Hybrid modelling for the stochastic simulation of multi-scale chemical kinetics

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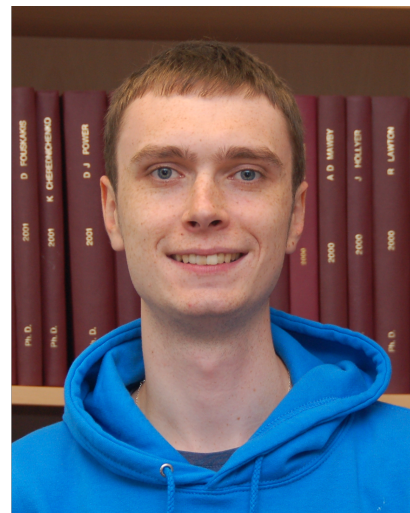
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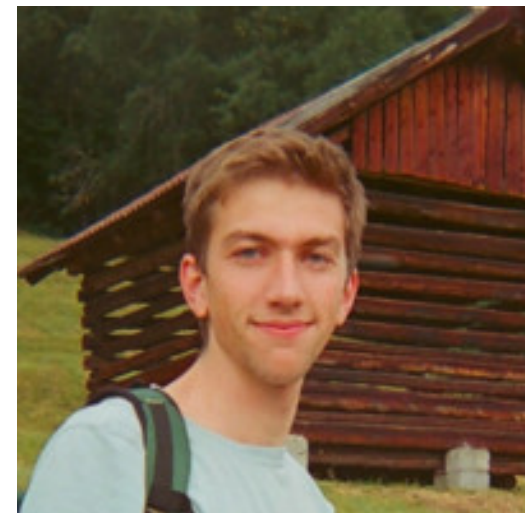
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Outline

1. Introduction
   - Models for non-spatial chemical kinetics
   - Models for spatial chemical kinetics

2. *Blending* the non-spatial models
   - Main idea: Kramers-Moyal expansion
   - Algorithms and numerical experiments
     - ★ Coupling algorithm
   - ★ Lotka Voltera model

3. *Blending* the spatial models
   - Main idea: Splitting methods
   - Conversion of quantities
   - Algorithms and numerical experiments
     - ★ Coupling algorithms
     - ★ Morphogen gradient

4. Conclusion and future work

Non-spatial chemical kinetics

- Chemical events, such as binding and disassociation, occur at random times. This leads to fluctuations in the chemical concentrations.

- Such fluctuations are called *internal* or *intrinsic* noise.

- Intrinsic noise is inherently due to the discrete nature of matter.

- A single reaction will cause the number of molecules to change by one or two. For systems with low number of molecules, such fluctuations can have a significant effect.
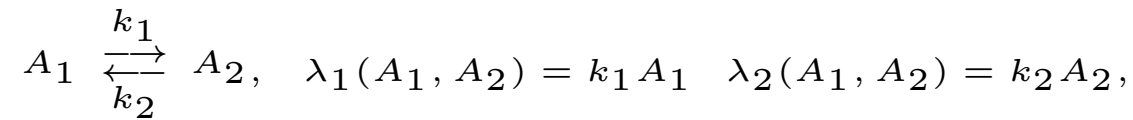
$$A + B \xrightleftharpoons[k_2]{k_1} C$$
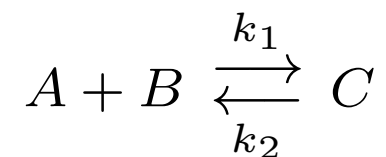
Deterministic Description:

$$\frac{dA}{dt} = k_2 C - k_1 AB$$

Stochastic Description:

- Chemical Master Equation

- Chemical Langevin Equation

Two stochastic descriptions

$$A_1 \; \underset{k_2}{\overset{k_1}{\rightleftarrows}} \; A_2, \quad \lambda_1(A_1, A_2) = k_1 A_1 \quad \lambda_2(A_1, A_2) = k_2 A_2,$$

$$\nu_1 = (-1, 1)^T, \quad \nu_2 = (1, -1)^T$$

Chemical master equation: The probability of the i-th reaction happening in $[t, t + \Delta t]$ is given by $\lambda_i(A_1(t), A_2(t))\Delta t$

$$\frac{dp(x, t)}{dt} = \sum_i^2 \lambda_i(x - \nu_i)p(x - \nu_i, t)$$
$$- \sum_{i=1}^2 \lambda_i(x)p(x, t), \quad x = (A_1, A_2)$$

How to simulate this?

- Let $\lambda_0 = \sum_{r=1}^R \lambda_r(X(t))$.

- Sample $\tau \sim -\log(u)/\lambda_0$, where $u \sim U[0, 1]$.

- Choose the next reaction r_j with probability $\lambda_r(X(t))/\lambda_0$, where $r = 1, \dots, R$.

- $X(t + \tau) = X(t) + \nu_r$.

Chemical Langevin equation: Here number of molecules are still behaving in a stochastic way but change continuously according to the following SDE

$$\frac{dA_1}{dt} = (-k_1 A_1 + k_2 A_2)dt + \sqrt{k_1 A_1 + k_2 A_2}\, dW$$
$$\frac{dA_2}{dt} = (k_1 A_1 - k_2 A_2)dt - \sqrt{k_1 A_1 + k_2 A_2}\, dW$$

How to simulate this? Simplest way is to use the Euler-Maruyama method

$$A_1(t + \tau) = A_1(t) + (-k_1 A_1(t) + k_2 A_2(t))\tau$$
$$+ \sqrt{\tau(k_1 A_1(t) + k_2 A_2(t)}\xi$$
$$A_2(t + \tau) = A_1(t) + (k_1 A_1(t) - k_2 A_2(t))\tau$$
$$- \sqrt{\tau(k_1 A_1(t) + k_2 A_2(t)}\xi, \xi \sim \mathcal{N}(0, 1)$$

