The auxiliary region method: A hybrid method for coupling a PDE to Brownian-based dynamics for reaction-diffusion systems
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Abstract

Reaction-diffusion systems are used to model many biological and physical phenomena. They model the random motion of particles (diffusion) and interactions between them (reactions). Such systems can be modelled at multiple scales with varying degrees of accuracy and computational efficiency. When representing genuinely multiscale phenomena, fine-scale models can be prohibitively expensive, whereas coarser models, although cheaper, often lack sufficient detail to accurately represent the phenomenon at hand. Spatial hybrid methods couple two or more of these representations in order to improve the efficiency of a model without compromising accuracy.

In this paper, we present a novel spatial hybrid method, which we call the auxiliary region method (ARM), which couples PDE and Brownian representations of reaction-diffusion systems. Numerical PDE solutions on one side of the interface are coupled to Brownian dynamics on the other side using compartment-based “auxiliary regions”. We demonstrate that the hybrid method is able to simulate reaction-diffusion dynamics for a number of different test problems with high accuracy. Further, we undertake error analysis on the ARM which demonstrates that it is robust to changes in the free parameters in the model, where previous coupling algorithms are not. In particular, we envisage that the method will be applicable for a wide range of spatial multi-scales problems including, filopodial dynamics, intracellular signalling, embryogenesis and travelling wave phenomena.

1 Introduction

Reaction-diffusion models are important mathematical tools which are used to represent and understand complex biological and physical behaviours. They model the random movement of the particles (diffusion) and the interactions between particles, giving them a wide range of applications across multiple spatial scales. These applications range from the large-scale representation of striped vegetation patterns in semi-arid landscapes (Sherratt, 2005) and the spread of epidemics (Volpert and Petrovskii, 2009) to smaller-scale studies of pattern formation during embryogenesis (Mort et al., 2016; Turing, 1952) and at even smaller scales to the study of actin dynamics inside a cell’s filopodia (Erban et al., 2014) and intracellular dynamics (Khan et al., 2011).

Reaction-diffusion models can be specified at different levels of detail depending on the temporal, spatial and concentration scales involved in the application (see Table 1). At the finest scale are microscopic dynamics. These models (which include Brownian motion for purely diffusive systems and Smoluchowski dynamics (Smoluchowski, 1917) or Green’s function reaction dynamics (van Zon and ten Wolde, 2005) for reaction-diffusion systems) are amongst the more detailed representations of such systems, but consequently are relatively computationally expensive\textsuperscript{1}. They require not only the knowledge of the location

\textsuperscript{1}Throughout this paper, regardless of whether we have interactions between particles or not, we shall refer to models at this microscopic scale as “Brownian dynamics".
of all particles at all times, but in the case of second- and higher-order reactions, the pairwise distances between particles. In the case of diffusion-limited reactions, time-steps must be taken to be extremely small to ensure that reactive particles do not jump past each other and that the attendant reaction events are not missed. All update steps also require the production of a normally distributed random number for each co-ordinate of each particle which can be particularly computationally expensive for large numbers of particles in high dimensions. Micro-scale modelling is particularly useful when fine scale detail is required, for example, when considering the binding of particles to receptors (Dobramysl et al., 2015; English and Hammer, 2004; Moy et al., 2000).

| Scale | Advantages | Disadvantages |
|-------|------------|---------------|
| Micro | Most accurate representation. Can be used for low copy numbers. | Slow to compute reactions. Impractical for large numbers of particles. |
| Meso  | Fast for low particle numbers. Represents individual-level behaviour. | Can be slow for large copy numbers. Does not retain precise location or particle identity. |
| Macro | Fast to compute solutions. Suitable for high copy numbers. | Inaccurate for low copy numbers. Mean-field models diverge from individual dynamics for higher-order reactions. |

Table 1. A comparison of the advantages and disadvantages of the three most prominent scales at which reaction-diffusion processes are modelled.

At a coarser scale we have compartment-based or mesoscopic models. Like the fine-scale, microscopic models, these also account for stochastic variation, however particles are now considered to belong to compartments rather than having their exact locations tracked. Particles can either react with one another within a compartment, or can jump between adjacent compartments with given rates, simulating diffusion. Compartment-based models can be simulated using either exact but computationally expensive (Elf and Ehrenberg, 2004; Gibson and Bruck, 2000; Gillespie, 1977) or inexact but computationally cheaper (Gillespie, 2001) stochastic simulation algorithms (SSAs). The exact methods (so-called because they produce sample paths consistent with the associated chemical master equation) effectively assign exponential waiting times to every possible event (diffusive jump or reaction) and then choose the first of these to enact. In general, they are faster than the microscopic methods, since pairwise reaction distances do not need to be calculated for bi-molecular reactions and individual particle identities are not tracked, but are less accurate, since they only record a particle’s location up to the accuracy of the compartment size and generally particles are only allowed to react with others in the same compartment (Isaacson, 2013).

Finally, at the coarsest scale lie continuum or macroscopic models. The most commonly employed macroscopic models for reaction-diffusion systems comprise partial differential equations (PDEs)\textsuperscript{2}. These methods are generally only valid for high particle numbers. The stochastic variations, which are considered small enough to be neglected at high copy numbers, play a pivotal role in the dynamics at low copy numbers, leading to the PDE solutions diverging from the true underlying dynamics. There is a wealth of well established numerical methods that can quickly simulate the solution to a PDE, including finite-difference methods, finite-volume methods and finite-element methods (see for example, (Brenner and Carstensen, 2004; Eymard et al., 2000; Morton and Mayers, 2005; Smith, 1985)).

