Multiscale Diffusion Modeling in Charged and Crowded Biological Environments

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joint work with
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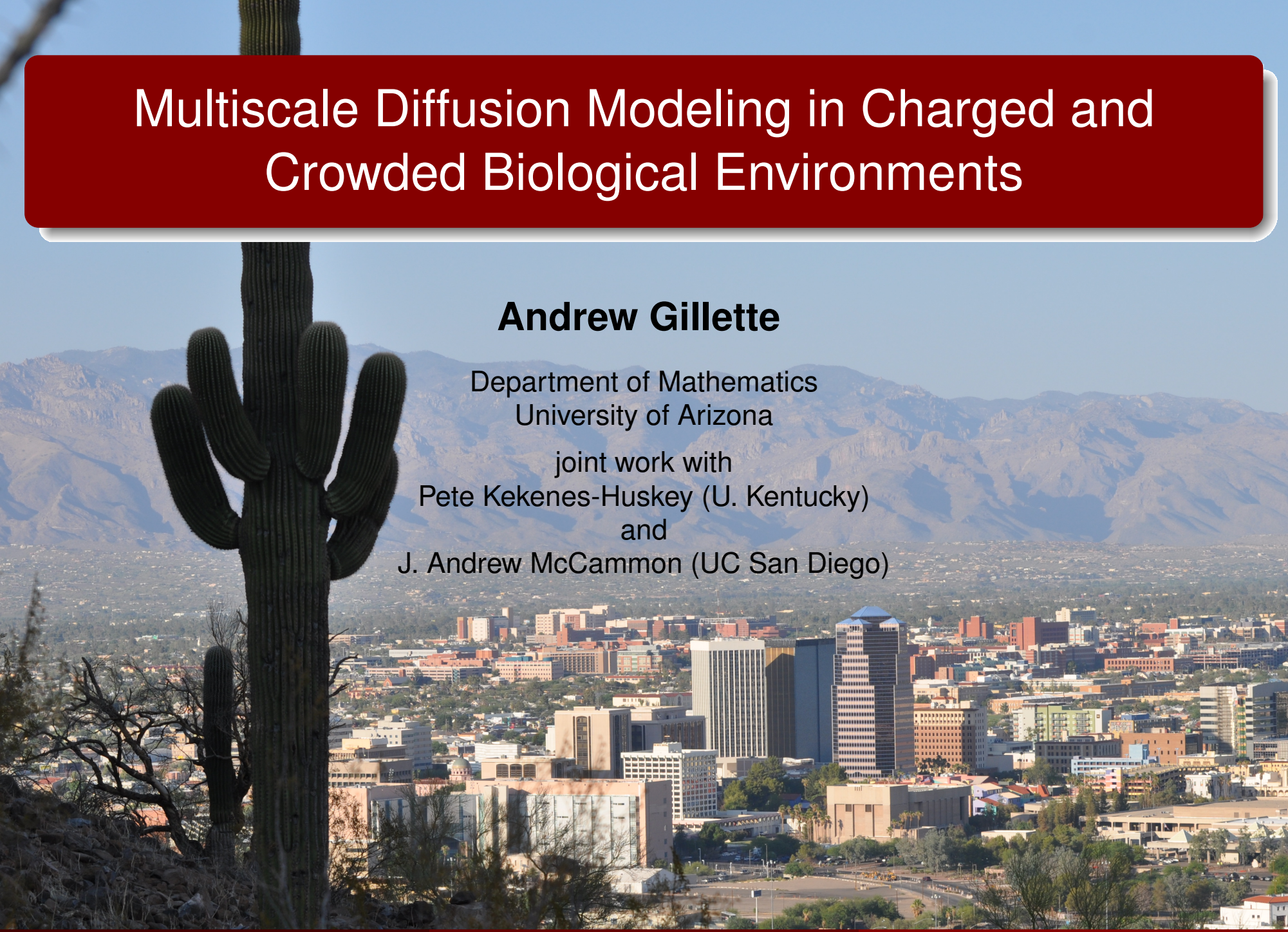
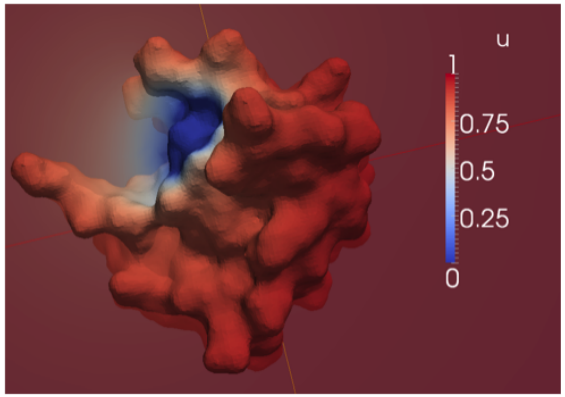
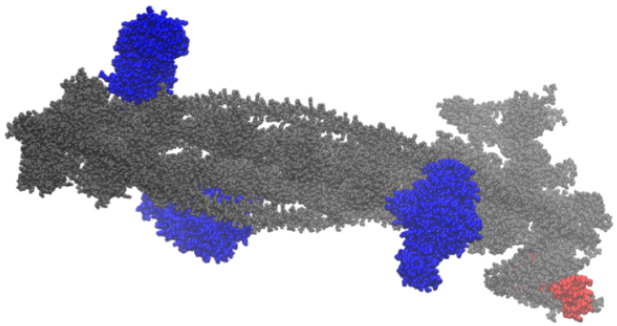
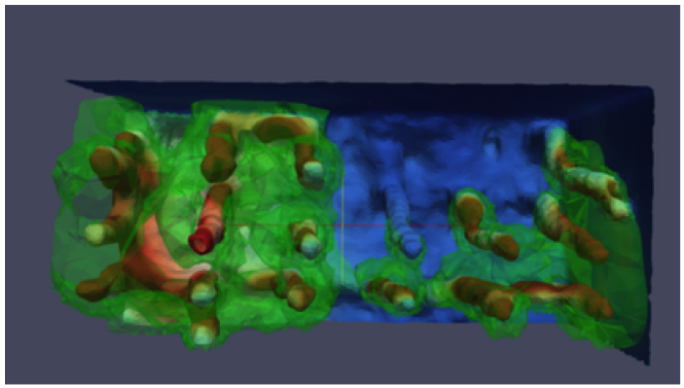


Diffusion in Crowded Biological Environments

Diffusion is a predominant signaling mechanism at multiple time and length scales and is constrained by the molecular and cellular environment.







Left: Troponin C protein, with steady state Ca^{2+} distribution shown.

Middle: Actin or 'thin' filament, with six bound **myosin heads** and **Troponin C**.

