assumption needs to be made about the volume where the reactants move. The complex geometry one needs to use in order to describe the living cell will be simplified. It will be assumed that the reactants and the product molecules are confined in a box of volume $V = L^d$, where L denotes the size of the system and d its dimension. Translational invariance is brought in by assuming periodic boundary conditions.

As will be discussed, the dimensionality of a system is the most important parameter that governs the validity of the mean field equations. It is assumed that

the typical size of molecules participating in a reaction is a. The setup for the $A + B$ reaction is shown in Fig. 1. (To visualize the $A + A$ case, just imagine that all B particles are changed into A.) P denotes the product of the reactions.

Note that the lattice models discussed in here can be used to describe other reaction-like phenomena. In such cases, the interpretation of A and B has to change. Particles A and B can be almost anything, molecules, excitons, electron-hole pairs, sellers and buyers on the stock market, sick or healthy individuals, etc.

Figure 1 depicts three distinct regimes. Panel (a) shows the situation when $L \gg a$ and the reactants have space to move and do not disturb each other. Such a situation is often modeled by assuming that the size of the reaction volume L is infinite. Also it is assumed that the product of the reactions, P, does not exert any influence on the reactants. In such a case it is possible to assume that the reactants annihilate, without worsening the validity of the models, and simply write $A + B \to \emptyset$ and $A + A \to \emptyset$. This approximation is very good when $L \gg a$. Panel (c) shows a different situation when $a \sim L$, but still $a < L$. In such a case the reactants do not have the space to move and one needs to consider exclusion effects. Panel (b) shows an intermediate case. In the following the two extreme cases (a) and (c) will be discussed. The living cell harbors reactions with both types of behaviors depending on the relative sizes of reactants and reaction volumes. As time goes on a reaction-diffusion system may exhibit a variety of behaviors, as discussed in Ref. [6] for the $A + B$ model.

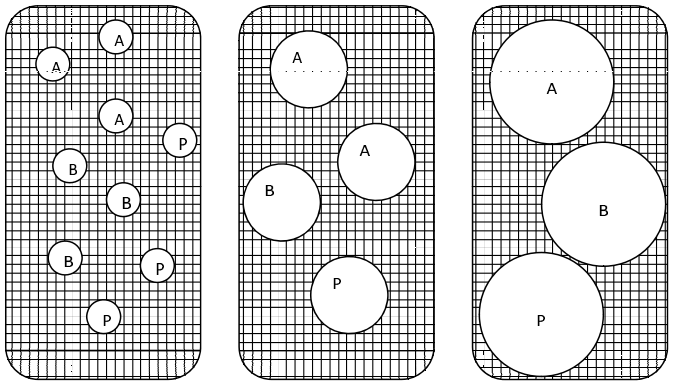

Figure 1. $A + B$ reaction in three different regimes. Panel (a): the reactants radii are much smaller than the size of the system L. In such a case, the reactants have a lot of space to move. Panel (c): a crowded situation where the typical reactant radius a is of the same order of magnitude as the system size L. Panel (b) represents an intermediate case.

The systems constructed so far are stochastic. To study their behavior one could perform stochastic simulations and there are a variety of techniques for doing that. For example, to simulate the systems shown in Fig. 1 one would need to take h very small by keeping the systems size L fixed. Also, particle radii should be kept fixed. While a simulation is done, it is important to chose the simulation parameters (the jump rate D_0 and "bare" reaction rates λ_0 and δ_0) according to the scaling recipe discussed previously. However, in the following, another approach will be presented that facilitates an analytic understanding of the problem. Equations will be constructed which describe the time evolution of quantities of interest, with a

particular emphasis on describing how averages of particle numbers change in time. Once the mathematical description is in place, the generic behavior of the diffusion-controlled reactions will be discussed at an intuitive level. The technical side of the problem will be presented later.

3 Qualitative Analysis of Diffusion-controlled Reactions in Infinite (Large) Volumes

Figure 2 shows a sketch of a snapshot of the $A+A \to \emptyset$ reaction-diffusion system. (Later on real figures from the simulation will be shown.) Interesting phenomena happen when the reaction rate λ is significantly larger than the diffusion rate D. Large spatial density fluctuations may develop with time. For that particular reason, it is far from trivial to predict how the number of A particles, $N_A(t)$, or the particle density $\rho_A(t) = N_A(t)/V$, vanish in time. The problem at hand is a complex many-body problem and the mechanism that governs its behavior is illustrated in Fig. 2.

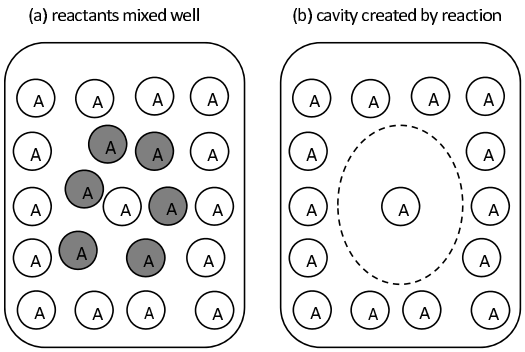

Figure 2. Reactions among A, A pairs create spatial fluctuations. The diffusion process is slow in filling in the cavity, and spatial fluctuations remain for a long time. Such behavior leads to the breakdown of mean field equations where the reaction volume is implicitly assumed to be well-mixed. The kinetics in such a case is fluctuation-dominated (anomalous).

