Reaction rates for mesoscopic reaction-diffusion kinetics

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Abstract

The mesoscopic reaction-diffusion master equation (RDME) is a popular modeling framework, frequently applied to stochastic reaction-diffusion kinetics in systems biology. The RDME is derived from assumptions about the underlying physical properties of the system, and it may produce unphysical results for models where those assumptions fail. In that case, other more comprehensive models are better suited, such as hard-sphere Brownian dynamics (BD). Although the RDME is a model in its own right, and not inferred from any specific microscale model, it proves useful to attempt to approximate a microscale model by a specific choice of mesoscopic reaction rates. In this paper we derive mesoscopic reaction rates by matching certain statistics of the RDME solution to statistics of the solution of a widely used microscopic BD model: the Smoluchowski model with a mixed boundary condition at the reaction radius of two molecules. We also establish fundamental limits for the range of mesh resolutions for which this approach yields accurate results, and show both theoretically and in numerical examples that as we approach the lower fundamental limit, the mesoscopic dynamics approach the microscopic dynamics.
I. INTRODUCTION

The reaction-diffusion master equation (RDME) is a commonly used mesoscopic model in the field of computational systems biology. As a natural extension of the classical well-mixed Markov-process formalism for reaction kinetics [1], it has been successfully applied to study diverse biological phenomena such as yeast polarization [2], Min oscillations in *E. Coli* [3], and noisy oscillations of Hes1 in embryonic stem cells [4, 5].

In the RDME framework, spatial heterogeneity is modeled by dividing space into voxels in a computational mesh, where molecules are assumed to be well mixed inside each voxel. In individual voxels, reactions are simulated using the Stochastic Simulation Algorithm (SSA) [1], while diffusion is accounted for through discrete jumps of molecules between voxels. Discrete diffusion and well-mixed SSA are combined in the Next Subvolume Method (NSM) [6], an efficient kinetic Monte Carlo method. For moderate mesh resolutions, simulations of the RDME are typically orders of magnitude faster than microscopic particle-tracking models, such as the popular Green’s Function Reaction Dynamics (GF RD) algorithm [7–9]. This contributes to the popularity of the method for applications where the system of interest needs to be studied on minute to hour timescales, typical for cellular events like gene expression, signaling and cell division. The RDME underlies software for spatial stochastic simulation such as MesoRD [10], URDME [11], pyURDME (www.pyurdme.org), and STEPS [12].

Despite the proven usefulness of the RDME—and the extensive work put into speeding up simulations using approximate [13–15] and hybrid [16] methods, as well as extending it to include additional transport phenomena [17, 18] and to simulate it on complex geometries [19, 20]—its fundamental numerical properties and its ability to approximate microscopic particle tracking models at high mesh resolution remains poorly understood. In order to discuss the accuracy of the RDME on small length- and timescales, we need to specify a fine-scaled alternative as our gold standard. A microscale model often utilized for that purpose is the Smoluchowski model, in which particles are modeled by hard spheres that diffuse according to Brownian motion, and reactions are modeled by a partially absorbing boundary condition at the surfaces of the spheres. This model has a long history in chemical physics, going back to ideas by Smoluchowski [21]. In systems biology, the Smoluchowski model is being popularized through software packages such as E-Cell [22] and Smoldyn [23].
This paper is concerned with the accuracy of the RDME when viewed as an approximation of the Smoluchowski model.

The principal way in which the mesoscale and the microscale are connected is through the mesoscopic bimolecular reaction constant. A classical result by Collins and Kimball provides such a constant where the microscopic, intrinsic, reaction parameters in the Smoluchowski model are related to mesoscale reactions rates in the RDME for simulations in 3D [24]. The same constant was derived more recently from first principle physics by Gillespie [25]. The constant is valid when voxels are large in comparison to the molecules. Since, in the conventional implementation, reactions occur only between molecules occupying the same voxel, the average time until molecules react diverges with vanishing size of the voxels [26–28]. A consequence is a lower bound on the size of the voxels, below which no mesoscopic reaction rate can make the average reaction times match in the RDME and Smoluchowski model [28].

In previous work we analyzed the scenario of a single, irreversible, bimolecular reaction on a Cartesian mesh. For the case of perfect absorption, we obtained analytical lower limits on the mesh size in both 2D and 3D. Above those limits, it is theoretically possible to construct a mesoscopic rate such that the mean binding time in the two models match. Below that critical mesh size, no such rate can be constructed [28]. Hence, in the presence of bimolecular reactions, a fundamental limitation of the RDME results from the inherent bound on the accuracy to which we can represent diffusion. As a direct consequence of our previous analysis, we also obtained mesoscopic reaction rates which ensure that the mean binding time in the RDME matches that of the Smoluchowski model for an irreversible bimolecular reaction.

In this paper we extend our previous analysis. First, we study the case of reversible reactions, and ask whether there are additional constraints on the admissible mesh sizes compared to the irreversible case. We derive a critical voxel size under the following three assumptions: the average time until a reaction fires should match between mesoscopic and microscopic models, the steady state levels should match, and the mesoscopic dissociation rate should be smaller than or equal to the intrinsic dissociation rate. The last condition is necessary for the dissociation to make physical sense, and if we are to match not only equilibrium distributions but also transient solutions. The result establishes the previously obtained critical voxel sizes—in the perfectly absorbing, irreversible, case—as an upper
bound on the critical sizes for the more general reversible case. Importantly, this means that there will be a non-trivial lower limit for the mesh size, independent of the intrinsic microscopic reaction parameters. We also study the accuracy of our reaction rates as compared to the Smoluchowski model, and show good agreement, both at steady state and during the transient phase, between mesoscopic and microscopic simulations as the mesh size approaches the critical lower limit. In particular, we show how the multiscale propensities can provide a better mesoscopic approximation to a diffusion limited model of a MAPK cascade, compared to the widely used propensities of Collins and Kimball [24]. This model has not previously been possible to simulate accurately with a fully local RDME, although it has been simulated successfully with a non-local extension of it [29], and using a hybrid microscale-mesoscale method [30].

For simplicity we have chosen not to write out units explicitly. We are using SI units throughout.