Often though, important biological and physical phenomena are genuinely multiscale (Black and McKane, 2012; Gillespie et al., 2013; Markevich et al., 2004; Robinson et al., 2014). In spatial reaction-diffusion systems, concentration may vary over orders of magnitude. In regions of low concentration it is often important to employ detailed individual-based models in order to correctly represent the

\textsuperscript{2}However, with the increasing awareness of the importance of randomness, stochastic partial differential equations (SPDEs) are also becoming popular macroscopic representations.
dynamics. If these models were to be employed indiscriminately throughout the domain, however, the
regions of high concentration, in which there are many individual particles to be evolved, might render
the system computationally intractable. In these regions, it might be acceptable to employ a coarser and
less computationally expensive model. A canonical example of this phenomenon is the stochastic Fisher
wave (Breuer et al., 1994, 1995). The wave speed is determined by the stochastic activity at the pulled
front, so it is important to employ an accurate individual-based representation of the dynamics in this
region. Conversely, behind the wave front, the detailed dynamics are of little importance. It is possible,
therefore, to employ a coarser, cheaper representation of the dynamics in this region.

Spatial hybrid models have been developed for precisely this purpose: to simulate spatially inhomoge-
neous domains both accurately and efficiently. In general, such methods are designed to accelerate
expensive computations whilst maintaining tolerable levels of accuracy. The majority of spatial hybrid
models divide the computational domain into distinct regions using interfaces. The dynamics of adjacent
regions are represented using different methods. Regions in which detailed representations of the dynam-
ics are required for accuracy are simulated using a fine-scale model, whereas regions in which less detail
is required are modelled with a coarser, less computationally expensive model.

There exist hybrid methods that couple each of the different scales described above (and indeed
many more (Smith and Yates, 2017)). Macroscopic-to-mesoscopic methods have been proposed which
employ averaged fluxes in order to calculate appropriate boundary conditions for each regime at the
interface(s) (Moro, 2004; Wagner and Flekkoy, 2004), as well as using an extra compartment within
the macroscopic region (Yates and Flegg, 2015). Mesoscopic-to-microscopic methods, which also employ
extra compartments, this time in the microscopic regime, have been developed (Flegg et al., 2015), and
a class of methods using adapted rates of diffusion from the mesoscopic to the microscopic domains have
been developed and successfully applied to represent biologic processes (Dobramysl et al., 2015; Erban
et al., 2014; Flegg et al., 2012, 2014; Robinson et al., 2014). There are fewer macroscopic-to-microscopic
hybrid methods in the literature. Macro-to-micro methods that allow mass to flow over the interface in
both directions in order to initialise particles (Franz et al., 2013) or that average solutions on either side
of the interface to find a flux (Alexander et al., 2002) can be found in the literature. For a more detailed
review of spatially extended hybrid methods, see (Smith and Yates, 2017).

Two of the above-mentioned hybrid methods are of particular relevance for the purposes of this paper.
The pseudo-compartment method, presented by Yates and Flegg (2015), is a macroscopic-to-mesoscopic
(specifically PDE-to-compartment) method in which the coupling is achieved using an extra compartment,
known as the “pseudo-compartment”, adjacent to the interface within the macroscopic domain. In this
compartment, mass is represented using both the PDE solution and the compartment-based method (with
particle numbers found by direct integration of the PDE over this region). Particles are then allowed
to cross the interface in both directions using the compartment-based method. We give a schematic
representation of this method in Figure 1 (a).

The ghost cell method proposed by Flegg et al. (2015) is a mesoscopic-to-microscopic method which
uses an extra compartment in the microscopic domain. The number of particles in this “ghost cell” is
simply the number of Brownian particles which reside in this region. Again, particles are allowed to jump
across the interface using the compartment-based mesoscopic method. A schematic representation of the
method is given in Figure 1 (b).

In this paper, we make use of these two methods in order to couple a macroscopic PDE description
for reaction-diffusion systems to a corresponding microscopic Brownian dynamics representation through
the use of “auxiliary regions”. These regions are compartments, which lie either side of the interface,
and allow mass to pass between the two regimes via a mesoscopic jump process (see Figure 4 on page 8
for a schematic representation). Within the auxiliary regions, mass is simultaneously represented using
both the description for the region in which they reside (i.e. PDE or Brownian) and the mesoscopic
description. Changes (i.e. reactions or diffusion events) implemented under one modelling paradigm
(e.g. the compartment-based representation of the auxiliary region) are simultaneously implemented in
Figure 1. Schematics for (a) the pseudo-compartment method and the (b) the ghost cell method. The green line represents the PDE solution, the blue boxes the solution to the mesoscopic region of the respective hybrid methods, and the yellow dots denote the Brownian particles. These particles are shown with a volume, but in the simulations do not have a mass or volume. The particles reside on the one-dimensional line, but have been illustrated in the plane in order to show the directions and magnitudes of their next movement clearly (black arrows). The green boxes in (a) denote the number of particles in the pseudo-compartment, and similarly, the yellow boxes in (b) are the number of particles in the ghost cell, with each box representing a single particle. In each case, the red line denotes the point interface between the two regimes.

The paper is organised as follows. In Section 2, a previous attempt at hybridising a Brownian dynamics model to its corresponding mean-field PDE description is discussed in more detail (Franz et al., 2013). A description of our novel auxiliary region method (ARM) is presented in Section 3 alongside the relevant justifications and pseudocode. Numerical results, verifying the accuracy of our hybrid method, are presented in Section 4. Numerical error analysis is conducted in Section 5 where we also discuss restrictions on the model parameters for the effective functioning of the coupling algorithm. We conclude with a discussion of the effectiveness of our new hybrid method and suggest avenues for further exploration in Section 6.

2 An existing PDE-to-Brownian coupling

In this section we summarise the pioneering work of Franz et al. (2013), who were among the first to couple PDE and Brownian dynamics representations of reaction-diffusion. By recapitulating their results, we demonstrate that their “PDE-assisted Brownian dynamics” algorithm is not robust to simulation parameter choice, even for simple diffusive processes. This motivates the need for a more robust coupling method, which we provide in the form of the ARM in Section 3.
2.1 PDE-assisted Brownian dynamics

Hybrid methods that couple the PDE description of a reaction-diffusion system to its corresponding Brownian dynamics representation have been relatively poorly investigated in comparison to PDE-to-compartment-based and compartment-based-to-Brownian couplings. In part, this is a result of the fact that such hybrid algorithms neglect meso-scale representations of particle dynamics, meaning that they must bridge a greater scale separation than either of the other two hybrid paradigms. Mainly though, the absence of many examples of PDE-to-Brownian hybrid methods is due to the inherent difficulty when converting PDE mass to individual particles (and vice-versa) when coupling Brownian dynamics models to continuum PDE representations.