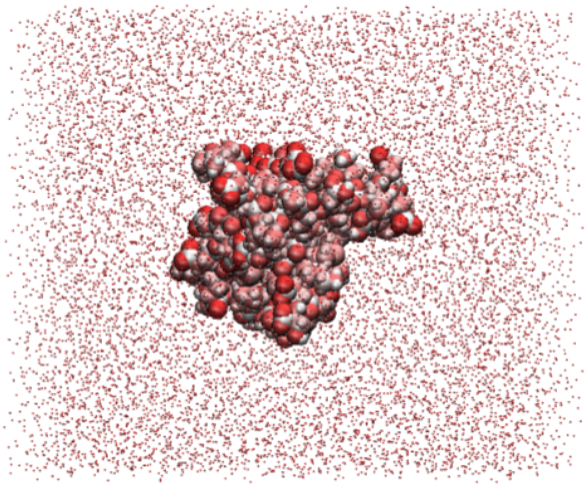
Right: Transverse tubules with Ca^{2+} diffusion in progress.
As the thin and thick filaments bind (horizontal; not shown),
the muscle fiber contracts.

Big question in biology

How does the molecular environment (e.g. arrangement of physical obstacles, electrostatic forces, chemical properties, etc.) influence diffusion of substrates?

Particle-based Models of Diffusion

Particle-based models accurately describe diffusional processes, but do so at a significant computational expense



- Molecular dynamics

  → Solve Newton's equations of motion for a flexible molecule

  → Account for trajectory + high-frequency molecular motions

  → 1 binding event can take 24 hours to simulate

- Brownian dynamics

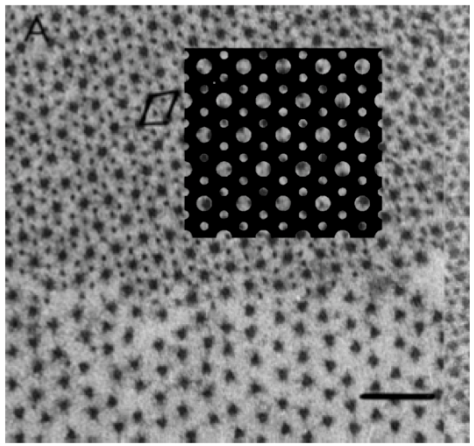
  → Solve Newton's equations of motion for rigid bodies

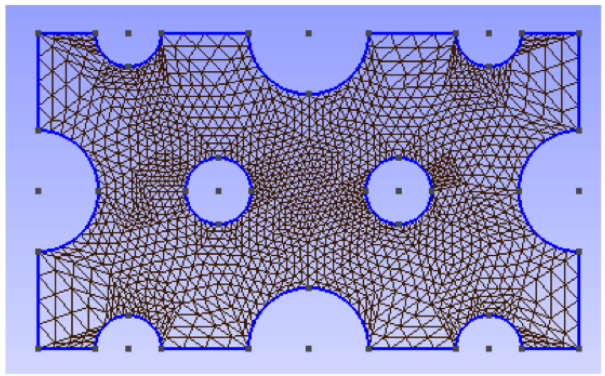
  → Account for translational / rotational trajectories

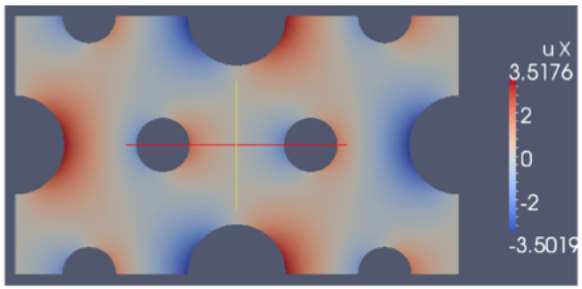
  → 1 million events can take 24 hours to simulate

Homogenization Approach to Diffusion

Homogenization approaches allow the computation of macro-scale quantities from a representative micro-scale region.







Macro-scale information

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Homogenization of Elliptic PDEs

Elliptic problem: Find $c^\epsilon : \Omega \to \mathbb{R}$ s.t.

$$\begin{cases} \nabla \cdot A^\epsilon \nabla c^\epsilon = f, & \mathbf{x} \in \Omega, \\ c^\epsilon = 0, & \text{on } \partial\Omega. \end{cases}$$

A standard homogenization approach assumes the following:

Periodicity: The solution c^ϵ and diffusion tensor A^ϵ are periodic on Ω with respect to a lattice of cubes of side length ϵ.

Scale separation: $\epsilon \ll \text{diam } \Omega$

Express c^ϵ as a function of the two length scales of interest: $\mathbf{x}$ and $\mathbf{y} := \mathbf{x}/\epsilon$:

$$c^\epsilon(\mathbf{x}, \mathbf{y}) = c_0(\mathbf{x}, \mathbf{y}) + \epsilon\, c_1(\mathbf{x}, \mathbf{y}) + \epsilon^2\, c_2(\mathbf{x}, \mathbf{y}) + \cdots$$

The ∇ operator becomes:

$$\nabla := \left[\frac{\partial}{\partial x_i} + \epsilon^{-1} \frac{\partial}{\partial y_i} \right]$$

Expand $\nabla \cdot A^\epsilon \nabla c^\epsilon$, then collect terms by powers of ϵ, yielding two separate problems: the order ϵ^0 problem (at the $\mathbf{x}$-scale) and the order ϵ^1 problem (at the $\mathbf{y}$-scale).

Homogenization of Elliptic PDEs

Suppose the diffusion tensor A^ϵ is known on a representative ϵ-cube Ω_ϵ. First solve:

Unit cell problem: Find $\chi : \Omega_\epsilon \to \mathbb{R}$ s.t. $$\frac{\partial}{\partial y_i}\left[A^\epsilon\right]_{ij}\left(\delta_{jk} + \frac{\partial \chi_k}{\partial y_j}\right) = 0, \qquad \mathbf{y} \in \Omega_\epsilon$$

with χ 1-periodic. *(Note: this is only required on one ϵ-cube!)*

Use the solution to compute:

Effective diffusion tensor: $$\left[\,\overline{A}\,\right]_{ij} := \int_{\Omega_\epsilon} \left[\,A^\epsilon\,\right]_{ij}\left(\delta_{jk} + \frac{\partial \chi_k}{\partial y_j}\right) dy$$

Use the effective diffusion tensor to solve:

Homogenized problem: Find $c : \Omega \to \mathbb{R}$ s.t. $$\begin{cases} \nabla \cdot \overline{A}\,\nabla c &= f, & \mathbf{x} \in \Omega, \\ c &= 0, & \text{on } \partial\Omega, \end{cases}$$

Prove that c is a good approximation to c^ϵ, defined by:

Elliptic problem: Find $c^\epsilon : \Omega \to \mathbb{R}$ s.t. $$\begin{cases} \nabla \cdot A^\epsilon\,\nabla c^\epsilon &= f, & \mathbf{x} \in \Omega, \\ c^\epsilon &= 0, & \text{on } \partial\Omega. \end{cases}$$

The Smoluchowski Equation

We now introduce an additional function $\psi^\epsilon : \Omega \to \mathbb{R}$, where

$$\psi^\epsilon(\mathbf{x}) := \text{strength (+ or -) of the electrostatic field at } \mathbf{x}.$$

Smoluchowski problem: Find $\tilde{c}^\epsilon : \Omega \times [0, T] \to \mathbb{R}$ s.t.

$$\frac{\partial \tilde{c}^\epsilon}{\partial t} = \underbrace{\nabla \cdot \tilde{A}^\epsilon \nabla \tilde{c}^\epsilon}_{\substack{\text{Regular diffusion} \\ \text{(Fick's law)}}} + \underbrace{\nabla \cdot \tilde{A}^\epsilon (\beta\, \tilde{c}^\epsilon\, \nabla \psi^\epsilon)}_{\substack{\text{drift in an electric field} \\ \text{(Ohm's law)}}} - f \qquad \text{on } \Omega,$$

where

$\tilde{A}^\epsilon$ = unknown tensor for unobstructed ionic diffusion, possibly dependent on $\mathbf{x}$

β = $\frac{1}{k_B T}$ with k_B the Boltzmann constant and T the temperature

f = net forcing effect of any ionic sinks or sources in Ω.

Suppose that $\tilde{A}^\epsilon$, $\tilde{c}^\epsilon$, and ψ^ϵ are all periodic with respect to the lattice of ϵ-cubes.

The Smoluchowski Equation

$$\frac{\partial \tilde{c}^{\,\epsilon}}{\partial t} = \nabla \cdot \tilde{A}^{\epsilon} \nabla \tilde{c}^{\,\epsilon} + \nabla \cdot \tilde{A}^{\epsilon} (\beta\, \tilde{c}^{\,\epsilon}\, \nabla \psi^{\epsilon}) - \quad f \qquad \text{on } \Omega,$$

We can re-write the right side using a bit of calculus (ignoring superscripts):

$$\begin{aligned}
\nabla \cdot A(\nabla c + \beta\, c\, \nabla \psi) &= \nabla \cdot A \frac{(\nabla c + c\, \beta\, \nabla \psi)\, e^{\beta \psi}}{e^{\beta \psi}} \\
&= \nabla \cdot A \left(\frac{e^{\beta \psi} \nabla c + c \nabla e^{\beta \psi}}{e^{\beta \psi}} \right) && \textit{chain rule!} \\
&= \nabla \cdot A\, e^{-\beta \psi} \nabla (e^{\beta \psi} c) && \textit{product rule!}
\end{aligned}$$

Set $\boxed{A^{\epsilon} := \tilde{A}^{\epsilon}\, e^{-\beta \psi^{\epsilon}}}$ and $\boxed{c^{\,\epsilon} := e^{\beta \psi^{\epsilon}} \tilde{c}^{\,\epsilon}}$ to get the Laplacian-like

Slotboom formulation (of the Smoluchowski problem): Find $c^{\,\epsilon} : \Omega \times [0, T] \to \mathbb{R}$ s.t.

$$\frac{\partial \tilde{c}^{\,\epsilon}}{\partial t} = \nabla \cdot A^{\epsilon} \nabla c^{\,\epsilon} - \quad f, \qquad \text{on } \Omega.$$

At steady state, this looks like the elliptic problem and is amenable to homogenization.

Computation of Diffusion Coefficients

The **unit cell problem** is: Find $\chi : \Omega_\epsilon \to \mathbb{R}$ such that:

$$\begin{cases} \dfrac{\partial}{\partial y_i}\left[A^\epsilon(\mathbf{y})\right]_{ij}\left(\delta_{jk} + \dfrac{\partial \chi_k}{\partial y_j}\right) = 0, & \text{on } \Omega_\epsilon, \\ \left[A^\epsilon(\mathbf{y})\right]_{ij}\left(\delta_{jk} + \dfrac{\partial \chi_k}{\partial y_j}\right) \cdot \hat{n}_i = 0, & \text{on } \partial\Omega_\epsilon. \end{cases}$$

The coefficients a_{ij} of the effective diffusion tensor $\overline{A}$ at the **x**-scale are then

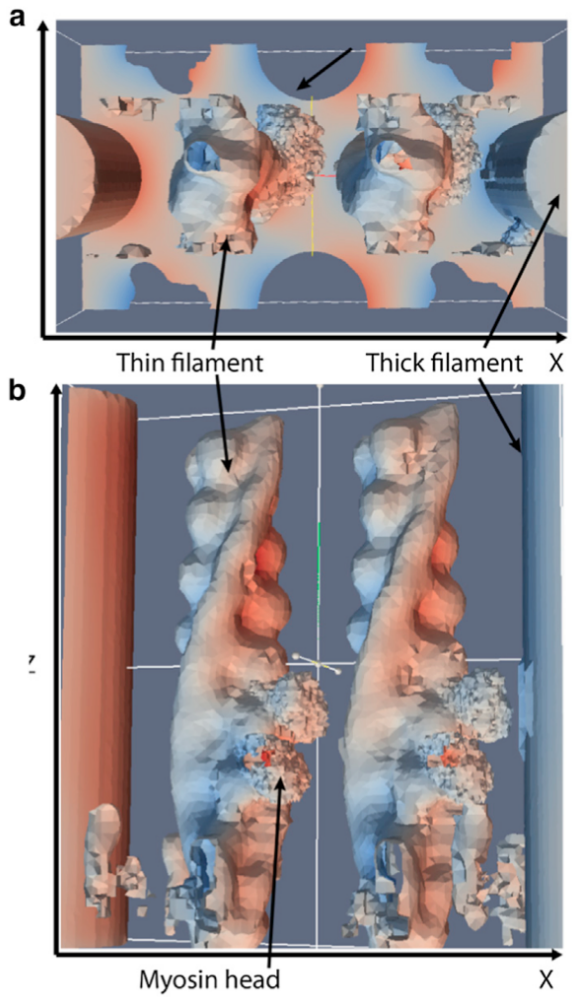
$$a_{ij} = \underbrace{\int_{\Omega_\epsilon}}_{\substack{\text{integral at} \\ \mathbf{y} \text{ scale}}} \left[A^\epsilon(\mathbf{y})\right]_{ij} \underbrace{\left(\delta_{jk} + \frac{\partial \tilde{\chi}_k}{\partial y_j}\right)}_{\substack{\text{from sol'n of} \\ \text{unit cell problem}}} dy,$$

where $A^\epsilon := \tilde{A}^\epsilon \, e^{-\beta \psi^\epsilon}$ with

$\to \tilde{A}^\epsilon(\mathbf{y})$ estimated by theoretical models (e.g. statistical mechanics or molecular dynamics) or physical experiments (e.g. diffusion spectroscopy)