Even if the reactants were well mixed initially, the reactions between A, A pairs, indicated in darker gray, create spatial fluctuations that the diffusion process cannot smear out. Figure 2, panel (b), shows a cavity that is created when the A particles, emphasized by gray shade in panel (a), annihilate. The A particle left in the middle of the cavity will not be annihilated, unless the diffusion process fills in the cavity by other A particles. However, if the diffusion processes is much slower than the reaction process, $D \ll \lambda$, it takes a much longer time to fill the cavity. Even if this cavity is filled by particles, there will be other cavities that emerge due to reactions between other pairs. In such a case, the dynamics of the system is plagued by spatial fluctuations in the particle density. Since particles are not well mixed, it takes a longer time to annihilate all the particles that were put in the system.

The fluctuation-dominated regimes for the $A + B$ and $A + A$ reactions are very different. In the following discussion, we assume $D_A = D_B$. Figure 3 shows how $A + B$ reactions can lead to spontaneous formation of domains. Assume that the

system arrives in a configuration where particles are clustered into domains, as depicted in panel (a). For such a configuration, even if diffusion mixes particles slightly, the minority species is immediately annihilated, as shown in panels (b) and (c). In principle, the domains that are rich in A or B particles are rather stable, while domains with smaller sizes are unstable due to the presence of diffusion.

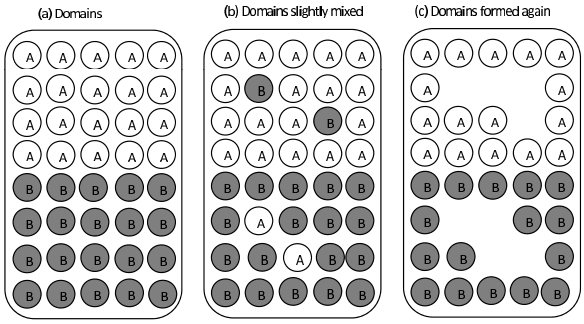

Figure 3. Spontaneous formation of domains for A+B reaction. Panel (a): Assumption is made that domains are formed. Panel (b): domains are mixed by diffusion. Diffusion process should ruin domain structure. Panel (c): Domains get reestablished due to the presence of reactions.

The mechanism discussed above shows up in the snapshots of the particle distribution that originate from stochastic computer simulations. As can be clearly seen in Fig. 4, the simulation (done using the Gillespie algorithm[7]) shows the formation of domains. This is a well-known result[8].

4 Mathematical Analysis of Diffusion-controlled Reactions: the Pair Approach

The type of kinetics discussed in the previous section is normally referred to as *fluctuation-dominated kinetics* since the presence of reactions leads to the appearance of spatio-temporal fluctuations. Equally often, the term *anomalous kinetics* is used to describe such systems where in this context "anomalous" indicates a deviation from mean-field kinetics. Fluctuation-dominated kinetics cannot be described using mean-field equations and in this section we will discuss where the problem is.

The problem at hand, i.e., a set of particles moving and reacting on a lattice, can be described in terms of the so-called *master equation*:

$$\dot{P}(c,t) = \sum_{c'} \left(R(c',c)P(c',t) - R(c,c')P(c,t) \right) \tag{4}$$

where $P(c,t)$ is the probability that the system is in state c at time t, and $R(c,c')$ is the rate of transition from c to c'. The transition rate expression can be constructed from the details of the model, but this will not be done in here, as it is a rather standard procedure. Here and in the following, the dot over a symbol denotes the time derivative. In practice, it virtually impossible to solve the master equation directly. Instead, another approach needs to be followed. In the following, the equations of motion for observables of interest will be constructed without dealing with the master equation directly.