Theoretical/Computational Issues

Chemical Master equation:

- exact

However

- computationally expensive when copy numbers are high

Chemical Langevin Equation

- speed independent of copy numbers (you just need to choose τ sensibly)

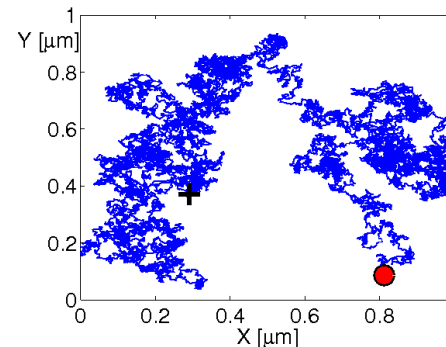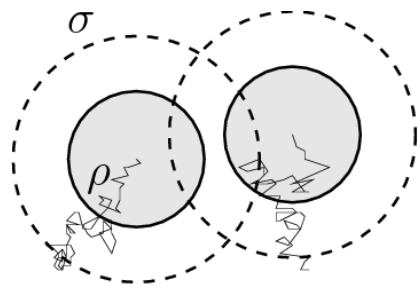- working with a stochastic differential equation which in some sense is easier to manipulate/analyse

However

- Not a good approximation for small copy numbers

- Solution might actually become negative (unphysical)

Question: Can we get best of both worlds?
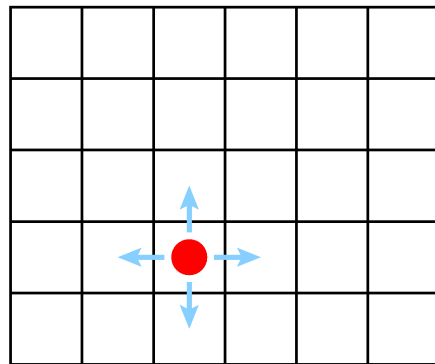
Spatial chemical kinetics

- Brownian dynamics *(microscopic description)*

$$X(t + \Delta t) = X(t) + \sqrt{2\Delta t}\xi_x,$$
$$Y(t + \Delta t) = Y(t) + \sqrt{2\Delta t}\xi_y$$

- Reaction-diffusion master equation *(mesoscopic description)*

each box spatially homogeneous

$$X_{i,j} \underset{D/h^2}{\overset{D/h^2}{\rightleftharpoons}} X_{i,j+1}, \quad X_{i,j} \underset{D/h^2}{\overset{D/h^2}{\rightleftharpoons}} X_{i,j-1}$$

$$X_{i,j} \underset{D/h^2}{\overset{D/h^2}{\rightleftharpoons}} X_{i+1,j}, \quad X_{i,j} \underset{D/h^2}{\overset{D/h^2}{\rightleftharpoons}} X_{i-1,j}$$

- Reaction-diffusion partial differential equation *(macroscopic description)*

$$\frac{\partial c}{\partial t} = \nabla \cdot (D\nabla c) + R(c)$$

Similarly to the non-spatial case: How can we combine different descriptions in a multi-scale system?

Blending the non-spatial models

Main idea (*non-spatial model*)

Now consider $\tilde{\beta}(x) = 1 - \beta(x)$ and the CME can be written as

$$\frac{dp(x,t)}{dt} = \sum_{k=1}^{R} \lambda_k(x - \nu_k)\beta(x - \nu_k)p(x - \nu_k, t) - \sum_{k=1}^{m} \lambda_k(x)\beta(x)p(x,t)$$

$$+ \sum_{k=1}^{m} \lambda_k(x - \nu_k)\tilde{\beta}(x - \nu_k)p(x - \nu_k, t) - \sum_{k=1}^{R} \lambda_k(x)\tilde{\beta}(x)p(x,t)$$

Perform Kramers-Moyal expansion for the terms containing $\tilde{\beta}(x)$

$$\frac{dp(x,t)}{dt} = \sum_{k=1}^{R} \lambda_k(x - \nu_k)\beta(x - \nu_k)p(x - \nu_k, t) - \sum_{k=1}^{R} \lambda_k(x)\beta(x)p(x,t)$$

$$+ \nabla \cdot \left(-\tilde{D}_1(x)p(x,t) + \frac{1}{2}\nabla \cdot \left(\tilde{D}_2(x)p(x,t) \right) \right),$$

where

$$\tilde{D}_1(\mathbf{x}) = \sum_{k=1}^{R} \tilde{\beta}(x)\tilde{\lambda}_k(\mathbf{x})\nu_k \quad \text{and} \quad \tilde{D}_2(\mathbf{x}) = \sum_{k=1}^{R} \tilde{\beta}(x)\tilde{\lambda}_k(\mathbf{x})\nu_k \otimes \nu_k.$$

