Diffusion of Proteins on Cell Membranes
1D Finite Element Method

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Abstract

Protein delivery to a cell membrane consists of two alternative fusion modes that contrast in energy expenditure and resource-cost. Thus, identifying a cell's bias to either of the two modes can suggest the process acting in the cell. However, current experimental and observational methods for time-dependent fusion events are limited in resolution, obscuring the differences between the two modes. We model both modes, simulate over the parameters spaces of known values for mammalian cells, and compare the theoretical evolution of the fusion and diffusion process. Failure to distinguish the two modes in simulation with infinite resolution can suggest the impossibility in making distinctions with limited resolution. On the other hand, successful distinctions in simulations can suggest the type of observations that may provide further resolution of the process in the laboratory setting.

Part I

Cell and Protein Dynamics

Chapter 1

Structure

1.1 Cells

1.2 Vesicles

1.3 Proteins

Chapter 2

Dynamics

2.1 Fusion

2.2 Diffusion

Chapter 3

Observations

3.1 TIRF Microscopy

3.1.1 Observation Zone

3.2 Electron Micrography

Part II

Mathematical Model

3.3 Mathematical Background

The following description is of a model built on the theory of differential equations, finite element method,

The mathematical symbols utilized for model derivation and expression are consistently used as given in table TODO.

Chapter 4

Diffusion

Protein delivery dynamics are here modelled as a scaled concentration diffusion on the surface of static membrane manifolds. Full fusion is modelled on the surface of a sphere, and kiss-and-run fusion on the surface of two truncated, connected spheres. The physical parameters involved in each model are derived from the pre-fusion cell and delivery vesicle parameters. The diffusion equation is then solved on the manifold defined by those parameters.

4.1 Conservation of Mass

The diffusion model assumes no source or sink for proteins, hence a conservation of mass expressed as follows.

$$\frac{\partial u}{\partial t} = -\nabla \cdot \vec{J}$$

4.2 Fick's First Law of Diffusion

$$J(\vec{x}, t) = -D(\vec{x}, t)\nabla u(\vec{x}, t)$$

4.3 Diffusion Equation

$$\frac{\partial u(\vec{x}, t)}{\partial t} = \nabla \cdot [D(\vec{x}, t)\ \nabla u(\vec{x}, t)]$$

In spherical coordinates with azimuthal symmetry on the surface of a sphere,

$$\rho^2 \sin(\varphi)\frac{\partial u}{\partial t} = \frac{\partial}{\partial \varphi}\left(D(\phi)\sin(\phi)\frac{\partial u}{\partial \phi}\right)$$

R_v Pre-Fusion Vesicle Radius
R_c Pre-Fusion Cell Radius

D_v Vesicle Diffusivity
D_c Cell Diffusivity

4.4 Total Concentration

$$\langle \bullet \rangle = 2\pi\rho^2 \int_0^{\pi} \bullet \sin(\varphi)\ \mathrm{d}\varphi$$

Chapter 5

Full Fusion

5.1 Fusion Parameters

$$
\begin{aligned}
D(\varphi) &= D_v H(\varphi_j - \varphi) + D_c H(\varphi - \varphi_j) \\
{R'}^2 &= R_v^2 + R_c^2 \\
\varphi_j &= \operatorname{acos}\left(\frac{R_c^2 - R_v^2}{{R'}^2}\right) \\
R'_s &= \frac{2 R_v R_c}{R'}
\end{aligned}
$$

5.2 Initial-and-Boundary Value Problem

$$\Omega = (0, \pi)$$

$$
\begin{aligned}
{R'}^2 \sin(\varphi) \frac{\partial u(\varphi,t)}{\partial t} &= \frac{\partial}{\partial \varphi}\left(D(\varphi) \sin(\varphi) \frac{\partial u(\varphi,t)}{\partial \varphi}\right) && \varphi \in \Omega \qquad t \in \mathbb{R}_0^+ \\
u(\varphi,t) &= H(\varphi_j - \varphi) && \varphi \in \Omega \qquad t \in \mathbb{R}_0^+
\end{aligned}
$$

5.3 Analytical Solution

The frontier of analytical solution methods for the diffusion problem specified above involves constant diffusivity.

