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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.

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

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

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

Steady-state Formation

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

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

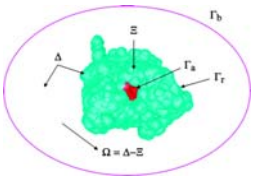
Or in flux operator J:

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

where

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

Boundary conditions for SSSE



- Δ -- whole domain
- Ξ -- biomolecular domain
- Ω -- free space in Δ
- Γ_a – reactive region
- Γ_r – reflective region
- Γ_b – boundary for Δ

(1) $p(\vec{r}) = p_{bulk}$ for $\vec{r} \in \Gamma_b$

(2) $p(\vec{r}) = 0$ (Dirichlet BC) for $\vec{r} \in \Gamma_a$
or $\vec{n} \cdot \vec{J}p(\vec{r}) = \alpha(\vec{r})\, p(\vec{r})$ (Robin BC)

(3) $\vec{n} \cdot \vec{J}p(\vec{r}) = 0$ for $x \in \Gamma_r$

Diffusion rate:

$$k = \frac{\int_{\Gamma_a} \vec{n} \cdot \vec{J}p(\vec{r})\, dS}{p_{bulk}}$$

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 of

$$p_h(\vec{r}) = \sum_i a_i v_i(\vec{r}), \quad p_h \in \bar{p}_h + V_h$$

2. The second derivatives of V_h are not well defined, thus need reformulation of SSSE by integrating it with a test function v:

$$\int_\Omega v(\vec{r}) \nabla \cdot \vec{J}p(\vec{r}) d\vec{r}^3 = 0$$

Weak form of SSSE

$$\Rightarrow \quad \int_\Omega \nabla v(\vec{r}) \cdot \vec{J}p(\vec{r}) d\vec{r}^3 - \int_{\Gamma_a} v(s)\alpha(s)p(s)ds - \int_{\Gamma_b} v(s)\vec{J}\bar{p}(s) \cdot \vec{n}(s)ds = 0$$

or $$\int_\Omega \nabla v(\vec{r}) \cdot \vec{J}p(\vec{r}) d\vec{r}^3 - \int_{\Gamma_a \cup \Gamma_b} v(s)\vec{J}\bar{p}(s) \cdot \vec{n}(s)ds = 0$$

http://www3.interscience.wiley.com/cgi-bin/fulltext/73503240/PDFSTART

Weak formation of SSSE

Find $p_h \in \bar{p}_h + V_h$ such as $< F(p_h), v_i >= 0$ for all $v_i \in V_h$

$$< F(p_h), v_i >= \int_\Omega \nabla v(x) \cdot Jp(x)dx - \int_{\Gamma_a} v(s)\alpha(s)p(s)ds - \int_{\Gamma_b} v(s)J\bar{p}(s) \cdot n(s)ds$$

$$< F(p_h), v_i >= \int_\Omega \nabla v(x) \cdot Jp(x)dx - \int_{\Gamma_a \cup \Gamma_b} v(s)J\bar{p}(s) \cdot n(s)ds$$

Note that the boundary integral on Γ_b vanishes due to the test function vanishes on the non-reactive boundaries.

Bilinear linearization form of SSSE

To apply a Newton iteration, we need to linearize $< F(u), v >$

$$\langle DF(u)w, v \rangle = \frac{d}{dt} \langle F(u + tw), v \rangle = \int_\Omega D\nabla w \cdot \nabla v dx$$

Algorithm 3.2. *(Damped-inexact-Newton)*

- *Given an initial* u
- *While* $(|\langle F(u), v \rangle| > TOL$ for some $v)$ *do:*
  (1) *Find* δ *such that* $\langle DF(u)\delta, v \rangle = -\langle F(u), v \rangle + r, \ \forall v$
  (2) *Set* $u = u + \lambda\delta$
- *end while*

Posteriori ERROR ESTIMATOR

$$\eta_s^2 = h_s^2 \| \nabla \cdot J_h \|_{L^2(s)}^2 + \frac{1}{2} \sum_{f \in I(s)} h_f^2 \| [n_f \cdot (D\nabla p(r))] \|_{L^2(f)}^2$$

h_s represent the size of the element.

$J_h(p;x)$ is the current estimate of the flux.

$f \in S$ denotes a face of simplex

h_s is the size of the face f

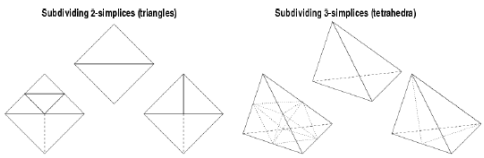
$[n \cdot J_h]$ denotes to the ``jump'' term across faces interior to the simplex.

