Computationally efficient simulation of cells that release diffusing compounds in their environment

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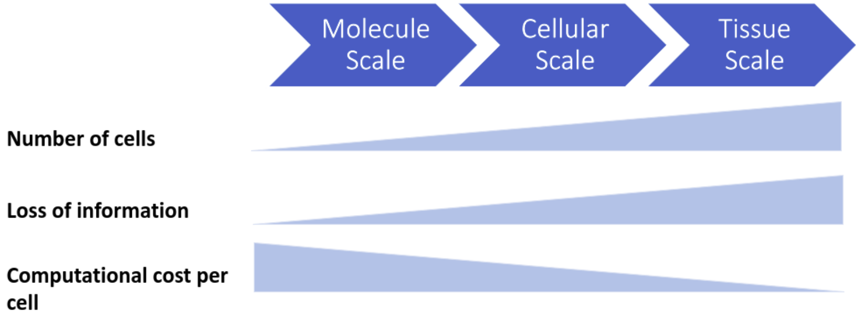
Motivations and Issues

Same long-term goal: to apply the model in clinical practice

- "Useful" and realistic model
- Computationally efficient
- Physically and mathematically *almost* correct



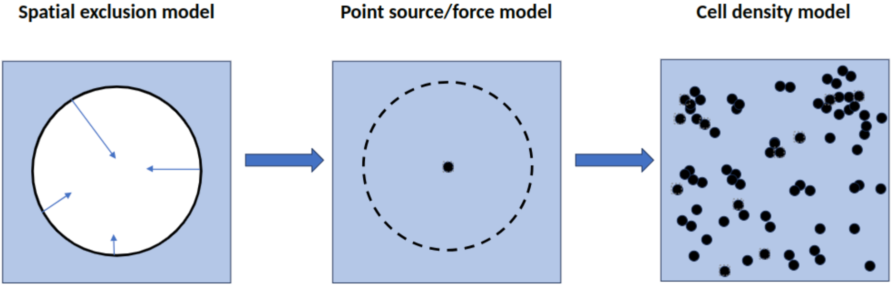
Wound Contraction and Cancer Cell Metastasis Model

Wound contraction
(C++, ~ 4000 cells, ~ 30 min)

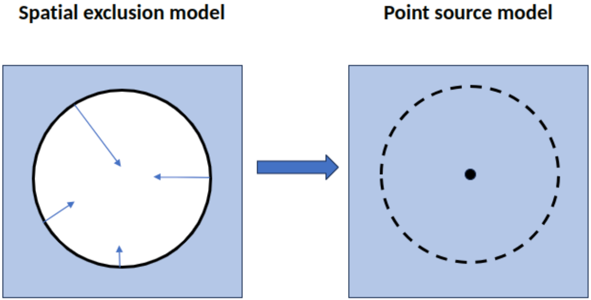
Cancer cell metastasis and invasion
(Python-Fenics, 3 cells, ~ 30 min/ cell)

Approaches to Improve the Computational Efficiency

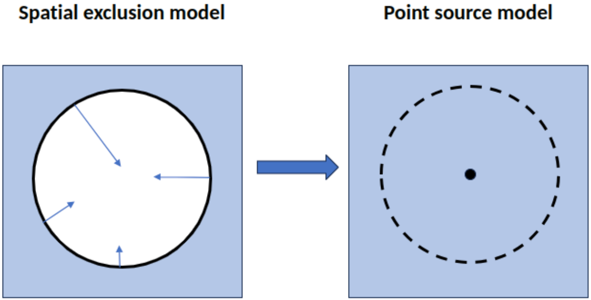
- **Computational perspective:** Neural Network (NN) approach
- **Mathematical perspective:** Upscaling the PDEs from microscale to (semi-)macroscale