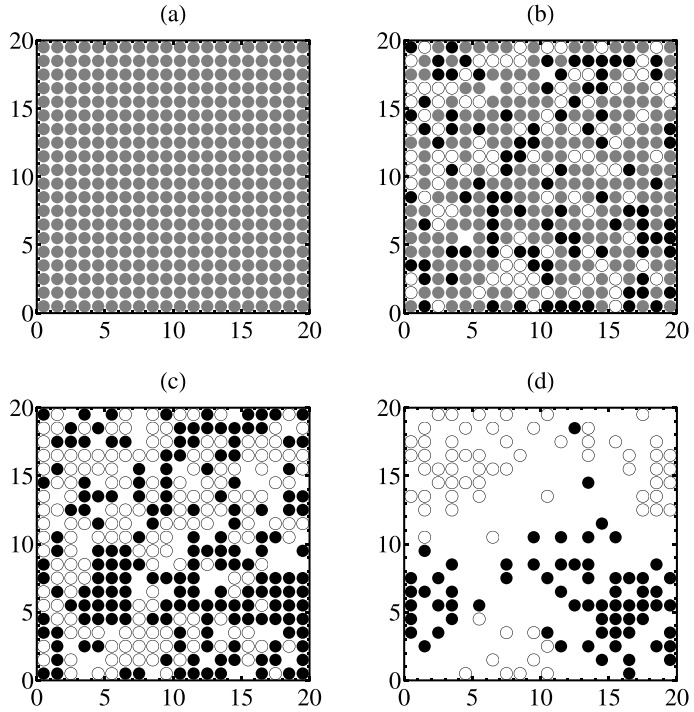

Figure 4. Snapshots of the $A + B$ model reaction dynamics in the fluctuation-dominated regime. The filled black circles denote A particles, the empty circles denote B particles, while a site that contains both A and B particles is denoted by a gray dot. The simulation is started by placing randomly 4000 A and 4000 B particles on the lattice. The size of the lattice is 20×20. The average density of particles is 10 per site per particle type. Panel (a): Initially, all sites are occupied with roughly equal numbers of A and B particles, and all sites are gray. Panel (b): As time goes on, reactions within each site deplete the lattice, and each lattice site decides on its identity, eventually turning into a black or a white circle. (c) Distinct domains rich in A or B particles start to form. Panel (d): A very late stage of the simulation with very few domains left.

4.1 Equations of motion

The observables of interest are average quantities such as the density of particles $\rho(r, t)$, or the pair (two-point) density function $\rho(r, r', t)$, where r, r' are lattice sites. Here, special care needs to be taken regarding how averaging is done. The averaging is done (conceptually) over trajectories and it not done over time. The one-point density function is exactly equivalent to the particle density. The two-point density function is slightly different as it measures the average number of pairs which can be formed from the particles at sites r and r'. For uncorrelated pairs, one would have $\rho(r, r', t) \approx \rho(r, t)\rho(r', t)$, but we cannot assume this *a priori*.

There are a couple of ways to obtain equations for these quantities. For example, one can map the problem in Eq. (4) to a field theory, and use various field-theoretic techniques to construct the equations of motion for the problem[9,10]. An alternative approach is to construct the equations directly starting from Eq. (4), as discussed in

Ref. [4]. In either case, calculations are rather technical and will be omitted. Only the final form of the equations will be stated here. Luckily, the final equations are rather intuitive.

In general, the equations of motion have the same form regardless of whether lattice sites can be multiply occupied or not (though the form of boundary conditions might differ). Reference [10] focuses on the multiple occupancy case, while Ref. [4] deals with the single occupancy one. For large volumes, both give essentially the same results.

4.1.1 Equations of motion for the $A + A$ model

To illustrate how the mean field equations emerge for the problem, it is useful to look at the simplest of the two models discussed so far, the $A + A$ annihilation process. To derive the equations of motion for the many-point density functions, a rather lengthy and technical route needs to be followed. In principle, the derivation is based on converting the master equation for the problem into something tractable. In the first step, the equations of motions for the observables of interest are derived in the lattice representation. In the second step, these equations are converted by taking the continuum limit (e.g., $x = hr$, $x' = hr'$, $h \to 0$). For example, if h is very small, the $x = hr$ can point to any point in the reaction volume. Once the procedure is carried out, the following equations are obtained. The one-point density is given by

$$\dot{\rho}(x,t) = D\nabla_x^2 \rho(x,t) - \int dV' \sigma(x-x')\rho(x,x',t) \tag{5}$$

and the two-point density is defined through

$$\begin{aligned}\dot{\rho}(x,x',t) = {} & D(\nabla_x^2 + \nabla_{x'}^2)\rho(x,x',t) - \sigma(x-x')\rho(x,x',t) \\ & - \int dV'' \left(\sigma(x-x'') + \sigma(x'-x'')\right) \rho(x,x',x'',t)\end{aligned} \tag{6}$$

The integrals are over the box that represents the reaction volume.

Please note that the both equations are exact. They only step that is needed in the continuation procedure discussed previously. In principle there are correction terms but they vanish in the $h \to 0$ limit. Also, the Laplace operators in the equation for the two-point density operate on two different coordinates (they are not equal).

The equations are rather intuitive. The first equation expresses the fact that particles can either diffuse or react in pairs, and one needs to sum over all available pairs for the reaction (second term in the right hand side of Eq. (5)). The second equation expresses the fact that a pair of particles located at x and x' can either diffuse (first term in the right hand side of (Eq. 6)), or annihilate on its own (second term in the right hand side of Eq. 6), or one of the pair constituents can get annihilated by a particle located at x'' (in such a case the third particle needs to be within the reaction range, and the integral sums over all such possibilities).

Eq. (6) shows that the two-point density $\rho(x,x',t)$ depends on the three-point density $\rho(x,x',x'',t)$. This continues and leads to an infinite hierarchy of equations. There are many examples of such equations, and they resurface in various disciplines. In all cases, the problem is how to cut an equation hierarchy. Various approximation methods have been developed to that end. The most common approach is to use a

pair approximation, and assume that effects related to particle pairs are the dominant ones. For example, a technique for performing a pair approximation for Fermionic models (where double occupancy of lattice sites is forbidden) is discussed in Ref. [4]. A similar discussion for Bosonic models (where double occupancy is allowed) can be found in Ref. [10].