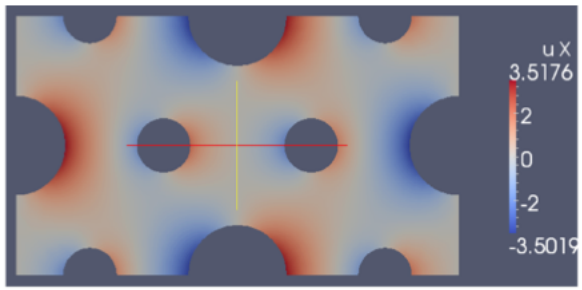
$\to \psi^\epsilon(\mathbf{y})$ estimated by a **y**-scale potential of mean force (e.g. electrostatic potential)

Computation of Diffusion Coefficients



→ Solutions of χ_x (top) and χ_z (bottom), with $\psi \equiv 0$ (pure diffusion only) using geometrically accurate thin filaments.

→ The χ_x solution resembles the solution for a mesh of perfect cylinders:



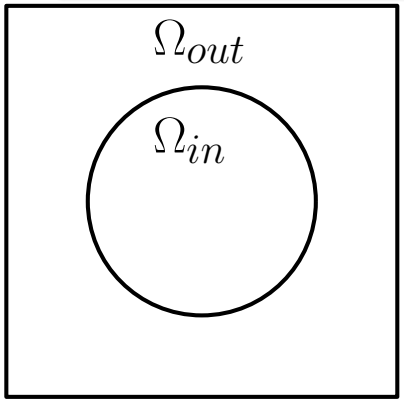
→ However, the myosin heads on the thin filament do seem to perturb the χ_x and χ_z solutions and affect the resulting diffusion rates, as we now quantify.

KEKENES-HUSKEY ET AL. *Molecular and Subcellular-Scale Modeling of Nucleotide Diffusion in the Cardiac Myofilament Lattice*, Biophysical Journal, Vol 105, Nov 2013.

Outline

Hashin-Shtrickman Theory

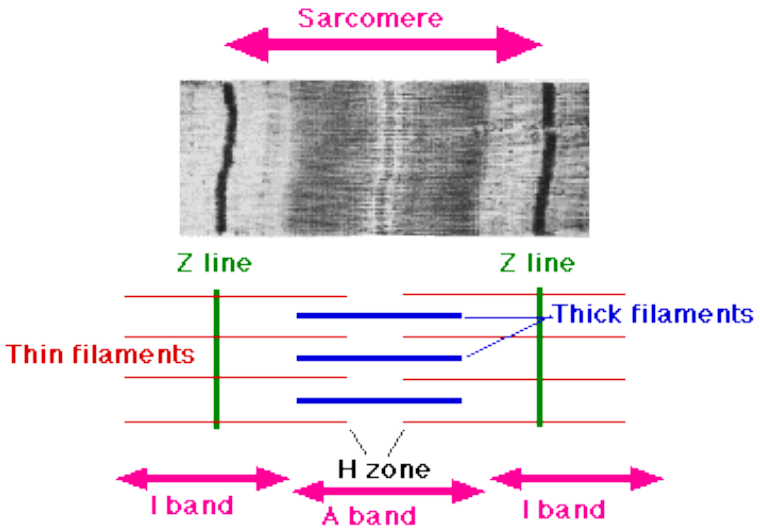
Hashin-Shtrickman Theory predicts effective diffusivities for a lattice of cylinders.



The H-S upper bound for the **x**-scale effective diffusion constant:

$$D = \frac{2\phi}{3-\phi} \quad \text{where} \quad \phi := \begin{matrix}\text{accessible} \\ \text{volume fraction}\end{matrix} = \frac{|\Omega_{out}|}{|\Omega_{in} \cup \Omega_{out}|}$$

The bound is normalized since $|\Omega_{in}| = 0 \;\Rightarrow\; \phi = 1 \;\Rightarrow\; D = 1$



(image from Wikipedia)

We hypothesized that:

$\rightarrow$ Increased thin-thick filament overlap influences diffusional anisotropy,

$\rightarrow$ Lattice spacing affects diffusion rates,

$\rightarrow$ Binding of myosin head affects diffusion rates,

in a manner correlating to the accessible volume fraction ϕ.

Computational experiments

Region	$[D_{xx}, D_{yy}, D_{zz}]$	ϕ	HS bound (D_{xx})
A-band (filament overlap region)	[0.42,0.45,0.59]	0.61	0.44
I-band (thin filament only)	[0.59,0.64,0.75]	0.77	0.62
H-zone (thick filament only)	[0.70,0.71,0.82]	0.82	0.69
Myosin-actin spacing			
16.43 nm	[0.26,0.26,0.37]	0.45	0.29
18.26 nm	[0.34,0.35,0.46]	0.53	0.36
20.08 nm	[0.44,0.44,0.57]	0.61	0.44
# cross-bridges (18.26 nm spacing)			
3	[0.34, 0.35, 0.46]	0.53	0.36
2	[0.38, 0.37, 0.50]	0.56	0.39
1	[0.38, 0.41, 0.54]	0.58	0.41
0	[0.42, 0.45, 0.59]	0.61	0.44

Observations:

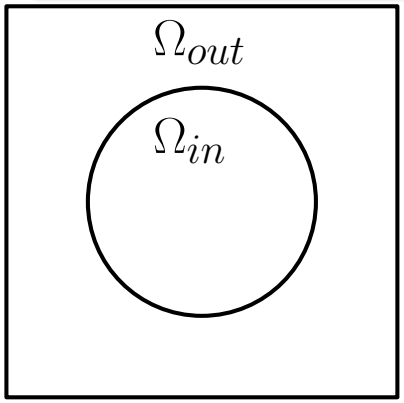
$\rightarrow$ Diffusion can be anisotropic in different sarcomere regions