Point Source in Diffusion Equation



Point Source in Diffusion Equation



Dirac delta distribution

$$< \delta, f >= f(\mathbf{0}), \text{ if } f \in C^{\infty}(\mathbb{R}^n)$$

$\Longleftrightarrow$

$$\int_{\Omega \ni \boldsymbol{x}_0} f(\boldsymbol{x}) \delta(\boldsymbol{x} - \boldsymbol{x}_0) d\Omega = f(\boldsymbol{x}_0)$$

Spatial exclusion and point source model

Spatial exclusion model

$$
(\mathrm{BVP_S})\begin{cases}
\dfrac{\partial u_S(\boldsymbol{x},t)}{\partial t} - D\Delta u_S(\boldsymbol{x},t) = 0, & \text{in } \Omega\backslash\bar{\Omega}_C, t>0,\\
-D\nabla u_S(\boldsymbol{x},t)\cdot\boldsymbol{n} = \phi(\boldsymbol{x},t), & \text{on } \partial\Omega_C, t>0,\\
D\nabla u_S(\boldsymbol{x},t)\cdot\boldsymbol{n} = 0, & \text{on } \partial\Omega, t>0,\\
u_S(\boldsymbol{x},0) = u_0(\boldsymbol{x}), & \text{in } \Omega\backslash\bar{\Omega}_C, t=0,
\end{cases}
$$

Point source model

$$
(\mathrm{BVP_P})\begin{cases}
\dfrac{\partial u_P(\boldsymbol{x},t)}{\partial t} - D\Delta u_P(\boldsymbol{x},t) = \Phi(\boldsymbol{x},t)\delta(\boldsymbol{x}-\boldsymbol{x}_c), & \text{in } \Omega, t>0,\\
D\nabla u_P\cdot\boldsymbol{n} = 0, & \text{on } \partial\Omega, t>0,\\
u_P(\boldsymbol{x},0) = \bar{u}_0(\boldsymbol{x}), & \text{in } \Omega, t=0.
\end{cases}
$$

Consistency between two models

Proposition

Denote by $u_S(\boldsymbol{x}, t)$ and $u_P(\boldsymbol{x}, t)$ the weak solutions to the spatial exclusion model (BVP_S) and the point source model (BVP_P), respectively, and let $\partial\Omega_C$ be the boundary of the cells, from which the compounds are released, with normal vector $\boldsymbol{n}$ pointing into Ω_C. Then

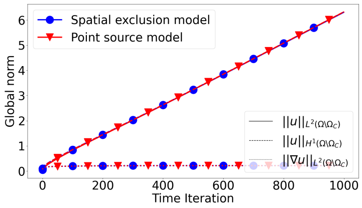
$$\frac{1}{2}\frac{d}{dt}\left\|u_S - u_P\right\|^2_{L^2(\Omega\setminus\Omega_C)} = -D\int_{\Omega\setminus\Omega_C}\left|\nabla(u_S - u_P)\right|^2 d\Omega + \int_{\partial\Omega_C}(u_s - u_P)(\phi - D\nabla u_P\cdot\boldsymbol{n})\, d\Gamma. \tag{1}$$

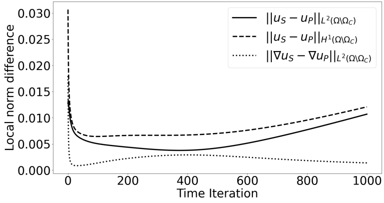
Assume moreover, that $u_S(\cdot, 0) = u_P(\cdot, 0)$ a.e. on $\Omega\setminus\Omega_C$. Then, $u_S(\boldsymbol{x}, t) = u_P(\boldsymbol{x}, t)$ a.e. in $\Omega\setminus\bar{\Omega}_C\times[0,\infty)$ if and only if

$$\boxed{\phi(\boldsymbol{x}, t) - D\nabla u_P(\boldsymbol{x}, t)\cdot\boldsymbol{n} = 0, \qquad \text{a.e. on } \partial\Omega_C\times[0,\infty).}$$