II. BACKGROUND

A system of \( N \) molecules of \( S \) different chemical species, diffusing and reacting inside a finite reaction volume, can be modeled at several different scales, and the accuracy of the different models depends on the properties of the system. In this section we briefly review the microscopic Smoluchowski model and the mesoscopic RDME model, and discuss previous work on connecting the two models.

A. Microscopic scale: the Smoluchowski model

Several microscopic models have been proposed and studied in some detail [27, 31, 32]. We have chosen to focus on the Smoluchowski model, given the extensive attention it has received for instance in [7–9]. In the Smoluchowski framework, molecules are modeled as hard spheres of radius \( \sigma \). The radii of the spheres are referred to as the reaction radius of the molecules. The Smoluchowski equation, extended with a mixed boundary condition at the sum of the reaction radii, determines the probability of a reaction occurring between colliding molecules.

Let \( \mathbf{x}_1 \) and \( \mathbf{x}_2 \) be the positions of two molecules, and consider the relative position \( \mathbf{r} = \)
\[ \frac{\partial p}{\partial t} = D \Delta p(r, t | r_n, t_n), \] (1)

where \( p(r, t | r_n, t_n) \) is the probability distribution function (PDF) of the relative position \( r \) at time \( t \), given the relative position \( r_n \) at time \( t_n \), and where \( D \) is the sum of the diffusion constants of the molecules. The boundary condition is given by

\[ K \frac{\partial p}{\partial n} \bigg|_{r=\sigma} = k_r p(r, t | r_n, t_n), \] (2)

where

\[ K = \begin{cases} 4\pi\sigma^2D & (3D) \\ 2\pi\sigma D & (2D) \end{cases} \] (3)

\( \sigma \) is the sum of the reaction radii, and \( k_r \) is the microscopic, intrinsic, reaction rate. The initial condition is \( p(r, t_n | r_n, t_n) = \delta(r - r_n) \).

To update a pair of molecules we solve for \( p(r, t | r_n, t_n) \), and then sample the new relative position at time \( t \). Single molecules are updated by sampling from a normal distribution in all directions. A system of \( N \) molecules becomes an \( N \)-body problem, and a direct solution is generally unattainable. Instead we can simulate the system with the Green’s function reaction dynamics (GFRD) algorithm \[7, 8\]. The core of the algorithm is a reduction of the problem to a collection of single- and two-body systems, accomplished through an appropriate restriction of the time step of the algorithm. In \[30\] the GFRD algorithm is extended to include complex boundaries, and in \[9\] improvements are suggested with the aim of making the algorithm more flexible and efficient.

The GFRD algorithm is efficient for dilute systems where the free space between molecules allows for an efficient grouping in pairs while using a relatively large time step, and the computational benefit over brute-force BD methods can be orders of magnitude. If the system contains some species that are present in higher copy numbers, or if a very high spatial resolution is not required, the mesoscopic RDME can in turn be orders of magnitude faster than GFRD.

B. Mesoscopic scale: The reaction-diffusion master equation

The RDME extends the classical well-mixed Markov-process model \[1\] to the spatial case by introducing a discretization of the domain into \( N \) non-overlapping voxels \[33\]. Molecules
are point particles and the state of the system is the discrete number of molecules of each of the species in each of the voxels. A common choice for the discretization is a uniform Cartesian lattice, where each voxel is a square with area $h^2$ (2D), or a cube with volume $h^3$ (3D). Simulations can also be conducted on unstructured triangular and tetrahedral meshes for better geometric flexibility [20]. The RDME is the forward Kolmogorov equation, governing the time evolution of the probability density of the system.

For brevity of notation, we write $p(x, t) = p(x, t|x_0, t_0)$ for the probability that the system can be found in state $x$ at time $t$, conditioned on the initial condition $x_0$ at time $t_0$. For a general reaction-diffusion system, the RDME can be written as

$$\frac{d}{dt} p(x, t) = \sum_{i=1}^{K} \sum_{r=1}^{M} a_{ir} (x_i - \mu_{ir}) p(x_1, \ldots, x_i - \mu_{ir}, \ldots, x_K, t) - \sum_{i=1}^{K} \sum_{r=1}^{M} a_{ir} (x_i) p(x, t) + \sum_{j=1}^{N} \sum_{i=1}^{K} \sum_{k=1}^{K} d_{ijk} (x_j - \nu_{ijk}) p(x_1, \ldots, x_j - \nu_{ijk}, \ldots, x_N, t) - \sum_{j=1}^{N} \sum_{i=1}^{K} \sum_{k=1}^{K} d_{ijk} (x_j) p(x, t),$$

(4)

where $x_i$ denotes the $i$-th row of $x$ and $x_j$ denotes the $j$-th column. The functions $a_{ir}(x_i)$ define the propensities of the $M$ chemical reactions, $\mu_{ir}$ are stoichiometry vectors associated with the reactions, $d_{ijk}(x_i)$ are propensities for the diffusion jump events, and $\nu_{ijk}$ are stoichiometry vectors for diffusion events. The RDME is too high-dimensional to permit a direct solution. Instead realizations of the stochastic process are sampled, using algorithms similar to the SSA but optimized for reaction-diffusion systems [6].

The propensity functions for the diffusion jumps, $d_{ijk}$, are selected to provide a consistent and local discretization of the diffusion equation, or equivalently the Fokker-Planck equation for a Brownian motion [34]. For a uniform Cartesian grid, a finite difference discretization results in diffusion jumps with propensities

$$X_{is} \xrightarrow{d_{ijs}} X_{js}, \quad d_{ijs} = \frac{\gamma_s}{h^2}.$$

(5)

For a triangular or tetrahedral unstructured mesh, finite element or finite volume discretizations result in propensities that account for the shape and size of each voxel [20]. With this
model of diffusion, setting reactions aside, the solution of the RDME will, with vanishing voxel sizes, converge in probability to a Brownian motion.