Franz et al. (2013) present two related algorithms. In the first, the non-overlapping PDE and Brownian domains are separated by an interface (see Figure 2). Both representations are updated using a time-driven algorithm, with the PDE time-step much smaller than the Brownian time-step. The discretised PDE is evolved (until the time reaches the next Brownian time-step) using a central finite-difference scheme with implicit Euler time-stepping, and PDE mass is allowed to cross the interface between the two regimes. Provided that the Brownian time-step is sufficiently small, the amount of mass that crosses the interface gives the probability that a new particle is placed within the Brownian domain. A uniformly distributed random number is used to determine whether a particle is initialised in the Brownian regime or not. If it is, this particle’s position is randomly initialised according to the normalised density profile of the PDE mass that crossed the interface in the previous Brownian time-step. If a Brownian particle crosses into the PDE domain, a particle’s worth of mass is added to the PDE solution at its new location as a $\delta$-function and the individual particle is removed. We have illustrated this method schematically in Figure 2.

Franz et al. (2013) found the variance in particle numbers in the Brownian region of the hybrid domain to be reduced in comparison to the variance that would be expected in a fully Brownian simulation. In order to counteract this problem, they introduced a second algorithm, in which an overlap region replaces the interface. Within the overlap region, mass can be simulated as either Brownian particles or as part of the PDE. The coupling works in the same way as in the interfacing algorithm, however the Brownian particles are subsumed into the PDE only once they have crossed the boundary of the overlap region closest to the fully-PDE domain. Similarly, PDE mass can only be converted to Brownian particles once it has flowed over the overlap boundary adjacent to the fully-Brownian domain.

The Brownian time-step in the algorithm is required to be small, in order that the total probability of initialising a particle in the Brownian regime is less than one. However, the algorithm runs into difficulties if the time-step is chosen to be too small. Specifically, the amount of mass that flows over the interface between updates of the Brownian dynamics is too small in comparison to that which would be predicted theoretically using the exact diffusion kernel. This gives rise to inaccuracies in the algorithm, particularly if long simulation times are required. This sensitivity to the choice of Brownian time-step restricts the physical scenarios to which the algorithm can be applied.

In figure 3 we present three snapshots of the evolution of the first version of the algorithm (interface rather than overlap region) which illustrate this problem. By time $t = 0.4$, in Figure 3 (c), there is a clear disparity between the hybrid model and the mean field solution (black dotted line). This is especially obvious in the PDE part of the domain (c.f. green curve). Clearly disparities of this nature are not acceptable when modelling real reaction-diffusion systems, irrespective of the computational savings the algorithm is able to produce.

3 The auxiliary region method

In this section we present our novel “auxiliary region method” (ARM) for coupling PDE and Brownian representations of reaction-diffusion. For simplicity we will present a version of the method with a single
Figure 2. A schematic for the method proposed by Franz et al. (2013). Descriptions are as in Figure 1. The PDE mass labelled $\alpha$ (orange) is the density of PDE mass that has flowed over the interface in the Brownian update-step. The peak in the PDE curve near the interface represents the addition of a $\delta$-function corresponding to a Brownian particle that crosses the interface.

Figure 3. The evolution of 100 particles worth of mass initialised at a single PDE point at position $x = -0.95$, at times (a) 0.2, (b) 0.3 and (c) 0.4 under the first hybrid model of Franz et al. (2013). The green line is the PDE part of the hybrid model, the yellow bars represent the Brownian dynamics for the hybrid model (appropriately binned for visualisation purposes), the red line is the interface and the black dashed line is the solution of the mean-field diffusion equation (equation (16)). Results shown are averaged over 100 repeats.
interface separating two regimes. However, the method can be easily generalised to multiple interfaces which separate alternating PDE and Brownian regions. Sequentially, we describe the composition of the domain and the models we employ in each region; the nature of the auxiliary regions; the implementation of movement of mass across the boundary; the implementation of reactions; and finally the specific details required for the simulation of the algorithm, including pseudocode for its implementation.

3.1 The domain composition

Recall that, for our coupling method, space is partitioned into two regions within which we use different modelling paradigms (PDE and Brownian motion) to simulate the underlying reaction-diffusion system. Separating the two regions is a point interface, over which particles can jump according to a compartment-based method.

Consider a one-dimensional domain\(^d\) \(\Omega = [L_1, L_2] \subseteq \mathbb{R}\) for some \(L_1 < 0 < L_2\). We split \(\Omega\) into two regions, \(\Omega_p = [L_1, 0]\) and \(\Omega_B = [0, L_2]\) (separated by an interface \(I\) at position 0), within which the evolution of the system will be represented using a PDE description and Brownian dynamics, respectively.

3.2 The auxiliary regions

Particles can move between the two domains (\(\Omega_p\) and \(\Omega_B\)) via the auxiliary regions \(\Omega_{pA}\) and \(\Omega_{BA}\); subsets of \(\Omega_p\) and \(\Omega_B\) respectively, each of width \(h > 0\). Within these regions, mass/particles are simultaneously represented according to the default methodology for their domain (either PDE in \(\Omega_p\) or Brownian dynamics in \(\Omega_B\)), but also as well-mixed particles in their respective auxiliary regions \(\Omega_{pA}\) and \(\Omega_{BA}\). These auxiliary regions act as a bridge between the fine- and coarse-scale descriptions. A schematic representation of domain’s composition is given in Figure 4.

We justify the use of the Brownian auxiliary region by following the methodology set out in Flegg et al. (2015). The entire Brownian domain can be simulated using a mesoscopic compartment-based regime, and equivalently using a microscopic simulation. In the absence of reactions, if the particles in the microscopic simulation are “binned” into the same compartments as the mesoscopic simulation, the expected numbers in each compartment for each simulation would be the same. At this scale, the two methods are equivalent ways of simulating the same diffusive process (Flegg et al., 2015).