5.4 Weak Form

$$
\begin{aligned}
{R'}^2 \sin(\varphi)\frac{\partial u(\varphi,t)}{\partial t} &= \frac{\partial}{\partial\varphi}\left(D(\varphi)\sin(\varphi)\frac{\partial u(\varphi,t)}{\partial\varphi}\right)\\
{R'}^2 \sin(\varphi)\frac{\partial u(\varphi,t)}{\partial t}w(\varphi) &= \frac{\partial}{\partial\varphi}\left(D(\varphi)\sin(\varphi)\frac{\partial u(\varphi,t)}{\partial\varphi}\right)w(\varphi)\\
{R'}^2 \int_\Omega \sin(\varphi)\frac{\partial u(\varphi,t)}{\partial t}w(\varphi)\mathrm{d}\varphi &= \int_\Omega \frac{\partial}{\partial\varphi}\left(D(\varphi)\sin(\varphi)\frac{\partial u(\varphi,t)}{\partial\varphi}\right)w(\varphi)\mathrm{d}\varphi\\
\frac{1}{2\pi}\left\langle \frac{\partial u(\varphi,t)}{\partial t}w(\varphi)\right\rangle &= \left[D(\varphi)\sin(\varphi)\frac{\partial u(\varphi,t)}{\partial\varphi}w(\varphi)\right]_\Omega - \int_\Omega D(\varphi)\sin(\varphi)\frac{\partial u(\varphi,t)}{\partial\varphi}\frac{\mathrm{d}w(\varphi)}{\mathrm{d}\varphi}\mathrm{d}\varphi\\
\frac{1}{2\pi}\left\langle \frac{\partial u(\varphi,t)}{\partial t}w(\varphi)\right\rangle &= -\int_\Omega D(\varphi)\sin(\varphi)\frac{\partial u(\varphi,t)}{\partial\varphi}\frac{\mathrm{d}w(\varphi)}{\mathrm{d}\varphi}\mathrm{d}\varphi\\
\frac{1}{2\pi}\left\langle \frac{\partial u(\varphi,t)}{\partial t}w(\varphi)\right\rangle &= -\frac{1}{2\pi {R'}^2}\left\langle D(\varphi)\frac{\partial u(\varphi,t)}{\partial\varphi}\frac{\mathrm{d}w(\varphi)}{\mathrm{d}\varphi}\right\rangle
\end{aligned}
$$

yielding the weak form

$$
0 = \left\langle \frac{\partial u(\varphi,t)}{\partial t}w(\varphi)\right\rangle + \frac{1}{{R'}^2}\left\langle D(\varphi)\frac{\partial u(\varphi,t)}{\partial\varphi}\frac{\mathrm{d}w(\varphi)}{\mathrm{d}\varphi}\right\rangle
$$

with total concentration

$$
\langle\bullet\rangle = 2\pi {R'}^2 \int_\Omega \sin(\varphi)\bullet\mathrm{d}\varphi
$$

5.4.1 Parameterisation by Arc Length

By foresight of the kiss-and-run fusion modelling, we parameterize the full fusion weak form by arc length.

$$
\varphi = \frac{s(\varphi)}{R'}
$$

so

$$
\begin{aligned}
\mathrm{d}\varphi &= \frac{1}{R'}\mathrm{d}s\\
\frac{\partial}{\partial\varphi} &= R'\frac{\partial}{\partial s}
\end{aligned}
$$

providing the new weak form

$$
0 = \left\langle \frac{\partial u(\varphi,t)}{\partial t}w(\varphi)\right\rangle + \left\langle D(\varphi)\frac{\partial u(\varphi,t)}{\partial\varphi}\frac{\mathrm{d}w(\varphi)}{\mathrm{d}\varphi}\right\rangle
$$

with

$$
\begin{aligned}
\omega(s) &= \frac{s}{R'}\\
\langle\bullet\rangle &= 2\pi R' \int_\Gamma \sin\left(\omega(s)\right)\bullet\mathrm{d}s
\end{aligned}
$$

Chapter 6

Kiss-and-Run Fusion

R_j Post-Fusion Junction Radius

6.1 Fusion Parameters

$$R'_v = \frac{2R_v^2}{\sqrt{4R_v^2 - R_j^2}}$$
$$R'_c = \frac{2R_c^2}{\sqrt{4R_c^2 - R_j^2}}$$
$$\phi_v = \pi - \operatorname{asin}\left(\frac{R_j}{R'_v}\right)$$
$$\psi_c = \pi - \operatorname{asin}\left(\frac{R_j}{R'_c}\right)$$

6.2 Initial-and-Boundary Value Problem

$$\Omega_v = (0, \phi_v)$$
$$\Omega_c = (\pi - \psi_c, \pi)$$

$$R_v'^{\,2} \sin(\phi) \frac{\partial v(\phi,t)}{\partial t} = D_v \frac{\partial}{\partial \phi}\left(\sin(\phi) \frac{\partial v(\phi,t)}{\partial \phi}\right) \qquad \phi \in \Omega_v \qquad t \in \mathbb{R}_0^+$$
$$R_c'^{\,2} \sin(\psi) \frac{\partial c(\psi,t)}{\partial t} = D_c \frac{\partial}{\partial \psi}\left(\sin(\psi) \frac{\partial c(\psi,t)}{\partial \psi}\right) \qquad \psi \in \Omega_c \qquad t \in \mathbb{R}_0^+$$