In the case of mass action kinetics, the propensity functions \( a_{ir}(x) \) for bimolecular reactions take the form

\[
a_{ir}(x_i) = k_{r}^{\text{meso}} x_{is} x_{is}'.
\]

We will refer to \( k_{r}^{\text{meso}} \) as the *mesoscopic association rate*. In practical modeling work, \( k_{r}^{\text{meso}} \) is often obtained by fitting the model to some phenotypic experimental observation, or provided directly as a macroscopic or mesoscopic model parameter obtained from experiments. If the association rate is instead given in terms of the microscopic reaction rate, \( k_{r} \), a classical result of Collins and Kimball \cite{24} couples the mesoscale and microscale in 3D through

\[
k_{r}^{\text{meso}} = k_{\text{CK}},
\]

where

\[
k_{\text{CK}} = \frac{4\pi\sigma D}{4\pi\sigma D + k_{r}}.
\]

Gillespie arrives at the same relation by using classical results from gas kinetics, and calls it the *diffusional propensity function* \cite{25}. From Gillespie’s physically rigorous derivation it is possible to relate the intrinsic reaction rate \( k_{r} \) to fundamental physical constants.

A natural question, given model parameters and a mesh size, is how well a mesoscopic simulation can capture the microscale dynamics. It has been shown that the solution of the RDME diverges with respect to the Smoluchowski model \cite{28,35}. Due to the point particle assumption, bimolecular reactions occur with successively lower probability, to eventually vanish in the limit of small voxels.

This means that there is a lower bound on the voxel size, below which bimolecular reactions cannot be accurately simulated in the RDME. There is also an upper bound on the voxel size, above which the reaction-diffusion dynamics will be insufficiently resolved. The question of how to choose the voxel size for sufficient accuracy has not yet been satisfactorily answered, but some attempts at establishing lower bounds on the voxel size have been made. A trivial bound on the voxel size follows from physical arguments \cite{36}; the voxels must be large enough for the reacting molecules to remain dilute and well mixed inside the voxel. This condition translates to

\[
h \gg \sigma.
\]
Apart from physical common sense, the above condition is an explicit assumption in the derivation of (7). Only if this assumption is valid can the rate constant (7) be expected to provide an accurate simulation with respect to the Smoluchowski model. Unfortunately, condition (8) offers little guidance on how to choose the mesh size in practice.

The reaction constant (7) depends on the microscopic parameters but not on the spatial discretization. By allowing the rate to depend on the mesh, and by matching certain properties of the microscopic model, it is possible to derive alternative forms for \( k_{r_{\text{meso}}} \) that perform better than (7) for diffusion limited systems and for fine meshes [28, 29]. Those approaches also yield constants in 2D, where no expression based on a physical derivation is available. In [29] the rates are derived by matching the mean equilibration time of a reversible reaction on a spherical discretization. These rates are then used on Cartesian lattices.

Let \( \tau_{\text{micro}}(k_r) \) be the mean binding time for two molecules in the Smoluchowski model. In the case of a single irreversible association reaction on a uniform Cartesian discretization of a square or cube of side length \( L \), Hellander et al. [28] showed that if the mesoscopic propensity \( k_{r_{\text{meso}}} \) is chosen as \( k_{r_{\text{meso}}} = \rho^{dd} \), where

\[
\rho^{dd}(k_r, h) = \begin{cases} 
\frac{(L/h)^2}{\tau_{\text{micro}}(k_r) - \frac{L^2}{2\pi D} \log\left(\frac{L}{h}\right) + \frac{2.1951}{4D} L^2} & d = 2 \\
\frac{(L/h)^3}{\tau_{\text{micro}}(k_r) - 1.5104L^3/(6Dh)} & d = 3,
\end{cases}
\]

then the mean binding time on the mesoscopic scale will match the mean binding time in the Smoluchowski model. For \( k_r \to \infty \), this is possible down to \( h_*^{\infty} \approx 3.2\sigma \) in 3D, and \( h_*^{\infty} \approx 5.1\sigma \) in 2D. Below \( h_*^{\infty} \), the matching of the mean binding time will not be possible in the perfectly absorbing case. For simple geometries, such as a disk or a sphere, \( \tau_{\text{micro}} \) can be obtained analytically. For other geometries, provided that \( h \ll L \), the analytical result for a disk or a sphere with matching volume provides an excellent approximation. The analytical lower bounds on the voxel sizes are obtained by considering the extreme case of \( k_r \to \infty \) and using the above mentioned approximation for \( \tau_{\text{micro}} \). In [27], based on another assumption not involving the microscopic Smoluchowski model, Erban and Chapman arrived at an expression in 3D that is similar to (9) and that establishes the same critical mesh size.

In what follows, we set out to expand on this theory with the aim of an improved understanding of the range of the mesh sizes for which the RDME will accurately approximate the Smoluchowski model. In particular, we derive critical mesh sizes for more realistic kinetics like reversible bimolecular reactions, and we show that under mild assumptions, the rates
are effectively independent of $L$. We will also obtain error estimates that provide a way to estimate the needed mesh resolution to achieve a certain accuracy in the rebinding time distributions.

III. RESULTS

The case of an irreversible reaction with $k_r \to \infty$ was studied in [28]. The analysis provided lower bounds on the mesh size in 2D and 3D, and reaction rates for matching mean association times. The reaction rates depended on the size $L$ of the domain. As reactions occur locally in space, that dependence is not intuitive.

In this section we expand on that theory. First we show that the reaction rates are independent of the size of the domain, under the assumption that the domain is much larger than the molecules. From this follows analytical lower bounds on the mesh size for the case of an irreversible reaction with $0 < k_r \leq \infty$.

Second, we study a reversible reaction on a square or cubical domain and proceed to derive mesoscopic reaction rates under the following three assumptions: the average reaction time should match between mesoscopic and microscopic models, the steady state levels should match, and the intrinsic dissociation rate should be larger than or equal to the mesoscopic dissociation rate. Under these assumptions we derive a lower bound on the mesh size independent of the reaction rates.

We also show how the multiscale mesoscopic reaction rates behave in the limit of small voxels as well as in the limit of large voxels, effectively connecting the microscopic and mesoscopic scales. Finally, we provide error estimates that relate the mesh size to the error in rebinding-time distributions, and show that the mean mesoscopic rebinding time approaches the mean microscopic rebinding time, as the mesoscopic mesh size approaches the lower bound.

A. Irreversible reactions

The analytical expressions for the lower bounds on the voxel size $h$ derived in [28] are valid for the case of irreversible reactions with perfect absorption. In this section we assume $L \gg \sigma$, to obtain analytical expressions for the lower bounds in the general case of $k_r > 0$. 
We show that the reaction rates are independent of the size $L$ of the domain, thus depending on local parameters only.