When a pair approximation is used, all density functions are expressed in terms of the pair correlation functions for the problem one deals with. For example, in the case of the $A + A$ model, it is common to use an approximation such as

$$\rho(x, x', x'', t) \approx \rho(x, t)\rho(x', t)\rho(x'', t)\chi(x, x', t)\chi(x', x'', t)\chi(x, x'', t) \tag{7}$$

where $\chi(x, x', t)$ denotes the pair correlation function for the problem, which is defined as

$$\rho(x, x', t) \equiv \rho(x, t)\rho(x', t)\chi(x, x', t) \tag{8}$$

Thus Eq. (7) is referred to as a pair approximation.

For a large system, it is expected that boundaries will not influence the dynamics of the system in any way. In such a case it is useful to assume periodic boundary conditions. Such an assumption simplifies the problem tremendously. If, in addition, initial conditions are uniform, the number of variables one needs to deal with reduces considerably. In particular, the density functions simplify greatly:

$$\rho(x, t) = \rho(t),\ \chi(x, x', t) = \chi(x - x', t) \tag{9}$$

Clearly, the assumption of translational invariance needs to be questioned for extremely small volumes, but when the size of the system is significantly larger than the size of reactants the boundaries should not play an important role.

Using the pair approximation in (7) and the translational invariance assumption (9), in (5) and (6), gives the following equations. The particle density equation becomes

$$\dot{\rho}(t) = -k(t)\rho(t)^2 \tag{10}$$

where the *effective* and *time-dependent* reaction rate $k(t)$ is given by

$$k(t) = \int dV \sigma(x)\chi(x, t) \tag{11}$$

The pair correlation function satisfies

$$\dot{\chi}(x, t) = 2D\nabla_x^2\chi(x, t) - \sigma(x)\chi(x, t) + \mathcal{O}(\rho) \tag{12}$$

where $\mathcal{O}(\rho)$ on the right hand side of the equation denotes the terms that drop out in the low density limit. These terms involve integrals of the particle density and become sub-leading when the system is dilute. Please note that Eq. (10) is always exact. The initial conditions for both equations are naturally given by

$$\rho(t = 0) = \rho_0 \tag{13}$$

and

$$\chi(x, t = 0) = 1 \tag{14}$$

The initial condition for the particle density describes a situation where reactants are spread uniformly throughout the reaction volume (Eq. 13), while the initial condition for the pair correlation function indicates that the state is well mixed (Eq. 14). This might seem slightly counterintuitive since one might ask: how could uniformly distributed particles fail to be well mixed?

Please keep in mind that these equations describe an ensemble and are meant to describe averages over many trajectories. The initial state that is being discussed is to be understood as a set of states where the system is started from. In fact, the initial condition specified above describe the Poisson state[4]. For example, such ensemble could be simulated by placing a fixed amount of particles randomly on a lattice and performing the stochastic simulation that starts from such a state. To obtain the density functions from the simulation one needs to repeat many runs and then average over trajectories. It is true that randomly throwing particles on the lattice there will be lattice sites that are empty, while some sites will contain a lot of particles, but on average there are no preferred sites that will pick more particles that others. However, for an initial configuration prepared in such a way the initial condition is uniform in a sense that there is no preference where particles are placed (which resurfaces later on, when averages are made resulting in Eq. 13). Also, the initial condition is well mixed since for a particle at a position r the probability of finding the reaction partner somewhere else at r' does not depend on the value of r'. Again when averages are made result in the Eq. (14) should be obtained.

One can see from Eq. (10) how the mean field equations for the problem emerge. If $\chi(x,t) = 1$, i.e. reactants are well mixed at all times, the effective reaction rate becomes a constant, $k(t) = \lambda$, where the time-independent reaction rate (the classical kinetic rate constant) is given by $\lambda = \int dV \sigma(x)$. In such a case, the law of classical chemical kinetics immediately follows, with the solution $\rho(t) = \rho_0/(1 + \lambda\rho_0 t)$. For large times the mean field solution behaves as

$$\rho(t) \approx \frac{1}{\lambda t} \propto t^{-1} \tag{15}$$

The exponent -1 is referred to as the *mean field exponent*.

However, the mean field description fails when $\chi(x,t) \neq 1$ due to the fact that diffusion cannot mix the reactants well. To see this, it is instructive to inspect Eq. (12). The first term on the right hand side of the equation describes mixing by diffusion, and the second term describes a process where the reaction "burns" a hole in the pair correlation function. These two processes work against each other. Once the equation is solved, one can see that for $D \ll \lambda$ and $d \leq 2$ the pair correlation function never equals one, and the reaction term dominates. In general, to get the correct kinetics, a rather technical analysis needs to be done for each problem one investigates. Such an analysis was conducted for the models studied in here, and it is beyond the scope of this paper to review all details of the computation.

For large times, the main findings for the $A + A$ reaction are as follows. The mean field result holds for $d > 2$. For $d < 2$ the correct result is given by

$$\rho(t) \approx \mathcal{A}(d)(Dt)^{-d/2} \tag{16}$$

where $\mathcal{A}$ is a constant which only depends on the dimensionality of the problem, and no longer on the reaction rate λ. The anomalous kinetics exponent is $d/2$ (different

from mean field exponent for $d < 2$). At $d = 2$ one obtains logarithmic corrections, $\rho(t) \propto \ln t/t$.