To justify the use of the PDE auxiliary region, we appeal to the arguments of Yates and Flegg (2015). We note that the PDE density can be thought of as the probability of finding a particle at a particular position and time, scaled by the number of particles within the PDE domain. Provided that the auxiliary region is sufficiently narrow, the PDE density within the auxiliary region can be thought of as being approximately uniformly distributed across the region with the appropriate number of particles. This is precisely the interpretation of the contents of a compartment within the mesoscopic, compartment-based framework.

3.3 The PDE regime, \(\Omega_p\)

Within \(\Omega_p\), we represent the mass of particles using a PDE of the form:

\[
\frac{\partial c}{\partial t}(x,t) = D \frac{\partial^2 c}{\partial x^2}(x,t) + f(c(x,t)); \quad x \in \Omega_p, \quad t \in [0, T],
\]

with zero flux boundary conditions at either end of \(\Omega_p\). Here, \(c(x,t) = (c_1(x,t), \ldots, c_K(x,t))^T\), denotes the density of species \(k = 1, \ldots, K\) at position \(x\) and time \(t\), \(D\) is a diagonal matrix containing the Fickian diffusion constants for each species, and \(f\) is a function that encapsulates the effect of any reactions on

\(^d\)Note that the method can be extended to different one-dimensional domains or higher dimensions with (hyper)-planar interfaces in a straight-forward manner.
Figure 4. A schematic for the auxiliary region method (ARM). The green line denotes the PDE solution, while the yellow dots denote the positions of the Brownian particles. The Brownian particles are shown with a volume, however in the simulation they are point particles with no mass or volume. All Brownian particles also lie on the one-dimensional line, but are shown here with different y-positions in order to clearly show the directions of their next movements (black arrows). The interface is the red line in the centre and the two auxiliary regions are shown with blocks to indicate the number of particles residing within them. In the PDE and Brownian auxiliary regions, each block represents a particle in the compartment-based representation and the number of blocks is determined by integrating the PDE over the auxiliary region $\Omega_{PA}$, and counting the number of Brownian particles in $\Omega_{BA}$, respectively.

For each species. For all the simulations presented in this paper we employ the finite-difference $\theta$-method (a general family of finite-difference methods). Although the Crank-Nicolson method ($\theta = 0.5$) is second-order accurate and unconditionally stable, we use $\theta = 0.51$ since the Crank-Nicolson method can give rise to spurious oscillations when implemented on step-function initial conditions of the sort we will consider (Smith, 1985).

3.4 The Brownian regime, $\Omega_B$

Within $\Omega_B$, all particles are tracked and their positions updated according to the following stochastic differential equation (SDE) which simulates Brownian motion:

$$y_{ik}^c(t+\Delta t) = y_{ik}^c(t) + \sqrt{2D_k \Delta t} \xi_i^k ; \quad \xi_i^k \sim N(0, 1); \quad \text{for} \quad i \in \{1, ..., N_{HB}^k(t)\} \quad \text{and} \quad k \in \{1, ..., K\},$$  \hspace{1cm} (2)

Note that this PDE can be simulated using any appropriate numerical solver, including the finite element method or finite-volume method.
where \( y_k^i(t) \) denotes the location of particle \( i \) of species \( k \) within \( \Omega_B \), \( \Delta t \) is the time-step for both the PDE and Brownian dynamics simulators\(^5\) and \( N_{\text{sim}}^k(t) \) is the number of particles of species \( k \) in \( \Omega_B \) at time \( t \). Once again, we set reflective boundary conditions at both ends of \( \Omega_B \) to ensure that no particles can leave this domain via a Brownian diffusion event. The zero-flux boundary conditions at the interface for both PDE and Brownian regimes ensure that mass can only cross the interface according to the compartment-based method.

### 3.5 Movement across the interface

Since both domains, \( \Omega_P \) and \( \Omega_B \), have zero-flux boundaries at the interface, particles can only cross over the interface via the auxiliary regions. In effect, these regions comprise a two-compartment reaction-diffusion master equation (RDME) model. Each particle in each auxiliary region jumps to its neighbouring region on the other side of the interface with a rate \( d_k \) (for species \( k \)), which is related to the macroscopic diffusion coefficient (for species \( k \)), \( D_k \), via

\[
d_k = \frac{D_k}{h^2}.
\]

Here, \( h \) is the width of each auxiliary region, which is assumed to be the same for both the Brownian and PDE auxiliary regions. In order to implement jumps (or reactions, where necessary) according to the RDME, we require particle numbers.

Borrowing terminology from Yates and Flegg (2015), the number of “pseudo-particles” of species \( k \) within the PDE auxiliary region, \( \Omega_{PA} \), at time \( t \), denoted \( N_{PA}^k(t) \), is calculated as

\[
N_{PA}^k(t) = \int_{\Omega_{PA}} c_k(x, t) \, dx.
\]

The number of particles of species \( k \) in the Brownian auxiliary region, \( \Omega_{BA} \), is given by

\[
N_{BA}^k(t) = |\{ j : y_j^k(t) \in \Omega_{BA}\}|.
\]

These particle numbers allow us to define propensity functions corresponding to diffusive jumps between, or reactions within, the auxiliary regions. For diffusive jumps between the two auxiliary regions, the propensity functions for species \( k \) within the PDE and Brownian auxiliary regions are (respectively):

\[
a_k^P(t) = d_k N_{PA}^k(t) \quad \text{for} \quad \Omega_{PA},
\]

\[
a_k^B(t) = d_k N_{BA}^k(t) \quad \text{for} \quad \Omega_{BA}.
\]

When a particle jumps from \( \Omega_{BA} \) to \( \Omega_{PA} \), a particle within the Brownian auxiliary region is chosen uniformly at random to be removed, and a particle’s worth of mass is added to the PDE solution uniformly across \( \Omega_{PA} \) for the species, \( k \), which has changed:

\[
c_k(x, t) = c_k(x, t) + \frac{1}{h} \mathbb{I}_{\{x \in \Omega_{PA}\}}.
\]

Similarly, if a jump is enacted in the opposite direction, from \( \Omega_{PA} \) to \( \Omega_{BA} \), we first remove a particle’s worth of mass uniformly from \( \Omega_{PA} \) for the appropriate species \( k \):

\[
c_k(x, t) = c_k(x, t) - \frac{1}{h} \mathbb{I}_{\{x \in \Omega_{PA}\}},
\]

and a new particle is initialised within the Brownian auxiliary region, \( \Omega_{BA} \), with position chosen uniformly at random.