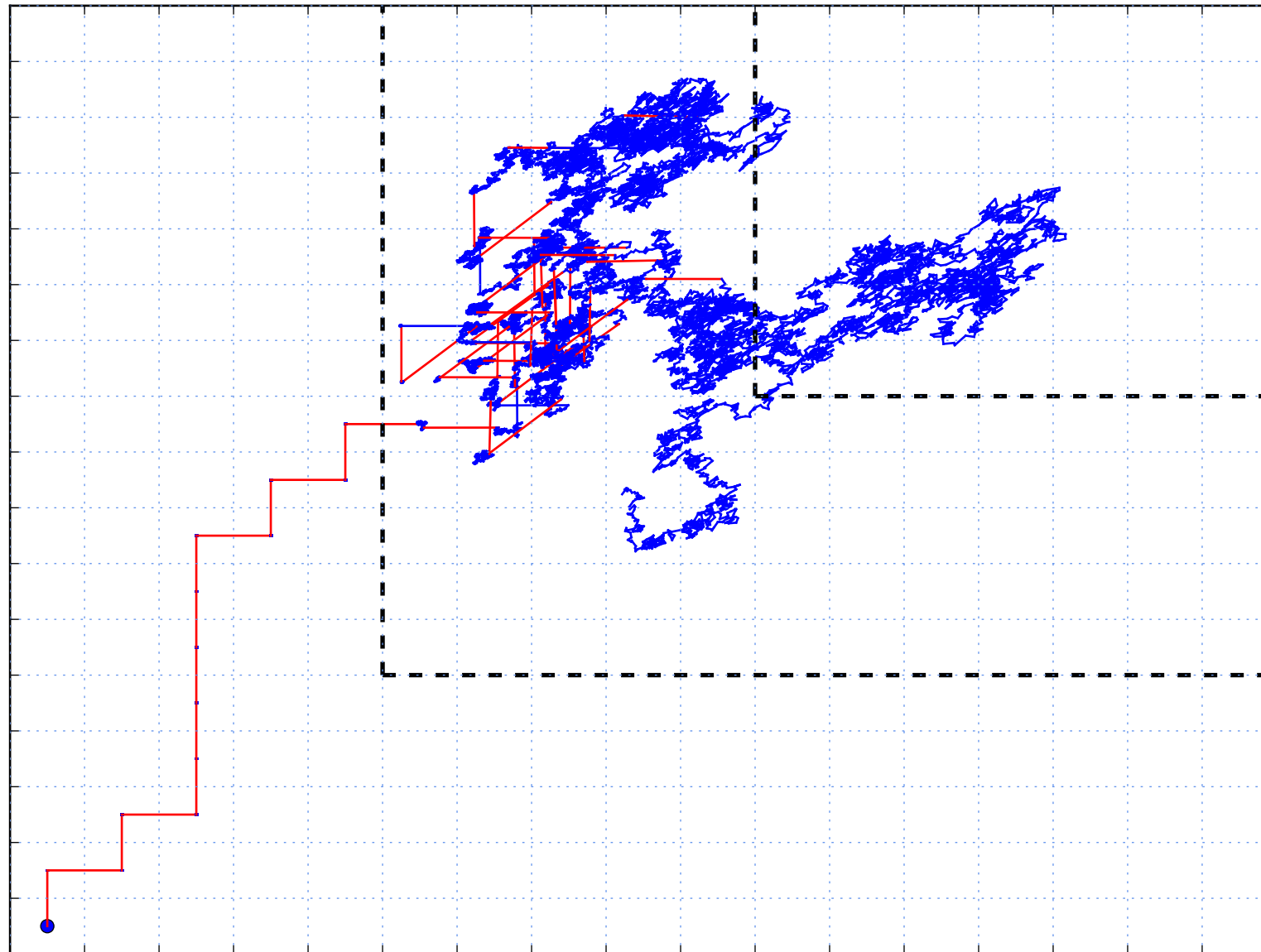# Main idea II

One can introduce more than one blending regions

$$\lambda_j(x) = \beta_j(x)\lambda_j(x) + (1 - \beta_j(x))\lambda_j(x)$$

to obtain in the general case

$$
\begin{aligned}
Z(t) &= Z(0) + \sum_{j=1}^{R} \nu_j \int_0^t (1 - \beta_j(Z(s)))\tilde{\lambda}_j(Z(s))\,ds \\
&+ \sum_{j=1}^{R} \int_0^t \nu_j \sqrt{(1 - \beta_j(Z(s)))\tilde{\lambda}(Z(s))}\,dW_j(s) + \sum_{j=1}^{M} P_j \left(\int_0^t \beta_j(Z(s))\tilde{\lambda}_j([Z(s)]) \right) \nu_j,
\end{aligned}
$$

But how does a typical path of this jump-diffusion looks like?

Hybrid Model: Typical trajectory

A theorem

We introduce the volume V and consider

$$\epsilon = V^{-1}, \quad X(t) = \frac{1}{\epsilon}X^{\epsilon}(t), \quad Z(t) = \frac{1}{\epsilon}Z^{\epsilon}(t)$$

and making the usual assumptions about how the rescaled propensity functions behave we have the following theorem

Theorem 1. *Let $g \in C^3(\mathbb{R}^N)$, then there exists a constant $C > 0$, independent of ϵ, such that*

$$|\mathbb{E}_x\left[g(X^{\epsilon}(t))\right] - \mathbb{E}_x\left[g(Z^{\epsilon}(t))\right]| \leq C\epsilon^2, \quad t \in [0, T],$$

where $X^{\epsilon}(0) = Z^{\epsilon}(0) = x \in \epsilon\Omega_0$.

Non spatial models: Algorithms and numerical experiments

Non-spatial blending algorithm

Set $t = 0$
while $t < T$ **do**
    if $\max_j \beta_j(\mathbf{X}(t)) = 0$ **then**
        Simulate Chemical Langevin up to time $t + \delta t$.
        Set $t = t + \delta t$.
    else if $\min_j \beta_j(\mathbf{X}(t)) = 1$ **then**
        Compute $\lambda_0 = \sum_{j=1}^{R} \lambda'_j(\mathbf{X}(t))$.
        Sample $\tau \sim -\log(u)/\lambda_0$ where $u \sim U[0, 1]$.
        Choose the next reaction r with probability $\lambda'_r(\mathbf{X}(t))/\lambda_0$.
        Set $\mathbf{X}(t + \tau) = \mathbf{X}(t) + \boldsymbol{\nu}_r$.
        Set $t = t + \tau$.
    else

