Continuum Diffusion Rate of Enzymes by Solving the Smoluchowski Equation

Finite element Method Application

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Outline

- To introduce the biological applications of the finite element tool kit (FEtk).
- To introduce the basic math background in solving diffusion problems.
- Examples to solve Steady-state SMOL equations and preliminary visualization.
  - Analytical tests (Aug. 10th)
  - mAChE monomer (Aug. 10th)
  - mAChE tetramer (Aug. 11th)

Smoluchowski Equation

Describes the over-damped diffusion dynamics of non-interacting particles in a potential field.

$$\frac{\partial p(\vec{r}, t | \vec{r}_0, t_0)}{\partial t} = -\nabla \cdot D[\nabla - \beta \nabla p(\vec{r}, t | \vec{r}_0, t_0)]$$

Or for $F(\vec{r}) = -\nabla U(\vec{r})$

$$\frac{\partial p(\vec{r}, t | \vec{r}_0, t_0)}{\partial t} = -\nabla \cdot D e^{-\beta U(\vec{r})} \nabla e^{\beta U(\vec{r})} p(\vec{r}, t | \vec{r}_0, t_0)$$

Steady-state Formation

$$\frac{\partial p(\vec{r}, t)}{\partial t} = 0$$

$$\Rightarrow \nabla \cdot D(\vec{r})[\nabla p(\vec{r}) + \beta p(\vec{r}) \nabla U(\vec{r})] = 0$$

Or in flux operator $J$:

$$\nabla \cdot \vec{J}(\vec{r}) = 0$$

where

$$\vec{J}(\vec{r}) = D(\vec{r})[\nabla p(\vec{r}) + \beta p(\vec{r}) \nabla U(\vec{r})]$$
Boundary conditions for SSSE

1. \( p(\mathbf{r}) = p_{\infty} \) for \( \mathbf{r} \in \Gamma_a \)
2. \( p(\mathbf{r}) = 0 \) (Dirichlet BC) for \( \mathbf{r} \in \Gamma_b \)
3. \( \mathbf{n} \cdot \mathbf{J}(\mathbf{r}) = a(\mathbf{r})p(\mathbf{r}) \) (Robin BC)
4. \( \mathbf{n} \cdot \mathbf{J}(\mathbf{r}) = 0 \) for \( x \in \Gamma_r \)

Diffusion rate:
\[
\frac{\partial}{\partial t} \cdot \mathbf{J}(\mathbf{r}) dS = k \mathbf{P}_{\text{diff}}
\]

Weak formation of SSSE

Find \( p_i \in \mathbb{P}_0 + V_i \) such as \( \langle F(p_i), v_i \rangle > 0 \) for all \( v_i \in V_h \)

\[
\langle F(p_i), v_i \rangle = \int_{\Omega} \nabla v_i \cdot \mathbf{J}(\mathbf{r}) d\mathbf{r} - \int_{\Gamma_a} v_i a(\mathbf{r}) \mathbf{J}(\mathbf{r}) dS
\]

\[
\langle F(p_i), v_i \rangle = \int_{\Omega} \nabla v_i \cdot \mathbf{J}(\mathbf{r}) d\mathbf{r} - \int_{\gamma_a} v_i \mathbf{J}(\mathbf{r}) dS
\]

Note that the boundary integral on \( \Gamma_a \) vanishes due to the test function vanishes on the non-reactive boundaries.

Finite element discretization of SSSE

1. Define a function space \( V_h = \{ v_i \} \) (\( v_i \): piece-wise linear FE basis functions defined over each tetrahedral vertex), and assume the solution to SSSE has the form
\[
p_i(\mathbf{r}) = \sum a_i v_i(\mathbf{r}), \quad p_i \in \mathbb{P}_0 + V_i
\]

2. The second derivatives of \( V_h \) are not well defined, thus need reformulation of SSSE by integrating it with a test function \( v \):
\[
\int_{\Omega} \nabla v(\mathbf{r}) \cdot \mathbf{J}(\mathbf{r}) d\mathbf{r} = 0
\]
\[
\int_{\Omega} \nabla v(\mathbf{r}) \cdot \mathbf{J}(\mathbf{r}) d\mathbf{r} = \int_{\Gamma_a} v(\mathbf{r}) \mathbf{J}(\mathbf{r}) dS = 0
\]

Weak form of SSSE

Bilinear linearization form of SSSE

To apply a Newton iteration, we need to linearize \( \langle F(u), v \rangle \)

\[
\langle D\mathbf{F}(u)w, v \rangle = \frac{d}{dt} \langle F(u + tw), v \rangle = \int_{\Omega} D\mathbf{F} \cdot \mathbf{V} v d\mathbf{r}
\]

Algorithm 3.2. (Damped-inexact-Newton)

1. Given an initial \( u \)
2. While \( ||\langle F(u), v \rangle|| > \text{TOL} \) for some \( v \) do:
   1. Find \( \delta \) such that \( \langle D\mathbf{F}(u)\delta, v \rangle = -\langle F(u), v \rangle + \varepsilon, \quad \forall v \)
   2. Set \( u = u + \lambda \delta \)
end while
Potential gradient mapping

Currently, we have three ways to obtain potential gradient \( \nabla U(r) \):

- **Boundary element method:**
  - **Pro:** it can easily calculate the \( \nabla U(r) \) at any spatial position.
  - **Con:** \( \nabla U(r) \) near the protein surface is hard to calculate accurately.