At the junction,

$$
\begin{aligned}
v(\phi,t) &= c(\psi,t) & \phi &= \sup\Omega_v & \psi &= \inf\Omega_c & t &\in \mathbb{R}_0^+\\
\frac{D_v}{R'_v}\frac{\partial v(\phi,t)}{\partial\phi} &= \frac{D_c}{R'_c}\frac{\partial c(\psi,t)}{\partial\psi} & \phi &= \sup\Omega_v & \psi &= \inf\Omega_c & t &\in \mathbb{R}_0^+
\end{aligned}
$$

Initially,

$$
\begin{aligned}
&v(\phi,t) = 1 && \phi\in\Omega_v && && t\in\mathbb{R}_0^+\\
&c(\psi,t) = 0 && && \psi\in\Omega_c && t\in\mathbb{R}_0^+\\
&v(\phi,t) = c(\psi,t) = 0.5 && \phi\in\Omega_v && \psi\in\Omega_c && t\in\mathbb{R}_0^+
\end{aligned}
$$

6.3 Weak Form

On the vesicle,

$$
\begin{aligned}
{R'_v}^2\sin(\phi)\frac{\partial v(\phi,t)}{\partial t} &= D_v\frac{\partial}{\partial\phi}\left(\sin(\phi)\frac{\partial v(\phi,t)}{\partial\phi}\right)\\
{R'_v}^2\sin(\phi)\frac{\partial v(\phi,t)}{\partial t}f(\phi) &= D_v\frac{\partial}{\partial\phi}\left(\sin(\phi)\frac{\partial v(\phi,t)}{\partial\phi}\right)f(\phi)\\
{R'_v}^2\int_{\Omega_v}\sin(\phi)\frac{\partial v(\phi,t)}{\partial t}f(\phi)\ \mathrm{d}\phi &= D_v\int_{\Omega_v}\frac{\partial}{\partial\phi}\left(\sin(\phi)\frac{\partial v(\phi,t)}{\partial\phi}\right)f(\phi)\ \mathrm{d}\phi\\
{R'_v}^2\int_{\Omega_v}\sin(\phi)\frac{\partial v(\phi,t)}{\partial t}f(\phi)\ \mathrm{d}\phi &= D_v\int_{\Omega_v}\frac{\partial}{\partial\phi}\left(\sin(\phi)\frac{\partial v(\phi,t)}{\partial\phi}\right)f(\phi)\ \mathrm{d}\phi\\
\frac{1}{2\pi}\left\langle\frac{\partial v(\phi,t)}{\partial t}f(\phi)\right\rangle_v &= D_v\left(\left[\sin(\phi)\frac{\partial v(\phi,t)}{\partial\phi}f(\phi)\right]_{\Omega_v} - \int_{\Omega_v}\sin(\phi)\frac{\partial v(\phi,t)}{\partial\phi}\frac{\partial f(\phi)}{\partial\phi}\ \mathrm{d}\phi\right)\\
\frac{1}{2\pi}\left\langle\frac{\partial v(\phi,t)}{\partial t}f(\phi)\right\rangle_v &= D_v\left(\left[\sin(\phi_v)\frac{\partial v(\phi_v,t)}{\partial\phi}f(\phi_v) - 0\right] - \frac{1}{2\pi {R'_v}^2}\left\langle\frac{\partial v(\phi,t)}{\partial\phi}\frac{\partial f(\phi)}{\partial\phi}\right\rangle\right)\\
\frac{1}{2\pi}\left\langle\frac{\partial v(\phi,t)}{\partial t}f(\phi)\right\rangle_v &= D_v\left(\sin(\phi_v)\frac{\partial v(\phi_v,t)}{\partial\phi}f(\phi_v) - \frac{1}{2\pi {R'_v}^2}\left\langle\frac{\partial v(\phi,t)}{\partial\phi}\frac{\partial f(\phi)}{\partial\phi}\right\rangle\right)
\end{aligned}
$$