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\(^5\)Note that there is no requirement for the PDE and Brownian time steps to be the same. In many situations it may be useful to have a significantly finer Brownian time-step than PDE time step in order to accurately resolve the individual-based dynamics. We employ the same time-step in our simulations for simplicity.
3.6 Reaction implementation

Throughout $\Omega$, all reactions are implemented using the reaction operator $f(c)$. The method we employ to implement reactions within $\Omega_B$ depends on the location of the reactant particles. Let $\mathcal{R}$ denote the set of reaction pathways (with $|\mathcal{R}| = R$). Define the subset of reactions $\mathcal{R}^*(t)$ at time $t$ as follows:

$$\mathcal{R}^*(t) = \{\text{all reactions for which at least one set of reactant particles lies exclusively within } \Omega_{BA}\}.$$

Reactions such that at least one of the reactive species lies within $\Omega_B \backslash \Omega_{BA}$ are implemented, in that region, using an appropriate microscopic approach, such as the $\lambda - \rho$ method (Erban and Chapman, 2009; Lipková et al., 2011). However, if at least one set of participating particles lie in $\Omega_{BA}$ (i.e., $r \in \mathcal{R}^*$), care needs to be taken over the interaction of such particles and the mass on the other side of the interface in $\Omega_P$. As explained below we will implement the reactions $r \in \mathcal{R}^*$ for these reactant particles using the compartment-based method.

For illustrative purposes, consider a reversible second-order reaction involving species $A$, $B$ and $C$:

$$A + B \xrightleftharpoons[\kappa_2]{\kappa_1} C. \quad (10)$$

Under the $\lambda - \rho$ method (Erban and Chapman, 2009), for the forward reaction, a particle of species $A$ and a particle of species $B$ are required to be within a distance $\rho$ of one another in order to react. They then react with a rate $\lambda$, where $\lambda$ is a function of both the reaction radius $\rho$ and the reaction rate $\kappa_1$. Imagine that an $A$ particle (without loss of generality) in $\Omega_B$ is close enough to the interface that the reaction radius $\rho$ is larger than the distance between itself and the interface. For consistency with the Brownian representation, the $A$ particle should be allowed to react with a $B$ particle in the PDE region. The implementation of such reactions would be extremely difficult. Instead, by ensuring bimolecular reactions within the auxiliary region are implemented according to the mesoscopic compartment-based method, we avoid such issues.

According to the backwards reaction, two particles are created after the reaction has occurred. These particles are placed a certain distance away from each other (called the dissociation radius) in order to avoid the possibility of geminate recombinations. If this radius intersects with the PDE regime, then there is the potential for individual particles to be initialised within $\Omega_P$. By again employing the mesoscopic representations for reactions we resolve this issue. All product particles are assumed to be placed uniformly throughout the Brownian auxiliary region. Particles that are products of the backwards dissociation reaction in $\Omega_B \backslash \Omega_{BA}$ are extremely unlikely to be placed in $\Omega_P$.

For these reasons, all of the reactions $r \in \mathcal{R}^*$ (for which at least one set of participating particles lie in $\Omega_{BA}$) are implemented using the compartment-based method, in which reactions are incorporated as events in the associated Markov chain, according to the RDME\footnote{Despite the fact that we are presenting our method in generality, for the purposes of this paper, the highest order of reaction we consider is first-order. For such systems, no moment closure assumptions are required in deriving the mean-field reaction-diffusion PDE and hence its behaviour agrees with the mean behaviour of the individual-based models. This allows us to efficiently verify accuracy by comparing the mean behaviour of our hybrid method to the known mean-field behaviour.}. We can write the following propensity functions for reactions within $\Omega_{BA}$:

$$\alpha_r(t) = g_r(N_{BA}(t))\kappa_r h^{1-\nu}, \quad (11)$$

for any reaction channel $r \in \mathcal{R}^*(t)$ of order $\nu$ and corresponding reaction rate $\kappa_r$, where $N_{BA}(t) = (N_{BA}^1(t), ..., N_{BA}^K(t))^T$ and $g_r$ is the appropriate number of possible combinations of the reactants for reaction $r$ from the particles that lie within $\Omega_{BA}$. Recall, however, that in $\Omega_B \backslash \Omega_{BA}$, any such reactions are implemented according to the chosen microscopic reaction method (Doi, 1976; Erban and Chapman, 2009; Lipková et al., 2011; van Zon and ten Wolde, 2005).
3.7 Simulation specifics

The Gillespie SSA (Gillespie, 1977) is used to simulate the above-described reactions in $\Omega_{BA}$, as well as the diffusive fluxes over the interface. The SSA requires the computation of an exponential random variable which gives the time, $\tau$, until the next event, and can be found by transforming a uniform random variable $u_1 \sim \text{Unif}(0, 1)$ via the following equation

$$\tau = \frac{1}{\alpha^0(t)} \ln \left( \frac{1}{u_1} \right). \quad (12)$$

Here, $\alpha^0(t)$ is the sum of all of the propensity functions:

$$\alpha^0(t) = \alpha^0_P(t) + \alpha^0_B(t) + \sum_{r \in R^*} \alpha_r(t), \quad (13)$$

where

$$\alpha^0_P(t) = \sum_{k=1}^{K} \alpha^k_P(t), \quad (14)$$

and

$$\alpha^0_B(t) = \sum_{k=1}^{K} \alpha^k_B(t). \quad (15)$$

The PDE solutions and Brownian dynamics are implemented using the same discrete time-step, $\Delta t$, and the diffusive jumps across the interface (and any required reactions, $r \in R^*$) are implemented in an event-driven manner, according to the Gillespie SSA. Event-driven time-steps are implemented until the putative time for the next event passes the next Brownian/PDE update time, at which point the PDE and Brownian dynamics are updated. Pseudocode for the ARM is given in Algorithm 1.