4.1.2 Equations of motion for the $A + B$ model

To simplify the discussion, only the case with equal diffusion constants and equal amounts of A and B particles will be discussed. Thus we assume $D_A = D_B = D$ and $\rho_A(x, 0) = \rho_B(x, 0) = \rho_0$. To derive the equations of motion in the pair approximation discussed above, it is necessary to introduce three correlation functions for the model. Two correlation functions are needed to describe correlations between A, A and B, B pairs and will be denoted by $\chi_{AA}(x, t)$ and $\chi_{BB}(x, t)$ respectively. The correlation function for A, B pairs will be denoted as $\chi_{AB}(x, t)$. By using standard techniques (e.g., as in Refs. [4,10]) one can obtain the following equation for the one-particle density

$$\dot{\rho}_A = \dot{\rho}_B = -k_{AB}(t)\rho_A(t)\rho_B(t) \tag{17}$$

where the effective reaction rate is given by

$$k_{AB}(t) = \int dV \sigma_{AB}(x)\chi_{AB}(x, t) \tag{18}$$

The correlation functions are governed by

$$\dot{\chi}_{AA}(x, t) = 2D\nabla_x^2\chi_{AA}(x, t) + \mathcal{O}(\rho) \tag{19}$$

$$\dot{\chi}_{BB}(x, t) = 2D\nabla_x^2\chi_{BB}(x, t) + \mathcal{O}(\rho) \tag{20}$$

$$\dot{\chi}_{AB}(x, t) = 2D\nabla_x^2\chi_{AA}(x, t) - \sigma_{AB}(x)\chi_{AB}(x, t) + \mathcal{O}(\rho) \tag{21}$$

Note that Eq. (19) and (20) are qualitatively different from Eq. (21) which has an extra sink term, and one expects very different dynamics for the A, A and B, B pairs and for the A, B ones. Figure 4 indicates that this is indeed the case. Because of the domain structure, particles A and B are anti-correlated, and $\chi_{AB}(x, t) < 1$, while particles of the same type tend to cluster, and $\chi_{XX}(x, t) > 1$ for $X = A, B$.

The mean field approximation is obtained by assuming $\chi_{XY}(x, t) = 1$ with $X, Y = A, B$. In such a case the equations of motion reduce to ordinary differential equations in time given by $\dot{\rho}_A(t) = \dot{\rho}_B(t) = -\delta\rho_A(t)\rho_B(t)$ with $\delta = \int dV \sigma_{AB}(x)$. For large times, one has the same scaling behavior as the $A + A$ reaction

$$\rho_A(t) = \rho_B(t) \approx \frac{1}{\delta t} \propto t^{-1} \tag{22}$$

Solving the equations of motion in the pair approximation has to be done differently when compared to the $A + A$ model. If $\mathcal{O}(\rho)$ terms are not kept in Eqs. (19-21) a wrong decay exponent is obtained. To obtain the correct decay exponent these terms have to be kept. After straight forward (and somewhat tedious) calculation it is possible to see that the exponent in the mean field asymptotic expression above is correct for $d > 4$. However, for $d < 4$ one has anomalous kinetics with exponent $d/4$,

$$\rho_A(t) = \rho_B(t) \approx \mathcal{B}(\rho_0, d)(Dt)^{-d/4} \tag{23}$$

and at $d = 4$ logarithmic corrections, as in the $A + A$ model. The constant $\mathcal{B}$ depends both on dimensionality and the initial concentration of particles. For the technical

details of the calculations leading to the asymptotic results (16) and (23), the reader can consult Ref. [11] and Refs. [8,12,13] respectively and references therein. The calculations are rather technical. The $A+B$ model has not been solved exactly below and at $d = 2$, although lower and upper bounds confirm the critical exponent (23).

4.1.3 Mathematical illustration

So far the discussion focussed on illuminating intuitive concepts. As a mathematical illustration (with limited rigor) we will present a solution to the $A + A$ model in the pair approximation and one dimension. To simplify calculations, we assume $\sigma(x) = \lambda_0\delta(x)$, which amounts to saying that A particles react only when in contact. Eq. (10) stays the same with the effective reaction rate given by

$$k(t) = \lambda_0\chi(0, t) \tag{24}$$

while Eq. (12) turns into

$$\dot{\chi}(x, t) = 2D\nabla_x^2\chi(x, t) - k(t)\delta(x) \tag{25}$$

Eq. (24) and (25) need to be solved self-consistently. We can use the Laplace transform technique to turn the problem into a much simpler problem of an ODE type. After straightforward algebra, one arrives at the following expression for the effective reaction rate

$$k(s) = \frac{\lambda_0}{s}\frac{1}{1+\frac{\lambda_0}{\sqrt{8Ds}}} \tag{26}$$

where the reaction rate expression is given in the Laplace space. It is possible to find the inverse Laplace transform of the rate expression, and it reads