$\rightarrow$ Myosin-actin spacing influences diffusion rates

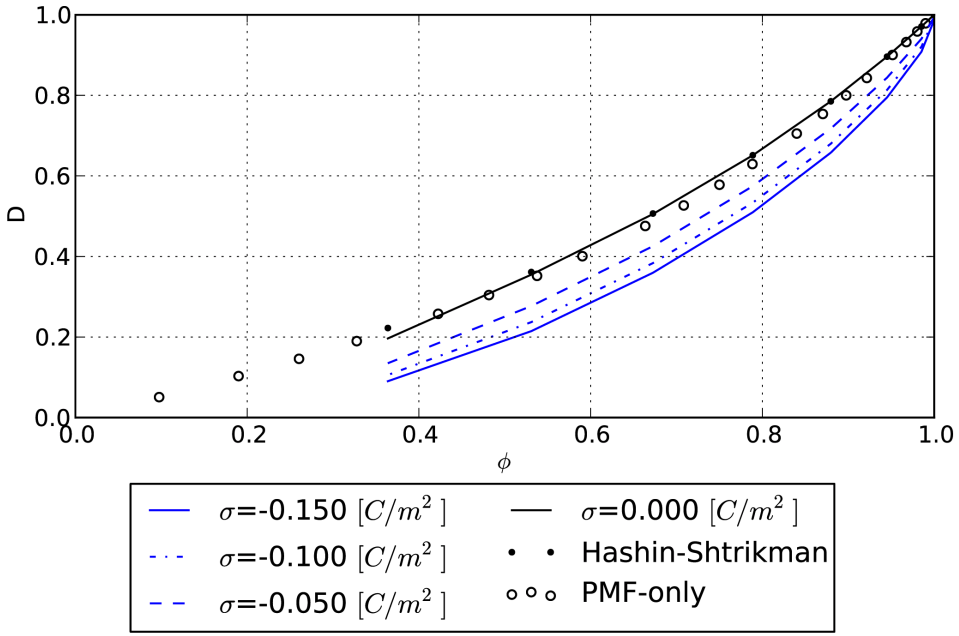
$\rightarrow$ The number of bound myosin heads influences diffusion rates.

Incorporating electrostatics

How does the electrostatic potential ψ influence the ***rate*** of decrease of diffusion with respect to accessible volume fraction ϕ?



- Instead of explicit obstacles, represent a cylindrical boundary implicitly by a potential of mean force ψ.
- Inside the cylinder, ψ is defined by a hard-sphere potential, effectively excluding particles from inside the cylinder.
- Outside the cylinder, ψ is defined in terms of a **surface charge** σ distributed uniformly on the surface of the cylinder.



$\sigma = 0 \implies$ diffusion unhindered by electric forces.

$\sigma < 0 \implies$ repulsive interaction with cylinder

Computing *D* via our method respects the H-S bound and confirms that repulsive interaction $\implies$ slower effective diffusion

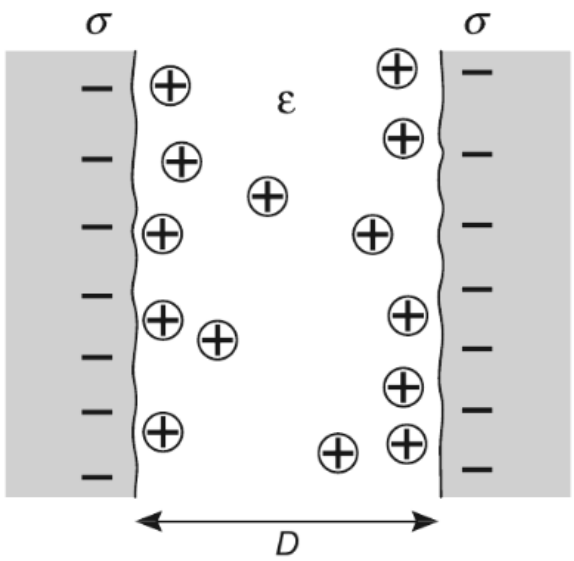
Van der Waals Forces

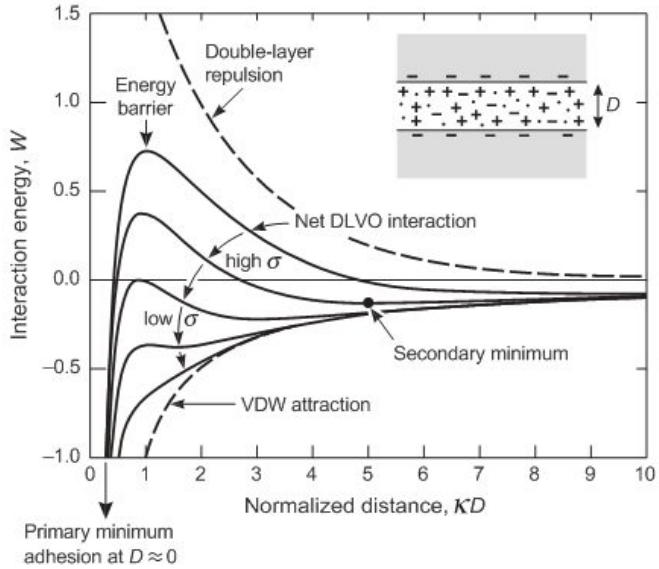
Show Van der Waals Forces video:

`http://www.youtube.com/watch?v=G1jGeeSWhXY`

Arbitrary Potentials of Mean Force

Derjaguin and Landau, Verwey and Overbeek or **DLVO theory** describes the force on a positively charged ion $\oplus$ located between surfaces with negative charge σ.





High σ, dilute $\oplus$: Surfaces repel strongly, up to van der Waals energy barrier

High σ, increased $\oplus$: A secondary minimum occurs where the ionic $\oplus$ "atmosphere" provides a "screen" to the surface repulsion.

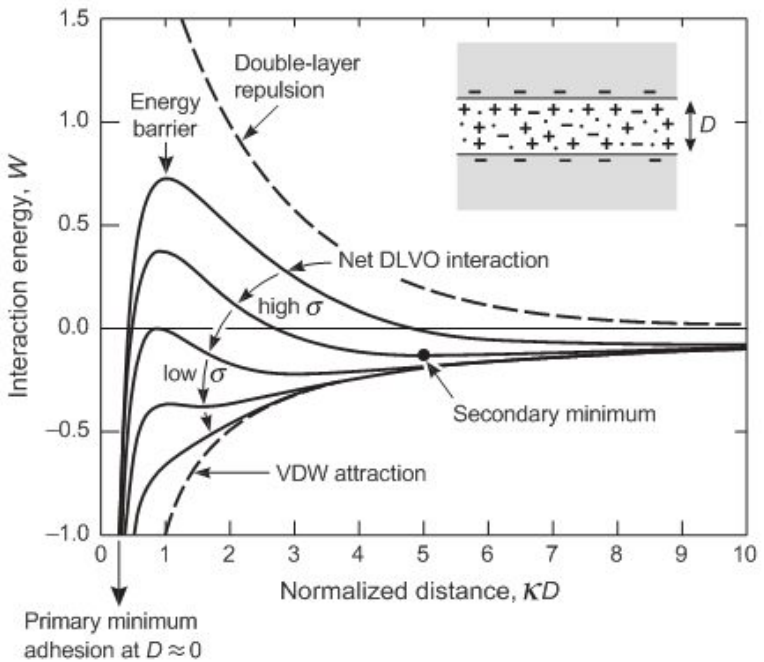
Low σ: Energy barrier is lower due to decreased surface charge.