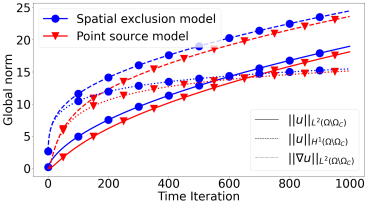
Homogeneous flux density: $\Phi = \int_{\partial\Omega_C} \phi \, d\Gamma = 2\pi R\phi$, $\phi = 1$

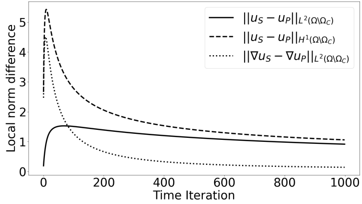
$D = 10$





$D = 0.1$





A systematic time delay between the solutions.

Gaussian-shaped initial conditions

- Fundamental solution of the diffusion equation is given by

$$P_t^D(\boldsymbol{x}, \boldsymbol{x}_c) = \begin{cases} \frac{1}{(4\pi D t)^{d/2}} \exp\left\{ -\frac{\|\boldsymbol{x} - \boldsymbol{x}_c\|^2}{4Dt} \right\}, & t > 0, \boldsymbol{x} \in \mathbb{R}^n, \\ 0, & t < 0, \boldsymbol{x} \in \mathbb{R}^n, \end{cases}$$

- We assume that the initial condition in the point source model is

$$\bar{u}_0(\boldsymbol{x}) = \begin{cases} p_0 P_{t_0}^D(\boldsymbol{x}, \boldsymbol{x}_c), & \boldsymbol{x} \in \bar{\Omega}_C, \\ 0, & \boldsymbol{x} \in \Omega \backslash \bar{\Omega}_C, \end{cases}$$

where $p_0, t_0 > 0$ determine the amplitude and the variance of the Gaussian kernel.

Gaussian-shaped initial condition helps

Flux over the cell boundary in the point source model

- Flux produced by the **Gaussian initial condition**:

$$\phi_1(R,t) = \frac{p_0 R}{2(t+t_0)} P^D_{t+t_0}(R).$$

- Flux produced by the **point source**:

$$\phi_2(R,t) = \frac{\Phi(\boldsymbol{x}_c)}{2\pi R} \exp\left\{-\frac{R^2}{4Dt}\right\}.$$

$$\begin{aligned}\Rightarrow \phi(\boldsymbol{x},t) \approx -D\nabla u_P \boldsymbol{n} := \phi_{sum} &= \phi_1(R,t) + \phi_2(R,t) \\ &= \frac{p_0 R}{2(t+t_0)} P^D_{t+t_0}(R) + \frac{\Phi(\boldsymbol{x}_c)}{2\pi R} \exp\left\{-\frac{R^2}{4Dt}\right\}.\end{aligned}$$

Let $t = 0$, then

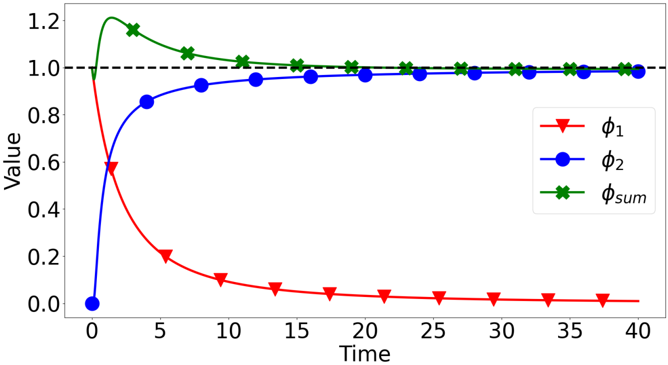
$$p_0(t_0) \approx \frac{2t_0 \phi(\boldsymbol{x},t)}{R P^D_{t_0}(R)}.$$

Various Options to select (p_0, t_0) (I/III)