$err = \sqrt{\sum_s \eta_s^2}$ Solve ⇒ Estimate ⇒ Refine

Mesh Mark and Refinement

Algorithm 3.1. *(Adaptive multilevel finite element approximation)*

- *While* $(\|u - u_h\|_X > \epsilon)$ *do:*
  - (1) *Find* $u_h \in \bar{u}_h + V_h \subset H_0^1(\Omega)$ *such that* $\langle F(u_h), v_h \rangle = 0, \ \forall\, v_h \in V_h \subset H_0^1(\Omega)$.
  - (2) *Estimate* $\|u - u_h\|_X$ *over each element.*
  - (3) *Initialize two temporary simplex lists as empty:* $Q1 = Q2 = \emptyset$.
  - (4) *Place simplices with large error on the "refinement" list* $Q1$.
  - (5) *Bisect all simplices in* $Q1$ *(removing them from* $Q1$*), and place any nonconforming simplices created on the list* $Q2$.
  - (6) $Q1$ *is now empty; set* $Q1 = Q2$, $Q2 = \emptyset$.
  - (7) *If* $Q1$ *is not empty, goto (5).*
- *End While.*

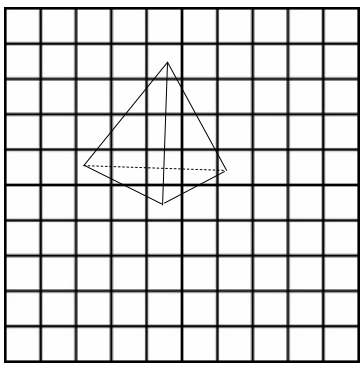


Potential gradient mapping

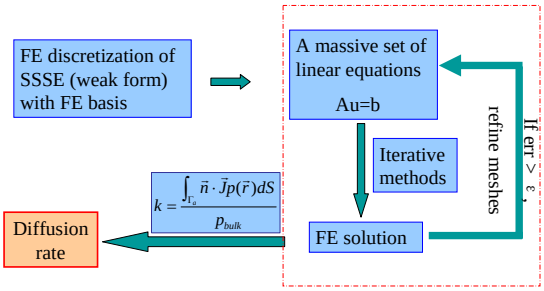
Currently, we have three ways to obtain potential gradient $\nabla U(r)$:

- 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: $\nabla U(r_j) = \frac{U(r_{j+1}) - U(r_{j-1})}{2h}$
- 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.

Potential gradient mapping



Solving SSSE by FEtk

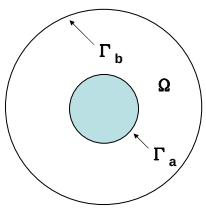


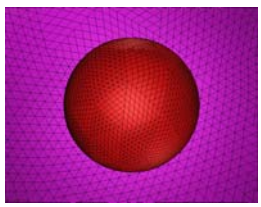
Example 1: Analytical test

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

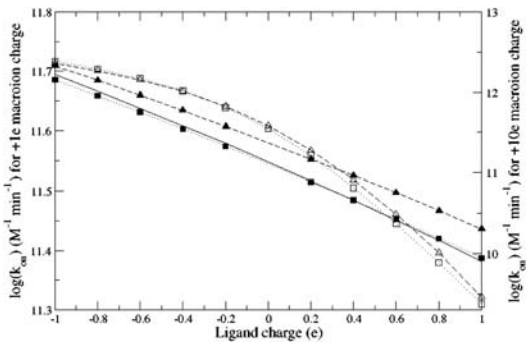
For a spherically symmetric system with a Coulombic form of the PMF, W(r) = q/(4 π ε r), the SSSE can be written as

$$\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 Jp) = \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 D(\frac{\partial p}{\partial r} - \beta p \frac{qq_l}{4\pi\varepsilon r^2})) = 0$$

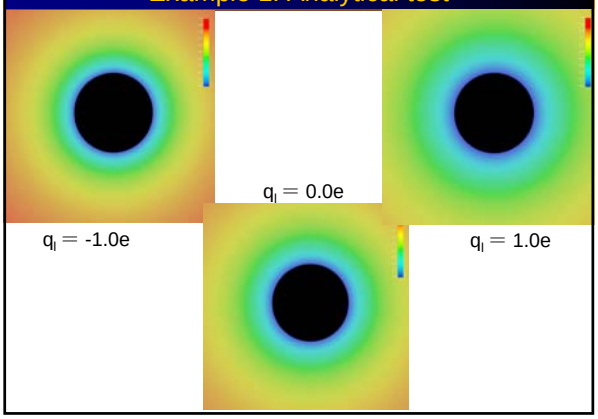
Suppose $Q = \frac{\beta q q_l}{4\pi\varepsilon}$, $p(r_1) = 0; p(r_2) = p_{bulk}$