Nearly zero σ: Essentially pure van der Waals attraction.

Arbitrary Potentials of Mean Force

Derjaguin and Landau, Verwey and Overbeek or **DLVO theory** describes the force on a positively charged ion $\oplus$ located between surfaces with negative charge σ.

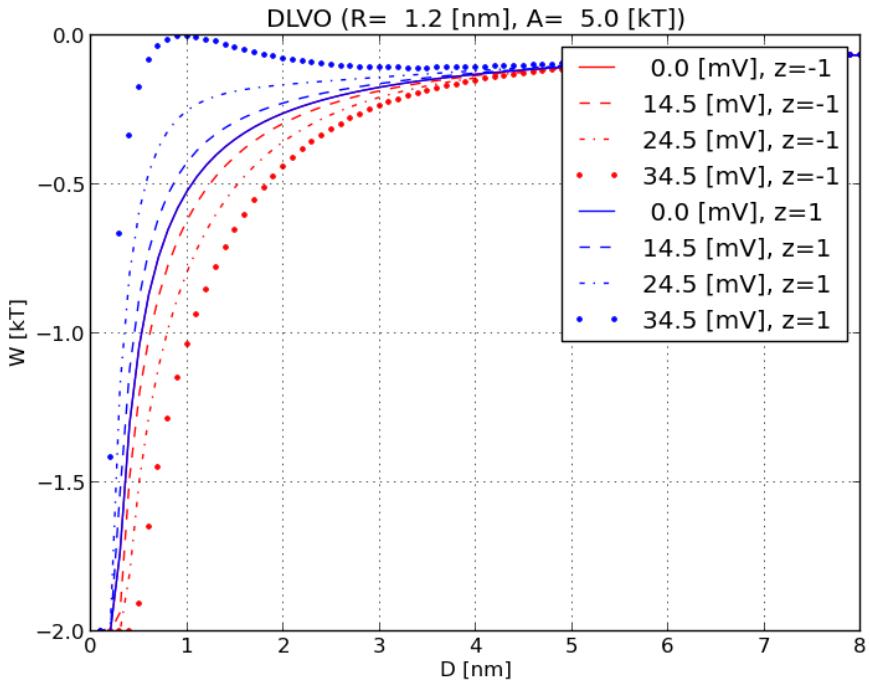
$$\psi(d) = \underbrace{\frac{R\,Z}{2\,e^{\kappa d}}}_{\text{screened electro-static interaction}} - \underbrace{\frac{A\,R}{12\,d}}_{\text{attractive Van der Waals interaction}}$$



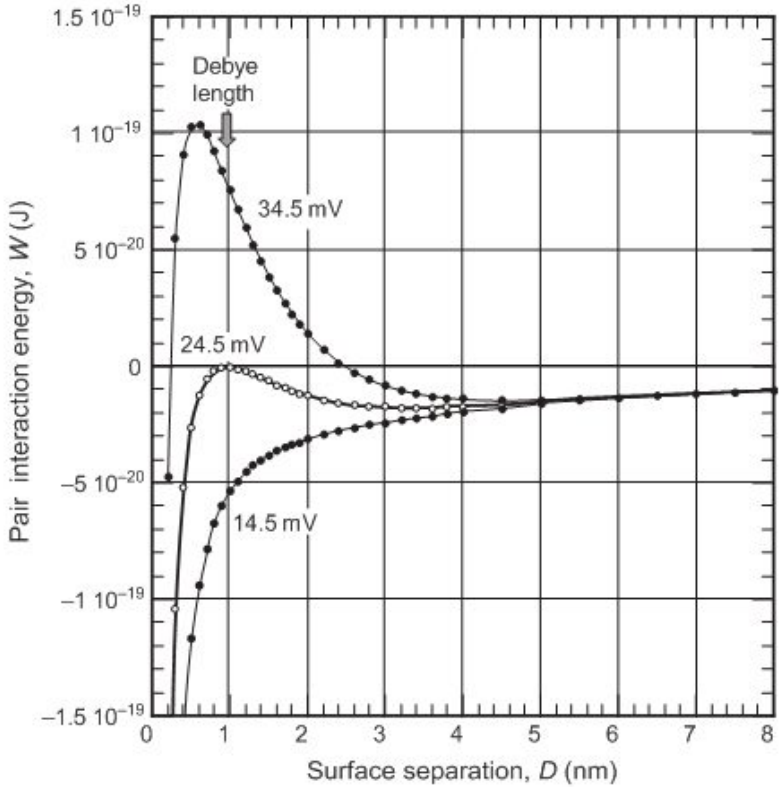
d	=	diffuser-obstacle separation distance
R	=	diffuser radius
Z	=	interaction constant
$1/\kappa$	=	Debye length
A	=	Hamaker constant
σ	=	surface charge density

ISRAELACHVILI *Intermolecular and surface forces*, 3rd ed., Academic Press, 2011.

DLVO Homogenized FEM Validation



Using our homogenized FEM approach, we compute the pair interaction energy (W) between a positively charged sphere with DLVO potential and another sphere of unit charge as a function of separation distance (D).



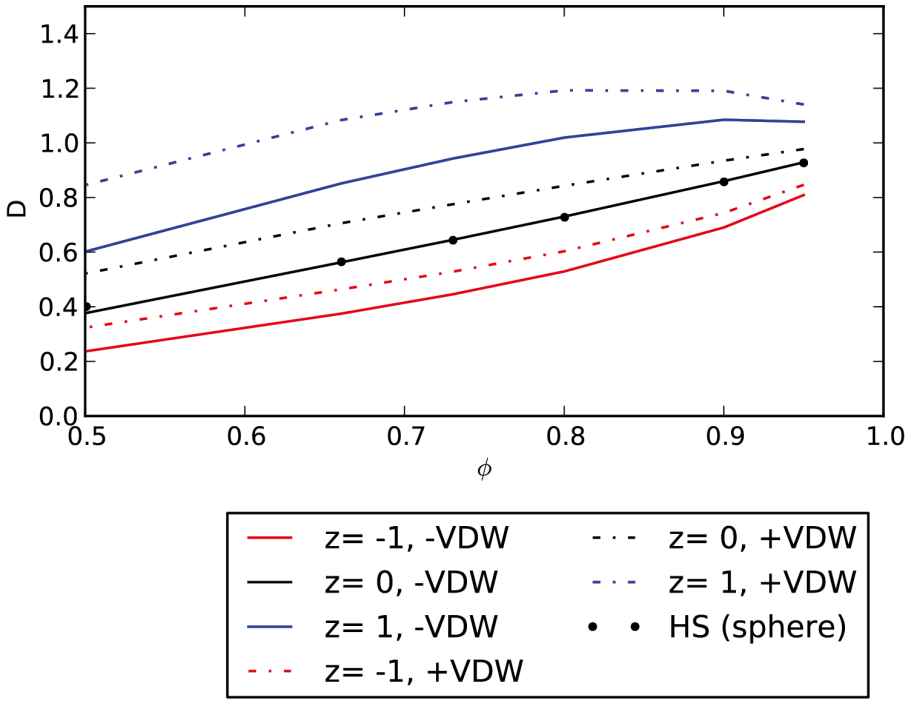
Our computations show the same behavior as DLVO theory; the right is Figure 14.14 from

ISRAELACHVILI *Intermolecular and surface forces*, 3rd ed., Academic Press, 2011.

