Reactions, Diffusion and Volume Exclusion in a Heterogeneous System of Interacting Particles

D. B. Wilson,1,a) H. Byrne,1 and M. Bruna1

1) Mathematical Institute, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, United Kingdom.

Recent experimental observations have shown that excluded-volume effects play an important role in reaction diffusion processes at the cellular and subcellular level. These findings have, in turn, increased interest in research focused on incorporating such effects into stochastic models that account explicitly for every single cell in the system. The high computational costs incurred by these models have motivated the development of macroscopic continuum models, in the form of partial differential equations, that can capture the microscopic effects. It has been shown that the volume exclusion leads to a nonlinear diffusion coefficient in the macroscopic model. For many biological processes it is important to consider reactions between heterogeneous cell populations that arise from direct physical interactions. In this paper we use the method of matched asymptotic expansions to derive macroscopic models that account for volume exclusion and reactions between subpopulations at the microscopic level. We show that for reactions due to contact interactions the appropriate reaction term in the macroscopic model is of lower order in the asymptotic expansion than the nonlinear diffusion term. However, we find that the next reaction term in the expansion is needed to ensure good agreement with simulations of the microscopic model.

a) Electronic mail: daniel.wilson@maths.ox.ac.uk
I. INTRODUCTION

Cellular migration plays an important role in many biological processes, including tumor growth and invasion through an extracellular matrix, the formation of blood vessels via the movement of endothelial cells during embryogenesis and the directed motion of immune cells to infected sites. Classical continuum modeling paradigms assume that cells move down spatial gradients (diffusion) or up a spatial gradient towards a signaling chemical (chemotaxis). However, these models are only valid when particles are treated as point particles. Recently, a significant amount of theoretical research has focused on how to incorporate excluded-volume effects, a crucial requirement in biological applications within confined environments. One approach is to discretize space into a regular lattice, and allow at most one cell to occupy each lattice site. An advantage of a lattice-based approach is that it is relatively easy to include many complex individual-based mechanisms, and to obtain a macroscopic model based on partial differential equations (PDEs). However, the form of the lattice can introduce artifacts into these models, such as a bias towards homogeneity.

An alternative approach is to derive continuum equations from an off-lattice individual-based model, simulating the Brownian motion and excluded-volume interactions of individual cells. Recent work by Bruna and Chapman shows that, in the context of off-lattice models of diffusion, accounting for the finite size of particles in a homogeneous population leads to a nonlinear diffusion equation with enhanced collective diffusion. This result was obtained systematically by applying the method of matched asymptotic expansions to the Fokker-Planck equation for the joint probability density of a system of identical hard spheres. The method reduces the high-dimensionality of the original problem and yields a low-dimensional PDE describing the evolution of the population density or concentration. Using the same method in a system with two types of particles with no reactions, results in a nonlinear cross-diffusion system for the evolution of the two subpopulations. Dyson and coauthors have derived continuum models for an off-lattice individual-based model of diffusion. However, the collision rules that they use are quite different to those used by Bruna and Chapman. Further when considering multiple subpopulations, the continuum equations in Refs. lack an obstruction term in the nonlinear diffusion coefficient.

As in the case of diffusion only, stochastic reaction-diffusion processes have been modeled
using either lattice- or off-lattice based approaches. An issue with lattice-based approaches is that it is difficult to combine reactions and finite-size interactions in the same model. As mentioned above, in the latter the lattice size is chosen so that at most one cell occupies a single lattice site. By contrast, the usual lattice-based approach for bimolecular reactions requires two cells to be in the same compartment in order to react.\textsuperscript{17} The standard off-lattice approach to model reaction-diffusion processes is based on the Smoluchowski model, which represents cells as point particles undergoing Brownian motion and reacting whenever they become closer than a given reaction radius.\textsuperscript{18} The reaction radius is chosen as a function of the reaction rate and diffusion constants of the reactants, and has no connection in general to their physical radii. In fact, it has been shown that the reaction radius may turn out to be unrealistically smaller than the radii of the reactants.\textsuperscript{17} Several methods have been proposed to overcome the shortcomings of these models,\textsuperscript{18,19} including one where the reaction radius can be fixed to represent the reactant radius,\textsuperscript{17} but to our knowledge none includes the excluded-volume effects. To this end, in this paper we extend the modeling framework of Bruna and Chapman\textsuperscript{13,14} to account for reactions between two subpopulations of Brownian hard-sphere particles. The advantage of our approach to model reactions is that the actual sizes of the cells (and therefore excluded-volume interactions) are included explicitly in our individual-based model, thereby circumventing the problem of unrealistically small reaction radii and providing a more natural way to describe diffusion-limited reactions.

We consider two types of reactions; first, unimolecular reactions to represent the spontaneous switching between subpopulations and, second, bimolecular reactions whereby a particle can change type due to a physical interaction with a particle in the other subpopulation. The spontaneous switching is motivated by phenotypic switching of tumor cells within a glioblastoma environment.\textsuperscript{2} A biological motivation for switching due to local interactions is the delta-notch signaling pathway.\textsuperscript{20}

The remainder of this paper is organized as follows. In Section \textsuperscript{II} we introduce spontaneous switching between subpopulations. We consider the discrete model and the Fokker-Planck equation for the joint probability density function of the system. Using the method of matched asymptotics, we derive population-level, reaction-diffusion-advection equations for the evolution of the density of the subpopulations. In Section \textsuperscript{III} we study the case when switching between subpopulations occurs in response to collisions. Finally in Section \textsuperscript{IV} we summarize our results and suggest possible directions for future investigations.
II. SPONTANEOUS SWITCHING: UNIMOLECULAR REACTIONS

In order to place our work in context, we summarize the results of Bruna and Chapman, where they incorporated excluded-volume effects into off-lattice stochastic models of diffusion for multiple subpopulations. Consider a population of \( N \) spheres within a bounded domain \( \Omega \subset \mathbb{R}^d \), where \( d \in \{2, 3\} \). There are two subpopulations of spheres, which we term “red” and “blue”. Let there be \( N_b \) blue spheres and \( N_r \) red spheres, where \( N = N_b + N_r \). The blue and red spheres have diameters \( \epsilon_b \) and \( \epsilon_r \), diffusion coefficients \( D_b \) and \( D_r \), and drift vectors \( f_b \) and \( f_r \), respectively. The center of the \( i \)th particle is denoted by \( X_i(t) \) and evolves according to the Langevin SDE:

\[
\begin{align*}
\text{d}X_i(t) &= \sqrt{2D_b}dW_i(t) + f_b(X_i(t))dt, \quad 1 \leq i \leq N_b, \\
\text{d}X_i(t) &= \sqrt{2D_r}dW_i(t) + f_r(X_i(t))dt, \quad N_b + 1 \leq i \leq N, 
\end{align*}
\]

where the \( W_i \) are independent, \( d \)-dimensional standard Brownian motions. Reflective boundary conditions are imposed whenever two spheres are in contact and also on the boundary of the domain \( \Omega \). From a particle-level description, the method of matched asymptotic expansions for a small but finite volume fraction was used to obtain a continuum model for the marginal probability density functions, \( b(x, t) \) and \( r(x, t) \) for blue and red spheres respectively. The continuum model comprises of the following system of nonlinear cross-diffusion equations

\[
\frac{\partial}{\partial t} \begin{pmatrix} b \\ r \end{pmatrix}(x, t) = \nabla_x \cdot \begin{pmatrix} D(b, r) \nabla_x b - F(b, r) \nabla_x b \\ D(b, r) \nabla_x r - F(b, r) \nabla_x r \end{pmatrix} \quad \text{in} \quad \Omega \subset \mathbb{R}^d,
\]

with zero-flux boundary conditions on \( \partial \Omega \). In equations (2a), the nonlinear diffusion \( D(b, r) \) and drift \( F(b, r) \) matrices are defined as follows:

\[
D(b, r) = \begin{pmatrix} D_b[1 + (N_b - 1)\epsilon_b^d \omega b - N_r \epsilon_b^d \eta_b r] & D_b N_r \epsilon_b^d \xi_b b \\ D_r N_b \epsilon_r^d \xi_r r & D_r[1 + (N_r - 1)\epsilon_r^d \omega r - N_b \epsilon_b^d \eta_r b] \end{pmatrix},
\]

\[
F(b, r) = \begin{pmatrix} f_b & N_r \epsilon_b^d \gamma_b (f_r - f_b) b \\ N_b \epsilon_r^d \gamma_r (f_b - f_r) r & f_r \end{pmatrix},
\]

with \( \epsilon_{br} = (\epsilon_b + \epsilon_r)/2 \) and the constants \( \omega, \xi, \eta \) are constants defined by

\[
\omega = \frac{2(d - 1)\pi}{d}, \quad \xi_i = \frac{2\pi}{d} \left[ (d - 1)D_i + dD_j \right]/D_i + D_j, \quad \gamma_i = \frac{2\pi}{d} \frac{D_i}{D_i + D_j},
\]

\[ ]
for $d \in \{2, 3\}$ and $i \in \{b, r\}$. The density-dependent terms in (2b) show how like particles enhance collective diffusion and also the competition that arises between subpopulations.