On the cell,

$$
\begin{aligned}
{R'_c}^2\sin(\psi)\frac{\partial c(\psi,t)}{\partial t} &= D_c\frac{\partial}{\partial\psi}\left(\sin(\psi)\frac{\partial c(\psi,t)}{\partial\psi}\right)\\
\frac{1}{2\pi}\left\langle\frac{\partial c(\psi,t)}{\partial t}g(\psi)\right\rangle_c &= D_c\left(\left[\sin(\psi)\frac{\partial c(\psi,t)}{\partial\psi}g(\psi)\right]_{\Omega_v} - \int_{\Omega_v}\sin(\psi)\frac{\partial c(\psi,t)}{\partial\psi}\frac{\partial g(\psi)}{\partial\psi}\ \mathrm{d}\psi\right)\\
\frac{1}{2\pi}\left\langle\frac{\partial c(\psi,t)}{\partial t}g(\psi)\right\rangle_c &= D_c\left(\left[0 - \sin(\pi-\psi_v)\frac{\partial c(\pi-\psi_v,t)}{\partial\psi}g(\pi-\psi_v)\right] - \frac{1}{2\pi {R'_c}^2}\left\langle\frac{\partial c(\psi,t)}{\partial\psi}\frac{\partial g(\psi)}{\partial\psi}\right\rangle\right)\\
\frac{1}{2\pi}\left\langle\frac{\partial c(\psi,t)}{\partial t}g(\psi)\right\rangle_c &= -D_c\left(\sin(\pi-\psi_v)\frac{\partial c(\pi-\psi_v,t)}{\partial\psi}g(\pi-\psi_v) + \frac{1}{2\pi {R'_c}^2}\left\langle\frac{\partial c(\psi,t)}{\partial\psi}\frac{\partial g(\psi)}{\partial\psi}\right\rangle\right)
\end{aligned}
$$

Adding the two expressions,

$$
\begin{aligned}
&\left\langle \frac{\partial v(\phi,t)}{\partial t} f(\phi) \right\rangle_v + \left\langle \frac{\partial c(\psi,t)}{\partial t} g(\psi) \right\rangle_c \\
&\quad = D_v \sin(\phi_v) \frac{\partial v(\phi_v,t)}{\partial \phi} f(\phi_v) - D_c \sin(\pi-\psi_v) \frac{\partial c(\pi-\psi_v,t)}{\partial \psi} g(\pi-\psi_v) \\
&\qquad - \left(\frac{D_v}{{R_v'}^2} \left\langle \frac{\partial v(\phi,t)}{\partial \phi} \frac{\partial f(\phi)}{\partial \phi} \right\rangle + \frac{D_c}{{R_c'}^2} \left\langle \frac{\partial c(\psi,t)}{\partial \psi} \frac{\partial g(\psi)}{\partial \psi} \right\rangle \right)
\end{aligned}
$$

then substituting the membrane angle sizes

$$
\begin{aligned}
&\frac{1}{2\pi} \left(\left\langle \frac{\partial v(\phi,t)}{\partial t} f(\phi) \right\rangle_v + \left\langle \frac{\partial c(\psi,t)}{\partial t} g(\psi) \right\rangle_c \right) \\
&\quad = D_v \frac{R_j}{R_v'} \frac{\partial v(\phi_v,t)}{\partial \phi} f(\phi_v) - D_c \frac{R_j}{R_c'} \frac{\partial c(\pi-\psi_v,t)}{\partial \psi} g(\pi-\psi_v) \\
&\qquad - \frac{1}{2\pi} \left(\frac{D_v}{{R_v'}^2} \left\langle \frac{\partial v(\phi,t)}{\partial \phi} \frac{\partial f(\phi)}{\partial \phi} \right\rangle + \frac{D_c}{{R_c'}^2} \left\langle \frac{\partial c(\psi,t)}{\partial \psi} \frac{\partial g(\psi)}{\partial \psi} \right\rangle \right)
\end{aligned}
$$

Select $f(\phi)$ and $g(\psi)$ such that

$$
f(\phi_v) = g(\pi - \psi_c).
$$

so

$$
\begin{aligned}
0 &= \left\langle \frac{\partial v(\phi,t)}{\partial t} f(\phi) \right\rangle_v + \left\langle \frac{\partial c(\psi,t)}{\partial t} g(\psi) \right\rangle_c \\
&\quad + \frac{D_v}{{R_v'}^2} \left\langle \frac{\partial v(\phi,t)}{\partial \phi} \frac{\partial f(\phi)}{\partial \phi} \right\rangle + \frac{D_c}{{R_c'}^2} \left\langle \frac{\partial c(\psi,t)}{\partial \psi} \frac{\partial g(\psi)}{\partial \psi} \right\rangle
\end{aligned}
$$