**Theorem 1.** Let $\rho^{dD}$ be the mesoscopic reaction rate in dimension $d$, and assume that $L \gg \sigma$. Then

$$\rho^{dD}(k_r, h) \approx \frac{k_r}{h^d} \left( 1 - \frac{k_r}{D} G^{dD}(h, \sigma) \right)^{-1}$$

where $d \in \{2, 3\}$, and

$$G^{dD}(h, \sigma) = \begin{cases} \frac{1}{4} \left( \frac{3}{2\pi} + C_{\alpha, 2} \right) - \frac{1}{2\pi} \log \left( \pi^{-\frac{1}{2}} \frac{h}{\sigma} \right) & (2D) \\ \frac{C_{\alpha, 3}}{6h} - \frac{1}{4\pi\sigma} & (3D) \end{cases}$$

where

$$C_{\alpha, d} \approx \begin{cases} 1.5164 & d = 3 \\ 0.1951 & d = 2. \end{cases}$$

Let

$$h^*_k = \inf_{h} \{ \rho^{dD}(k_r, h) > 0 \}.$$

Then $h^*_k$ is the smallest $h$ for which $\rho^{dD}$ is a well-defined reaction rate, and

$$h^*_k = \begin{cases} \sqrt{\pi e \frac{3+2C_{\alpha, 2}}{4} \frac{2\pi D}{k_r} \sigma} & (2D) \\ \frac{C_{\alpha, 3}}{6} \left( \frac{D}{k_r} + \frac{1}{4\pi\sigma} \right)^{-1} & (3D) \end{cases}$$

**Proof.** In [28], the reaction rate $k_r^{\text{meso}}$ was derived under the assumption that $L \gg h$. This effectively implies that $L \gg \sigma$, since we have adopted the basic assumption [8]. Let $\tau^{dD}_{\text{micro}}$ and $\tau^{dD}_{\text{meso}}$ be the mean association times for uniformly distributed particles in dimension $d$.

For $L \gg \sigma$, we can approximate $\tau^{3D}_{\text{micro}}$ by

$$\tau^{3D}_{\text{micro}} \approx \frac{L^3}{k_{\text{CK}}}$$

which, when inserted into [9], yields

$$\rho^{3D}(k_r, h) = \frac{h^{-3}}{k^{-1}_{\text{CK}} + \frac{C_{\alpha, 3}}{6Dh}}.$$
With \( k_{\text{CK}} \) defined by \((7)\), we obtain \( \rho^{3D} \) as in \((10)\). Thus, for large enough domains, the effect of the outer boundary is small in 3D, and the reaction rates are defined by local parameters only.

The situation in 2D is more complicated. From \([29]\) we know that

\[
\tau_{\text{micro}}^{2D} = \frac{[1 + \alpha F(\lambda)]V}{k_r},
\]

where

\[
\begin{cases}
\lambda = \left(\frac{4\pi}{3}\right)^{\frac{1}{3}} \frac{\sigma}{L} \\
\alpha = \frac{k_r}{2\pi\sigma} \\
F(\lambda) = \frac{\log(1/\lambda)}{(1-\lambda^2)^2} - \frac{3-\lambda^2}{4(1-\lambda^2)},
\end{cases}
\]

yielding

\[
\rho^{2D}(k_r, h) = \frac{h^{-2}}{1 + \alpha F(\lambda)} - \left(\frac{1}{2\pi D} \log(\frac{L}{h}) + \frac{C_{\alpha,2}}{4D}\right)
\]

\[
= \frac{1}{h^2} \left( (k_r)^{-1} + \frac{1}{2\pi D} \left\{ \log \left( \left( \frac{3}{4\pi} \right)^{\frac{1}{3}} \frac{L}{\sigma} \right) - \log \left( \frac{L}{h} \right) \right\} - \frac{1}{2\pi D} \left( \frac{3}{2\pi} + C_{\alpha,2} \right) \right)^{-1},
\]

For \( L \gg \sigma \) we have \( 1 - \lambda^2 \approx 1 \), and \( 3 - \lambda^2 \approx 3 \). Thus

\[
\rho^{2D}(k_r, h) = \frac{1}{h^2} \left( (k_r)^{-1} + \frac{1}{2\pi D} \left\{ \log \left( \left( \frac{3}{4\pi} \right)^{\frac{1}{3}} \frac{L}{\sigma} \right) - \log \left( \frac{L}{h} \right) \right\} - \frac{1}{4D} \left( \frac{3}{2\pi} + C_{\alpha,2} \right) \right)^{-1}.
\]

(15)

By noting that

\[
\log \left( \left( \frac{3}{4\pi} \right)^{\frac{1}{3}} \frac{L}{\sigma} \right) - \log \left( \frac{L}{h} \right) = \log \left( \left( \frac{3}{4\pi} \right)^{\frac{1}{3}} \frac{h}{\sigma} \right),
\]

we find that we can rewrite \((15)\) to obtain \((10)\) also in the case of \( d = 2 \). Consequently, for \( L \gg \sigma \), the reaction rate defined by \( \rho^{2D} \) is approximately independent of the global parameter \( L \).

Now \((14)\) follows by noting that \( \rho^{dD} > 0 \) holds if and only if

\[
\frac{k_r}{D} G^{dD}(h, \sigma) < 1,
\]

and then solving \( \frac{k_r}{D} G^{dD}(h, \sigma) = 1 \) for \( h \).
B. Reversible reactions

In this section we extend the analysis to the reversible case. We limit our considerations to the conventional RDME, thus allowing reactions only between molecules occupying the same voxel. The system consists of one \(A\)-molecule and one \(B\)-molecule, diffusing on a Cartesian lattice consisting of \(N\) voxels of width \(h\), with periodic boundary conditions. The molecules react reversibly through the reaction

\[
A + B \xleftrightarrow{k^{\text{meso}}_r} C. \tag{17}
\]

Henceforth we assume that \(k_r\) and \(k_d\) are given model parameters, and that \(k^{\text{meso}}_r\) is defined by (10).