In what follows we extend the model in Ref. 14 to incorporate switching between subpopulations. We introduce switching at the discrete level by allowing particles to spontaneously switch between the blue and red types at a constant rate independent of both time and space.

A. Particle-based model

We consider a population of $N$ spheres, all of diameter $\epsilon$, that can be either tagged blue or red. We denote the position and color of the $i^{th}$ individual as $X_i(t)$ and $s_i$ respectively, where $s_i = s_b (s_r)$ if the $i^{th}$ particle is blue (red). For our discrete model we consider the following set of overdamped Langevin SDEs:

\begin{align}
    dX_i(t) &= \sqrt{2D_b}dW_b(t) + f_b(X_i(t))dt, \quad s_i = s_b, \quad (4a) \\
    dX_i(t) &= \sqrt{2D_r}dW_r(t) + f_r(X_i(t))dt, \quad s_i = s_r, \quad (4b)
\end{align}

for $1 \leq i \leq N$. We also introduce two unimolecular reactions to account for spontaneous switching:

\[ B \xrightarrow{\alpha} R, \quad R \xrightarrow{\beta} B, \quad (4c) \]

where $\alpha$ and $\beta$ are the switching rates. When considering the probabilistic description of the discrete model, the color of the $i^{th}$ particle is a random variable. We therefore consider the joint probability density function $P(\vec{x}, \vec{s}, t)$, the probability of the $N$ particles being in the configuration $\vec{x} = (x_1, \ldots, x_N)$ with the colors of the particles being described by the vector of states $\vec{s} = (s_1, \ldots, s_N)$ at time $t$. The configuration space (set of legal configurations) is defined as $\Omega_\epsilon^N \times \{s_b, s_r\}^N$, where $\Omega_\epsilon^N = \Omega^N \setminus B_\epsilon$, and $B_\epsilon$ is the set of illegal spatial configurations,

\[ B_\epsilon = \{ \vec{x} \in \Omega^N : \exists i \neq j \text{ such that } \|x_i - x_j\| \leq \epsilon \} . \]

Using the Chapman-Kolmogorov equation\textsuperscript{21} we derive the following linear PDE for the
evolution of the density $P(\bar{x}, \bar{s}, t)$ in configuration space $\Omega_N \times \{s_b, s_r\}^N$, 
\[
\frac{\partial P}{\partial t}(\bar{x}, \bar{s}, t) = \nabla \cdot \left[ D_{\bar{x}} \nabla P(\bar{x}, \bar{s}, t) - \vec{F}_{\bar{s}}(\bar{x}) P(\bar{x}, \bar{s}, t) \right] + \alpha \sum_{\vec{c} \in \mathcal{B}(\bar{s})} P(\bar{x}, \vec{c}, t) + \beta \sum_{\vec{c} \in \mathcal{R}(\bar{s})} P(\bar{x}, \vec{c}, t) - (\alpha |\mathcal{R}(\bar{s})| + \beta |\mathcal{B}(\bar{s})|) P(\bar{x}, \bar{s}, t),
\]
where $D_{\bar{x}} = \text{diag}(D_{s_1}, \ldots, D_{s_N})$ and $\vec{F}_{\bar{s}}(\bar{x}) = (f_{s_1}(x_1), \ldots, f_{s_N}(x_N))$. We define $\mathcal{B}(\bar{s})$ ($\mathcal{R}(\bar{s})$) to be the set of state vectors that require one blue (red) switch to become the state vector $\bar{s}$. These sets can be formally described as,
\[
\mathcal{B}(\bar{s}) = \{(s_1, \ldots, s_{j-1}, s_b, s_{j+1}, \ldots, s_N) | j \in \{1, \ldots, N\} \text{ and } s_j = s_r\},
\]
\[
\mathcal{R}(\bar{s}) = \{(s_1, \ldots, s_{j-1}, s_r, s_{j+1}, \ldots, s_N) | j \in \{1, \ldots, N\} \text{ and } s_j = s_b\}.
\]
On the boundaries of the configuration space, $\partial \Omega_N$, we impose zero-flux boundary conditions
\[
\left[ D_{\bar{x}} \nabla P(\bar{x}, \bar{s}, t) - \vec{F}_{\bar{s}}(\bar{x}) P(\bar{x}, \bar{s}, t) \right] \cdot \vec{n} = 0,
\]
for all $\bar{s} \in \mathcal{C}^N$, where $\mathcal{C}^N$ denotes the set of all possible configurations of the states of $N$ particles and $\vec{n} \in S^{4N-1}$ denotes the unit outward normal. The initial conditions are $P(\bar{x}, \bar{s}, 0) = P_0(\bar{x}, \bar{s})$.

B. Population-based model

Although linear, the PDE for the particle-based model \cite{55} is very high-dimensional for large $N$. For this reason, we seek to derive a coupled set of low dimensional PDEs for the probability distribution of the position and state of a typical particle. Accordingly we introduce
\[
b(x, t) = \int_{\Omega_N} \left[ \sum_{\vec{c} \in \mathcal{C}^N} P(\bar{x}, \vec{c}, t) \delta(c_1 - s_b) \right] \delta(x - x_1) \, d\bar{x}, \tag{6a}
\]
\[
r(x, t) = \int_{\Omega_N} \left[ \sum_{\vec{c} \in \mathcal{C}^N} P(\bar{x}, \vec{c}, t) \delta(c_1 - s_r) \right] \delta(x - x_1) \, d\bar{x}. \tag{6b}
\]
We remark that the functions $b(x, t)$ and $r(x, t)$ are not marginal distribution functions, unlike in Ref. \cite{14} where switching between species is not considered (neglected). Here they represent the probabilities of finding a particle at position $x$ at time $t$, and the particle being either blue or red, respectively. We denote by $N_b(t)$ and $N_r(t)$ the number of blue
and red particles at time $t$ and note from equations [3] that $\int_{\Omega} b(x, t) dx = N_b(t)/N$ and $\int_{\Omega} r(x, t) dx = N_r(t)/N$. We shall refer to $b(x, t)$ and $r(x, t)$ as the blue and red density functions. As in Refs. [13,14] we are interested in the low volume fraction regime in which pairwise interactions dominate over those involving three or more particles. Thus, the problem reduces to the case when $N = 2$. We introduce the following notation, $P_{s_1s_2}(x_1, x_2, t) \equiv P(x_1, x_2, s_1, s_2, t)$. For simplicity, we describe the derivation for $f_b = f_r = 0$, but the case with drift can be obtained in a similar manner. Setting $N = 2$, equation (5a) can be rewritten as follows

$$\frac{\partial P_{bb}}{\partial t} = \nabla \cdot (D_{bb} \nabla P_{bb}) + \beta P_{br} + P_{rb} - 2\alpha P_{bb}, \tag{7a}$$

$$\frac{\partial P_{br}}{\partial t} = \nabla \cdot (D_{br} \nabla P_{br}) + \beta P_{rr} + \alpha P_{bb} - (\alpha + \beta) P_{br}, \tag{7b}$$

$$\frac{\partial P_{rb}}{\partial t} = \nabla \cdot (D_{rb} \nabla P_{rb}) + \beta P_{rr} + \alpha P_{bb} - (\alpha + \beta) P_{rb}, \tag{7c}$$

$$\frac{\partial P_{rr}}{\partial t} = \nabla \cdot (D_{rr} \nabla P_{rr}) + \alpha P_{br} + P_{rb} - 2\beta P_{rr}, \tag{7d}$$

and equations (6) become

$$b(x_1, t) = \int_{\Omega(x_1)} (P_{bb}(x_1, x_2, t) + P_{br}(x_1, x_2, t)) dx_2, \tag{8a}$$

$$r(x_1, t) = \int_{\Omega(x_1)} (P_{rr}(x_1, x_2, t) + P_{rb}(x_1, x_2, t)) dx_2. \tag{8b}$$