$$k(t) = \lambda_0 e^{\xi}\left[1 - \mathrm{erf}\sqrt{\xi}\right] \tag{27}$$

where

$$\xi = \frac{\lambda_0^2 t}{8D} \tag{28}$$

It is instructive to study Eq. (26) expression for $D/\lambda_0^2 \gg 1$ and $D/\lambda_0^2 \ll 1$ to see how the competition between (i) mixing by diffusion and (ii) creating spatial fluctuations by the reaction, determine the fate of the system. When $D \gg \lambda_0^2$, one has $k(s) \approx \lambda_0/s$ or $k(t) \approx \lambda_0$, which is the mean field result discussed previously. For the opposite case one gets $k(s) \approx \sqrt{8D/s}$ or

$$k(t) \approx \sqrt{\frac{8D}{\pi t}} \tag{29}$$

which through Eq. (10) leads to the pair approximation result

$$\rho_{pair}(t) \approx \sqrt{\frac{\pi}{32}}(Dt)^{-1/2} \tag{30}$$

which signals anomalous kinetics. Comparing these results with Eq. (16) for $d = 1$, we see that the exponent is right, and that the density decay amplitude does not

depend on λ, as already pointed out. However, the numerical value for the amplitude does not agree with the exact result which in the case of $d = 1$ is given by

$$\rho_{exact}(t) \approx \frac{1}{\sqrt{8\pi Dt}} \tag{31}$$

The analysis done so far suggests that for small times, the kinetics should always be mean-field like. This finding is rather generic. In the beginning, due to the choice of the initial conditions for the model, there are simply enough particles around for reactions to occur. For large time, particles lose their reacting partners, and since the diffusion cannot mix the particles well, the system enters into the regime of anomalous kinetics. The crossover between these two behaviors is given by the condition that $\frac{\lambda_0}{\sqrt{8Ds_*}} \sim 1$, where naturally $t_* \sim 1/s_*$. In the time domain, the condition becomes

$$t_* \sim D/\lambda_0^2 \tag{32}$$

It is possible to derive the expression for the crossover time (32) in a more exact way. This can be seen from the expression for the reaction rate given in Eq. (27) for large times. No matter which values are used for D and λ_0, the argument of the error function grows with time, and eventually becomes very large. The border case is given by $\xi \sim 1$, which, results in the condition (32).

Furthermore, using the asymptotic expansion of the error function for large arguments

$$1 - \mathrm{erf}(\sqrt{\xi}) \approx e^{-\xi}\left[\frac{1}{\sqrt{\pi\xi}} + \mathcal{O}\left(\frac{1}{\xi^{3/2}}\right)\right] \tag{33}$$

leads to the cancellation of the exponential terms, and one arrives at the form (29). Thus, the system always enters into the anomalous kinetics regime (provided the system is infinite in size). The intuitive side of such behavior was touched upon when discussing Fig. (2).

Please note that the crossover time involves the ratio of the two most important scales in the problem, the transport and the reaction scales. The larger the diffusion, the longer the crossover time, and the longer the systems stays in the mean field regime. Conversely, if the reaction rate is increased, the crossover time gets smaller, and the anomalous kinetics regime is reached faster. These findings are rather generic as well. However, the details differ significantly, since the expression for the crossover time t_* of a particular model is strongly model-dependent (type of reaction, dimensionality of the system, etc.).

4.1.4 An example of mean field failure

To illustrate the importance of fluctuation-dominated kinetics, an example will be discussed where the mean field description fails spectacularly. The model where $A+A$, $A+B$, and $B+B$ reactions occur at the same time was suggested previously[14,15,16,10]. The behavior of the system depends very much on the equality of diffusion constants. Assuming $D_A \neq D_B$[14] or $D_A = D_B$[15,16,10] will lead to very different behaviors of the system.

The $D_A = D_B$ case is a notorious example of how a mean field description can go wrong. In particular, the ABBA model suggested and studied in Refs. [15,16,10] shows dramatic failure of the mean field approach. The model arises when one wants

to include steric effects into the simplest possible way, and results in the following set of reactions: $A + A \to \emptyset$, $A + B \to \emptyset$, and $B + B \to \emptyset$ with rates λ, δ, and λ respectively. Please note that the $A + A \to \emptyset$ and $B + B \to \emptyset$ reactions have the same rate constant. Also, the rate constants are such that $\delta > \lambda$. (The opposite case can be also studied but this is not done here.) The mean field equations for the model are given by $\dot{\rho}_A = -\lambda\rho_A^2 - \delta\rho_A\rho_B$ and $\dot{\rho}_B = -\lambda\rho_B^2 - \delta\rho_A\rho_B$. By mapping the problem to the Poincaré sphere[16] large time behavior can be found, and is given by $\rho_A(t)/\rho_B(t) \propto t^{\delta/\lambda - 1}$, when $\rho_A(0) > \rho_B(0)$. The type of molecule that is in minority at $t = 0$ simply has to vanish asymptotically. However, the careful calculation in Refs. [16,10] reveals that the ratio $\rho_A(t)/\rho_B(t)$ saturates to a constant value for large times, and that the minority species vanishes as fast as the majority species.

5 Diffusion-controlled Reactions in Restricted Geometries

In the previous subsections, we have discussed diffusion-controlled reactions in infinite volumes. Here, we shift to discussing diffusion-controlled reactions in restricted geometries.