**Algorithm 1: Auxiliary region method (ARM)**

1a) Initialise time $t = 0$, set final time $T$, PDE/Brownian update time-step, $\Delta t$, the PDE discretisation grid size, $\Delta x$, and the auxiliary region spatial step, $h$. Initialise particles in both $\Omega_P$ and $\Omega_B$ as required. Calculate the time until the next PDE and Brownian update step $t_\Delta = \Delta t$.

1b) Calculate the number of particles $N^k_{PA}$ and $N^k_{BA}$ in the auxiliary regions, for each species $k \in \{1, 2, ..., K\}$, using formulae (4) and (5). Consequently, calculate the corresponding propensity functions, $\alpha^k_P(t)$ and $\alpha^k_B(t)$ as per equations (6) and (7), and their sums according to equations (14) and (15). Calculate $\alpha_r(t)$, for $r \in R^*$, using equation (11) and finally compute $\alpha^0(t)$ according to equation (13).

1c) Calculate the time, $\tau$, until the next auxiliary region event according to equation (12). Update the auxiliary region time $t_a = t + \tau$.

1d) If $t_a < t_\Delta$

   i) Draw two random numbers $u_1, u_2 \sim \text{Unif}(0, 1)$.

   ii) If $u_1 \alpha^0_P(t) < \alpha^0_B(t)$ (Corresponding to a jump from $\Omega_{PA}$ to $\Omega_{BA}$):

      • Use $u_2$ to determine the species, $k$, which the jump affects, with each species selected with probability proportional to its propensity function.
• Remove a particle from the PDE auxiliary region for species $k$ via equation (9).
• Initialise a new particle of species $k$ uniformly within $\Omega_{BA}$.

Else if $u_1\alpha^0(t) < \alpha^0_\nu(t) + \alpha^0_\phi(t)$ (Corresponding to a jump from $\Omega_{BA}$ to $\Omega_{PA}$):
• Use $u_2$ to determine the species, $k$, which the jump affects, with each species selected with probability proportional to its propensity function.
• Choose a particle of species $k$ uniformly at random from within the Brownian auxiliary region and remove it from the system.
• Add a new particle into the PDE auxiliary region for species $k$ via equation (8).

Else (Corresponding to a reaction in $\Omega_{BA}$)
• Use $u_2$ to choose the reaction $r \in \mathcal{R}^*(t)$ to be implemented with probability proportional to its propensity function.
• Update particle numbers (and initialise positions, if appropriate) in the Brownian representation accordingly.

(iii) Set $t = t_a$.

Else

(i) Update the PDE system (1) using an appropriate numerical method (see Section 3.1).
(ii) Update the positions of the Brownian particles according to equation (2).
(iii) Implement any reactions using an appropriate method (see Section 3.1). Note that production reactions should be implemented after any degradation reactions in order to prevent particles being created and destroyed in the same time-step.
(iv) Set $t = t_\Delta$, update $t_\Delta = t + \Delta t$.

(1e) If $t < T$, return to (1b), otherwise stop.

4 Results

Within this section, we present three test problems which are used to demonstrate that the ARM correctly simulates reaction-diffusion systems. Two of these problems are models of pure diffusion with different initial conditions and will demonstrate that the fluxes over the interface are consistent with the expected behaviour of the fully Brownian simulations. The final problem is the formation of a morphogen gradient, which demonstrates the successful implementation of reactions in the ARM.

For each of these test problems, we use $\Omega_{P} = [-1, 0]$ and $\Omega_{B} = [0, 1]$, meaning that the interface is the single point at 0. We take the value of the fixed PDE and Brownian update steps to be $\Delta t = 0.02$, the auxiliary regions have width $h = 0.05$ and the diffusion constant is $D = 0.025$. We will quantify the qualitative comparisons, presented here through density comparison snapshots, in Section 5. All simulations will comprise only a single species, so henceforth, all sub- or super-scripts, $k$, pertaining to species will be removed.

4.1 Test problem 1: maintaining equilibrium

For the first test problem, we simulate pure diffusion in the form of a simple Brownian motion with reflecting boundary conditions, which has Fokker-Planck equation given by the diffusion PDE and corre-
responding boundary conditions:

\[ \frac{\partial p}{\partial t} = D \frac{\partial^2 p}{\partial x^2}; \quad \frac{\partial p}{\partial x} \bigg|_{x=-1,1} = 0. \]  \hspace{1cm} (16)

Note that \( p(x,t) \) here represents the mean-field solution across the whole domain, whereas \( c(x,t) \) represents the PDE solution in \( \Omega_P \) in the hybrid method. We initialise particles uniformly across the computational domain. Figure 5 shows that the ARM passes the most basic test by maintaining the steady state without causing an accumulation of mass on either side of the interface.

4.2 Test problem 2: flux over the interface

The second test problem is a stress test for the interfacial flux. For the PDE part of the hybrid model we solve the same diffusion equation (16) as in Section 4.1. However this time we initialise by placing all particles uniformly within the PDE domain, \( \Omega_P \). The results from this simulation are displayed in Figure 6. As with the uniform initial condition in test problem 1, we see from Figure 6 that the hybrid method agrees with the solution of the mean-field model, indicating that the method simulates flux over the interface accurately. We have also tested our hybrid method with all the mass initialised uniformly across \( \Omega_B \) and found excellent agreement between the hybrid method and the mean-field solution (figures not shown).

4.3 Test problem 3: morphogen gradient

For the final test problem, we investigate the formation of a morphogen gradient from a uniform initial condition. The gradient is formed by allowing particles to diffuse throughout the domain as well as to degrade at a rate \( \mu \). We also have particles entering at the left-hand boundary, \( x = -1 \), at rate \( D \lambda \).