Combining equations (7a), (7b) and (8a) we arrive at the following equation

$$\frac{\partial b(x_1, t)}{\partial t} = \int_{\Omega(x_1)} \nabla x_1 \cdot \{D_b [\nabla x_1 P_{bb}(x_1, x_2, t) + \nabla x_1 P_{br}(x_1, x_2, t)] \} dx_2 \tag{9}$$

$$+ \int_{\Omega(x_1)} \nabla x_2 \cdot \{D_b \nabla x_2 P_{bb}(x_1, x_2, t) + D_r \nabla x_2 P_{br}(x_1, x_2, t) \} dx_2 \tag{9}$$

$$+ \beta r(x_1, t) - \alpha b(x_1, t).$$

By using the Divergence and the Reynolds Transport theorems (see Ref. 22) we simplify equation (9) as follows

$$\frac{\partial b(x_1, t)}{\partial t} = D_b \nabla^2 x_1 b(x_1, t) - \int_{\partial B(x_1)} \{2D_b \nabla x_1 (P_{bb} + P_{br}) + (D_b - D_r) \nabla x_2 P_{br}) \} \cdot n_2 dS_{x_2} \tag{10a}$$

$$+ \beta r(x_1, t) - \alpha b(x_1, t).$$
where $\partial B_r(x_1)$ is the collision surface for a sphere of radius $\epsilon$ at position $x_1$. Similarly we can derive the following equation for $r(x_1, t)$:

\[
\frac{\partial r}{\partial t}(x_1, t) = D_r \nabla^2_{x_1} r(x_1, t) - \int_{\partial B_r(x_1)} \{2D_r \nabla_{x_1} (P_{rb} + P_{rr}) + (D_r - D_b) \nabla_{x_2} (P_{rb})\} \cdot n_d dS_{x_2}
- \beta r(x_1, t) + \alpha b(x_1, t).
\] (10b)

The integrals (10) are on the contact surface of two interacting particles, where the particle positions are correlated. As a result, a closure approximation of the type $P_{bb}(x_1, x_2, t) = b(x_1, t)b(x_2, t)$ is not suitable. Instead we determine the collision integrals systematically, using the method of matched asymptotic expansions.

C. Matched asymptotic expansions for the densities $P_{bb}$ and $P_{rr}$

We define two regions in configuration space, the inner region where the two particles are close to each other, $\|x_1 - x_2\| \sim \epsilon$, and the outer region where they are far apart, $\|x_1 - x_2\| \gg \epsilon$. To evaluate the collision integral in equation (10a) we must first calculate an asymptotic expansion for $P_{bb}(x_1, x_2, t)$ in the inner region. In the outer region the positions of the two particles are assumed to be uncorrelated at leading order. Therefore

\[
P_{bb}^{\text{out}}(x_1, x_2, t) = q_b(x_1, t)q_b(x_2, t) + \epsilon P_{bb}^{\text{out},(1)}(x_1, x_2, t) + \cdots,
\] (11)

for some function $q_b$. In the inner region, we introduce the inner variables $\tilde{x}_1 = \hat{x}_1$ and $\tilde{x}_2 = \hat{x}_1 + \epsilon \hat{\hat{x}}$ and define $\tilde{P}_{bb}(\tilde{x}_1, \tilde{x}, t) = P_{bb}(x_1, x_2, t)$. Then equation (10a) becomes

\[
\epsilon^2 \frac{\partial \tilde{P}_{bb}}{\partial t} = 2D_b \nabla^2_{\hat{x}_1} \tilde{P}_{bb} - 2D_b \epsilon \nabla_{\hat{x}_1} \cdot \nabla_{\hat{\hat{x}}} \tilde{P}_{bb} + \epsilon^2 [D_b \nabla^2_{\hat{x}_1} \tilde{P}_{bb} + \beta (\tilde{P}_{bb} + \tilde{P}_{rb}) - 2\alpha \tilde{P}_{bb}].
\] (12a)

The zero-flux boundary condition (5b) becomes

\[
2\hat{x} \cdot \nabla_{\hat{x}} \tilde{P}_{bb} = \epsilon \hat{\hat{x}} \cdot \nabla_{\hat{x}_1} \tilde{P}_{bb}, \quad \text{on} \quad \|\hat{x}\| = 1.
\] (12b)

To match the inner and outer regions we expand the outer solution in the inner variables

\[
P_{bb}^{\text{out}}(x_1, x_2, t) = q_b(\hat{x}_1, t)q_b(\hat{x}_1 + \epsilon \hat{\hat{x}}) + \epsilon P_{bb}^{\text{out},(1)}(x_1, x_1 + \epsilon \hat{x}_1) + \cdots
= q_b^2(\hat{x}_1, t) + \epsilon [q_b(\hat{x}_1, t)\hat{x} \cdot \nabla_{\hat{x}_1} q_b(\hat{x}_1, t) + P_{bb}^{\text{out},(1)}(\hat{x}_1, \hat{x}_1, t)] + \cdots.
\] (12c)
We seek a regular power series expansion of the form \( \hat{P}_{bb} = \hat{P}_{bb}^{(0)} + \epsilon \hat{P}_{bb}^{(1)} + \cdots \). Substituting in (12) and equating terms of zeroth order we obtain the following problem

\[
\nabla_x^2 \hat{P}_{bb}^{(0)} = 0, \quad (13a)
\]
\[
\hat{x} \cdot \nabla_x \hat{P}_{bb}^{(0)} = 0, \quad \text{on } \|\hat{x}\| = 1, \quad (13b)
\]
\[
\hat{P}_{bb}^{(0)} \sim q_b^2(\hat{x}_1, t), \quad \text{as } \|\hat{x}\| \to \infty, \quad (13c)
\]

with solution \( \hat{P}_{bb}^{(0)} = q_b^2(\hat{x}_1, t) \). Similarly, the first order problem for \( \hat{P}_{bb}^{(1)} \) is

\[
\nabla_x^2 \hat{P}_{bb}^{(1)} = 0, \quad (14a)
\]
\[
\hat{x} \cdot \nabla_x \hat{P}_{bb}^{(1)} = q_b(\hat{x}_1, t)\hat{x} \cdot \nabla_x q_b(\hat{x}_1, t), \quad \text{on } \|\hat{x}\| = 1, \quad (14b)
\]
\[
\hat{P}_{bb}^{(1)} \sim q_b(\hat{x}_1, t)\hat{x} \cdot \nabla_x q_b(\hat{x}_1, t) + P_{bb}^{\text{out},(1)}(\hat{x}_1, \hat{x}_1, t), \quad \text{as } \|\hat{x}\| \to \infty, \quad (14c)
\]

with solution \( \hat{P}_{bb}^{(1)} = q_b(\hat{x}_1, t)\hat{x} \cdot \nabla_x q_b(\hat{x}_1, t) + P_{bb}^{\text{out},(1)}(\hat{x}_1, \hat{x}_1, t) \). We conclude that, to first order in \( \epsilon \), the expansion of \( P_{bb}(x_1, x_2, t) \) in the inner region is

\[
\hat{P}_{bb}(\hat{x}_1, \hat{x}, t) = q_b^2(\hat{x}_1, t) + \epsilon \left[ q_b(\hat{x}_1, t)\hat{x} \cdot \nabla_x q_b(\hat{x}_1, t) + P_{bb}^{\text{out},(1)}(\hat{x}_1, \hat{x}_1, t) \right] + \cdots. \quad (15)
\]

Similarly, to first order we can write the expansion of \( P_{rr}(x_1, x_2, t) \) in the inner region as

\[
\hat{P}_{rr}(\hat{x}_1, \hat{x}, t) = q_r^2(\hat{x}_1, t) + \epsilon \left[ q_r(\hat{x}_1, t)\hat{x} \cdot \nabla_x q_r(\hat{x}_1, t) + P_{rr}^{\text{out},(1)}(\hat{x}_1, \hat{x}_1, t) \right] + \cdots. \quad (16)
\]

**D. Matched asymptotic expansions for the densities \( P_{br} \) and \( P_{rb} \)**

In order to evaluate the collision integral in equation (10a) we require an asymptotic expansion for \( P_{br}(x_1, x_2, t) \) in the inner region. In the outer region, our assumption of independence enables us to write

\[
P_{br}^{\text{out}} = q_b(x_1, t)q_r(x_2, t) + \epsilon P_{br}^{\text{out},(1)}(x_1, x_2, t) + \cdots, \quad (17)
\]

for some functions \( q_b \) and \( q_r \).