Define arc-length transformation such that

$$
\begin{aligned}
s_j &= R_v' \phi_v \\
s_P &= s_j + R_c' \psi_c \\
s &= \begin{cases} R_v' \phi & \phi \in \Omega_v \\ s_j + R_c'(\psi + \psi_c - \pi) & \psi \in \Omega_c \end{cases}
\end{aligned}
$$

so inverse transformations are

$$
\begin{aligned}
\Gamma_v &= (0, s_j) \\
\Gamma_c &= (s_j, s_P) \\
\Gamma &= \operatorname{conv}(\Gamma_v \cup \Gamma_c) \\
\phi(s) &= \frac{s}{R_v'} \\
\psi(s) &= \frac{s - s_j}{R_c'} + \pi - \psi_c \\
\omega(s) &= \begin{cases} \phi(s) & s \in \Gamma_v \\ \psi(s) & s \in \Gamma_c \end{cases}
\end{aligned}
$$

and define $u(s,t)$ such that

$$u(s,t) = \begin{cases} v(\phi(s),t) & s \in \Gamma_v \\ c(\psi(s),t) & s \in \Gamma_c \end{cases}$$

so derivatives become

$$\begin{aligned}
\mathrm{d}\phi &= \frac{1}{R_v'}\,\mathrm{d}s \\
\mathrm{d}\psi &= \frac{1}{R_c'}\,\mathrm{d}s \\
\frac{\partial v(\phi,t)}{\partial \phi} &= R_v' \frac{\partial u(s,t)}{\partial s} \\
\frac{\partial c(\psi,t)}{\partial \psi} &= R_c' \frac{\partial u(s,t)}{\partial s}
\end{aligned}$$

and define

$$w(s) = \begin{cases} f(\phi(s),t) & s \in \Gamma_v \\ g(\psi(s),t) & s \in \Gamma_c \end{cases}$$

so our weak form becomes

$$\begin{aligned}
0 &= \left\langle \frac{\partial v(\phi,t)}{\partial t} f(\phi) \right\rangle_v + \left\langle \frac{\partial c(\psi,t)}{\partial t} g(\psi) \right\rangle_c \\
&\quad + \frac{D_v}{{R_v'}^2} \left\langle \frac{\partial v(\phi,t)}{\partial \phi} \frac{\partial f(\phi)}{\partial \phi} \right\rangle + \frac{D_c}{{R_c'}^2} \left\langle \frac{\partial c(\psi,t)}{\partial \psi} \frac{\partial g(\psi)}{\partial \psi} \right\rangle \\
0 &= {R_v'}^2 \int_{\Omega_v} \sin(\phi) \frac{\partial v(\phi,t)}{\partial t} f(\phi) \mathrm{d}\phi + {R_c'}^2 \int_{\Omega_c} \sin(\psi) \frac{\partial c(\psi,t)}{\partial t} g(\psi) \mathrm{d}\psi \\
&\quad + D_v \int_{\Omega_v} \sin(\phi) \frac{\partial v(\phi,t)}{\partial \phi} \frac{\partial f(\phi)}{\partial \phi} \mathrm{d}\phi + D_c \int_{\Omega_c} \sin(\psi) \frac{\partial c(\psi,t)}{\partial \psi} \frac{\partial g(\psi)}{\partial \psi} \mathrm{d}\psi \\
0 &= R_v' \int_{\Gamma_v} \sin(\phi(s)) \frac{\partial u(s,t)}{\partial t} w(s)\,\mathrm{d}s + R_c' \int_{\Gamma_c} \sin(\psi(s)) \frac{\partial u(s,t)}{\partial t} w(s)\,\mathrm{d}s \\
&\quad + D_v \int_{\Gamma_v} \sin(\phi(s)) \frac{\partial u(s,t)}{\partial s} \frac{\mathrm{d}w(s)}{\mathrm{d}s}\,\mathrm{d}s + D_c \int_{\Gamma_c} \sin(\psi(s)) \frac{\partial u(s,t)}{\partial s} \frac{\mathrm{d}w(s)}{\mathrm{d}s}\,\mathrm{d}s \\
0 &= \int_\Gamma \sin(\omega(s)) R'(s) \frac{\partial u(s,t)}{\partial t} w(s) + \int_\Gamma \sin(\omega(s)) D(s) \frac{\partial u(s,t)}{\partial s} \frac{\mathrm{d}w(s)}{\mathrm{d}s}\,\mathrm{d}s
\end{aligned}$$

yielding our weak form in arc-length

$$0 = \left\langle \frac{\partial u(s,t)}{\partial t} w(s) \right\rangle + \left\langle \frac{D(s)}{R'(s)} \frac{\partial u(s,t)}{\partial s} \frac{\mathrm{d}w(s)}{\mathrm{d}s} \right\rangle$$

with

$$
\begin{aligned}
R'(s) &= \begin{cases} R'_v & s \in \Gamma_v \\ R'_c & s \in \Gamma_c \end{cases} \\
\langle \bullet \rangle &= 2\pi \int R'(s) \sin\left(\omega(s)\right) \bullet \, \mathrm{d}s
\end{aligned}
$$