It remains to define \(k^{\text{meso}}_d\). A plausible approach would be to match the steady-state levels of the species at the mesoscopic and microscopic scales; we choose \(k^{\text{meso}}_d\) such that

\[
\tau^{\text{meso}}_{\text{rebind}} = \frac{k^{\text{meso}}_r}{k^{\text{meso}}_d + 2dh} \tag{18}
\]

where \(\tau^{\text{meso}}_{\text{rebind}}\) and \(\tau^{\text{micro}}_{\text{rebind}}\) are the respective times until an \(A\)- and a \(B\)-molecule rebind, given that they have just dissociated. The quantities \(\tau^{\text{meso}}_d\) and \(\tau^{\text{micro}}_d\) are the average times until a \(C\)-molecule dissociates (thus \(\tau^{\text{meso}}_d = 1/k^{\text{meso}}_d\) and \(\tau^{\text{micro}}_d = 1/k^{\text{micro}}_d\)).

We can compute \(\tau^{\text{meso}}_{\text{rebind}}\) analytically. Let \(\tau_e := 1/(k^{\text{meso}}_r + 2dh)\), where \(d\) is the dimension. Then \(\tau_e\) is the average time until the next event, given that the molecules are in the same voxel. Now \(\tau^{\text{meso}}_{\text{rebind}}\) satisfies

\[
\tau^{\text{meso}}_{\text{rebind}} \frac{\tau^{\text{meso}}_{\text{rebind}}}{\tau^{\text{meso}}_d + \tau^{\text{meso}}_{\text{rebind}}} = \frac{\tau^{\text{micro}}_{\text{rebind}}}{\tau^{\text{micro}}_d + \tau^{\text{micro}}_{\text{rebind}}}, \tag{19}
\]

where the first term on the right hand side represents the probability that the first event after a dissociation is an association event, and where the second term represents the probability that the first event is a diffusion event (note that \(N - 1\) is the average number of steps until the molecules again occupy the same voxel [28].)

Solving (19) for \(\tau^{\text{meso}}_{\text{rebind}}\) yields

\[
\tau^{\text{meso}}_{\text{rebind}} = \frac{N}{k^{\text{meso}}_r}. \tag{20}
\]

Unfortunately \(\tau^{\text{micro}}_{\text{rebind}}\) is not easily computed by analytical means (for general geometries), but by noting that \(\tau^{\text{micro}}_{\text{rebind}} = \tau^{dD}_{\text{micro}}(k_r) - \tau^{dD}_{\text{micro}}(\infty)\) we obtain the estimate

\[
\tau^{\text{micro}}_{\text{rebind}} = \frac{L^d}{k_r}. \tag{21}
\]
for $L \gg \sigma$. By using (20) and (21) in (18) it follows that
\[
\frac{N}{k_{\text{meso}}} + \frac{N}{k_{r}^{\text{meso}}} = \frac{V}{k_{r}} \frac{1}{k_{d}} + \frac{V}{k_{r}}
\]
which, after some simplifications, results in
\[
k_{d}^{\text{meso}} = h \frac{k_{d} k_{r}^{\text{meso}}}{k_{r}}.
\]
When rearranged, (23) can be recognized as the detailed balance condition. Maintaining this relation between the rate constants is sufficient to ensure that the equilibrium values of $A$ and $B$ are the same in the two models.

However, even if we match the mean association time for a given voxel size, we may be in a region where the mesoscopic dissociation rate is higher than the microscopic, intrinsic, rate. This is unphysical and may lead to incorrect transient dynamics compared to the microscopic model. The inverse of the mesoscopic dissociation rate is a combination of the expected time for a complex to break apart and the time for the products to become separated a certain length scale due to diffusion. Therefore, the intrinsic microscopic dissociation rate is an upper bound on the mesoscopic rate. We therefore ask for what size of $h$ we can match the mean binding times while satisfying
\[
k_{d}^{\text{meso}} \leq k_{d}.
\]
\[\textbf{Theorem 2.} \text{ The condition } k_{d}^{\text{meso}} \leq k_{d} \text{ holds if and only if the inequality }
\]
\[
k_{r} \frac{D G^{D}(h, \sigma)}{D} < 0
\]
\[\text{is satisfied for } G^{D}(h, \sigma) \text{ as defined in (11)}. \]

Let
\[
h_{k_{r}, k_{d}}^{*} = \max \left\{ h_{k_{r}, k_{d}}^{*}, \inf_{h} \left\{ k_{r} \frac{D G^{D}(h, \sigma)}{D} < 0 \right\} \right\}.
\]
Then $h_{k_{r}, k_{d}}^{*}$ is the smallest $h$ for which we can satisfy $\tau_{\text{micro}} = \tau_{\text{meso}}$ as well as $k_{d}^{\text{meso}} \leq k_{r}^{\text{meso}}$, and we have
\[
h_{k_{r}, k_{d}}^{*} = h_{\infty}^{*} \approx \begin{cases} 5.1\sigma & (2D) \\ 3.2\sigma & (3D). \end{cases}
\]
Proof. We obtain $h_{kr,kd}^*$ by using (23) in (24):

$$h_d k_{micro} k_{meso} \leq k_{micro}^d,$$

which holds if and only if

$$h_d k_{meso} \leq 1. \quad (28)$$

However, from (10) we have

$$h_d k_{meso} = \left(1 - \frac{k_r}{D} G^{dd}(h, \sigma)\right)^{-1}.\quad (29)$$

Thus we find that equation (28) is equivalent to

$$\frac{k_r}{D} G^{dd}(h, \sigma) < 0,$$

since $(k_r/D) G^{dd}(h, \sigma) > 1$ is excluded by the condition $\rho^{dd} > 0$ as shown in (16), and (25) follows.

In Figure 1 we show how $h_{kr,kd}^*$ relates to $h_{kr}^*$.

C. Reaction rates in the limits

In this section we investigate the behavior of the reaction rate $\rho^{dd}(k_r, h)$ in the limits. We would expect $\rho^{dd}$ to behave similarly to $k_{CK}$ for large voxels. In the limit of small voxels, it is of interest to see how the mesoscopic reaction rates relate to the microscopic reaction rates.