        Compute $\lambda'_0 = \sum_{j=1}^{R} \lambda'_j(\mathbf{X}(t))$.
        Sample $\tau \sim -\log u/\lambda'_0$, where $u \sim U[0, 1]$.
        Choose the next reaction r with probability $\lambda'_r(\mathbf{X}(t))/\lambda'_0$.
        if $\tau < \Delta t$ **then**
            Simulate Chemical Langevin up to time $t + \tau$ and set $\mathbf{X}(t + \tau) = \mathbf{X}(t + \tau) + \boldsymbol{\nu}_r$.
            Set $t = t + \tau$.
        else
            Simulate Chemical Langevin up to time $t + \Delta t$.
            Set $t = t + \Delta t$.
        end
end

Lotka-Voltera

$$A \xrightarrow{k_1} 2A, \qquad A + B \xrightarrow{k_2} 2B \qquad B \xrightarrow{k_3} \emptyset.$$
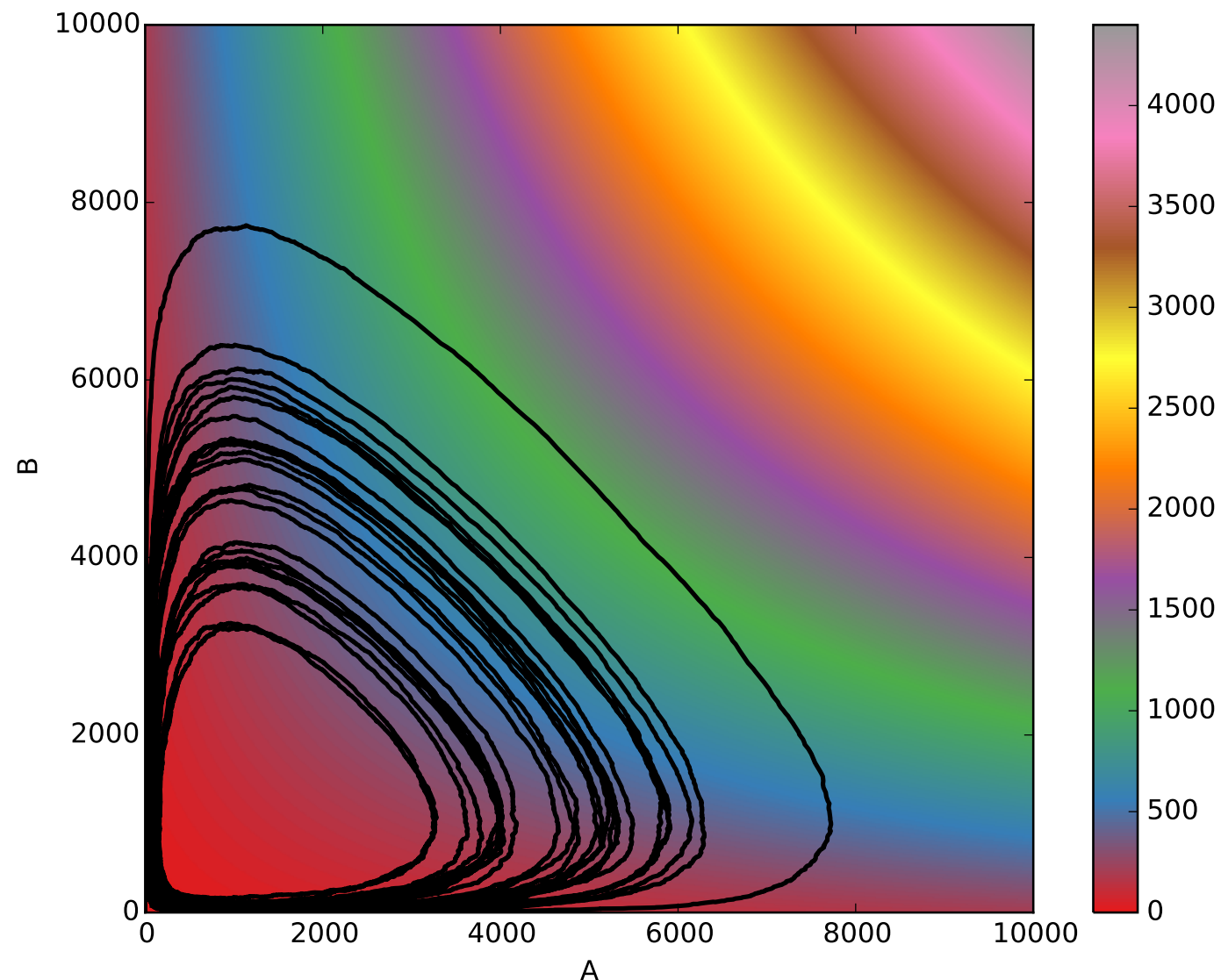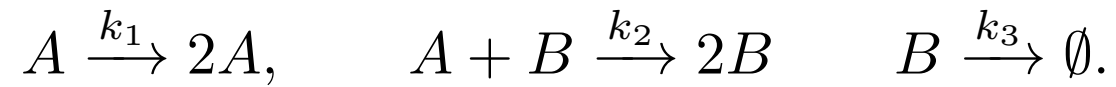