In the inner region, we define \( \hat{P}_{br}(\hat{x}_1, \hat{x}, t) = P_{br}(x_1, x_2, t) \) and transform equation (7b) into inner variables as before, yielding

\[
\epsilon^2 \frac{\partial \hat{P}_{br}}{\partial t} = (D_b + D_r)\nabla_{x}^2 \hat{P}_{br} - 2\epsilon D_b \nabla_{x_1} \cdot \nabla_{x} \hat{P}_{br} + \epsilon^2 [D_b \nabla_{x_1}^2 \hat{P}_{br} + \alpha \hat{P}_{bb} + \beta \hat{P}_{rr} - (\alpha + \beta) \hat{P}_{br}] + \cdots. \quad (18a)
\]
The boundary condition (5b) becomes
\[
\hat{x} \cdot \nabla_{\hat{x}} \hat{P}_{br} = \epsilon \frac{D_b}{D_b + D_r} \hat{x} \cdot \nabla_{\hat{x}} \hat{P}_{br} \quad \text{on} \quad \|\hat{x}\| = 1. \quad (18b)
\]
Expanding (17) in inner variables gives
\[
P_{br}^{\text{out}} = q_b(\hat{x}_1, t)q_r(\hat{x}_1, t) + \epsilon q_b(\hat{x}_1, t)\hat{x} \cdot \nabla_{\hat{x}_1} q_r(\hat{x}_1, t) + \epsilon P_{br}^{\text{out},(1)}(\hat{x}_1, \hat{x}_1, t) + \cdots. \quad (18c)
\]
As before, we seek a solution of the form \( \hat{P}_{br} = \hat{P}_{br}^{(0)} + \epsilon \hat{P}_{br}^{(1)} + \cdots \). Repeating the same procedure as in the previous section, the inner region solution for a blue and a red particle is
\[
\hat{P}_{br} = q_b(\hat{x}_1, t)q_r(\hat{x}_1, t) + \epsilon q_b(\hat{x}_1, t)\hat{x} \cdot \nabla_{\hat{x}_1} q_r(\hat{x}_1, t) + \epsilon P_{br}^{\text{out},(1)}(\hat{x}_1, \hat{x}_1, t) + \frac{\epsilon \hat{x}}{(D_b + D_r)(d-1)\|\hat{x}\|^d} \cdot [D_r q_b(\hat{x}_1, t)\nabla_{\hat{x}_1} q_r(\hat{x}_1, t) - D_b q_r(\hat{x}_1, t)\nabla_{\hat{x}_1} q_b(\hat{x}_1, t)]. \quad (19)
\]
Similarly, to first order we find that the expansion of \( P_{rb}(\hat{x}_1, \hat{x}_2, t) \) in the inner region is
\[
\hat{P}_{rb} = q_r(\hat{x}_1, t)q_b(\hat{x}_1, t) + \epsilon q_r(\hat{x}_1, t)\hat{x} \cdot \nabla_{\hat{x}_1} q_b(\hat{x}_1, t) + \epsilon P_{rb}^{\text{out},(1)}(\hat{x}_1, \hat{x}_1, t) + \frac{\epsilon \hat{x}}{(D_b + D_r)(d-1)\|\hat{x}\|^d} \cdot [D_r q_r(\hat{x}_1, t)\nabla_{\hat{x}_1} q_b(\hat{x}_1, t) - D_b q_b(\hat{x}_1, t)\nabla_{\hat{x}_1} q_r(\hat{x}_1, t)]. \quad (20)
\]

E. Evaluating the collision integral

We use the inner solutions of \( P_{bb}(\hat{x}_1, \hat{x}_2, t) \) and \( P_{br}(\hat{x}_1, \hat{x}_2, t) \), (19) and (19) respectively, to evaluate the collision integral in equation (10a). First we transform the integral into inner variables
\[
\mathcal{I} = - \int_{\partial B_1(\hat{x}_1)} [2D_b \nabla_{\hat{x}_1} (P_{bb} + P_{br}) + (D_b - D_r) \nabla_{\hat{x}_2}(P_{br})] \cdot \hat{n}_2 \, dS_{\hat{x}_2}
\]
\[
= -\epsilon^d - 2D_b \int_{\partial B_1(0)} \nabla_{\hat{x}_1}(\hat{P}_{bb} + \hat{P}_{br}) \cdot \hat{x}dS_{\hat{x}} + (D_r - D_b) \int_{\partial B_1(0)} \nabla_{\hat{x}_1} \hat{P}_{br} \cdot \hat{x} \, dS_{\hat{x}} \quad (21)
\]
\[
+ 2\epsilon^{d-1}D_b \int_{\partial B_1(0)} \nabla_{\hat{x}_1}(\hat{P}_{bb} + \hat{P}_{br}) \cdot \hat{x} \, dS_{\hat{x}}.
\]
Using the boundary conditions (12b) and (18b), \( \mathcal{I} \) can be rewritten as
\[
\mathcal{I} = \epsilon^{d-1}D_b \int_{\partial B_1(0)} \nabla_{\hat{x}_1}(\hat{P}_{bb} + \hat{P}_{br}) \cdot \hat{x} \, dS_{\hat{x}}. \quad (22)
\]
Inserting (15) and (19) into (22), we find
\[
\mathcal{I} \sim \epsilon^d D_b \int_{\partial B_1(0)} \nabla_{\hat{x}_1}(\hat{P}_{bb}^{(1)} + \hat{P}_{br}^{(1)}) \cdot \hat{x} \, dS_{\hat{x}} \quad (23)
\]
\[
= \epsilon^d \nabla_{\hat{x}_1} \cdot \left\{ D_b \omega q_b(\hat{x}_1, t) \nabla_{\hat{x}_1} q_b(\hat{x}_1, t) + D_b \left[ \xi_b q_b(\hat{x}_1, t) \nabla_{\hat{x}_1} q_r(\hat{x}_1, t) - \eta_b q_r(\hat{x}_1, t) \nabla_{\hat{x}_1} q_b(\hat{x}_1, t) \right] \right\},
\]
where the constants $\omega$, $\xi$, and $\eta$ are given in (3). Using the normalization condition 
$$\int_{G^2} (P_{bb} + P_{br} + P_{rb} + P_{rr}) = 1,$$
we find that $q_b(x_1, t) = b(x_1, t) + O(\epsilon^3)$ and $q_r(x_1, t) = r(x_1, t) + O(\epsilon^3)$ (see Appendix for details). This allows us to write $I$ in terms of $b(x_1, t)$ and $r(x_1, t)$.

Substituting the asymptotic expansion for the collision integral (23) into equation (10a) we arrive at the following equation for the blue particles’ density

$$\frac{\partial b}{\partial t}(x_1, t) = \beta r(x_1, t) - \alpha b(x_1, t) + \nabla_{x_1} \cdot \left\{ D_b[1 + \omega \epsilon d b(x_1, t)] \nabla_{x_1} b(x_1, t) + \epsilon d D_b [\xi b(x_1, t) \nabla_{x_1} r(x_1, t) - \eta r(x_1, t) \nabla_{x_1} b(x_1, t)] \right\}, \quad (24)$$

A similar calculation on (10b) yields an equation for the density of red particles, $r(x_1, t)$.

For the case of $N$ particles there is a contribution from every potential pairwise interaction. This allows us to write down the population-level equation for the general case, where we reintroduce the drift contributions, as follows

$$\frac{\partial}{\partial t} \begin{pmatrix} b \\ r \end{pmatrix}(x, t) = \nabla_x \cdot \left[ D(b, r) \nabla_x \begin{pmatrix} b \\ r \end{pmatrix} - F(b, r) \begin{pmatrix} b \\ r \end{pmatrix} \right] + \begin{pmatrix} \beta r - \alpha b \\ \alpha b - \beta r \end{pmatrix}, \quad (25a)$$

where the diffusion matrix is

$$D(b, r) = \begin{pmatrix} D_b[1 + (N - 1)(\epsilon d \omega b - \epsilon d \eta r)] & D_b(N - 1)\epsilon d \xi b \\ D_r(N - 1)\epsilon d \xi r & D_r[1 + (N - 1)(\epsilon d \omega r - \epsilon d \eta b)] \end{pmatrix}, \quad (25b)$$

and the drift matrix is

$$F(b, r) = \begin{pmatrix} f_b & (N - 1)\epsilon d \gamma b(f_r - f_b)b \\ (N - 1)\epsilon d \gamma r(f_b - f_r)r & f_r \end{pmatrix}. \quad (25c)$$

The diffusion and drift matrices (25b) and (25c) can be compared to the matrices (2b) and (2c) corresponding to the case of two subpopulations without switching. In Ref. 14 the numbers of blue and red particles, $N_b$ and $N_r$, were fixed and appeared explicitly in the matrices. As now there is a non zero probability of being either blue or red we see contributions from all $(N - 1)$ possible collisions in (25b) and (25c).