Thus, the PDE half of the hybrid domain is governed by the mean-field model representing the expected behaviour of the fully Brownian dynamics:

\[ \frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - \mu c ; \quad \frac{\partial c}{\partial x} \bigg|_{x=-1} = -\lambda, \quad \frac{\partial c}{\partial x} \bigg|_{x=0} = 0. \]  \hspace{1cm} (17)
Figure 6. The evolution of test problem 2 at times (a) 0, (b) 25 and (c) 100. All figure descriptions and parameter values are the same as in Figure 5.

For the corresponding microscopic dynamics we implement Brownian motion for the diffusion of particles and a time-based method in order to enact the degradation reactions. We note that the production reaction is not implemented within the microscopic domain since it occurs at $x = -1$. 500 particles (the number of particles found at steady state under the parameters given in Figure 7) are initialised uniformly across the domain.

Figure 7. The evolution of test problem 3 at times (a) 0, (b) 25 and (c) 100. The value for the diffusion coefficient is $D = 0.025$, for the production rate is $\lambda = 400$ and for the degradation rate is $\mu = 0.02$. All other figure descriptions and parameter values are the same as Figure 5.

As demonstrated in Figure 7 the solution of the hybrid method matches that of the corresponding mean-field model, as with the previous two test problems.

5 Error analysis

We have seen in Section 4 that the solutions provided by the hybrid method visually match the mean-field solution. Within this section we quantify the difference between the solutions of these test problems. We compare the mass in the PDE and Brownian regions of the domain between the two methods. Separately we compare the density profile across the whole domain using the histogram distance error (HDE). We then proceed to investigate the changing accuracy of the hybrid model as we vary the two free simulation
parameters ($\Delta t$ and $h$) within the method.

5.1 Quantitative comparisons

In order to evaluate the accuracy of the ARM, we compare its mean behaviour (averaged over 1000 repeat simulations) to the mean-field model for which we compute the analytical solution across the entire domain $\Omega$, for each of our test problems. Figure 8 contains nine plots which demonstrate the error for the three test problems above; (a)-(c) are for test problem 1, (d)-(f) are for test problem 2 and (g)-(i) are for test problem 3. The first and second columns show particle number comparisons between the hybrid and analytical solutions. Specifically, in the first column we compare

$$N_{MP}(t) = \int_{-1}^{0} p(x, t)dx,$$

the expected number of particles in $\Omega_P$ in the mean-field model to

$$N_{HP}(t) = \frac{1}{S} \sum_{s=1}^{S} \int_{-1}^{0} c^s(x, t)dx,$$

the expected number of particles in $\Omega_P$ in the hybrid model. Here, as before, $p(x, t)$ represents the mean-field PDE solution at position $x$ at time $t$ and $c^s(x, t)$ represents the PDE part of the solution in the hybrid model for repeat $s$ of $S$. Explicitly, we plot $(N_{HP} - N_{MP})/N_{MP}$, which shows no bias around zero for any of the three test problems.

For completeness, in the second column we also compare

$$N_{MB}(t) = \int_{0}^{1} p(x, t)dx,$$

the expected number of particles in $\Omega_B$ in the mean-field model to

$$N_{HB}(t) = \frac{1}{S} \sum_{s=1}^{S} N_{sHB}(t),$$

the expected number of particles in $\Omega_B$ in the hybrid models. Here, $N_{sHB}(t)$ is the number of particles in the Brownian region of the hybrid method at time $t$ for repeat $s$ of $S$. Explicitly we plot $(N_{HB} - N_{MB})/N_{MB}$, which again shows no bias around zero for any of the three test problems.

The last column contains the histogram distance error (HDE), which is defined by

$$HDE(t) = \frac{1}{2} \left| \sum_{\ell=1}^{L} |c^H_\ell(t) - c^P_\ell(t)| \right|,$$

where $\ell$ indexes a common mesh on which the solutions are compared. $c^H_\ell(t)$ is the normalised solution of the hybrid method at mesh point $\ell$ and time $t$, and $c^P_\ell(t)$ is the normalised solution of the mean-field model at the same common mesh point and time, where

$$\sum_{\ell=1}^{L} c^H_\ell(t) = \sum_{\ell=1}^{L} c^P_\ell(t) = 1 \quad \forall \quad t \geq 0.$$

This ensures a value of the HDE between 0 and 1. Here, 0 means that the two solutions are exactly the same, and 1 corresponds to the two solutions having non-overlapping supports. All figures were produced using the same number of repeats ($S = 1000$).
Figure 8. Error plots for test problems 1 (a)-(c), 2 (d)-(f) and 3 (g)-(i). The first column contains the relative errors \((N_{HP} - N_{MP})/N_{MP}\), while the second column contains the relative errors \((N_{HB} - N_{MB})/N_{MB}\), and the third column contains the HDE comparison using equation (22).

In all cases, the relative errors between the mean-field and hybrid models, in Figure 8, are low with no discernible bias about zero. Similarly, all HDE plots, in Figure 8, are low for the majority of the simulations. This demonstrates numerically that the hybrid scheme presented in this paper is correctly reproducing the behaviour of the Brownian model, at least in the mean-field. These error plots confirm the visual concurrence shown in Figures 5–7.

5.2 Parameter restrictions

Within the method, there are two free parameters that need to be chosen – the width of the auxiliary regions \(h\) and the time-step for the PDE and Brownian updates \(\Delta t\). These need to be chosen so that the
quantity $D\Delta t/h^2$ remains small enough that the particle numbers in the auxiliary regions do not become overly equilibrated between PDE/Brownian update steps. That is to say, if there is a gradient across the interface, $\Delta t$ should be small enough that the closed system of the two auxiliary regions should not reach steady state between PDE/Brownian update steps. In order to demonstrate why $D\Delta t/h^2$ must be small, we consider the evolution of particle numbers in the two auxiliary regions between PDE/Brownian update steps. We form an ODE for particle numbers in one of these boxes (using the fact that particle numbers are conserved between PDE/Brownian updates) assuming particles can only transfer between auxiliary regions.