Recall the important equation in Proposition:

$$\phi(\boldsymbol{x}, t) - D\nabla u_P(\boldsymbol{x}, t) \cdot \boldsymbol{n} = 0, \text{ over } \partial\Omega_C,$$

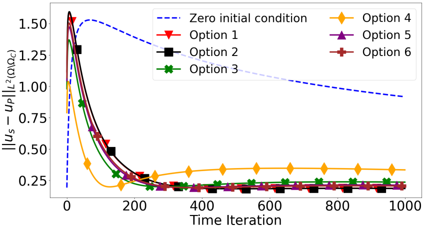
and the shape of the analytical expression of ϕ_{sum} (i.e. $D\nabla u_P(\boldsymbol{x}, t) \cdot \boldsymbol{n}$):



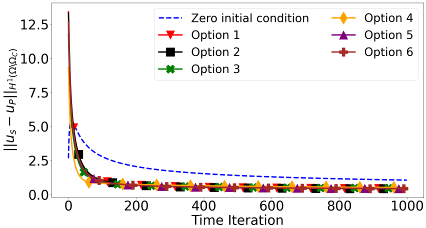
Various Options to select (p_0, t_0) (II/III)

Options	Objective	Constraints
Option 1	$\min_{(p_0,t_0)} \int_0^T \lvert\phi_{sum}(R,t) - \phi(\boldsymbol{x},t)\rvert dt$	-
Option 2		$p_0(t_0) = \frac{2t_0\phi(\boldsymbol{x},t)}{RP^D_{t_0}(R)}$
Option 3	$\min_{(p_0,t_0)}(\lvert\max_{0\leqslant t\leqslant T}(\phi_{sum} - \phi(\boldsymbol{x},t))\rvert$	-
Option 4	$+\lvert\min_{0\leqslant t\leqslant T}(\phi_{sum} - \phi(\boldsymbol{x},t))\rvert)$	$p_0(t_0) = \frac{2t_0\phi(\boldsymbol{x},t)}{RP^D_{t_0}(R)}$
Option 5	$\min_{(p_0,t_0)}(\int_0^T \lvert\phi_{sum}(R,t) - \phi(\boldsymbol{x},t)\rvert dt +$ $\lvert\max_{0\leqslant t\leqslant T}(\phi_{sum} - \phi(\boldsymbol{x},t))\rvert$	-
Option 6	$+\lvert\min_{0\leqslant t\leqslant T}(\phi_{sum} - \phi(\boldsymbol{x},t))\rvert)$	$p_0(t_0) = \frac{2t_0\phi(\boldsymbol{x},t)}{RP^D_{t_0}(R)}$

Various Options to Compute (p_0, t_0) (III/III)



(a) $\|u_S(\boldsymbol{x},t) - u_P(\boldsymbol{x},t)\|_{L^2(\Omega\backslash\Omega_C)}$

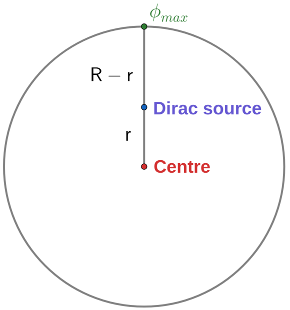


(b) $\|u_S(\boldsymbol{x},t) - u_P(\boldsymbol{x},t)\|_{H^1(\Omega\backslash\Omega_C)}$

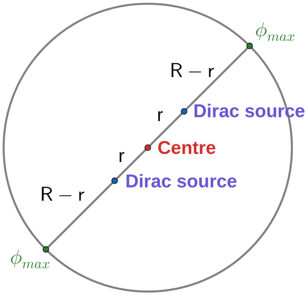
Computational Efficiency

CPU Time (s) $h = 0.127$	One Cell		Ten Cells	
	Generating Mesh	Solving BVP (per iteration)	Generating Mesh	Solving BVP (per iteration)
Spatial Exclusion Model	1.233	0.199	12.080	0.194
Point Source Model	0.257	0.198	0.323	0.199
Computing (p_0, t_0) in Gaussian-shaped IC	0.116			