F. Numerical results

In this section we present numerical simulations of the discrete stochastic model (4) and the population-based model (25). The discrete model was simulated using the software package Smoldyn via the standard Euler-Maruyama method.
If two particles are found to be overlapping then we incorporate volume exclusion by using the ballistic collision update rule implemented in the software package Smoldyn. This method assigns to each particle a post-collision velocity by comparing both particles’ current and previous positions. Then it uses conservation of momentum to compute their positions had they undergone an elastic collision.

When considering spontaneous switching of particles between subpopulations, at each timestep in the algorithm we generate a random number $\rho$ uniformly on the interval $[0, 1]$. A blue particle becomes red if $\rho < \alpha \Delta t$. Similarly, a red particle becomes blue if $\rho < \beta \Delta t$. In order for this implementation to be accurate we assume $\Delta t$ to be small enough such that $\alpha \Delta t \ll 1$ and $\beta \Delta t \ll 1$, and so are good approximations to the probability of a switch occurring in a time interval of length $\Delta t$. We also require that the timestep is small enough that each particle moves, on average, a distance much less than the particle’s diameter. This requirement ensures that most collisions are detected.

We solved the PDEs numerically using the method of lines. In this technique only the spatial variables are discretized and time is viewed as a continuous variable, resulting in a system of Ordinary Differential Equations (ODEs) that are solved using MATLAB’s inbuilt ode15s solver (which performs the discretization of the time variable adaptively).

Initially we have 350 blue particles and 50 red particles in the domain $\Omega = [-1/2, 1/2]^2$. We select an initial Gaussian density of particles with zero mean and a standard deviation of 0.09 for both the blue and red subpopulations. We set $D_b = 0.5$ and $D_r = 1$ for the diffusion coefficients of the blue and red populations respectively, as well as switching parameters $\alpha = \beta = 10$. We ignore drift terms, setting $f_b = f_r = 0$. The data from the stochastic simulations of the SDEs (4a) and (4b) were generated using $10^4$ realizations, which resulted in $4 \times 10^6$ individual trajectories, where a timestep of $\Delta t = 10^{-5}$ was used.

Figure 1 shows the densities $b(x_1, t)$ and $r(x_1, t)$ of the blue and red particles respectively at time $t = 0.05$. Panels (I) and (II) respectively show the PDE solution and the histogram produced from the simulated trajectories for point particles ($\epsilon = 0$), whereas panels (III) and (IV) respectively show the same for finite size particles of diameter $\epsilon = 0.01$. Figure 2(a) shows a one dimensional slice of the histograms in Figure 1 for a clearer comparison of the PDEs and the stochastic data. We see good agreement between the particle-based model and the derived population-level equations. For further quantitative comparison we consider how the population numbers, $N_b(t)$ and $N_r(t)$, evolve over time. Recall that
FIG. 1. Population-level equations (25a) for both blue ([I-IV]-b) and red ([I-IV]-r) particles at time $t = 0.05$, with data being initially Gaussian with zero mean and standard deviation 0.09. (I) Solutions to equations (25a) for point particles, $\epsilon = 0$. (II) Histograms for point particles, $\epsilon = 0$. (III) Solutions to equations (25a) for finite size particles, $\epsilon = 0.01$. (IV) Histograms for finite size particles, $\epsilon = 0.01$. The data was calculated from $10^4$ stochastic simulations with $\Delta t = 10^{-5}$. Parameter values: $D_b = 0.5$, $D_r = 1$, $\alpha = \beta = 10$ and $N = 400$. Initial conditions were $N_b(0) = 350$ and $N_r(0) = 50$.

$$\int_{\Omega} b(x_1, t) \, dx_1 = N_b(t)/N$$ and $$\int_{\Omega} r(x_1, t) \, dx_1 = N_r(t)/N.$$ We can then integrate equations (25a) over the domain $\Omega$ to obtain, using zero-flux boundary conditions, the following ODE

$$\frac{dN_b(t)}{dt} = \beta N_r(t) - \alpha N_b(t), \quad N_r(t) = N - N_b(t).$$ (26)

In Figure 2(b) we plot the solution of (26) and compare these results with those from the stochastic simulations. We only plot the results for finite size particles but note that the curves for point particles are identical. That is, the finite size particles have no effect on the evolution of the population number when the switching rates are constant on $\Omega$, and so the ODEs are exactly the same as if we had considered the non-spatial model originally.

G. Environmental Switching

We now consider the case when the switching rates depend on the particle’s position, i.e., $\alpha(x)$ and $\beta(x)$. Following a derivation analogous to that for the constant rates case, we
FIG. 2. a) A slice of the histograms in Figure 1 at y = 0. b) The evolution of the blue and red population for 0 ≤ t ≤ 0.05 for finite size particles (ε = 0.01). Solid (dashed) lines represent the PDE and ODE solutions for finite size (point) particles. Asterisks (circles) represent data from stochastic simulations for finite size (point) particles. Parameter values: $D_b = 0.5$, $D_r = 1$, $\alpha = \beta = 10$ and $N = 400$. The initial numbers of particles were $N_b(0) = 350$ and $N_r(0) = 50$.

obtain the following population-level equations

$$
\frac{\partial}{\partial t} \begin{pmatrix} b \\ r \end{pmatrix} = \nabla_x \cdot \begin{pmatrix} D(b, r) \nabla_x b \\ F(b, r) \end{pmatrix} + \begin{pmatrix} \beta(x)r - \alpha(x)b \\ \alpha(x)b - \beta(x)r \end{pmatrix},
$$

where the matrices $D(b, r)$ and $F(b, r)$ are defined by equations (25b) and (25c), respectively. If we consider the evolution of the population number, then we arrive at the following integro-differential equations

$$
\frac{dN_b(t)}{dt} = N \int_{\Omega} (\beta(x)r(x, t) - \alpha(x)b(x, t)) \, dx, \quad N_r(t) = N - N_b(t).
$$

As an illustrative example, we consider the following choice for our spatially dependent switching parameters:

$$
\alpha(x, y) = \begin{cases} 1000, & (x, y) \in \mathcal{A} \\ 0, & \text{otherwise} \end{cases}, \quad \beta(x, y) = \begin{cases} 0, & (x, y) \in \mathcal{A} \\ 100, & \text{otherwise} \end{cases},
$$

where $\mathcal{A} = \{(x, y) : (0.2)^2 \leq x^2 + y^2 \leq (0.35)^2\}$. This corresponds to blue particles becoming red inside the annulus $\mathcal{A}$, at a rate 1000, and red particles becoming blue outside the annulus at a rate 100. The initial conditions were 400 blue particles normally distributed with zero mean and standard deviation 0.09 in both the $x$ and $y$ coordinates.
FIG. 3. Population-level equations (27) for both blue ([I-IV]-b) and red ([I-IV]-r) particles at time $t = 0.05$, with data being initially Gaussian with zero mean and standard deviation 0.09. (I) Solutions to equations (25a) for point particles, $\epsilon = 0$. (II) Histograms for point particles, $\epsilon = 0$. (III) Solutions to equations (25a) for finite size particles, $\epsilon = 0.01$. (IV) Histograms for finite size particles, $\epsilon = 0.01$. The data was calculated from $10^4$ stochastic simulations with $\Delta t = 10^{-5}$. Parameters were: $D_b = 1$, $D_r = 0.5$ and $N = 400$. Initial conditions were $N_b(0) = 400$ and $N_r(0) = 0$.

Figure 3 shows the histograms for the evolution of the densities with the spatially dependent rates. We see a good agreement between the numerical solutions of (27) and the stochastic data, for both point particles ($\epsilon = 0$) and for finite particles ($\epsilon = 0.01$). In Figure 4(a) we present a one dimensional slice of the histograms in Figure 3 to emphasize the good agreement between the PDEs and the stochastic data. In Figure 4(b) we plot the evolution of the population number of both red and blue particles and we note a difference in population number due to the finite size effects: the finite size of the particles obstructs their movement into and out of the annulus and so fewer reactions can occur.

III. SWITCHING UPON COLLISION: BIMOLECULAR REACTIONS

In this section we assume that particles switch between subpopulations as a result of a pairwise collision or interaction and consider bimolecular reactions of the form $B + R \rightarrow 2R$. 
We first describe how this effect changes our particle-level description and then derive the corresponding population-level equations.