Corollary 1. We have

$$\rho^{dd}(k_r, h_{\infty}^*) \approx \frac{k_r}{(h_{\infty}^*)^d}. \quad (30)$$

Also, as $h \to \infty$, with $L/h$ constant and $L/h \gg 1$, we have

$$\rho^{dd}(k_r, h) \to \frac{k_{CK}}{h^3}. \quad (31)$$

In the limit of $k_r/D \to 0$ we obtain

$$\rho^{dd}(k_r, h) \to \frac{k_r}{h^d}. \quad (32)$$
FIG. 1. The bound $h^*_{kr}$ for the irreversible case in 2D depends on $kr$, and decreases with decreasing $kr$. However, in order to satisfy (24), we must have $h > h^*_{kr,kd}$, shown as the red dashed line in the figure above. For large $kr$, $h^*_{kr} \approx h^*_{kr,kd}$, and $h^*_{kr,kd} = h^*_{\infty}$ for all $kr, k_d > 0$. The remaining parameters are given by $\sigma = 2 \cdot 10^{-9}$ and $D = 2 \cdot 10^{-14}$.

In 3D, (32) implies that

$$\rho^{3D}(kr, h) \to \frac{k_{CK}}{h^3}. \quad (33)$$

as $kr/D \to 0$.

Proof. Since $G^{dd}(\sigma, h^*_{\infty}) = 0$, (30) follows immediately. By noting that

$$G^{3D}(h, \sigma) \to -\frac{1}{4\pi \sigma}, \text{ as } h \to \infty,$$

we get (31) from some straightforward algebra. We obtain (32) immediately from (11). Finally, (33) follows from the fact that $k_{CK} \to kr$ as $kr \to 0$ or $D \to \infty$.

In words, as we approach the critical mesh size $h^*_{\infty}$ in the mesoscopic model, the mesoscopic rates approach the microscopic, intrinsic rates. For large voxels in 3D, we note that $\rho^{3D}$, as expected, approaches $k_{CK}$.

As an immediate consequence we have
Corollary 2. For $h = h^*_\infty$, the following holds:

$$
\begin{align*}
\rho^{3D}(k_r, h^*_\infty) &= \frac{k_r}{(h^*_\infty)^\alpha} \\
\tau_{meso}^{dD} &= k_d \\
\tau_{rebind}^{meso} &= \tau_{rebind}^{micro}.
\end{align*}
$$

For $h = h^*_\infty$, we match the mean association time, dissociation time, and the mean rebinding time. For any $h$ below $h^*_\infty$, we cannot simultaneously match both the association and dissociation times.

In Figure 2 we illustrate these limits in 3D for different values of the intrinsic reaction rate $k_r$. The more diffusion limited the reaction is, the larger the discrepancy between $\rho^{3D}$ and $k_{CK}$ becomes.

D. Error estimates

Given a system with known intrinsic reaction rates, we would ideally want to know how to choose the mesh size for sufficiently accurate mesoscopic simulations. While solving this is hard for a general system, we can choose the mesh size such that we limit the relative error in the average rebinding times. We do not guarantee an accurate mesoscopic solution by doing so, but if the error in the average rebinding time is large, and we have fine-grained dynamics that we wish to capture, we may have to reduce the voxel size to decrease the error.

Now consider a reversible reaction in a given system, with intrinsic reaction rates given by $k_r$ and $k_d$.

Corollary 3. For a given error tolerance $\epsilon$, the following holds:

$$
|k_r - k_r^{meso}| < \epsilon k_r
$$

if and only if

$$
h \leq F(k_r, \sigma, D, \epsilon),
$$

where

$$
F(k_r, \sigma, D, \epsilon) = \left\{ \begin{array}{ll}
\frac{C_{\alpha,3}}{\sigma} \left[ \frac{1}{4\pi \sigma} + (1 - (1 - \epsilon)^{-1}) \frac{D}{k_r} \right]^{-1} \\
\sqrt{\pi} \exp \left[ -\frac{2\pi D}{k_r} (1 - (1 - \epsilon)^{-1}) + \frac{3 + 2\pi C_{\alpha,2}}{4} \right] \sigma.
\end{array} \right. 
$$
FIG. 2. Limits in 3D. In (a), where $k_r = 10^{-18}$, the difference between $k_{\text{CK}}$ and $\rho^{3D}$ is orders of magnitude; in (b), where $k_r = 10^{-20}$, the difference is much smaller. The other parameters are given by $D = 2 \cdot 10^{-12}$, $\sigma = 2 \cdot 10^{-9}$, and $L = 5.145 \cdot 10^{-7}$. 
Furthermore, for $h \leq F$, we have

$$|\tau_{\text{meso}} - \tau_{\text{micro}}|_{\tau_{\text{rebind}}} \leq \epsilon + O(\epsilon^2). \quad (38)$$

In 2D we have

$$F \to \infty, \text{ as } D/k_r \to \infty. \quad (39)$$

In 3D, we obtain

$$F \to \infty \quad (40)$$

as

$$\left\{ \begin{array}{l}
\frac{D}{k_r} \to \frac{1}{4\pi \sigma}, \text{ or } \\
\epsilon \to \frac{k_{\text{CK}}}{4\pi \sigma D} =: \epsilon_{\text{max}}
\end{array} \right. \quad (41)$$

For all $h$, it holds that

$$\frac{|\tau_{\text{meso}} - \tau_{\text{micro}}|}{\tau_{\text{rebind}}} \leq \frac{k_{\text{CK}}}{4\pi \sigma D} + O \left( \frac{k_{\text{CK}}}{4\pi \sigma D}^2 \right), \quad (42)$$

in 3D.

Proof. Assume that

$$|k_r - h^d k_r^{\text{meso}}| < \epsilon k_r \quad (43)$$

holds. Using (10) we obtain

$$\left| 1 - \left( 1 - \frac{k_r}{D} G^{dd} \right)^{-1} \right| < \epsilon. \quad (44)$$

From (29) we know that $(k_r/D)G^{dd} < 0$, and thus (44) becomes

$$1 - \left( 1 - \frac{k_r}{D} G^{dd} \right)^{-1} < \epsilon. \quad (45)$$

Some straightforward algebra now yields

$$G^{dd} > \frac{D}{k_r} (1 - (1 - \epsilon)^{-1}). \quad (46)$$

By inserting $G^{dd}$, for $d = 2$ and $d = 3$, into (46) and solving for $h$, we obtain (37).
We obtain (38) by noting that \( k_r \approx V/\tau_{\text{micro}} \) and \( k_{r\text{meso}} = N/\tau_{\text{meso}} \), and using that in (43), together with the observation that \( (1 - (1 - \epsilon)^{-1}) = -\epsilon + O(\epsilon^2) \).