Figure: Line depicts the trajectory of a single realisation in phase–space. The heatmap indicates the average number of chemical reactions which take place within a timestep of $\Delta t = 10^{-2}$ at a given state.
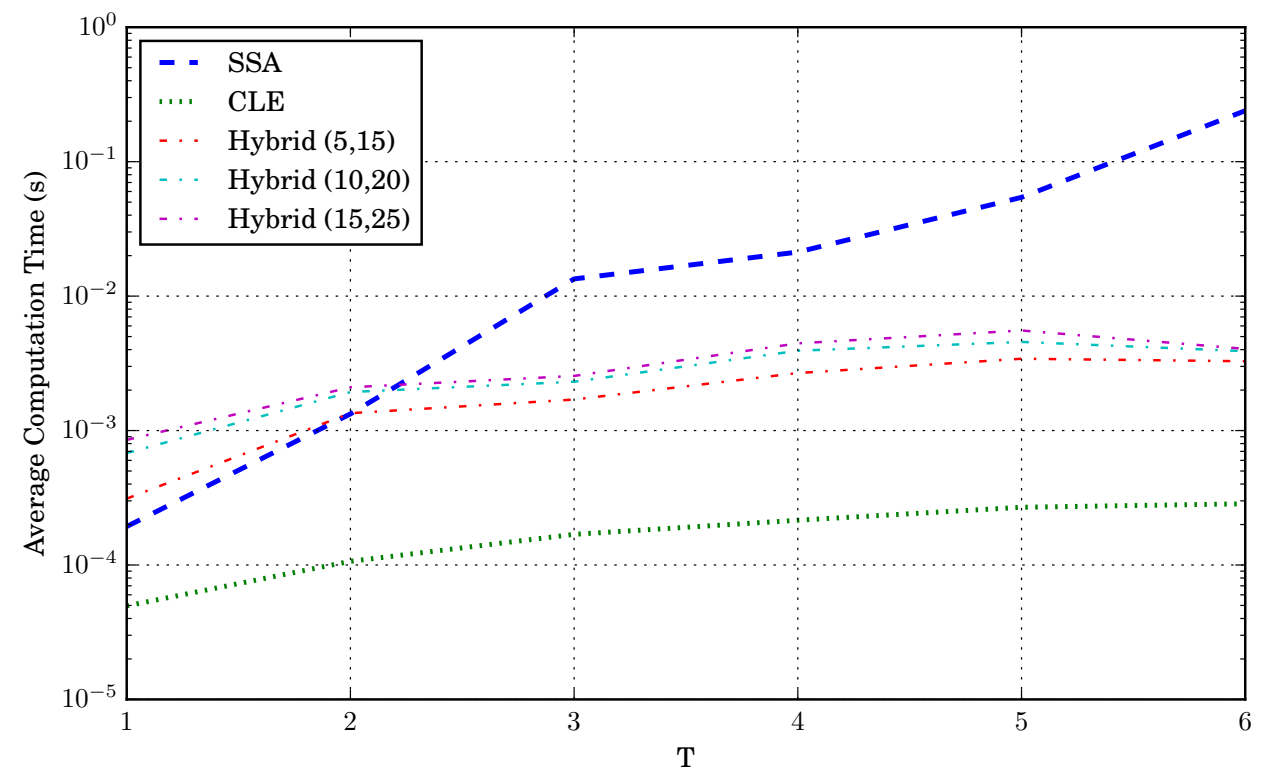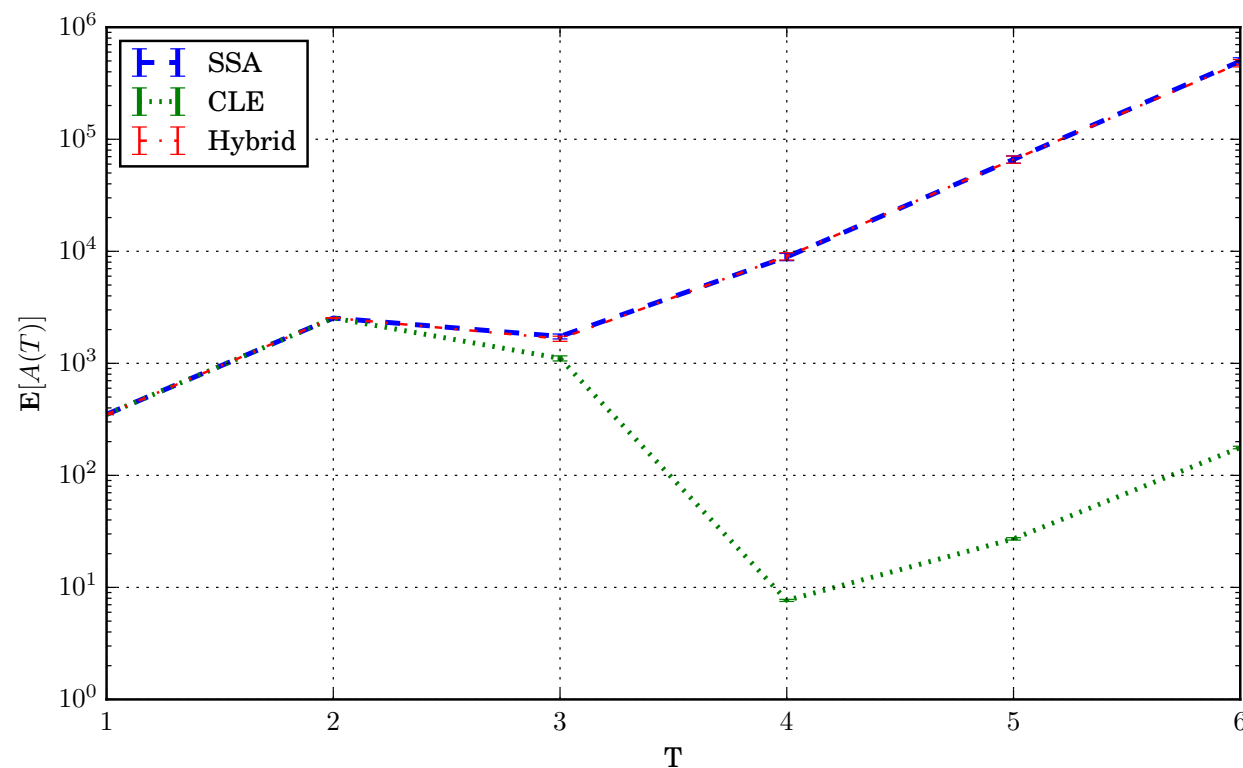
Average behaviour/computational cost

