The auxiliary region method for coupling Brownian dynamics and PDE representations of reaction-diffusion systems

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Motivation

Reaction-diffusion systems are important tools for the modelling of many biological systems. Formulated in general by Alan Turing in his paper "the chemical basis of morphogenesis" [Turing, 1952], they are useful for modelling **travelling waves, cell migration and pattern formation** amongst many other phenomena. They combine the movement of particles down a concentration gradient (diffusion) with the interaction of particles within the system (reactions).

One such example is that of **piebaldism** in mice. During the embryonic development, melanocytes migrate from the dorsal to the ventral. Piebaldism is the failure of the cells to do this properly, resulting in a white belly spot.

Modelling paradigms

There are **many different ways** to model reaction diffusion systems:
Macro scale: partial differential equations (PDEs) – valid for high copy numbers, can be simulated quickly. Lack stochastic variation.
Meso scale: compartment-based models – include stochastic variation but do not record exact particle locations. Costly to simulate.
Micro scale: individual-based model – positions of all particles are tracked. Diffuse using a Brownian motion, react using any suitable technique, such as the λ-ρ method [Lipková et al., 2011].

Paradigm	Type	Particle numbers	Simulation speed
Macro	Deterministic	High	Fast
Meso	Stochastic	Medium/Low	Medium/Slow
Micro	Stochastic	Low	Slow

Spatial hybrid modelling

The aim of spatial hybrid modelling is to **compliment the strengths** of different representations, whilst **limiting their deficiencies**, by utilising them in different regions of the computational domain.

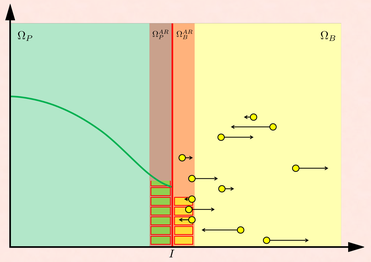
Spatial hybrid models have been extensively studied:

- **[Yates and Flegg, 2015]** (macro → meso) [pseudo-compartment method].
- **[Flegg et al., 2015]** (meso → micro) [ghost cell method].
- **[Franz et al., 2013]** (macro → micro)

However, there is little work on hybrid methods which combine the PDE to the individual-based dynamics.

Auxiliary region method (ARM)

A new method for coupling the PDE and individual-based dynamics for reaction-diffusion systems, using an "auxiliary region" which bridges the gap between the coarsest (PDE) and finest (Brownian) resolutions.



Domain: $\Omega = (0, L)$, split into two disjoint regions Ω_P (PDE) and Ω_B (Brownian).
Interface: Single point $I = \bar{\Omega}_P \cap \bar{\Omega}_B$.
Auxiliary regions: $\Omega_P^{AR} \subseteq \Omega_P$ and $\Omega_B^{AR} \subseteq \Omega_B$, each of width h.

PDE evolution: Second-order finite difference approximation to the PDE $\partial_t u = D\partial_{xx} u + \mathcal{R}(u)$ plus zero-flux boundary conditions.
Brownian position evolution: Update using fixed time-stepping algorithm $X(t + \delta t) = X(t) + \sqrt{2D\delta t}\xi$ with $\xi \sim N(0, 1)$ and reflective boundaries.
Auxiliary region evolution: Use a compartment-based method, simulating using a stochastic simulation algorithm (SSA) such as the Gillespie direct method [Gillespie, 1977].

The **algorithm** proceeds as follows (for any given time):

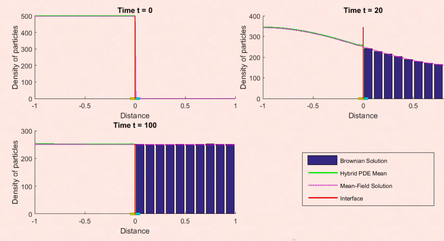
1. **Find the time until the next event within the auxiliary regions occurs.**
2. **If this is less than the time until the next PDE/Brownian update, find the corresponding event and enact it.**
3. **Otherwise, evolve the PDE and Brownian domains.**
4. **Update time and return to step 1.**

Reactions: All reactions in Ω_P and $\Omega_B \backslash \Omega_B^{AR}$ completed using an appropriate method for their regime. Within Ω_B^{AR}, reactions are completed using the compartment-based model.

Results

Results from the algorithm:
Initial condition: All particles on left hand side – demonstrates that the interfacial flux is correct.
What does this show?

- The algorithm matches that of the mean-field model (solution of the PDE) ⇒ Process does not "see" the interface.
- Reaches and maintains the steady state.
- Flux over the interface is correct.



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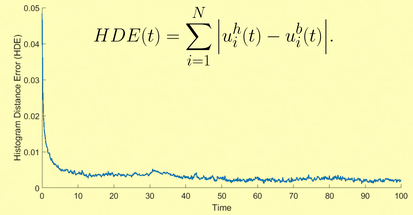
Error analysis

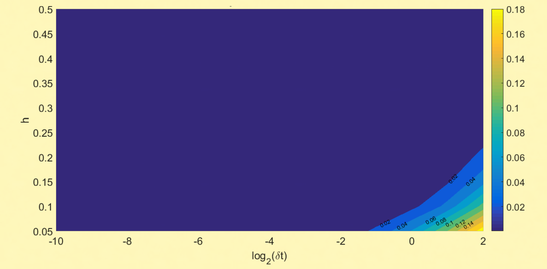
The **histogram distance error (HDE)** is a measurement of how similar the hybrid method is to the equivalent fully Brownian simulation:

$$HDE(t) = \sum_{i=1}^{N} \left| u_i^h(t) - u_i^b(t) \right|.$$



Here, $u_i^h(t)$, $u_i^b(t)$ are the densities of the hybrid and fully Brownian solutions at mesh-point i of the common histogram mesh with N points.

Parameter sensitivity



The error is only large when the value of the width of the auxiliary regions is small and the time step is large. This is due to the **diffusive limit**, which requires the quantity $\delta t/h^2$ to be small.

Conclusions

Created a **hybrid method** which couples a PDE for reaction-diffusion systems to its corresponding individual-based model.
Hybrid method **concurs** with the mean-field solution – the solution to the PDE which arises from forming the Fokker-Planck equation related to the SDE for the Brownian motion.
The **HDE** is low over time ⇒ emphasises the agreement.
The method is relatively **insensitive to parameter choices**.

Future work

Adaptive interfaces – interfaces that move with the density.
SPDEs – Swap the PDE for an SPDE to correct for variance problems.
Growing domain – Add biological realism by allowing the domain to grow.

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