As an immediate consequence of (37) we obtain (39). We get (40)-(41) from (37), and by noting that

\[
\frac{1}{4\pi\sigma} + (1 - (1 - \epsilon)^{-1}) \frac{D}{k_r} \to 0 \quad (47)
\]

as

\[
\epsilon \to \frac{k_{\text{CK}}}{4\pi\sigma D} \quad (48)
\]

Finally we get (42) immediately from (38) and (40)-(41).

We see that as the reactions become very diffusion limited, the difference between the mesoscopic and microscopic reaction rates can grow large, since \( k_{\text{CK}} \to 4\pi\sigma D \) as \( k_r \to \infty \). The less diffusion limited a reaction is, the closer the reaction rates will be (and the difference is bounded). This makes intuitive sense, since less diffusion-limited reactions mean that the system is more well-mixed; thus the system can be accurately simulated on a coarser mesh.

In Section IV B we demonstrate how this theory can be applied to increase the understanding of the behavior of a relevant biological system.

IV. NUMERICAL EXPERIMENTS

In this section we present two numerical examples that will demonstrate the scope of validity of the mesoscopic reaction rates derived above. In the first example we consider the rebinding time of a pair of molecules. We compute the distributions and compare mesoscopic results for varying \( h \) to microscopic simulations.

In the second example we study a model proposed by Takahashi et al. in [37]. It was shown to have fine-grained dynamics, captured at the microscale but not at the deterministic level; we will simulate it at the mesoscopic scale, and show that as the mesh size \( h \) approaches \( h_\infty^* \), the mesoscopic and microscopic scales agree.
A. Rebinding-time distribution

Consider one molecule of species $A$ and one molecule of species $B$, subject to a reversible reaction

$$A + B \xrightleftharpoons[kt]{kr} C.$$  \hspace{1cm} (49)

in a cubic domain of width $L$.

We showed in Section III C that for $h = h^*_\infty$ the mean rebinding time at the mesoscopic scale will agree with the mean rebinding time at the microscopic scale. This does not, however, automatically guarantee that this particular choice of mesh size will yield the best agreement between the distributions of the rebinding times at the different scales.

In Figure 3 we plot the distribution of the rebinding times for different mesh sizes, and compare to the distribution obtained by simulations at the microscopic scale. For $h = h^*_\infty$ we get a distribution that matches the microscopic results well for $t \gtrsim h^2/(2D)$. For other values of $h$, we get a distribution shifted relative to the microscopic distribution. For $t \lesssim h^2/(2D)$, the microscopic simulations behave differently than the mesoscopic ones, regardless of mesh size. This is due to the fact that at this timescale the spatial resolution is coarser than the temporal resolution, thus being the limiting factor for the accuracy. During a time $t$, a molecule diffuses an average distance proportional to $\sqrt{2Dt}$ in each direction. Thus, for $t \lesssim h^2/(2D)$, the distance the molecule diffuses is less than the size $h$ of a voxel.

In Figure 4 we plot the mean rebinding time as a function of $h$, and show that for $h = h^*_\infty$ the mean rebinding times match between the different scales.

B. MAPK cascade

An example of when small errors in the transient dynamics of bimolecular equilibration processes can have a large impact on the system’s dynamics was given in [37] to illustrate the need of the microscale resolution provided by the GFRD algorithm. The model considered is two steps of the omnipresent mitogen activated phosphatase kinase (MAPK) cascade. Here, a transcription factor $MAPK$ is phosphorylated in two steps by a kinase $MAPKK$ and dephosphorylated by a phosphatase $P$: 
(a) Rebinding-time distributions in 3D.

(b) Rebinding-time distributions in 2D

FIG. 3. The width $L = 5.145 \cdot 10^{-7}$ of the domain has been chosen such that $h \approx h_\infty^*$ for $N = 81^3$ in (a). In (b), $L = 5.2 \cdot 10^{-7}$ so that $h \approx h_\infty^*$ for $N = 51^2$. The mesoscopic rebinding-time distribution matches the microscopic rebinding-time distribution well for $h = h_\infty^*$ and $t \gtrsim (h_\infty^*)^2/(2D)$. Refining the mesh further, we find that the mean rebinding time decreases, and that the distribution is shifted correspondingly. For coarser meshes, the mean rebinding time increases, and consequently the distribution is shifted in the opposite direction. In (a), the other parameters are given by $\sigma = 2 \cdot 10^{-9}$, $D = 2 \cdot 10^{-12}$, and $k_r = 10^{-18}$. In (b), the parameters are $\sigma = 2 \cdot 10^{-9}$, $D = 2 \cdot 10^{-14}$, and $k_r = 10^{-12}$. 
FIG. 4. The mean rebinding times in 3D (a) and 2D (b) as a function of the voxel size $h$. For $h > h^*_\infty$ the rebinding time is overestimated, while for $h < h^*_\infty$ it is underestimated. We match the mean rebinding time perfectly for $h = h^*_\infty$. The parameters are the same as in Figure 3.
\[ MAPK + MAPKK \xrightarrow[k_1]{k_2} MAPK_{\cdot}MAPKK \]  
(50)

\[ MAPK_{\cdot}MAPKK \xrightarrow[k_3]{k_4} MAPKK^* + MAPK_p \]  
(51)

\[ MAPKK^* \xrightarrow[k_7]{k_7} MAPKK \]  
(52)

\[ MAPK_p + MAPKK \xrightarrow[k_9]{k_5} MAPK_p_{\cdot}MAPKK \]  
(53)

\[ MAPK_{pp\cdot}MAPKK \xrightarrow[k_9]{k_6} MAPKK + MAPK_{pp} \]  
(54)

\[ MAPK_{pp} + P \xrightarrow[k_1]{k_2} MAPK_{pp\cdot}P \xrightarrow[k_3]{k_4} P^* + MAPK_p \]  
(55)

\[ P^* \xrightarrow[k_7]{k_7} P \]  
(56)

\[ MAPK_p + P \xrightarrow[k_4]{k_5} MAPK_p_{\cdot}P \xrightarrow[k_6]{k_6} P + MAPK \]  
(57)