Figure: (a) *Plots of $\mathbb{E}(A(T))$ as a function of T for the SSA, CLE and hybrid schemes; (b) the corresponding average computational (CPU) time in seconds as a function of T.*

Blending the spatial models

Revisiting simple diffusion PDE

Consider the following PDE on $\Omega = [a, b]$

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial x}\right), \quad D\frac{\partial c}{\partial x}\bigg|_{x=a} = D\frac{\partial c}{\partial x}\bigg|_{x=b} = 0.$$

We will break the domain, Ω, into three subdomains $\Omega_1 = [a, I_1]$, $\Omega_2 = [I_1, I_2]$, $\Omega_3 = [I_2, b]$ and write the constant diffusion coefficient $D = D_1(x) + D_2(x)$ where

$$D_1(x) = \begin{cases} D, & a \le x < I_1, \\ f_1(x), & I_1 \le x < I_2, \\ 0, & I_2 \le x < b, \end{cases} \quad D_2(x) = \begin{cases} 0, & a \le x < I_1, \\ f_2(x), & I_1 \le x < I_2, \\ D, & I_2 \le x < b, \end{cases}$$

with $f_1(I_1) = f_2(I_2) = D$ and $f_1(I_2) = f_2(I_1) = 0$

Splitting into two parts

$$\frac{\partial c}{\partial t} = \underbrace{\frac{\partial}{\partial x}\left(D_1(x)\frac{\partial c}{\partial x}\right)}_{1} + \underbrace{\frac{\partial}{\partial x}\left(D_2(x)\frac{\partial c}{\partial x}\right)}_{2},$$

with corresponding boundary conditions

$$(D_1(x)+D_2(x))\frac{\partial c}{\partial x}\bigg|_{x=a} = D\frac{\partial c}{\partial x}\bigg|_{x=a} = 0 \quad \text{and} \quad (D_1(x)+D_2(x))\frac{\partial c}{\partial x}\bigg|_{x=b} = D\frac{\partial c}{\partial x}\bigg|_{x=b} = 0,$$

We can thus consider two PDEs

$$\frac{\partial c^1}{\partial t} = \frac{\partial}{\partial x}\left(D_1(x)\frac{\partial c^1}{\partial x}\right), \quad D_1(a)\frac{\partial c^1}{\partial x}\bigg|_{x=a} = D_1(I_2)\frac{\partial c^1}{\partial x}\bigg|_{x=I_1} = 0$$

$$\frac{\partial c^2}{\partial t} = \frac{\partial}{\partial x}\left(D_1(x)\frac{\partial c^2}{\partial x}\right), \quad D_2(I_2)\frac{\partial c^2}{\partial x}\bigg|_{x=I_2} = D_2(b)\frac{\partial c^2}{\partial x}\bigg|_{x=b} = 0$$
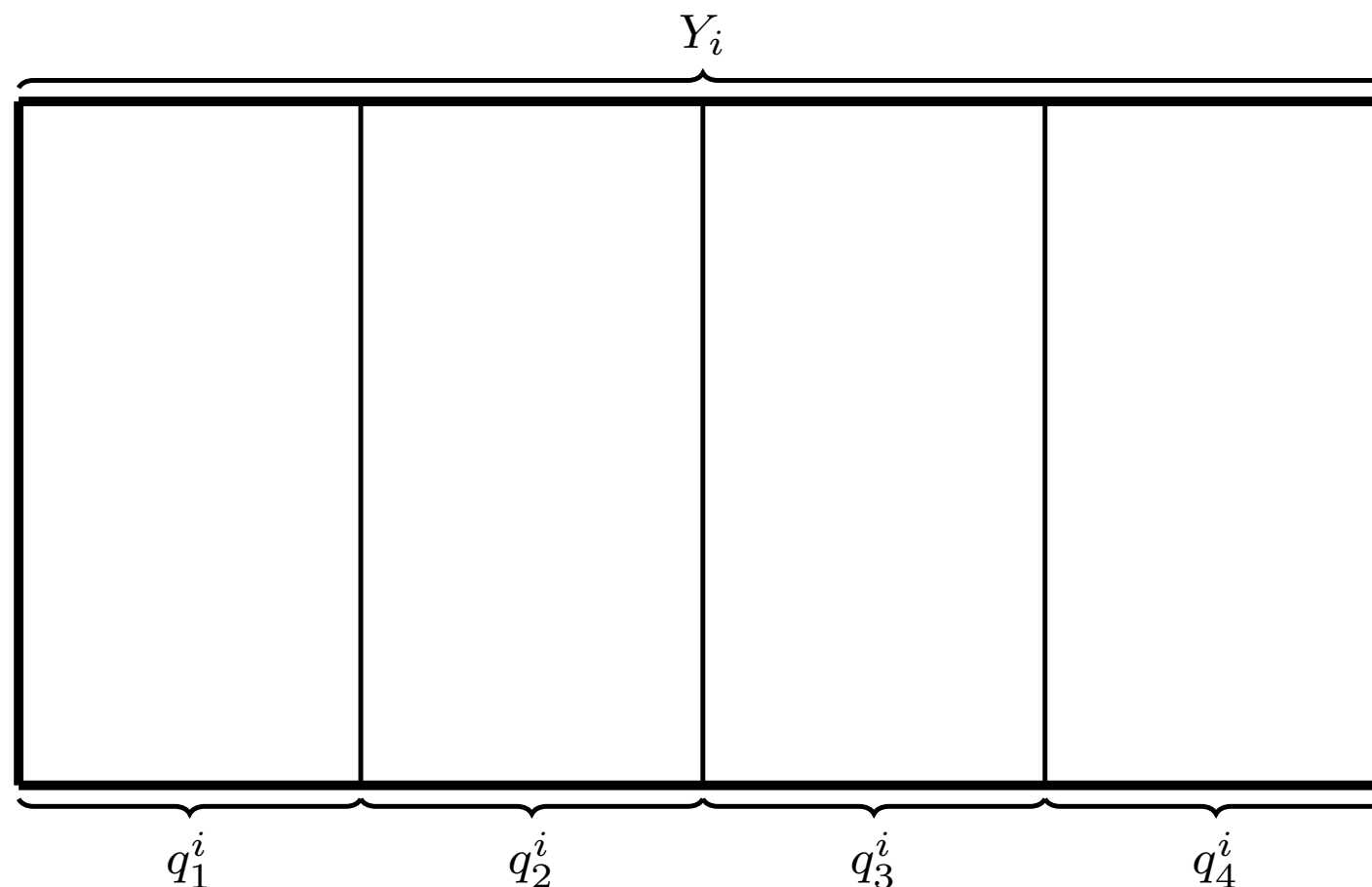
Main idea: splitting methods