A. Particle-based model

Our discrete model has the same Langevin dynamics as before

\[ dX_i(t) = \sqrt{2D_b}dW_b(t) + f_b(X_i(t))dt, \quad s_i = s_b, \quad (30a) \]
\[ dX_i(t) = \sqrt{2D_r}dW_r(t) + f_r(X_i(t))dt, \quad s_i = s_r, \quad (30b) \]

for \( 1 \leq i \leq N \). When two blue (red) particles are in contact we impose standard reflective boundary conditions. However, when a blue and a red particle are in contact the blue particle can either become red or remain blue when it is reflected.

As before the joint probability density function \( P(\vec{x}, \vec{s}, t) \) obeys the linear Fokker-Planck equation

\[ \frac{\partial P(\vec{x}, \vec{s}, t)}{\partial t} = \nabla \cdot \left[ D_s \nabla P(\vec{x}, \vec{s}, t) - F_s(\vec{x})P(\vec{x}, \vec{s}, t) \right] \quad \text{in} \quad \Omega^N, \quad (31) \]
where \( \mathbf{D_s} = \text{diag}(D_{s_1}, \ldots, D_{s_N}) \) and \( \vec{F}_s = (f_{s_1}, \ldots, f_{s_N}) \). However, the boundary conditions require more careful treatment. We define a flux for each configuration of particle states

\[
\mathbf{J}_s := \left[ \mathbf{D_s} \nabla \vec{x} P(\vec{x}, \vec{s}, t) - \vec{F}_s(\vec{x}) P(\vec{x}, \vec{s}, t) \right] \cdot \vec{n}.
\]  
(32)

In the case of spontaneous switching on the internal boundaries \( \partial \Omega^N \setminus \partial \Omega^N \) we had that \( \mathbf{J}_s = 0 \) for all \( \vec{s} \in \mathcal{C}^N \). However there are now non-zero fluxes across these internal boundaries in the configuration space, where the reactivity parameter for these boundaries is \( \lambda \). To make this explicit, we consider the boundary between a pair of particles, \( \| \mathbf{x}_i - \mathbf{x}_j \| = \epsilon \) for \( i \neq j \).

If \( (s_i, s_j) = (s_b, s_b) \) then \( \mathbf{J}_s = 0 \) on this boundary, as there is no reaction between two blue particles. If \( (s_i, s_j) = (s_b, s_r) \) (or \( (s_r, s_b) \)) then we have \( \mathbf{J}_s = \lambda P_s \) on \( \| \mathbf{x}_i - \mathbf{x}_j \| = \epsilon \). This is because there is a flux out of the configuration state \( \vec{s} \) due to the bimolecular reaction.

Finally if \( (s_i, s_j) = (s_r, s_r) \) no reaction occurs for two red particles; however there is a flux into the configuration state \( \vec{s} \) on the boundary \( \| \mathbf{x}_i - \mathbf{x}_j \| = \epsilon \) from the blue and red reactions. Therefore on this boundary \( \mathbf{J}_s = -\lambda \left( P_{c_i} + P_{c_j} \right) \), where \( \vec{c}_i = (s_1, \ldots, s_{i-1}, s_b, s_{i+1}, \ldots, s_N) \) and \( \vec{c}_j = (s_1, \ldots, s_{j-1}, s_b, s_{j+1}, \ldots, s_N) \).

\section*{B. Population-based model}

To reduce the particle-level description to the population-level we consider as before the density functions \([\mathbf{P}]\). We restrict our attention to the case for \( N = 2 \) and introduce the notation \( P_{s_1,s_2}(\mathbf{x}_1, \mathbf{x}_2, t) = P(\mathbf{x}_1, \mathbf{x}_2, s_1, s_2, t) \). For simplicity we set again \( f_b = f_r = 0 \); however the derivation with drift terms can be done similarly. For \( N = 2 \) we only have one inner boundary, \( \| \mathbf{x}_1 - \mathbf{x}_2 \| = \epsilon \), with the following boundary conditions

\[
\begin{align*}
\mathbf{J}_{bb} &= D_b \nabla \mathbf{x}_1, P_{bb} \cdot \mathbf{n}_1 + D_b \nabla \mathbf{x}_2, P_{bb} \cdot \mathbf{n}_2 = 0, \\
\mathbf{J}_{br} &= D_b \nabla \mathbf{x}_1, P_{br} \cdot \mathbf{n}_1 + D_r \nabla \mathbf{x}_2, P_{br} \cdot \mathbf{n}_2 = \lambda P_{br}, \\
\mathbf{J}_{rb} &= D_r \nabla \mathbf{x}_1, P_{rb} \cdot \mathbf{n}_1 + D_b \nabla \mathbf{x}_2, P_{rb} \cdot \mathbf{n}_2 = \lambda P_{rb}, \\
\mathbf{J}_{rr} &= D_r \nabla \mathbf{x}_1, P_{rr} \cdot \mathbf{n}_1 + D_r \nabla \mathbf{x}_2, P_{rr} \cdot \mathbf{n}_2 = -\lambda (P_{br} + P_{rb}).
\end{align*}
\]  
(33)
Then, from (31) the equations for the blue and red densities with the collision integrals can be written as

\[
\frac{\partial b}{\partial t}(x_1, t) = D_b \nabla^2 b - \int_{\partial B_r(x_1)} [2D_b \nabla x_1 (P_{bb} + P_{br}) + (D_b - D_r) \nabla x_2 (P_{br})] \cdot n_2 \, dS_{x_2}, \tag{34a}
\]

\[
\frac{\partial r}{\partial t}(x_1, t) = D_r \nabla^2 r - \int_{\partial B_r(x_1)} [2D_r \nabla x_1 (P_{rb} + P_{rr}) + (D_r - D_b) \nabla x_2 (P_{rb})] \cdot n_2 \, dS_{x_2}. \tag{34b}
\]

We must derive asymptotic expansions for \( P_{bb}, P_{br}, P_{rb} \) and \( P_{rr} \) in the inner region in order to evaluate the collision integrals in equations (34).

C. Matched asymptotic expansions and collision integral

First we consider \( P_{bb}(x_1, x_2, t) \). As the boundary condition on \( ||x_1 - x_2|| = \epsilon \) is \( J_{bb} = 0 \), we can use the results of Section II C to write down the inner solution as

\[
\hat{P}_{bb}(\hat{x}_1) = q_b^2(\hat{x}_1, t) + \epsilon q_b(\hat{x}_1, t) \hat{x} \cdot \nabla \hat{x}_1 q_b(\hat{x}_1, t) + \cdots, \tag{35}
\]

for some function \( q_b \). We construct the inner solution to \( P_{br}(x_1, x_2, t) \) by matching the solutions in the outer and inner regions. Introducing the inner variables \( x_1 = \hat{x}_1 \) and \( x_2 = \hat{x}_1 + \epsilon \hat{x} \) as before, we transform equations (31) and (33b) to get the following problem

\[
\epsilon^2 \frac{\partial \hat{P}_{br}}{\partial t} = (D_b + D_r) \nabla^2 \hat{P}_{br} - 2\epsilon D_b \nabla \hat{x}_1 \cdot \nabla \hat{P}_{br} + \epsilon^2 D_b \nabla^2 \hat{x}_1 \hat{P}_{br}, \tag{36a}
\]

with boundary conditions

\[
\hat{x} \cdot \nabla \hat{x} \hat{P}_{br} = \epsilon \left( \frac{D_b}{D_b + D_r} \hat{x} \cdot \nabla \hat{x}_1 \hat{P}_{br} + \frac{\lambda}{D_b + D_r} \hat{P}_{br} \right) \quad \text{on} \quad ||\hat{x}|| = 1. \tag{36b}
\]

We seek a regular power series expansion of the form \( \hat{P}_{br} = \hat{P}_{br}^{(0)} + \epsilon \hat{P}_{br}^{(1)} + \cdots \), and as seen in Section II for the zeroth order problem we obtain the solution \( \hat{P}_{br}^{(0)} = q_b(\hat{x}_1, t) q_r(\hat{x}_1, t) \). The first order problem for \( \hat{P}_{br}^{(1)} \) is

\[
\nabla^2 \hat{P}_{br}^{(1)} = 0, \tag{37a}
\]

\[
\hat{x} \cdot \nabla \hat{x} \hat{P}_{br}^{(1)} = \frac{D_b}{D_b + D_r} \hat{x} \cdot \nabla \hat{x}_1 (q_b q_r) + \frac{\lambda}{D_b + D_r} q_b q_r, \quad \text{on} \quad ||\hat{x}|| = 1, \tag{37b}
\]

\[
\hat{P}_{br}^{(1)} \to \hat{x} \cdot q_b \nabla \hat{x}_1 q_r, \quad \text{as} \quad ||\hat{x}|| \to \infty. \tag{37c}
\]