DLVO Homogenized FEM Results

$\longrightarrow$ We compute the effective diffusion constant D as a function of accessible volume fraction ϕ around a charged spherical protein.

$\longrightarrow$ We consider **repulsive**, **attractive**, and **neutral** diffusers.



$\longrightarrow$ Solid lines show that attractive differs have *faster* diffusion relative to neutral or repulsive diffusers (somewhat surprising).

$\longrightarrow$ Dotted lines show that inclusion of Van der Waals interactions (via the DLVO potential) increase D for every diffuser type, with most significant effects at small ϕ when the attractive region represents a greater percentage of the free volume.

DLVO Homogenized FEM Results

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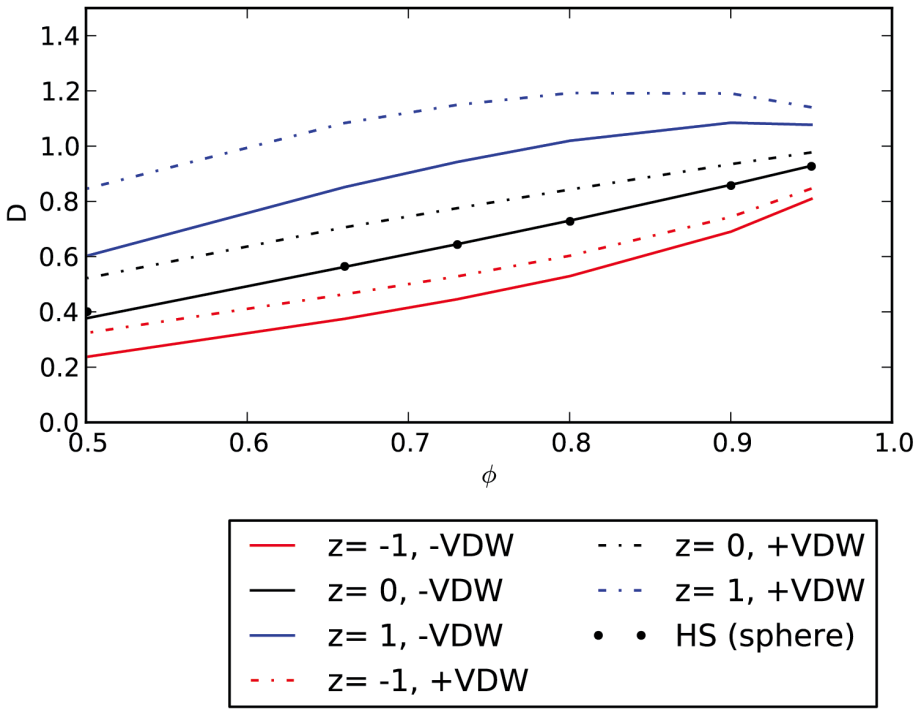
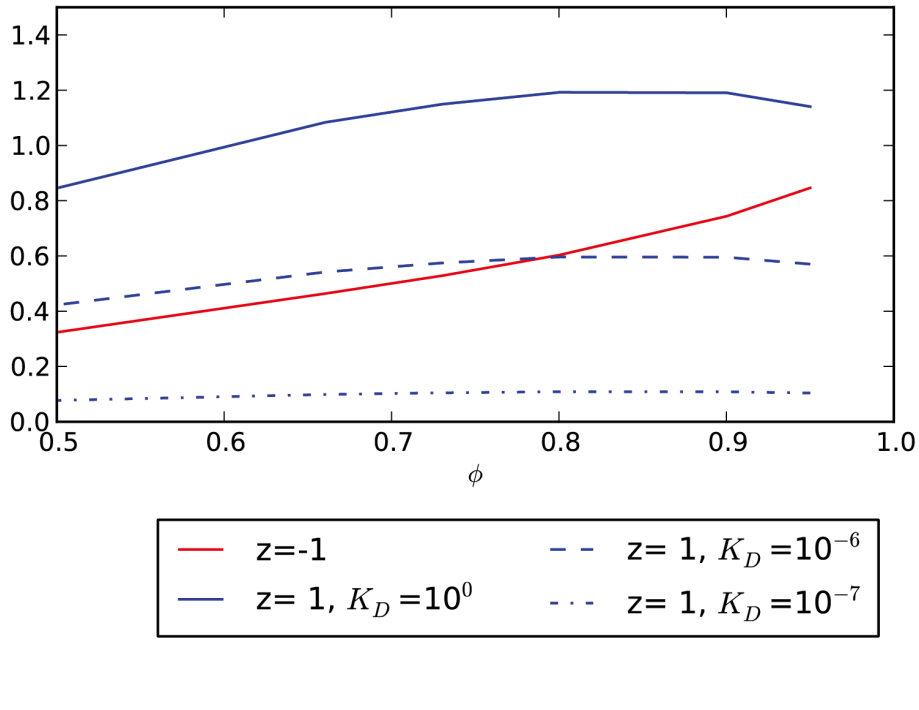
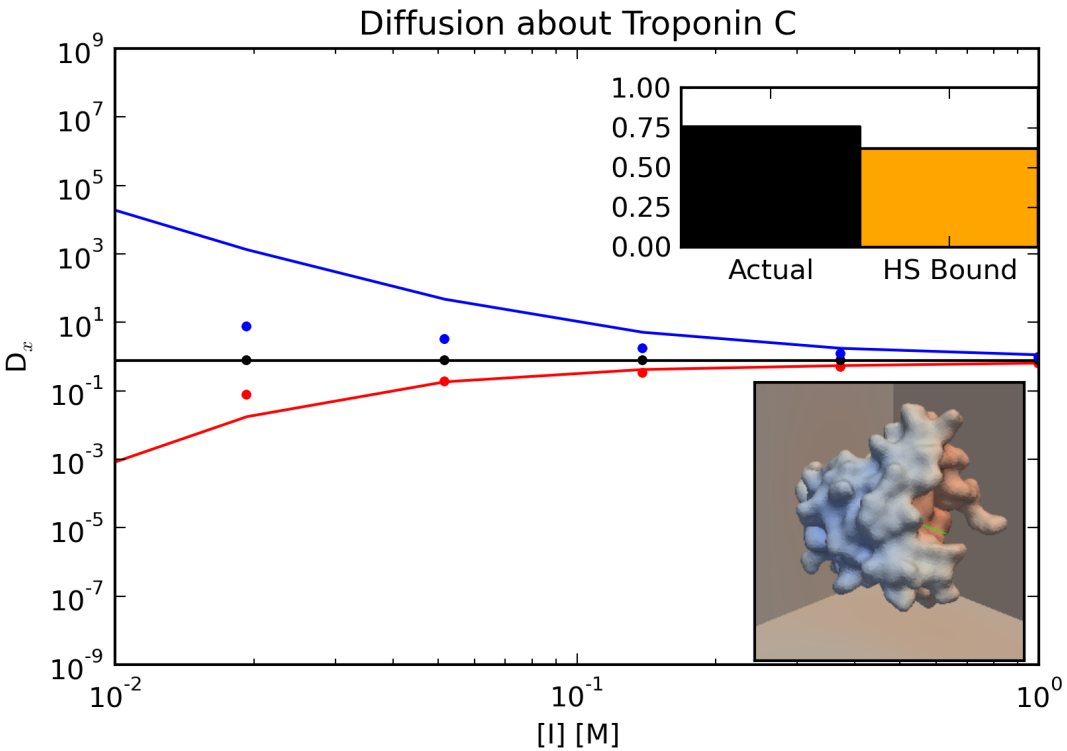