A typical situation of interest is depicted in Fig. 1, panel (c). When the size of the reactants is comparable to the size of the system, extreme crowding conditions arise. In a situation like this, one cannot neglect the presence of the product molecules (or the associated backward reactions). Interestingly, compared to the infinite volume case, diffusion-controlled reactions in small (restricted) volumes are relatively unexplored. There are some pioneering efforts in this area, e.g., the work by Khairutdinov and Serpone, Tachiya, or Ramamurthy. See Refs. [17,18,19] for reviews on the subject. In such systems, the number of reactants tends to be small, and the effects of fluctuations are enhanced. The methods used to study the bulk situation (infinite volume), if they indeed work, have to be heavily modified.

The main difference with the case of infinite volumes is that the particle decay is governed by an exponential decay law, instead of the power law found in infinite systems. Such behavior comes from the fact that the configuration space becomes strictly discrete. When the number of particles becomes low, one needs to count them one by one. The average of the number of particles behaves as $n(t) = c_1 + c_2 e^{-E_1 t} + c_3 e^{-E_2 t} + \ldots$, and the transition rate operator R in the master equation has eigenvalues that are well separated. When time is large enough, one has $(E_1 - E_i)t \gg 1$ for $i \geqslant 2$, and the first two terms in the expansion of $n(t)$ dominate, which results in the exponential decay.

Even a very large system, with a large number of particles, might eventually arrive in the regime where particle/density decay is exponential (e.g., as discussed in Ref. [6]). When the reaction volume is finite, there is an additional time-scale that is important, the time needed for a molecule to "realize" it is in a finite volume. A rough estimate for such time is

$$t_{mix} \sim L^2/D \tag{34}$$

which will be also referred to as the mixing time. In reality, the mixing time can have a rather complicated behavior. The spatial scales for the problem (the size of a reaction volume, and the size of reactants) combine in a non trivial way[19,6,20].

It should be mentioned that, in general, there is the problem of extremely low copy numbers. The methods proposed here may not represent the situation very

accurately, as one uses a truncated description of the master equation. In this context, one naturally wonders about the usefulness of the pair approach. It was shown that the truncation of the master equation for the $A + B$ model can have a severe impact on the accuracy of the pair approximation when the number of particles is low. The flaw of the methods described in here, can be traced to the breaking of a symmetry law which is implicit in the $A + B$ model: the difference in the number of A and B particles is constant in time. The issue was studied very carefully in Ref. [6], where it was shown that it is possible to devise an extrapolation technique which takes care of the problem.

6 Relevance for Understanding the Living Cell Biochemistry

Is there a need for modeling the living cell biochemistry by using the framework of diffusion-controlled reactions? This question has been already addressed to some extent, e.g., in Refs. [21,22]. After all, many important biochemical details are not included in the reaction-diffusion framework, such as effects related to structured water, chain-like structure of molecules, or processes on time scales much smaller than the reaction times. Also, the formalism is rather technical, and there are other alternatives that can be used. This question will be approached both from the theoretical (modeling) and the practical (applied) points of view, in the two subsections that follow. At the end of this section, a few open problems will be discussed as well.

6.1 Modeling aspects

The usefulness of the formalism comes from its conceptual simplicity. The most important aspect is that there is a clear conceptual separation between transport and reaction processes. The structure of the configuration space and transitions among the states are well defined. The calculation of observables is straightforward, though technically complicated. Besides, the formalism suggests itself naturally in the context of the modelling of the living cell biochemistry, as diffusion is the ubiquitous transport mechanism in the living cell, and there are one million reactions happening in the cell per second.

There are series of modeling activities where the validity of mean field equations might be an issue. Typical examples would be studies related to the stability, sensitivity, or robustness analysis, which are often based on the use of mean field equations. The example of the ABBA model discussed previously shows that, even at the qualitative level, the mean field framework can fail miserably and, accordingly, any conclusions drawn from mean field equations will be incorrect. Thus in general, mean field kinetics should be used with caution. It is important to be aware of the risks.

In general, one cannot say when the classical chemical kinetics is applicable and when to expect fluctuation-dominated kinetics. In principle, every new process studied in the cell should be approached with caution from that point of view. Unfortunately, for a given process in the living cell, it is hard to make a precise mathematical statement regarding whether the formalism of classical chemical kinetics can be used. To determine this, a rather lengthy and technical analysis needs to be done for each new model. A central issue is to identify the critical

dimension of a system. For example, $d_c = 2$ for the $A + A$ reaction in an infinite volume, and $d_c = 4$ for the $A + B$ one.

The value of the critical dimension governs the validity of the mean field equations for a problem. For example, in three dimensions ($d = 3$), the $A + A$ reaction does not suffer from anomalous kinetics, and mean field classical kinetics can be safely used. However, if one studies reactions on surfaces ($d = 2$) or lines ($d = 1$), one has to be careful. The situation is more alarming for the $A + B$ reaction as it is always has anomalous kinetics, regardless of whether occurring in the bulk ($d = 3$), at the surface ($d = 2$) or on a line ($d = 1$), since its critical dimension equals $d_c = 4$.