Inhomogeneous flux density: multiple Dirac delta points



(a) $\phi(\theta) = \phi_0 + A\sin(\theta)$



(b) $\phi(\theta) = \phi_0 + A\sin(2\theta)$

Extreme points over the cell boundary (I/II)

In the **Point Source Model**, the flux density is computed by

$$\begin{aligned}\phi_P(\boldsymbol{x},t) &= D\nabla u_P(\boldsymbol{x},t)\cdot\boldsymbol{n}\\ &= \sum_{i=0}^{N}\int_0^t \frac{\Phi_i(s)}{4\pi D(t-s)}\exp\left\{-\frac{\|\boldsymbol{x}-\boldsymbol{x}^{(i)}\|^2}{4D(t-s)}\right\}\frac{(\boldsymbol{x}-\boldsymbol{x}_C)\cdot(\boldsymbol{x}-\boldsymbol{x}^{(i)})}{2(t-s)R}ds.\end{aligned}$$

Extreme points over the cell boundary (I/II)

In the **Point Source Model**, the flux density is computed by

$$\phi_P(\boldsymbol{x},t) = D\nabla u_P(\boldsymbol{x},t)\cdot\boldsymbol{n}$$
$$= \sum_{i=0}^{N}\int_0^t \frac{\Phi_i(s)}{4\pi D(t-s)}\exp\left\{-\frac{\|\boldsymbol{x}-\boldsymbol{x}^{(i)}\|^2}{4D(t-s)}\right\}\frac{(\boldsymbol{x}-\boldsymbol{x}_C)\cdot(\boldsymbol{x}-\boldsymbol{x}^{(i)})}{2(t-s)R}ds.$$

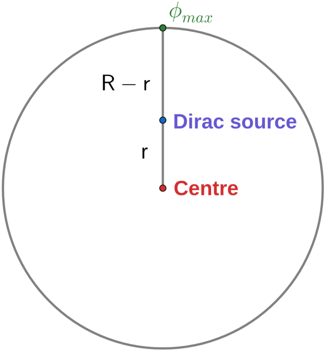
Assume $\Phi_i(s) = \widetilde{\Phi}_i(t) + \delta_t(s)$, $s \in [0,t]$. Then the flux density above yields

$$\hat{\phi}(\boldsymbol{x},t) := \sum_{i=0}^{N}\frac{\widetilde{\Phi}_i(t)}{2\pi R}\frac{(\boldsymbol{x}-\boldsymbol{x}_C)\cdot(\boldsymbol{x}-\boldsymbol{x}^{(i)})}{\|\boldsymbol{x}-\boldsymbol{x}^{(i)}\|^2}\exp\left\{-\frac{\|\boldsymbol{x}-\boldsymbol{x}^{(i)}\|^2}{4Dt}\right\},$$

and at steady state

$$\hat{\phi}_\infty(\boldsymbol{x}) := \sum_{i=0}^{N}\frac{\widetilde{\Phi}_i^\infty}{2\pi R}\frac{(\boldsymbol{x}-\boldsymbol{x}_C)\cdot(\boldsymbol{x}-\boldsymbol{x}^{(i)})}{\|\boldsymbol{x}-\boldsymbol{x}^{(i)}\|^2}$$

Extreme points over the cell boundary (II/II)



$$\begin{cases} \frac{\widetilde{\Phi}_D(t)}{2\pi(R-r)} \exp\left\{-\frac{(R-r)^2}{4Dt}\right\} + \frac{\widetilde{\Phi}_C(t)}{2\pi R} \exp\left\{-\frac{R^2}{4Dt}\right\} = \phi_0 + A \\ \frac{\widetilde{\Phi}_D(t)}{2\pi(R+r)} \exp\left\{-\frac{(R+r)^2}{4Dt}\right\} + \frac{\widetilde{\Phi}_C(t)}{2\pi R} \exp\left\{-\frac{R^2}{4Dt}\right\} = \phi_0 - A \end{cases}$$