In two dimensions \((d = 2)\), problem (37) does not have a solution satisfying both the inner and outer boundary conditions, indicating that a more intricate method is required.
For the case $d = 3$ the solution is

$$
\hat{P}_{br}^{(1)} = q_b \hat{x} \cdot \nabla_{x_1} q_r + \frac{\hat{x}}{2(D_b + D_r)\|\hat{x}\|^3} (D_r q_b \nabla_{x_1} q_r - D_b q_r \nabla_{x_1} q_b) - \frac{\lambda}{(D_b + D_r)\|\hat{x}\|} q_b q_r. \tag{38}
$$

Combining the above results we deduce that the inner solution for $P_{br}$ is therefore

$$
\hat{P}_{br} = q_b q_r + \varepsilon \left[q_b \hat{x} \cdot \nabla_{x_1} q_r + \frac{\hat{x}}{2(D_b + D_r)\|\hat{x}\|^3} (D_r q_b \nabla_{x_1} q_r - D_b q_r \nabla_{x_1} q_b) \right. 
\left. - \frac{\lambda}{(D_b + D_r)\|\hat{x}\|} q_b q_r \right] + \cdots. \tag{39}
$$

We denote by $I$ the collision integral in equation (34a),

$$
I = -\int_{\partial B_r(x_1)} [2D_b \nabla_{x_1} (P_{bb} + P_{br}) + (D_b - D_r) \nabla_{x_2}(P_{br})] \cdot n_2 \, dS_{x_2}. \tag{40}
$$

We transform $I$ into inner variables and use the boundary condition (36b) and the inner solutions (35) and (39) and get

$$
I = -4\pi \varepsilon^2 \lambda q_b q_r + 4\pi \varepsilon^3 \left[\frac{D_b}{3} q_b \nabla_{x_1} q_b + D_b \left(\xi_3 q_b \nabla_{x_1} q_r - \eta_3 q_r \nabla_{x_1} q_b\right) + \frac{\lambda^2}{D_b + D_r} q_b q_r \right] + \cdots, \tag{41}
$$

where the constants $\xi_i$ and $\eta_i$ are defined in (34). Using the normalization condition (see Appendix) we find $q_b(x_1, t) = b(x_1, t) + O(\varepsilon^2)$ and $q_r(x_1, t) = r(x_1, t) + O(\varepsilon^2)$. Combining these results we deduce that the population-level equation for a blue particle satisfies

$$
\frac{\partial b}{\partial t} = \nabla_{x_1} \cdot \left[D_b \left(1 + \frac{4\pi}{3} \varepsilon^3 b\right) \nabla_{x_1} b + D_b \varepsilon^3 \left(\xi_3 b \nabla_{x_1} r - \eta_3 r \nabla_{x_1} b\right)\right] 
- 4\pi \varepsilon^2 \lambda \left(1 - \varepsilon \frac{\lambda}{D_b + D_r}\right) br. \tag{42}
$$

From (34b) a similar equation can be derived for the red density. For the general case of $N$ particles, by considering only pairwise interactions and reintroducing drift terms, we have the following system of nonlinear reaction-diffusion-advection equations

$$
\frac{\partial}{\partial t} \begin{pmatrix} b \\ r \end{pmatrix} = \nabla_x \cdot \left[\mathcal{D}(b, r) \nabla_x \begin{pmatrix} b \\ r \end{pmatrix} - \mathcal{F}(b, r) \begin{pmatrix} b \\ r \end{pmatrix}\right] + \mathcal{R}(b, r, \varepsilon) \quad \text{in} \quad \Omega, \tag{43}
$$

where the diffusion matrix, $\mathcal{D}(b, r)$, and the drift matrix, $\mathcal{F}(b, r)$, are defined by equations (25b) and (25c). The reaction terms $\mathcal{R}(b, r, \varepsilon)$ are given by

$$
\mathcal{R}(b, r, \varepsilon) = \lambda(N - 1)4\pi \varepsilon^2 \left(1 - \varepsilon \frac{\lambda}{D_b + D_r}\right) br \begin{pmatrix} -1 \\ 1 \end{pmatrix}. \tag{44}
$$
We interpret the reaction terms as follows: \((N - 1)4\pi\epsilon^2\) is the total surface area of the \((N - 1)\) spheres with which the sphere under consideration could react. The factor \((1 - \epsilon\lambda/(D_b + D_r))\) represents a correction to the source and sink terms, and indicates that only a fraction of the available surface area is used. If the diffusion coefficients are large relative to the reactivity parameter \(\lambda\) then this correction term approaches one, which can be interpreted as the case when the particle is moving fast enough that the entire surface area is available to it for collisions.

Our result (44) can be related to the \(\lambda - \bar{\rho}\) model introduced by Erban and Chapman as follows. In their model, a bimolecular reaction can only take place when the distance between two particles is less than \(\bar{\rho}\), and it occurs at a rate \(\lambda\). They distinguish between two cases depending on whether the relative mean-square displacement between the particles in one timestep, \(\sqrt{2(D_b + D_r)\Delta t}\), is small or large compared to the reaction radius \(\bar{\rho}\). We consider the former case, since we already perform simulations in this regime so that we do not miss collisions between particles (as discussed in Section II F). Taking the limit \(\lambda\) small, the reaction rate was found to be proportional to the volume of the reactive region (see Eq. (31) in Ref. 17). By contrast, the leading order of our reaction rate is proportional to the surface area of the collision surface (see (44)). This discrepancy arises because we have incorporated the excluded-volume effect directly into our microscopic model and, further, particles are not allowed to get closer to each other than the reaction radius, that is, \(\bar{\rho} \equiv \epsilon\) in our case.

D. Numerical Results

In this section we show how the inclusion of bimolecular reactions affects the time dependent behavior of our model. The stochastic simulations are implemented as described previously in Section II F with the exception of the reaction terms. When considering particle switching due to the collisions we proceed as follows. When a red and blue particle overlap, the reaction is implemented by generating a random number \(\rho\) uniformly on the interval \([0, 1]\). If \(\rho < \mathcal{P}\sqrt{\Delta t}\), where \(\mathcal{P}\sqrt{\Delta t}\) is the reaction probability, we switch the color of the blue particle to red and then update the positions due to the collision. We note that the relationship between the reactivity parameter, \(\lambda\), and the reaction probability parameter,
\[ P, \text{ has been shown to be}^{23} \]
\[ P = \frac{\lambda \sqrt{\pi}}{\sqrt{D_b + D_r}}. \]  

(45)

In order to increase the accuracy of this method we may also want to account for the possibility, that during the interval \([t, t + \Delta t]\), the red and blue particles may have overlapped and then moved apart, and a reaction may have occurred that otherwise would be missed. This correction, first pointed out by Andrews and Bray,\(^{18}\) is not included in our implementation of the bimolecular reactions. Instead, the timestep \(\Delta t\) is taken to be small enough that the probability of particles overlapping and separating during \(\Delta t\) is negligible.

We consider the evolution of the population numbers by integrating equations (43) over the domain \(\Omega\) to obtain the following integro-differential equation for the number of blue particles

\[ \frac{dN_b(t)}{dt} = -4\pi \epsilon^2 \lambda N(N - 1) \left(1 - \epsilon \frac{\lambda}{D_b + D_r}\right) \int_{\Omega} b(x, t) r(x, t) dx, \]

(46)

and \(N_r(t) = N - N_b(t)\). Since the leading-order reaction term in equation (46) is at order \(\epsilon^2\), it is natural to ask if retaining terms to \(O(\epsilon^2)\) provides sufficient detail to accurately predict the evolution of the population numbers. In Figure 5(a) we present the solutions to equation (46) correct to \(O(\epsilon^2)\) and \(O(\epsilon^3)\). We note that the \(O(\epsilon^3)\) terms are needed to accurately model the evolution of the population number. We also consider how the total volume fraction occupied by spheres affects the evolution of the population of particles. To investigate the effect of volume fraction we plotted the evolution of the blue population for a variety of different diameters \(\epsilon\) in Figure 5(b), keeping \(N\) fixed. We see that the time to extinction decreases as volume fraction increases. In particular, when only 6.55% of the domain is filled with particles we observe rapid extinction of the blue particles population.