Chapter 7

Finite Element Method

The finite element method expressed generically for the fusion modes of full and kiss-and-run takes a weak formulation

$$0 = \left\langle \frac{\partial u(s,t)}{\partial t} w(s) \right\rangle + \left\langle \frac{D(s)}{R(s)} \frac{\partial u(s,t)}{\partial s} \frac{\mathrm{d}w(s)}{\mathrm{d}s} \right\rangle$$

with

$$\langle \bullet \rangle = 2\pi \int_{\Gamma} R(s) \sin\left(\omega(s)\right) \bullet \mathrm{d}s$$

for Γ, s, $D(s)$, $R(s)$, and $\omega(s)$ defined by the fusion mode model.

7.1 Spatial Discretisation

Select positive integers p_j and P such that

$$p_j < P$$

Define

$$\mathbb{P} = \{0, 1, 2, ..., P\}$$

Select values s_p for $p \in \mathbb{P}$ such that

$$0 = s_0 < s_1 < \cdots s_{p_j - 1} < s_{p_j} = s_j < s_{p_j + 1} < \cdots < s_{P-1} < s_P$$

Define their spacing,

$$h_p = s_p - s_{p-1} \qquad\qquad s \in \mathbb{P}^+$$

Define hat functions such that

$$\Lambda_p(s) = \begin{cases} 1 & s = s_p \\ \dfrac{s - s_{p-1}}{h_p} & s \in (s_{p-1}, s_p) \\ \dfrac{s_{p+1} - s}{h_{p+1}} & s \in (s_p, s_{p+1}) \\ 0 & \text{otherwise} \end{cases}$$

Transform the weak form into a system of equations by selecting

$$w(s) = \Lambda_p(s) \qquad p \in \mathbb{P}$$

so

$$0 = \left\langle \frac{\partial u(s,t)}{\partial t} \Lambda_p(s) \right\rangle + \left\langle \frac{D(s)}{R(s)} \frac{\partial u(s,t)}{\partial s} \frac{\partial \Lambda_p(s)}{\partial s} \right\rangle \qquad p \in \mathbb{P}$$

Project the solution $u(s,t)$ onto the space of piecewise-linear functions defined on the discrete grid s_p, and define this projection as

$$u_h(s,t) = \sum_{q=0}^{P} U_q(t) \Lambda_q(s)$$

and impose this by substitution so

$$0 = \frac{\partial U_q(t)}{\partial t} \langle \Lambda_q(s) \Lambda_p(s) \rangle + U_q(t) \left\langle \frac{D(s)}{R(s)} \frac{\partial \Lambda_q(s)}{\partial s} \frac{\partial \Lambda_p(s)}{\partial s} \right\rangle$$

in Einstein notation.

Define

$$\begin{aligned} \vec{U}(t) &= [U_0(t)\ U_1(t)\ \cdots\ U_P(t)]^{\mathrm{T}} \\ [M]_{pq} &= \langle \Lambda_q(s) \Lambda_p(s) \rangle \\ [S]_{pq} &= \left\langle \frac{D(s)}{R(s)} \frac{\partial \Lambda_q(s)}{\partial s} \frac{\partial \Lambda_p(s)}{\partial s} \right\rangle \end{aligned}$$

so we have our system

$$0 = M \frac{\mathrm{d}\vec{U}(t)}{\mathrm{d}t} + S\vec{U}(t)$$

7.1.1 Taming Discontinuity

A Heaviside transition of parameter values is located at the junction in both fusion modes. An optimal selection of spatial grid spacing minimizes the possibility of violating the law of conservation. This motivates placing a large concentration of points around the junction point. The junction itself must also be a grid point.

We apply cubic spacing on the vesicle and cell domains separately.