Then, $k_{on} = \frac{4\pi Q D r_1^2}{e^{-\frac{Q}{r_2}} - e^{-\frac{Q}{r_1}}}$ If Q = 0, $k_{on} = \frac{4\pi D r_1^2}{\frac{1}{r_1} - \frac{1}{r_2}}$

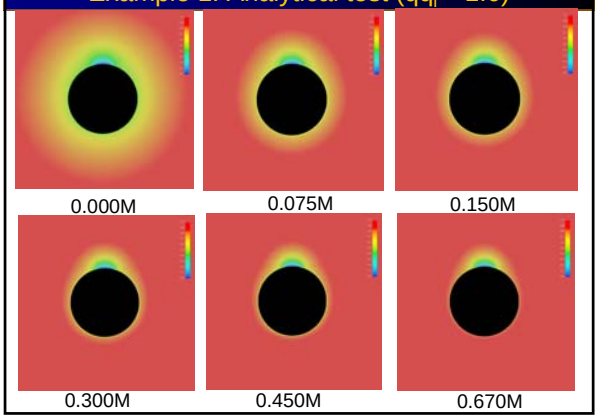
Example 1: Analytical test



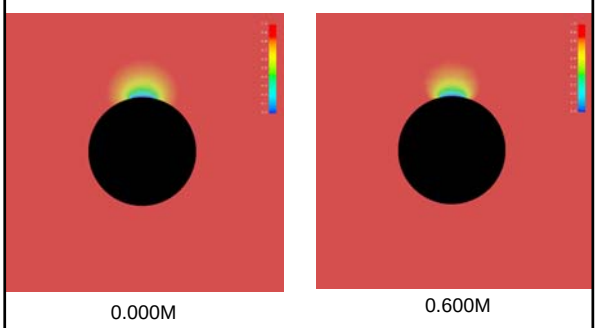
Example 1: Analytical test



Example 1: Analytical test (qq_l = 1.0)

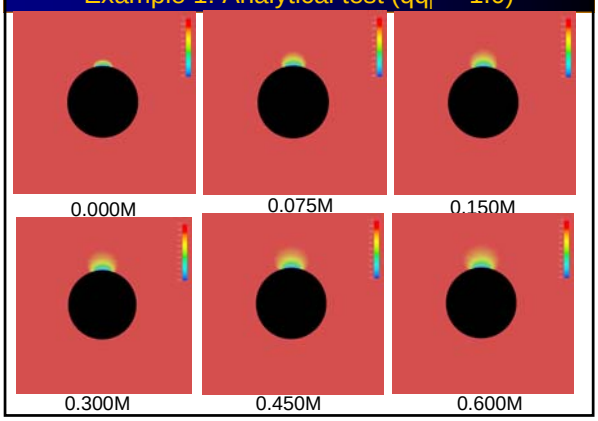


Example 1: Analytical test (qq_l = 0.0)



Certainly, there is no difference at any ionic strength.

Example 1: Analytical test (qq_l = -1.0)



Example 2: mAChE monomer

Why Study AChE?

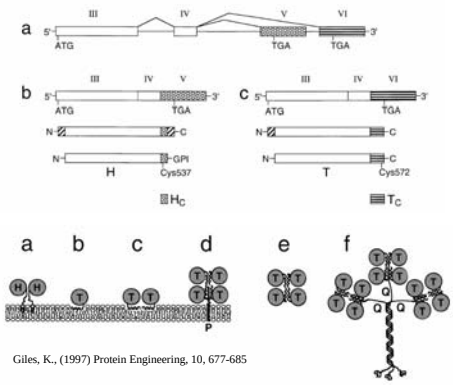
- AChE breaks down ACh at the post-synapse in the neuromuscular junction, terminating the neural signal
- Because of its critical function, AChE is a target for medical agents, insecticides, chemical warfare agents
- The reaction is extremely fast, approaching diffusion limit. Thus a good target to study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