IV. DISCUSSION

In this paper we have extended existing off-lattice, stochastic models of diffusion with excluded-volume effects to account for switching between two subpopulations of particles, which we termed by “blue” and “red” particles.

In Section II we considered the case of spontaneous switching. We formulated the discrete model, a system of Langevin SDEs, to allow particles to switch their color at a spatially dependent rate. The resulting system of nonlinear reaction-diffusion-advection equations \([25a]\) are similar to those for multiple populations without switching with additional linear
source and sink terms. We then presented numerical solutions of the PDEs and showed that they are in good agreement with stochastic simulations of the discrete model.

In Section III we considered the bimolecular reaction $B + R \rightarrow 2R$, where a change in a blue particle’s color could only occur, with a prescribed probability, after a collision with a red particle. We considered the effects on the particle-level equation and instead of including source and sink terms in the equation as for the unimolecular reactions we modified the boundary conditions on the interior boundaries in the configuration space. We then used the method of matched asymptotic expansions to derive the population-level equations in three spatial dimensions. Surprisingly, the case of two dimensions is more complicated. The problem can be compared to solving for the steady state of a random walker. In two dimensions the walker will hit the surface of the sphere infinitely many times and so will always be absorbed by the sphere. This means that we cannot match the inner and outer solutions for our current method of matched asymptotic expansions. In contrast, in three dimensions there is a non-zero probability of the walker never hitting the sphere. A possible way to solve the two-dimensional case using matched asymptotic expansions would be to

FIG. 5. a) Plots of the numerical solutions to equation (46) correct to $O(\epsilon^2)$ and $O(\epsilon^3)$, where $\epsilon = 0.02$. b) Plots of the evolution of the blue population number, $N_b(t)$, for a variety of diameters $\epsilon = \{0.00, 0.01, 0.02, 0.03, 0.04, 0.05\}$. Parameter values: $D_b = 0.5$, $D_r = 1$, $\lambda = 10$, $f_b = f_r = 0$ and $N = 1000$. The initial conditions were $N_b(0) = 650$ and the particles were uniformly distributed in $\Omega = [-1/2, 1/2]^3$ and $N_r(0) = 350$ which were normally distributed with zero mean and standard deviation 0.09 in the $(x, y)$ plane and uniformly distributed in the $z$ coordinate.
consider an intermediate region between the inner and outer regions.

An interesting extension of the model would be to incorporate cell proliferation and death. The main difficulty when including reactions of this type into the modeling framework is that the total number of cells in the system, \( N(t) \), becomes a random variable. A further consideration is that of the volume fraction occupied in the domain; if the cells produced via proliferation were the same size as their parents the volume occupied in the domain would increase.

A further application under consideration is to study the phenotypic switching behavior of cells within a glioblastoma. A third population of point particles could be introduced to represent a chemo-attractant which interacts with the different glioma cell populations. This application fits naturally into the framework we have introduced in this paper.

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Appendix: Normalization condition

In this Appendix we prove the following relationship

\[
q_b(x_1,t) = b(x_1,t) + O(\epsilon^2), \tag{A.1}
\]

for the case \( N = 2 \). We recall that the blue particles' density, defined in (8a), satisfies \( \int b(x_1,t)dx_1 = N_b(t)/N \). Similarly, \( \int r(x_1,t)dx_1 = N_r(t)/N \). We split the domain of integration in (8a) into an outer and inner region using an arbitrary parameter \( \delta \) such that \( \epsilon < \delta < 1 \).

\[
b(x_1,t) = \int_{\Omega_{\text{out}}(x_1)} [P_{bb}(x_1,x_2,t) + P_{br}(x_1,x_2,t)] \, dx_2 \\
+ \int_{\Omega_{\text{in}}(x_1)} [P_{bb}(x_1,x_2,t) + P_{br}(x_1,x_2,t)] \, dx_2. \tag{A.2}
\]
We consider the outer region integral in (A.2) first, for which we use the outer solutions (11) and (17). We note that we did not solve for the first-order corrections $P_{bb}^{\text{out}(1)}$ and $P_{br}^{\text{out}(1)}$ in the outer, since they did not affect the collision integral. In fact, it can be shown they are zero in the low-volume fraction limit since the excluded volume scales as $O(\epsilon^2)$. Using this, the first integral in (A.2) reads

$$q_b(x_1, t) \int_{\Omega_{\text{out}}} [q_b(x_2, t) + q_r(x_2, t)] \, dx_2 + O(\epsilon^2)$$

$$= q_b(x_1, t) \left\{ \int_{\Omega} [q_b(x_2, t) + q_r(x_2, t)] \, dx_2 - \int_{||x_2-x_1||<\delta} [q_b(x_2, t) + q_r(x_2, t)] \right\} + O(\epsilon^2)$$

$$= q_b(x_1, t) \left\{ \int_{\Omega} [q_b(x_2, t) + q_r(x_2, t)] \, dx_2 - \left| B_d \right| \delta^d [q_b(x_1, t) + q_r(x_1, t)] \right\} + O(\delta^{d+1}, \epsilon^2) \quad (A.3)$$

where $|B_d|$ is the area of a unit sphere in $d$ dimensions. Changing to inner variables in the second integral in (A.2) and using the inner solutions yields

$$\epsilon^d \int_{1 \leq ||\hat{x}|| \leq \delta_\epsilon} \left[ \hat{P}_{bb}(\hat{x}_1, \hat{x}, t) + \hat{P}_{br}(\hat{x}_1, \hat{x}, t) \right] \, d\hat{x}$$

$$= \epsilon^d \int_{1 \leq ||\hat{x}|| \leq \delta_\epsilon} \left[ q_b^2(\hat{x}_1, t) + q_b(\hat{x}_1, t)q_r(\hat{x}_1, t) \right] \, d\hat{x} + O(\epsilon^{d+1})$$

$$= |B_d| (\delta^d - \epsilon^d) \left[ q_b^2(x_1, t) + q_b(x_1, t)q_r(x_1, t) \right] + O(\epsilon \delta^d), \quad (A.4)$$

where $\delta_\epsilon = \delta/\epsilon$. Substituting equations (A.3) and (A.4) into equation (A.2) gives

$$b(x_1, t) = q_b(x_1, t) \left[ \int_{\Omega} q_b(x_1, t) + q_r(x_1, t) \, dx \right] - \epsilon^d |B_d| q_b(x_1, t)[q_b(x_1, t) + q_r(x_1, t)] + O(\delta^{d+1}, \epsilon^2). \quad (A.5)$$

Integrating equation (A.5) over the domain $\Omega$ yields

$$\frac{N_b(t)}{N} = \left[ \int_{\Omega} q_b(x_1, t) \, dx_1 \right] \left[ \int_{\Omega} [q_b(x, t) + q_r(x, t)] \, dx \right]$$

$$- \epsilon^d |B_d| \int_{\Omega} q_b(x_1, t)[q_b(x_1, t) + q_r(x_1, t)] \, dx_1 + O(\delta^{d+1}, \epsilon^2). \quad (A.6)$$

Similarly we can show that

$$\frac{N_r(t)}{N} = \left[ \int_{\Omega} q_r(x_1, t) \, dx_1 \right] \left[ \int_{\Omega} [q_b(x, t) + q_r(x, t)] \, dx \right]$$

$$- \epsilon^d |B_d| \int_{\Omega} q_r(x_1, t)[q_b(x_1, t) + q_r(x_1, t)] \, dx_1 + O(\delta^{d+1}, \epsilon^2). \quad (A.7)$$
Adding equations (A.6) and (A.7) and noting \( N = N_b(t) + N_r(t) \) we get

\[
1 = \left[ \int_{\Omega} \left[ q_b(x, t) + q_r(x, t) \right] \, dx \right]^2 - \epsilon^d |B_d| \int_{\Omega} \left[ q_b(x_1, t) + q_r(x_1, t) \right]^2 \, dx_1 + O(\delta^{d+1}, \epsilon^2) \tag{A.8}
\]

Equation (A.8) implies

\[
\int_{\Omega} \left[ q_b(x, t) + q_r(x, t) \right] \, dx = 1 + \frac{\epsilon^d |B_d|}{2} \int_{\Omega} \left[ q_b(x, t) + q_r(x, t) \right]^2 \, dx + O(\delta^{d+1}, \epsilon^2). \tag{A.9}
\]

We then substitute equation (A.9) into equation (A.5) to get,

\[
b(x_1, t) = q_b(x_1, t) + O(\delta^{d+1}, \epsilon^2). \tag{A.10}
\]

Choosing \( \delta = \epsilon^{2/d+1} \) leads to the required result.

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