The vesicular gridding must satisfy

$$s_0 = 0 s_{p_j} \qquad = s_j$$

and be concave down, which leads to

$$s_p = s_j\left(1-\left(1-\frac{p}{p_j}\right)^3\right)$$

The cellular gridding similarly must satisfy

$$\begin{aligned} s_{p_j} &= s_j \\ s_P &= s_P \end{aligned}$$

and must be concave up, leading to

$$s_p = s_j + (s_P - s_j)\left(\frac{p-p_j}{P-p_j}\right)^3$$

7.2 Temporal Discretisation

Due to stiffness, we select a backward Euler dynamic timestepping scheme. Define

$$\begin{aligned} 0 &= t_0 < t_1 < \cdots \\ \vec{U}^n &= \vec{U}(t_n) && n \in \mathbb{Z}_0^+ \end{aligned}$$

so

$$\begin{aligned} 0 &= M\frac{\vec{U}^n - \vec{U}^{n-1}}{\Delta t_n} + S\vec{U}^n \\ 0 &= M\left(\vec{U}^n - \vec{U}^{n-1}\right) + \Delta t_n S\vec{U}^n \\ 0 &= (M + \Delta t_n S)\vec{U}^n - M\vec{U}^{n-1} \end{aligned}$$

yielding the matrix equation

$$(M + \Delta t_n S)\vec{U}^n = M\vec{U}^{n-1}$$

Due to accuracy needing small h_p, Simpson's Rule with two subintervals is used to evaluate the integral for the mass matrix to avoid machine rounding errors via division by small h_p values.

$$\int_a^b f(x)\,\mathrm{d}x \approx \frac{b-a}{6}\left[f(a) + 4f\left(\frac{a+b}{2}\right) + f(b)\right]$$

Additionally, note the diagonalism, i.e.

$$
\begin{aligned}
[M]_{pq} &= [M]_{qp} \\
[S]_{pq} &= [S]_{qp}
\end{aligned}
$$

thus, WLOG we calculate

$$
\begin{aligned}
&[M]_{pp}, [S]_{pp} && p \in \mathbb{P} && \text{(diagonal)} \\
&[M]_{p-1,p}, [S]_{p-1,p} && p \in \mathbb{P}^{+} && \text{(off-diagonal)}
\end{aligned}
$$

For clarity, define

$$
\begin{aligned}
\mathbb{P}_{-} &= \{0, ..., P-1\} \\
\mathbb{P}_{+} &= \{1, ..., P\} \\
R'(s) &= R(s)\sin(\omega(s)) \\
D'(s) &= D(s)\sin(\omega(s))
\end{aligned}
$$

7.3 Mass Matrix

$$
\begin{aligned}
[M]_{pp} &= \left\langle \Lambda_p^2(s) \right\rangle \\
&= 2\pi \int_{\Gamma} R'(s)\Lambda_p^2(s)\,\mathrm{d}s \\
&= 2\pi\left(I_{\mathbb{P}_+}(p) \int_{s_{p-1}}^{s_p} R'(s)\frac{s-s_{p-1}}{h_p}\,\mathrm{d}s + I_{\mathbb{P}_-}(p) \int_{s_p}^{s_{p+1}} R'(s)\frac{s_{p+1}-s}{h_{p+1}}\,\mathrm{d}s \right)
\end{aligned}
$$

$$
\begin{aligned}
&\int_{s_{p-1}}^{s_p} R'(s)\frac{s-s_{p-1}}{h_p}\,\mathrm{d}s \\
&\quad= \frac{1}{h_p}\int_{s_{p-1}}^{s_p} R'(s)(s-s_{p-1})\,\mathrm{d}s \\
&\quad\approx \frac{1}{6}\left[R'(s_p)h_p + 4R'(s_{p-1/2})\left(\frac{s_{p-1}+s_p}{2} - s_{p-1}\right)\right] \\
&\quad= \frac{1}{6}\left[R'(s_p)h_p + 2R'(s_{p-1/2})h_p \right]
\end{aligned}
$$

$$
\begin{aligned}
&\int_{s_p}^{s_{p+1}} R'(s)\frac{s_{p+1}-s}{h_{p+1}}\,\mathrm{d}s \\
&\quad= \frac{1}{h_p}\int_{s_p}^{s_{p+1}} R'(s)(s_{p+1}-s)\,\mathrm{d}s \\
&\quad\approx \frac{1}{6}\left[R'(s_p)h_{p+1} + 4R'(s_{p+1/2})\left(s_{p+1} - \frac{s_p+s_{p+1}}{2}\right)\right] \\
&\quad= \frac{1}{6}\left[R'(s_p)h_{p+1} + 2R'(s_{p+1/2}h_{p+1}) \right]
\end{aligned}
$$