Sub-types of AChE

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

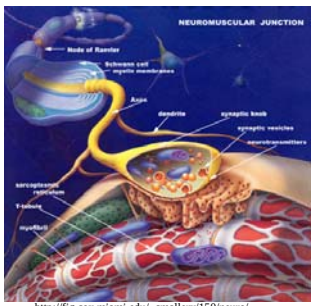
- Type R ('readthrough') produce soluble monomers; they are expressed during development and induced by stress in the mouse brain.
- Type H ('hydrophobic') produce GPI-anchored dimers, but also secreted molecules; they are mostly expressed in red blood cells, where their function is unknown.
- Type T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

From Gene to protein



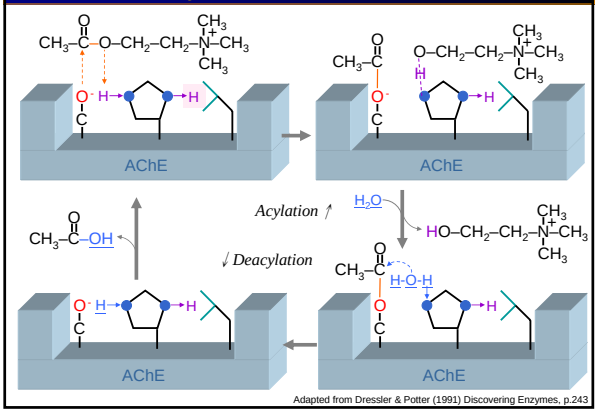
Giles, K., (1997) Protein Engineering, 10, 677-685

Neuromuscular Junction



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

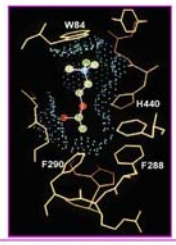
Catalytic Mechanism in AChE

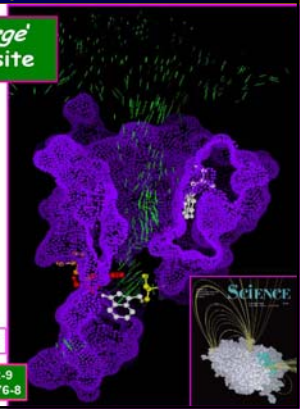


Adapted from Dressler & Potter (1991) Discovering Enzymes, p.243

AChE Catalytic Center

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

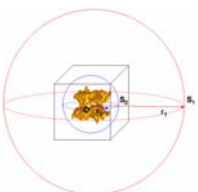




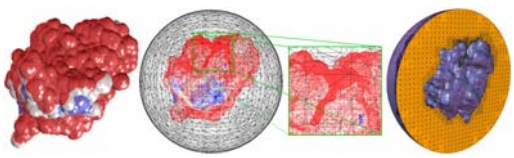
ACh bound in AChE active site

Sussman *et al* Silman (1991) *Science* 253, 872-9
Gilson *et al* Sussman (1994) *Science* 263, 1276-8

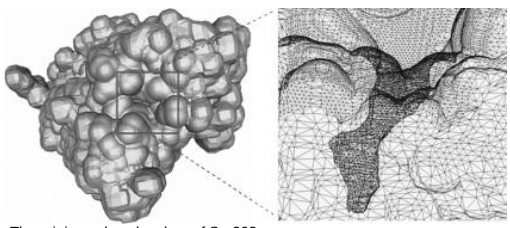
Finite element mesh generation



- LBIE-mesher (Bajaj group at UT, Austin): (http://www.ices.utexas.edu/CCV/software/)
- $r_1 \sim 40r_0$ (r: biomolecule size)
- Adaptive tetrahedral mesh generation by contouring a grid-based inflated vdW accessibility map for region S_0
- Extend mesh to region S_1 spatial adaptively