- **Finite difference method:**
  - **APBS:** \( \frac{U(r_{ext}) - U(r_{int})}{2h} \)

- **Finite element method:**
  - Treat the cubic grid as the FE cubic mesh
  - Use basis functions to calculate the force on the tetrahedral FE node position.
Solving SSSE by FEtk

**FE discretization of SSSE (weak form)**

with FE basis

**A massive set of linear equations**

\[ Au = b \]

**Iterative methods**

**FE solution**

\[ \int_{\Gamma} \sigma \cdot n dS = \int_{\Omega} \nabla J \cdot \mathbf{r} \]

**Diffusion rate**

\[ \text{Diffusion rate} \]

Example 1: Analytical test

Mesh preparation: Netgen 4.4 (http://www.hpfem.jku.at/netgen/)

Netgen is an excellent mesh generator, especially for the spherical shaped objects.

The finite problem domain is the spherical test case.

Example 1: Analytical test

For a spherically symmetric system with a Coulombic form of the PMF, \( W(r) = q/(4 \pi r) \), the SSSE can be written as

\[
\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \cdot f(r)) = \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 D \frac{\partial p}{\partial r} - \beta p \frac{q^2}{4 \pi \varepsilon r^2}) = 0
\]

Suppose \( Q = \frac{\beta q q}{4 \pi \varepsilon} \), \( p(r_1) = 0 \), \( p(r_2) = P_{\text{bulk}} \)

Then, \( k_{\text{on}} = \frac{4 \pi Q D r_1^2}{Q} \)

If \( Q = 0 \), \( k_{\text{on}} = \frac{4 \pi D r_1^2}{1 + \frac{1}{r_1}} \)
Example 1: Analytical test

Example 1: Analytical test (q_{1} = 1.0)

Example 1: Analytical test (q_{1} = 0.0)

Example 1: Analytical test (q_{1} = -1.0)

Certainly, there is no difference at any ionic strength.
Example 2: mAChE monomer

**Why Study AChE?**

- AChE breaks down ACh at the post-synapse in the neuromuscular junction, terminating the neural signal
- Because of its critical function, AChE is a target for medical agents, insecticides, chemical warfare agents
- The reaction is extremely fast, approaching diffusion limit. Thus, a good target to study diffusion both experimentally and computationally
- Part of efforts toward synapse simulation at cellular level

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Sub-types of AChE

Three different types of AChE subunits from the same gene, but with alternative splicing of the C-terminal:

- Type R (‘readthrough’) produce soluble monomers; they are expressed during development and induced by stress in the mouse brain.
- Type H (‘hydrophobic’) produce GPI-anchored dimers, but also secreted molecules; they are mostly expressed in red blood cells, where their function is unknown.
- Type T (‘tailed’) represent the forms expressed in brain and muscle. This is the dominate form of AChE, and also exists for butyrylcholinesterase (BChE).

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From Gene to protein

Giles, K., (1997) Protein Engineering, 10, 677-685

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Neuromuscular Junction

http://fig.cox.miami.edu/~cmallery/150/neuro/neuromuscular-sml.jpg
Catalytic Mechanism in AChE

Acetylcholinesterase (AChE) catalyzes the hydrolysis of acetylcholine (ACh) to acetate and choline.

\[
\begin{align*}
\text{ACh} + \text{AChE} & \rightarrow \text{Acetate} + \text{Choline} + \text{AChE} \\
\text{Acetate} + \text{H}_2\text{O} & \rightarrow \text{Acetic Acid} + \text{H}_2\text{O}
\end{align*}
\]

Adapted from Dressler & Potter (1991) Discovering Enzymes, p.243

AChE Catalytic Center

AChE has a 'deep gorge' leading to its active site.

Finite element mesh generation

- LBIE-mesher (Bujal group at UT, Austin):
  (http://www.ices.utexas.edu/CCV/software/)
- \( r_1 \sim 40 \text{r}_0 \) (r: biomolecule size)
- Adaptive tetrahedral mesh generation by contouring a grid-based inflated vDW accessibility map for region S0
- Extend mesh to region S1 spatial adaptively

Reactive boundary assignment

The origin: carbonyl carbon of Ser203

Sphere 1: (0.0, 16.6, 0.0) \( r = 12\text{Å} \)
Sphere 2: (0.0, 13.6, 0.0) \( r = 6\text{Å} \)
Sphere 3: (0.0, 10.6, 0.0) \( r = 6\text{Å} \)
Sphere 4: (0.0, 7.6, 0.0) \( r = 6\text{Å} \)
Sphere 5: (0.0, 4.6, 0.0) \( r = 6\text{Å} \)
Sphere 6: (0.0, 1.6, 0.0) \( r = 6\text{Å} \)
Reactive boundary assignment

mAChE wild-type ligand binding rate

Debye-Hückel limiting law:

\[ k_{on} = (k_{on}^0 - k_{on}^H) 10^{1.18z_ew} \sqrt{\tau} + k_{on}^H \]

Mesh quality and refinement

Why do we need to refine the mesh?

Mesh quality and refinement:
- Original: 121,670 nodes, 656,823 simplexes.
- Final: 1,144,585 nodes, 6,094,440 simplexes.

\[ \epsilon < 5.0 \times 10^5 \]
Visualization of ligand concentration distribution

0.000M 0.025M 0.100M 0.150M 0.300M 0.600M

What can we learn from last several cases?

- The concentration distribution is affected by the ionic strength substantially.

- $k_{on}$ exhibits an ionic strength dependence strongly indicative of electrostatic acceleration. The high ionic strength environment lessens the electrostatic interactions between the active site and the ligand, (cf. J. Mol. Biol. 1999, 291, 149-162)

Additional reading materials

3. advanced diffusion materials:
   http://www.ks.uiuc.edu/Services/Class/PHY349NSM/