Let $\nu_0$ be the (constant) number of particles in the two auxiliary regions combined, $M_P(t)$, $M_B(t)$ be the mean number of particles in the PDE and Brownian auxiliary regions respectively at time $t$, and $\mu_P$, $\mu_B$ be the number in the PDE and Brownian auxiliary regions respectively at time 0. Then, the equation for the mean number of particles in the PDE auxiliary region can be calculated from a simple probability master equation as

$$\frac{dM_P}{dt} = dM_B - dM_P = d(\nu_0 - M_P) - d\nu_0 - 2dM_P,$$

where we recall that $d$ is the jumping rate between the two auxiliary regions and is linked to the diffusion constant, $D$, via equation (3). Solving this ODE gives

$$M_P(t) = \frac{1}{2} \left[ \nu_0 - (\nu_0 - 2\mu_P)e^{-2dt} \right]. \quad (23)$$

Assuming a small time-step, $\Delta t$, we can approximate $M_P(\Delta t)$ by Taylor expanding equation (23) to first order:

$$M_P(\Delta t) = M_P(0) + \Delta t M_P'(0) + o(\Delta t)$$

$$\approx \frac{1}{2} [\nu_0 - (\nu_0 - 2\mu_P)] + \frac{\Delta t}{2} [2d(\nu_0 - 2\mu_P)]$$

$$= (1 - 2d\Delta t)\mu_P + d\Delta t \nu_0.$$ 

Fixing the value of $D$ and using equation (3), we find that

$$M_P(\Delta t) \approx \left( 1 - \frac{2D\Delta t}{h^2} \right) \mu_P + \frac{D\Delta t}{h^2} \nu_0.$$ 

We require the change in the number of particles over the small time-step to be small, and so we like $M_P(\Delta t) \approx \mu_P$. Thus we need to choose our parameters such that the quantity $D\Delta t/h^2$ small. This elucidates an important relationships between the fixed and free parameters of the model. If the diffusion coefficient is large then we must choose a small update time-step or a larger auxiliary region length to compensate.

Figure 9 shows that a large region of the $\Delta t - h$ space has a very low histogram distance error, meaning that our method is robust to parameter change, and only breaks down once the value of $D\Delta t/h^2$ becomes very large. The plot also shows that, given any choice of the width, $h$, of the auxiliary regions, there is a value for the time-step, $\Delta t$, which will give a low level of error. The same is true for a given value of $\Delta t$.

### 6 Discussion

We have presented a new spatial hybrid method for coupling a Brownian dynamics representation of a reaction-diffusion system to its corresponding mean-field PDE description. By bridging the gap in spatial scales with intermediate auxiliary regions, we have produced an algorithm that is not only accurate, but
is also robust to the choice of the free parameters within the problem, namely the width of the auxiliary regions, $h$, and the fixed time-step, $\Delta t$ used to update both the PDE and Brownian dynamics. This is in direct contrast to a previously presented PDE-to-Brownian hybrid, which we demonstrated to be extremely parameter-sensitive. In order to make the ARM even more robust, applicable and efficient, we now discuss several areas for possible extension, which will be addressed in future works.

In the interests of completeness we should point out that, as with the pseudo-compartment method of Yates and Flegg (2015), the auxiliary region method requires that the mass in the PDE auxiliary region $\Omega_{PA}$ be sufficient for a step function, corresponding to the mass of a particle, to be removed uniformly from across the auxiliary region. This will lead to difficulties in situations in which particle numbers are low around the interface. Arguably though, we should not employ such hybrid methods in situations for which particle density is low around the interface as the PDE will be a poor model of the true stochastic, microscopic dynamics in these regions. A possible solution to this inconvenience, which could be implemented in this PDE-to-Brownian hybrid method in a straightforward manner, is the incorporation of an adaptive interface. Such interfaces evolve with the particle density, ensuring the appropriate model is employed for the corresponding particle density (Robinson et al., 2014).

A related issue is that of multiple interfaces. Multiple interfaces will allow the efficient simulation of stochastic reaction diffusion systems in which multiple regions of high and low concentration are expected. Such patterns will require interfaces to be dynamic in number and transient in nature. Although we have not implemented such interfaces in this work we expect it to be a relatively straightforward extension. Similarly, although we have only presented the algorithm in a single spatial dimension, we expect the extension to higher dimensions with (hyper-)planar interfaces to be relatively straightforward. Non-planar interfaces and complex domain geometries present deeper challenges that we hope to address in a future publication.

Failing to maintain stochastic variation is a problem which is common amongst many spatial hybrid methods. As a result of the deterministic nature of the PDE, the noise in the Brownian dynamics region of the domain is damped in comparison to the fully microscopic model. In the literature, two approaches
have been used in order to rectify this. The first is an overlap region, which has been employed in several papers (Franz et al., 2013; Harrison and Yates, 2016). These methods introduce a region of space which lies in the intersection of the two domains. In these regions, mass is simultaneously represented using both scales of description. The second is to replace the deterministic PDE with an appropriately chosen stochastic partial differential equation (SPDE). Alexander et al. (2002) consider such a coupling and demonstrate they can indeed fix the discrepancy by using an SPDE as their continuum macro-scale model. We will address both the use of SPDEs and buffer regions (in which the region between the PDE and the Brownian dynamics regions is simulated using a purely compartment-based method) in forthcoming work.

The auxiliary region method provides a simple yet accurate method to couple an individual Brownian dynamics representation of a reaction-diffusion system to a corresponding PDE representation. Our hybrid algorithm will be of particular interest to researchers modelling reaction-diffusion systems whose concentrations vary significantly across the spatial domain. By reducing the computational expense of simulations, the ARM will facilitate the investigation of stochastic effects in such systems, in some cases, making the difference between being able to interrogate the system and not. In particular, we suggest that our method will be useful for the investigation of stochastic Turing patterns (Flegg, 2016), Fisher waves (Breuer et al., 1994, 1995), oscillatory dynamics (Hoffmann and Schwarz, 2014) and excitatory dynamics (Gerisch et al., 2013) with applications in embryogenesis (Mort et al., 2016), intracellular dynamics (Khan et al., 2011) and pattern formation (Flegg, 2016) amongst others. It may also be worthwhile to interface the methods presented here with commonly used Brownian dynamics simulation software packages such as Smoldyn (Andrews and Bray, 2004).

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