Intensities of Dirac delta points

$$\begin{cases} \widetilde{\Phi}_D(t) = \dfrac{4\pi A(R+r)(R-r)}{(R+r)\exp\left\{-\frac{(R-r)^2}{4Dt}\right\} - (R-r)\exp\left\{-\frac{(R+r)^2}{4Dt}\right\}} \\ \widetilde{\Phi}_C(t) = 2\pi R \exp\left\{\dfrac{R^2}{4Dt}\right\}\left(\phi_0 + A - \dfrac{2A(R+r)}{(R+r)-(R-r)\exp\left\{-\frac{Rr}{Dt}\right\}}\right) \end{cases}$$

Take $t \to +\infty$:

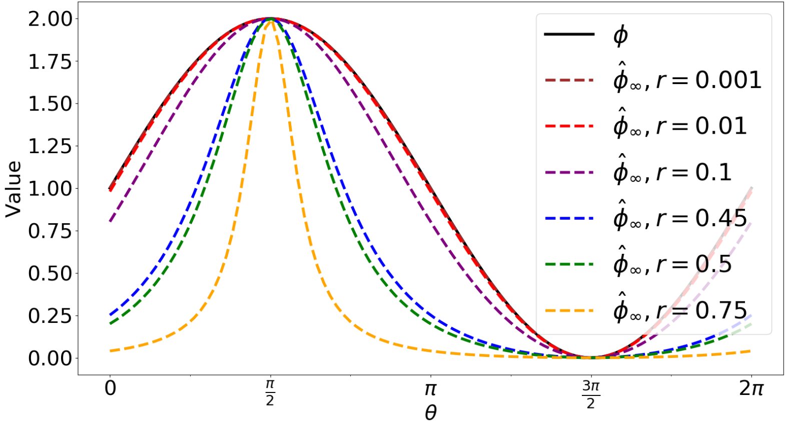
$$\begin{cases} \widetilde{\Phi}_D^{\infty} = \dfrac{2\pi A(R+r)(R-r)}{r} \\ \widetilde{\Phi}_C^{\infty} = 2\pi R\left(\phi_0 - A\dfrac{R}{r}\right) \end{cases}$$

Parameter Values

$D = R = \phi_0 = A = 1.0,\ r = 0.1,\ T = 40.0,\ dt = 0.04$

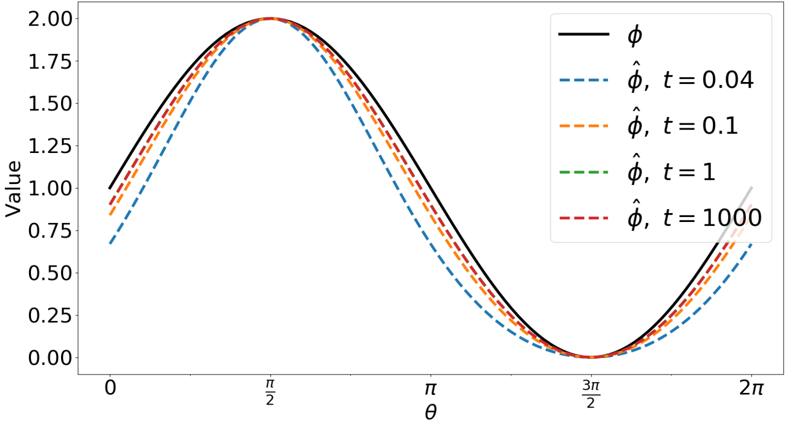
Flux density over the cell boundary: $t \to +\infty$

$$\hat{\phi}_\infty(\boldsymbol{x}) := \sum_{i=0}^{N} \frac{\widetilde{\Phi}_i^\infty}{2\pi R} \frac{(\boldsymbol{x}-\boldsymbol{x}_C)\cdot(\boldsymbol{x}-\boldsymbol{x}^{(i)})}{\|\boldsymbol{x}-\boldsymbol{x}^{(i)}\|^2}$$