So

$$[M]_{pp} \approx \frac{\pi}{3}\left(I_{\mathbb{P}_+}(p)h_p\big[R'(s_p)+2R'(s_{p-1/2})\big]+I_{\mathbb{P}_-}(p)h_{p+1}\big[R'(s_p)+2R'(s_{p+1/2})\big]\right)$$

$$\begin{aligned}
[M]_{p-1,p} &= \langle \Lambda_{p-1}(s)\Lambda_p(s)\rangle \\
&= 2\pi\int_\Gamma R'(s)\Lambda_{p-1}(s)\Lambda_p(s)\,\mathrm{d}s \\
&= \frac{2\pi}{h_p^2}\int_{s_{p-1}}^{s_p} R'(s)(s_p-s)(s-s_{p-1})\,\mathrm{d}s \\
&\approx \frac{\pi}{3h_p}\left[4R'(s_{p-1/2})\left(s_p-\frac{s_{p-1}+s_p}{2}\right)\left(\frac{s_{p-1}+s_p}{2}-s_{p-1}\right)\right]
\end{aligned}$$

yielding

$$[M]_{p-1,p} \approx \frac{\pi h_p}{3}R'(s_{p-1/2})$$

7.4 Stiffness Matrix

$$\begin{aligned}
[S]_{pp} &= \left\langle \frac{D(s)}{R(s)}\left(\frac{\partial\Lambda_p(s)}{\partial s}\right)^2\right\rangle \\
&= 2\pi\int_\Gamma D'(s)\left(\frac{\partial\Lambda_p(s)}{\partial s}\right)^2\mathrm{d}s \\
&= 2\pi\left(I_{\mathbb{P}_+}(p)\int_{s_{p-1}}^{s_p} D'(s)\frac{1}{h_p^2}\,\mathrm{d}s + I_{\mathbb{P}_-}(p)\int_{s_p}^{s_{p+1}} D'(s)\frac{1}{h_{p+1}^2}\,\mathrm{d}s\right) \\
&= 2\pi\left(\frac{I_{\mathbb{P}_+}(p)}{h_p^2}\int_{s_{p-1}}^{s_p} D'(s)\,\mathrm{d}s + \frac{I_{\mathbb{P}_-}(p)}{h_{p+1}^2}\int_{s_p}^{s_{p+1}} D'(s)\,\mathrm{d}s\right)
\end{aligned}$$

$$\begin{aligned}
[S]_{p-1,p} &= \left\langle \frac{D(s)}{R(s)}\frac{\partial\Lambda_{p-1}(s)}{\partial s}\frac{\partial\Lambda_p(s)}{\partial s}\right\rangle \\
&= 2\pi\int_\Gamma D'(s)\frac{\partial\Lambda_{p-1}(s)}{\partial s}\frac{\partial\Lambda_p(s)}{\partial s}\,\mathrm{d}s \\
&= 2\pi\int_{s_{p-1}}^{s_p} D'(s)\frac{-1}{h_p^2}\,\mathrm{d}s \\
&= \frac{-2\pi}{h_p^2}\int_{s_{p-1}}^{s_p} D'(s)\,\mathrm{d}s
\end{aligned}$$

Chapter 8

TIRF Microscopy Model

The final component of the intended model incorporation of parameters involved in TIRF Microscopy which limit the resolution of observations for fusion and diffusion dynamics in space and time.

8.1 TIRF Microscopy Zone

Due to the TODO, observations are limited to a depth below the TODO.

Let this depth be denoted $d_m > 0$. The viewing angle for full and KNR fusion is thus

$$\varphi_m = \min\left\{\pi, \operatorname{acos}\left(1 - \frac{d_m}{R'}\right)\right\}$$
$$\phi_m = \max\left\{\pi, \operatorname{acos}\left(1 - \frac{d_m}{R'_v}\right)\right\}$$
$$\psi_m = \min\left\{\pi, \operatorname{acos}\left(1 - \frac{d_m}{R'_c}\right)\right\}$$

8.2 Spot Intensity

8.3 Ring Intensity

Part III

Implementation

Chapter 9

API

9.1 Fusion Modes

9.2 Diffusion

9.3 Intensity

9.3.1 Point Spread Function

9.3.2 TIRF Zone

9.3.3 Spot Intensity

9.3.4 Ring Intensity

Chapter 10

Model Usage

Due to the diminutive nature of cells and vesicles, the model implementation would require a very small stepping size. Fortunately, the units used in the model only require consistency, thus input units are specified when used.

Part IV

Mode Discernment

Chapter 11

Total Concentration on Fused Vesicle Membrane

One metric for mode discernment in the theoretical space is the rate of decrease of total concentration on the vesicle.

Chapter 12

TIRF Microscopy Simulation

Chapter 13

Regional Intensity

13.1 Spot Intensity

13.2 Ring Intensity

13.3 Point Spread

13.4 TIRF Zone

13.5 Frame Rate

Chapter 14

Discernment