We now have
$$c(x, \tau) \approx \phi_\tau^1(\phi_\tau^2(c_0(x))).$$

By allowing the flow maps ϕ_τ^1 and ϕ_τ^2 to represent propagation operators for two different model types it will allows us to seamlessly blend the different modelling regimes.

Only thing that we have to worry about is how to convert between different regimes in the blending region

Spatial models: algorithms and numerical experiments

Coupling PDE to compartments

Input: PDE mesh size – Δx; compartment size – h; time-step for the solution of the PDE – Δt; left and right ends of the blending region – I_1, I_2 ; initial concentration for the PDE – c_{init} ; initial particle numbers – C_{init} ; final time – T.
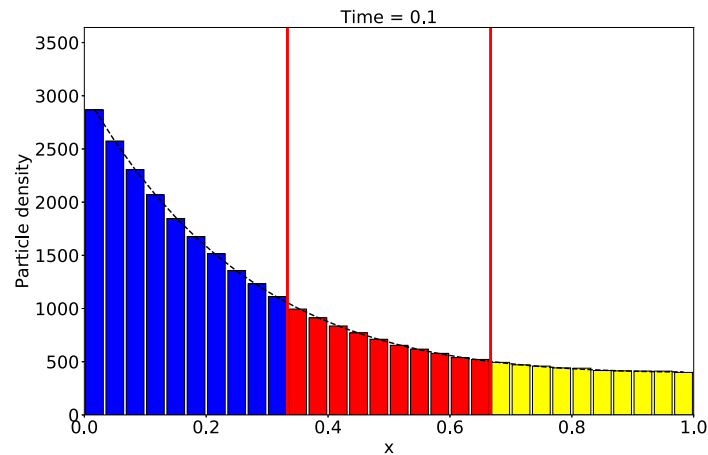
1 Set $t = 0$.

2 **while** $t < T$ **do**

3 Simulate the partial differential equation in $[a, I_1]$ between t and $t + \Delta t$ for diffusion coefficient given by D_1 using an appropriate numerical solver.

4 Update the particle numbers in $[I_1, I_2]$

5 Simulate the compartment-based approach in $[I_1, b]$ between t and $t + \Delta t$ for diffusion coefficient given by D_2 using an appropriate stochastic simulation algorithm, taking as an initial condition the updated particle numbers from line 4.

6 Update the PDE solution in $[I_1, I_2]$,

7 Set $t = t + \Delta t$.

8 **end**

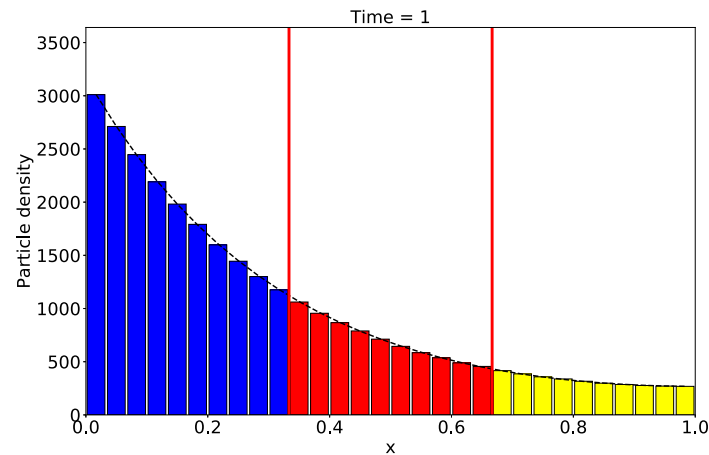# Coupling compartments to individual particles

Input: Compartment size – h; time-step for the solution update of the Brownian dynamics – Δt; left and right ends of the blending region – I_1, I_2; initial particle numbers – C_{init} ; initial Brownian particle positions – y; final time – T.

1 Set $t = 0$.

2 **while** $t < T$ **do**

3   Simulate the compartment-based approach in $[a, I_2]$ between t and $t + \Delta t$ for diffusion coefficient given by D_1 using an appropriate stochastic simulation algorithm.

4   Update the Brownian particle positions in $[I_1, I_2]$.

5   Simulate the Brownian particle dynamics in $[I_1, b]$ between t and $t + \Delta t$ for diffusion coefficient given by D_2.