During the phosphorylation and dephosphorylation steps, the kinase and phosphatase turns into an inactivated form \( MAPKK^* \) and \( P^* \). This can model e.g. a conformation change due to conversion of ATP to ADP, resulting in the need to reactivate the enzymes before proceeding with the next reaction. If the timescale for this reactivation step is short and the system very diffusion limited, rapid rebinding of \( MAPKK \) to the newly phosphorylated molecules can have a big impact on the overall system dynamics, as illustrated and discussed from a biological perspective in [37]. Numerically, this means that the system is very challenging to simulate with lattice based methods, due to the need of very high spatial resolution in order to resolve the rebindings on the fast timescale. This was noted by Fange et al. in [29] where length scale dependent rates were derived based on the ansatz that the equilibration time should match on the two scales for a spherical discretization. They managed to resolve the microscale dynamics of the model by considering these propensities evaluated in a non-local fashion, aggregating the values in one layer of neighbors of the voxel on a Cartesian grid.

In Figure 5 we show results of simulation of this model using our local rates for different mesh resolutions. As can be seen, when \( h \) is close to \( h^* \), we obtain a good approximation of the results of the GFRD algorithm from [37]. In the figure, we show the time until half-activation (i.e. the time to reach half the steady state level of \( MAPK_{pp} \)) for varying diffusion constants, making the system range from reaction limited to diffusion limited. As can be seen, for large values of \( D \), as expected, the rates proposed here and the rates of
Collins and Kimball give similar results, but for the strongly diffusion limited cases, our rates result in a much better agreement with the microscale model. Notably, for small $D$ we obtain comparable accuracy to using $k_{CK}$ with $h = h^*_\infty$ for $h = 4h^*_\infty$, resulting in simulations that run approximately sixteen times faster, due to the $O(h^{-2})$ scaling of the computational time.

In Figure 6a we have computed the upper bound on $h$ obtained by requiring that the relative error in the average rebinding time is bounded by 0.05. As expected, we can see that for the less diffusion limited cases, when $D/k_r$ is larger, we can choose the voxel size larger and still obtain accurate results. As $D$ becomes even larger, the well-mixed assumption will be satisfied, and the system can be simulated at a much coarser scale. For smaller values of $D$ the restriction on $h$ is quite severe, and we are required to approach $h^*_\infty$ in order to accurately simulate the system. This has an implication for the computational complexity of the simulations; a small $D$ makes the system less stiff, but also forces us to choose a smaller voxel size, while a large $D$ makes the system more stiff, but on the same time allows for a larger voxel size. In Figure 6b we have computed the maximum error in the average rebinding time, as a function of $D$ but independent of the size $h$ of the voxels.

V. DISCUSSION

As we have seen, by taking a multiscale approach and deriving reaction constants by matching certain statistics of the Smoluchowski model, more accurate simulations can be obtained compared to the classical approach due to Collins and Kimball. An important factor for why this is possible is that we start out with a given discretization of space, and then derive propensities, while the CK rate is derived only using an assumption of the size of the mesh. While it is important to be able to resolve the reaction kinetics of a given diffusion limited system, it may also be important to accurately resolve complex geometries. In the latter case, uniform Cartesian grids have drawbacks compared to unstructured triangular and tetrahedral discretizations [11, 20]. What fundamental limits on the discretization that applies to triangular and tetrahedral grids, and whether it is possible to extend the approaches taken herein to general grids is yet to be seen. Another approach to the problem of making an RDME-type model approximate a microscopic model is taken in [35], where a mesoscale model is constructed by discretizing the Doi model [38]. This approach seems
FIG. 5. We compare the results of mesoscopic simulations using both our proposed multiscale reaction rates (HHP), as well as the classical rates by Collins and Kimball (CK), for different sizes of the mesh. As we can see, for coarser meshes, while capturing the qualitative behavior, we are still not reproducing the microscopic GFRD results accurately. As we refine the mesh and approach $h = h^*_\infty$, we approach the microscopic results. The parameters are chosen as in [37].

more directly amenable to be used on general grids, but it has not yet been applied to the Smoluchowski model, and except for the case of irreversible, perfect absorption [31], the relationship between the Doi and Smoluchowski models is not well understood.

We have illustrated in numerical examples that by using the propensities proposed here it is possible to accurately simulate the MAPK system [37] on the mesoscale using a purely local RDME implementation, and we have shown theoretically why $h^*_\infty$ is the optimal mesh size. The same system has previously been successfully simulated with an RDME-type model by Fange et al. [29], using another set of multiscale propensities and by relying on a non-local implementation of the RDME in which molecules occupying adjacent voxels are
(a) Upper bound on $h$ for $\epsilon = 0.05$.

(b) $\epsilon_{\text{max}}(D)$

FIG. 6. As we can see in (a), the restriction on the voxel size $h$ is severe for small $D$. This is seen in Figure 5 by noting the relatively large error even for smaller $h$. For larger values of $D$, the error is smaller. In accordance with that observation, we see in (a) that the relative error in mean rebinding time decreases with increasing $D$. In (b) we have plotted $\epsilon_{\text{max}}$, the maximum error in average rebinding time, as a function of $D$; for larger values of $D$ we note that the maximum relative error in the mean rebinding time is bounded by around 0.19. This shows that with increasing $D$, as the system gets more and more well-mixed, coarser methods will yield acceptable results. In [37] they show that the microscopic simulations agree with deterministic methods for large enough $D$.

allowed to react. Although more efficient than a non-local implementation, the simulations herein require a uniformly fine mesh and hence expensive simulations. Unless there are components in the model present in high copy numbers, it is not unlikely that an efficient implementation of e.g. GFRD is more efficient than the purely mesoscopic simulation, since the RDME in this limit can be thought of as a microscopic lattice method. Therefore, for very diffusion limited systems with multiscale properties, a compelling approach is the use of hybrid methods. Such a method, blending the RDME and GFRD algorithms, has previously been proposed by the present authors [30], in which it was demonstrated that an accurate hybrid simulation of the MAPK model [37] can yield accurate results with only a small part of the system simulated on the microscopic scale. In this paper we advance the fundamental understanding of the RDME when viewed as an approximation to the Smoluchowski model, which is ultimately necessary to achieve adaptive implementations of such hybrid methods.
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