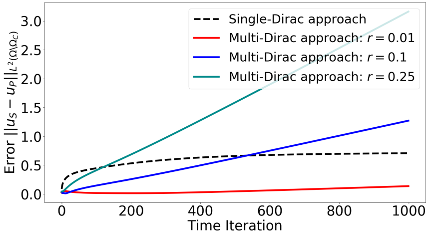
Flux density over cell boundary: $r = 0.05$

$$\hat{\phi}(\boldsymbol{x}, t) := \sum_{i=0}^{N} \frac{\widetilde{\Phi}_i(t)}{2\pi R} \frac{(\boldsymbol{x}-\boldsymbol{x}_C)\cdot(\boldsymbol{x}-\boldsymbol{x}^{(i)})}{\|\boldsymbol{x}-\boldsymbol{x}^{(i)}\|^2} \exp\left\{-\frac{\|\boldsymbol{x}-\boldsymbol{x}^{(i)}\|^2}{4Dt}\right\}, \text{ with } r = 0.05$$

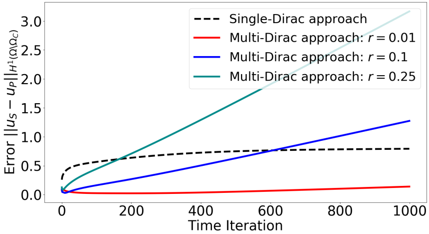


Numerical results of model comparison

L_2−norm difference in $\Omega \setminus \Omega_C$



H_1−norm difference in $\Omega \setminus \Omega_C$



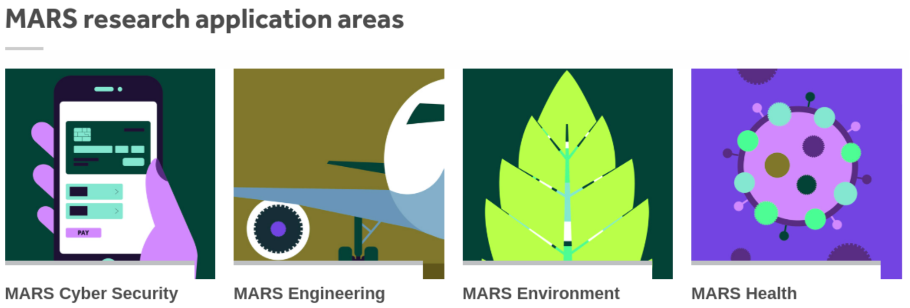
Conclusions

- Due to the necessary assumptions and simplifications, mathematical modelling is a trade off between loss of information and computational efficiency.
- Upscalling between the models at different scales from the PDE perspective improves the computational efficiency with controlling the information loss.
- The essential and necessary condition has been derived analytically for the consistency between the diffusion models at different scales.
- For **homogeneous** flux density, **one Dirac delta point at cell center** combined with extra initial condition for the intracellular environment is needed for producing the consistent solutions.
- To reproduce the **inhomogeneous** flux density over the cell boundary, **multiple Dirac delta points** are used to represent one cell.

Further Reading...

- Q. Peng and S.C. Hille. *Quality of approximating a mass-emitting object by a point source in a diffusion model*. Journal of Computers & Mathematics with Applications 151, 491 - 507 (2023).
- Q. Peng and S.C. Hille. *Using multiple Dirac delta points to describe inhomogeneous flux density over a cell boundary in a single-cell diffusion model.* arXiv:2401.16261 (2024).
- X. Yang, Q. Peng and S.C. Hille. *Approximation of a compound-exchanging cell by a Dirac point.* arXiv:2410.09495 (2024).

PhD Vacancies and Thank you!



Questions or Comments?

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