Reactive boundary assignment



The origin: carbonyl carbon of Ser203

Sphere 1: (0.0, 16.6, 0.0) r = 12Å

Sphere 2: (0.0, 13.6, 0.0) r = 6Å

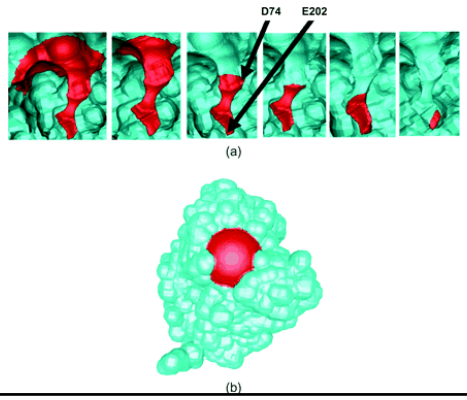
Sphere 3: (0.0, 10.6, 0.0) r = 6Å

Sphere 4: (0.0, 7.6, 0.0) r = 6Å

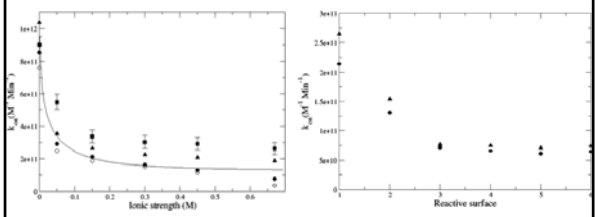
Sphere 5: (0.0, 4.6, 0.0) r = 6Å

Sphere 6: (0.0, 1.6, 0.0) r = 6Å

Reactive boundary assignment



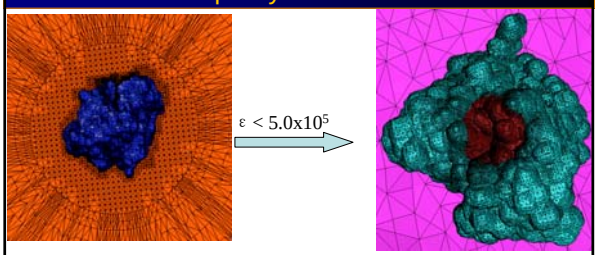
mAChE wild-type ligand binding rate



Debye-Huckel limiting law:

$$k_{on} = (k_{on}^{0} - k_{on}^{H})10^{-1.18|z_E z_I|\sqrt{I}} + k_{on}^{H}$$

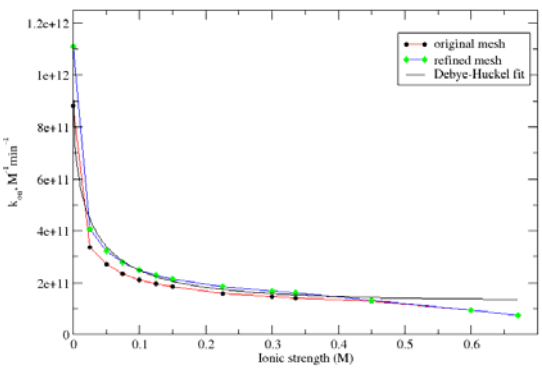
Mesh quality and refinement



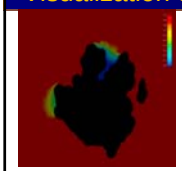
original: 121,670 node, 656,823 simplexes.

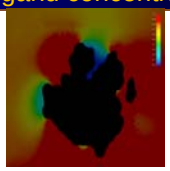
final: 1,144,585 node, 6,094,440 simplexes.

Why do we need to refine the mesh?



Visualization of ligand concentration distribution


0.000M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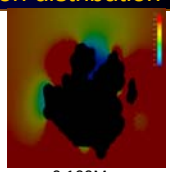
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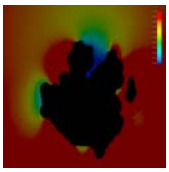
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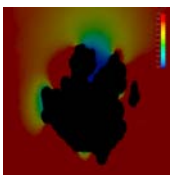
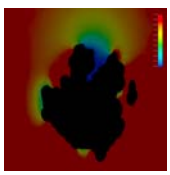

0.300M


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

1. http://en.wikipedia.org/wiki/Diffusion
2. Berg, H C. *Random Walks in Biology*. Princeton: Princeton Univ. Press, 1993
3. advanced diffusion materials:

http://www.ks.uiuc.edu/Services/Class/PHYS498NSM/

4. Adaptive Multilevel Finite Element Solution of the Poisson-Boltzmann Equation I: Algorithms and Examples. *J. Comput. Chem.*, 21 (2000), pp. 1319-1342.
5. Finite Element Solution of the Steady-State Smoluchowski Equation for Rate Constant Calculations. *Biophysical Journal,* 86 (2004), pp. 2017-2029.
6. Continuum Diffusion Reaction Rate Calculations of Wild-Type and Mutant Mouse Acetylcholinesterase: Adaptive Finite Element Analysis. *Biophysical Journal,* 87 (2004), pp.1558-1566.
7. Tetrameric Mouse Acetylcholinesterase: Continuum Diffusion Rate Calculations by Solving the Steady-State Smoluchowski Equation Using Finite Element Methods. *Biophysical Journal,* 88 (2005), pp. 1659-1665.