$\longrightarrow$ The dissociation constant K_D represents the probability that the counter-ion (attractive diffuser) is in a bound state.

$\longrightarrow$ If K_D is small, more counter-ions bind to the protein (instead of diffusing away), which decreases D.

Combining Shape and Charge Effects



$\longrightarrow$ We compute the effective diffusion constant as a function of ionic strength for the Troponin C molecule.

$\longrightarrow$ We consider **repulsive**, **attractive**, and **neutral** diffusers and compare uniform charge distribution (dots) to charge localized on TnC (lines)

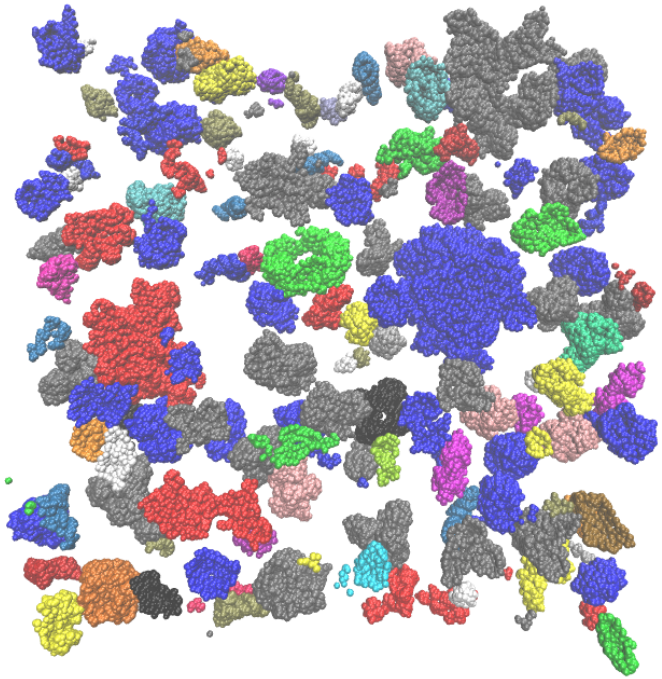
$\longrightarrow$ Non-uniform charge distribution appears to amplify the electrostatic effects

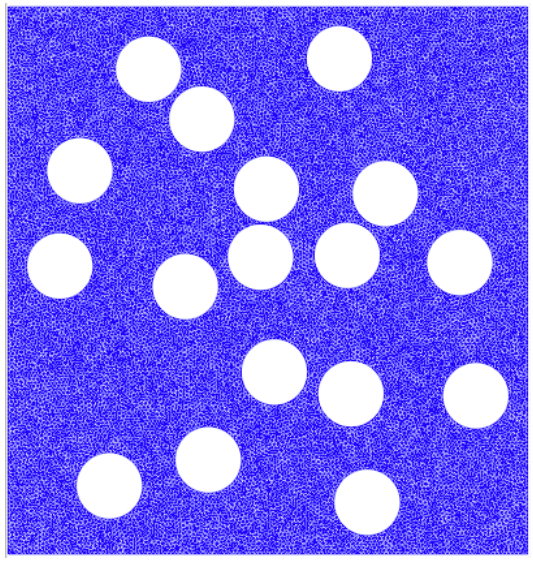
$\longrightarrow$ At physiological ionic strength ($\approx$150 *mM*) the combined effects of geometry and charge give an effective *D* beyond the H-S bound.

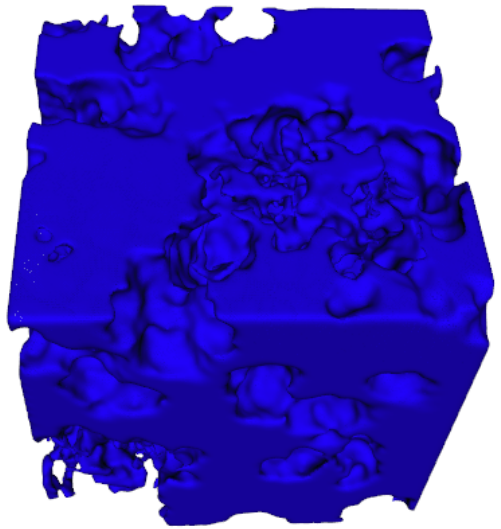
KEKENES-HUSKEY, GILLETTE, MCCAMMON *Predicting the influence of long-range molecular interactions on macroscopic-scale diffusion by homogenization of the Smoluchowski equation,* Accepted pending revisions (yesterday!) to J. Chemical Physics.

Outline

The crowded cellular environment







$\longrightarrow$ The cellular environment is more crowded and random than our current models can describe.

$\longrightarrow$ Determining which quantities and scales are most relevant to effective diffusion rates via homogenization requires the development of new computational and mathematical techniques, especially in biological environments with less geometrical regularity.

Various Future Directions

- Generalize approach to Poisson-Nernst-Planck equation to account for ion-ion interactions
- Incorporate hydrodynamic interactions and finite size effects.
- Use recent mathematics results on homogenization in imperfect or perturbed lattices to derive new unit cell problems and accompanying computational methods.
- Software development
  ← Smolfin source available at
  `https://bitbucket.org/huskeypm/smolfin`

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Many more. . .

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J. Andrew McCammon
National Biomedical Computation Resource

Slides available at

`http://math.arizona.edu/~agillette/`