To determine the critical dimension for a problem is a rather non-trivial task. There is simply no well-defined recipe for how to do such an analysis. For example, the power counting techniques from the field theory framework do not always work: using the power counting, one can predict the critical dimension for the $A + A$ problem, but not for the $A + B$ reaction.

Should one use a computer simulation to understand a particular problem, there are a couple of issues to be aware of. If one solely counts the particles in the cell, then perfect mixing is assumed. In such a case, effects related to spatio-temporal fluctuations are ignored. To go beyond that simplification, and account for the position of particles, one needs to formalize the problem in mathematical terms. This naturally leads to the use of the framework of diffusion-controlled reactions. Simulations done at that level account for the most important aspects of the problem. Also, fluctuation-dominated kinetics (if it appears) is automatically taken care of. For example, one does not need to worry about the validity of mean field equations. In that respect, there is no need to perform a rather technical and time-consuming analysis, such as finding the critical dimension of the system. Simulations are a very attractive approach to describe the living cell.

Though extremely useful, *in silico* experiments are heavily dependent on the computer resources, the cpu power, the memory, etc. There is certainly an upper limit on the number of particles one can simulate. The equations of motion approach discussed in this review can be an interesting alternative in the situation when the number of particles is large, and there are not that many particle types. Admittedly, the situation in the living cell is the opposite (a large number of particle types in low copy numbers). Nevertheless, the equations of motion approach could be useful since it could be adjusted to describe the low particle number limit as shown in Ref. [6].

6.2 Applied aspects

The properties of diffusion-controlled reactions discussed in the previous sections might have profound effects on our understanding of the living cell biochemistry. Many processes in the cell are noise driven or influenced by noise.[23] Given this fact, the two most important questions that need to be asked at this point are: are there processes in the living cell where fluctuation-dominated kinetics or anomalous kinetics sets in, and does the living cell exploit the characteristic features of fluctuation-dominated kinetics in any way to successfully perform its functions? After all, the living cell environment exhibits kinetics in all dimensions. As a rule of thumb, lowering the dimensionality of a system results in anomalous kinetics. The two-dimensional

reactions at the membrane surface are certainly very different from the ones in the bulk. In that sense fluctuation-dominated kinetics should be abundant in the living cell. Answering such questions is beyond the scope of this paper, but an attempt will be made to discuss some specific cases.

Two scales determine whether the anomalous kinetics sets in, t_* and t_{mix}. For $t_* \ll t_{mix}$ one expects anomalous kinetics in the interval $t_* \ll t \ll t_{mix}$. However, such a regime is relatively hard to find in the living cell. A typical living cell is very small in size, and in such cases t_{mix} can get very small, which easily invalidates the $t_* \ll t_{mix}$ condition. For example, in E. Coli, the mixing time is relatively fast for small metabolites, being roughly $t_{mix} \sim 1\ msec$. For proteins, the time is somewhat larger $t_{mix} \sim 0.1\,sec$. Also, for larger cells, such as human fibroblasts, the mixing times are somewhat larger, being roughly $t_{mix} \sim 0.1\,sec$ ($t_{mix} \sim 100\,sec$) for small molecules (proteins). The data were taken from Ref. [24].

Clearly, in general, it is hard to find a process in the living cell for which $t_* \ll t_{mix}$. Interestingly, despite this fact, a few examples have been discussed in the literature. For example, the importance of understanding the influence of diffusion on enzymatic kinetics has been pointed out a long time ago[25,26], and has been investigated ever since[27,29,28,30]. Figure 4 in Ref. [29], which depicts the spatial distribution of an enzyme and a substrate molecule, appears very similar to Fig. 4 which describes the $A + B$ model. Despite the fact that the occurrence of anomalous kinetics implies a special choice of the parameters that describe a system, it is possible to find instances where enzymatic kinetics is anomalous. References [28,30] discuss fractal pharmacokinetics of the drug mibefradil in the liver. In these cases, the anomalous kinetics observed has to do with the fact that the space where reactants move have a fractal-like structure.

6.3 Open problems

The problems discussed so far get even more complicated when the structure of the cell is taken into account. New issues emerge that need to be addressed. Understanding the interplay between the geometrical shape that sustains the reactions and the topological structure of the pathways is one of the central problems. Ultimately, the question is whether we can understand the shape of the organelles with reference to the set of reactions they sustain. Unfortunately, the role that the geometry plays for cell function is poorly understood, see the review papers[31,22] and references therein. In that context, diffusion-controlled reaction can provide useful tools for that type of analysis. A mathematical framework for studying the geometry and reaction interplay (GRIP) is suggested in Refs. [22,32].

7 Conclusions

The framework of diffusion-controlled reactions is studied extensively in the statistical physics and chemistry communities. In particular, the study of the fluctuation-dominated, or anomalous kinetics, has been done extensively within the statistical physics community. Interestingly, in publications that address computational cell biology, comparatively little attention has been payed to the effects related to the fluctuation-dominated kinetics, and in particular to the validity of mean field equations, though some work exists (e.g., Refs. [21,29,20]). The goal of

this study is to point out these facts and motivate future investigations.

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