6   Update the compartment-based particle numbers in $[I_1, I_2]$.
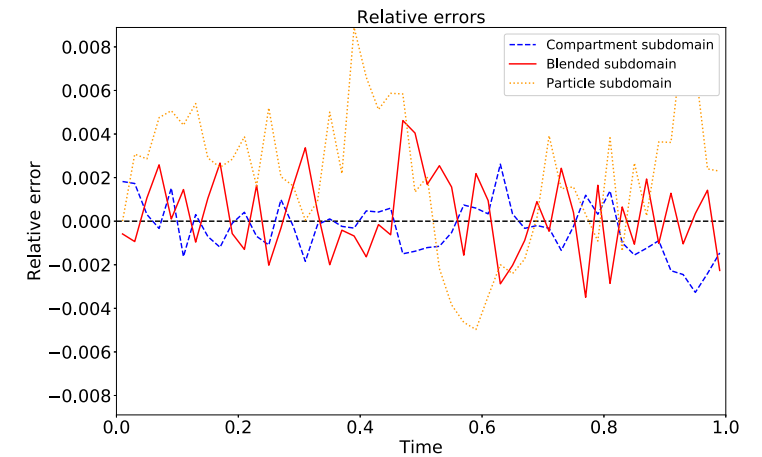
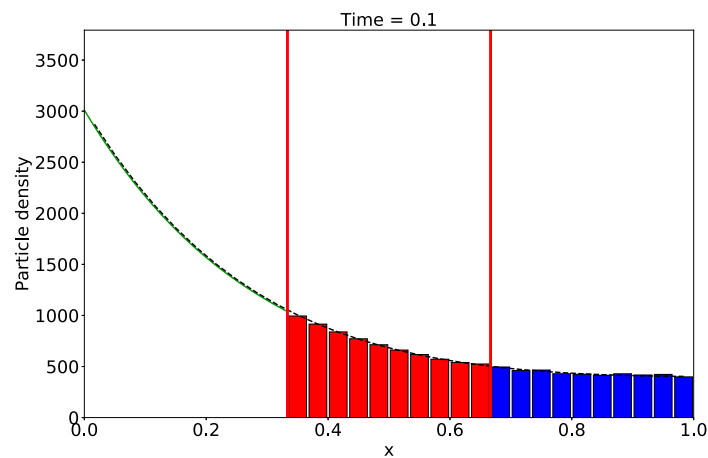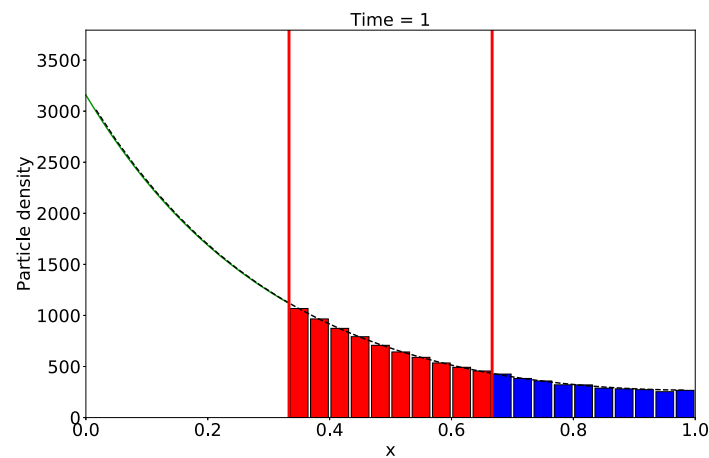7   Set $t = t + \Delta t$.

8 **end**
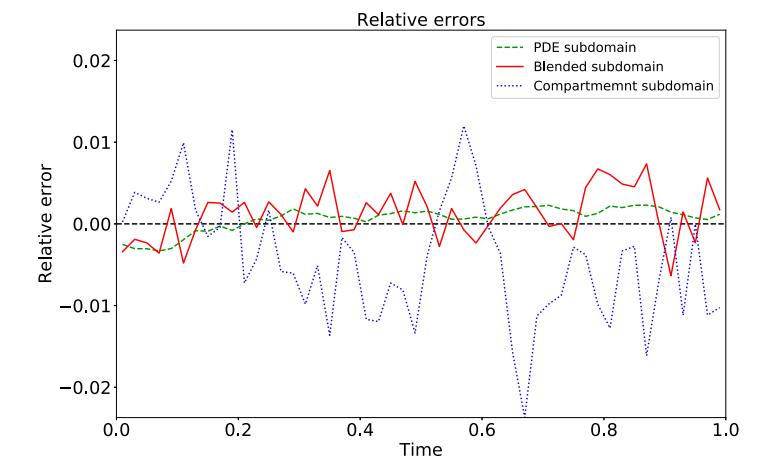
Morphogen gradient

(a)

(b)

(c)

(d)

(e)

(f)

PDE : $\dfrac{\partial c}{\partial t} = D\dfrac{\partial^2 c}{\partial x^2} - \mu c;\quad x \in (-1, 0);\quad t \in (0, T),$

BCs : $\dfrac{\partial c}{\partial x}(0, t) = -\lambda;\quad \dfrac{\partial c}{\partial x}(1, t) = 0;\quad t \in (0, T),$

IC : $c(x, 0) = c_0;\quad x \in [0, 1].$

Conclusions and future work

Conclusions

1. Non-spatial models
   - We have defined a very simple procedure that provides good approximation to the CME
   - Hybrid scheme doesn't require apriori knowledge of *fast* and *slow* species.
   - The hybrid model does not have the pitfalls associated with the CLE

2. Spatial models
   - Extended the idea from non-spatial models to spatial ones
   - Scheme can be understood as a splitting method
   - The blending area doesn't introduce any visible bias

Future work

1. Non spatial models
   - Extend the model to include a reaction rate regime
   - Use our simulation to perform Bayesian inference for unknown parameters

2. Spatial model
   - Allow for moving blending areas
   - Simulate more complicated multi scale systems such as calcium puff dynamics

Thank you for your time