Computational Bioelectrostatics

Matthew Knepley

Computation Institute
University of Chicago

Computational and Applied Mathematics Colloquium
Rice University
Houston, TX   February 9, 2015

Begins with the numerics of BIEs and PDEs,

and mathematics of the computation,

Begins with the numerics of BIEs and PDEs,

and mathematics of the computation, is

Distilled into

high quality numerical libraries, and

Begins with the numerics of BIEs and PDEs,

and mathematics of the computation, is

Distilled into

high quality numerical libraries, and

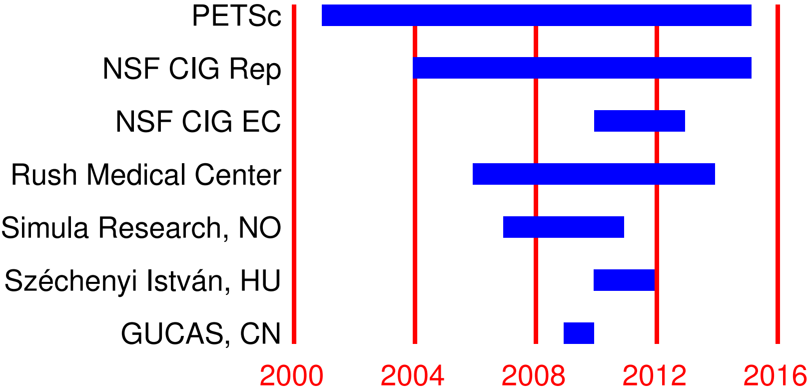
Culminates in scientific discovery.

Research Areas

- Mathematics
  - Scalable solution of Nonlinear PDE
  - Discretization on unstructured meshes
  - Massively parallel algorithms
  - Fast methods for integral equations
- Applications
  - Bioelectrostatics
  - Crustal and Magma Dynamics
  - Wave Mechanics
  - Fracture Mechanics

Funding

Community Involvement



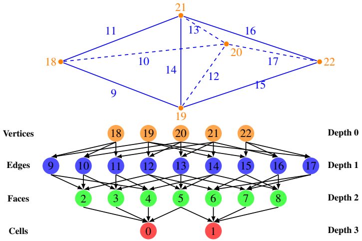
PETSc is one of the most popular software libraries in scientific computing.

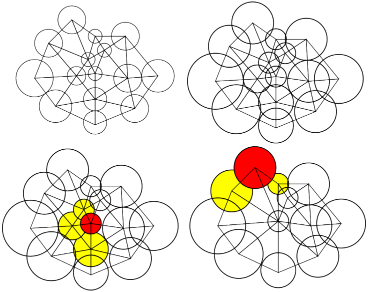
As a principal architect since 2001, I developed

- unstructured meshes (model, algorithms, implementation),
- nonlinear preconditioning (model, algorithms),
- FEM discretizations (data structures, solvers optimization),
- optimizations for multicore and GPU architectures.

What is PETSc?

Knepley, Karpeev, Sci. Prog., 2009. Brune, Knepley, Scott, SISC, 2013.





As a principal architect since 2001, I developed

- unstructured meshes (model, algorithms, implementation),
- nonlinear preconditioning (model, algorithms),
- FEM discretizations (data structures, solvers optimization),
- optimizations for multicore and GPU architectures.

What is PETSc?

Brune, Knepley, Smith, and Tu, SIAM Review, 2015.

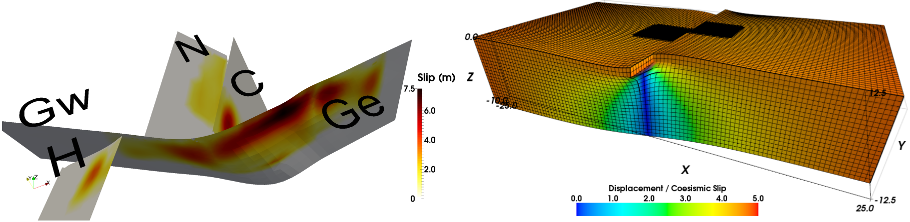
Type	Sym	Statement	Abbreviation
Additive	$+$	$\vec{x} + \alpha(\mathcal{M}(\mathcal{F}, \vec{x}, \vec{b}) - \vec{x})$ $+ \beta(\mathcal{N}(\mathcal{F}, \vec{x}, \vec{b}) - \vec{x})$	$\mathcal{M} + \mathcal{N}$
Multiplicative	$*$	$\mathcal{M}(\mathcal{F}, \mathcal{N}(\mathcal{F}, \vec{x}, \vec{b}), \vec{b})$	$\mathcal{M} * \mathcal{N}$
Left Prec.	$-_L$	$\mathcal{M}(\vec{x} - \mathcal{N}(\mathcal{F}, \vec{x}, \vec{b}), \vec{x}, \vec{b})$	$\mathcal{M} -_L \mathcal{N}$
Right Prec.	$-_R$	$\mathcal{M}(\mathcal{F}(\mathcal{N}(\mathcal{F}, \vec{x}, \vec{b})), \vec{x}, \vec{b})$	$\mathcal{M} -_R \mathcal{N}$
Inner Lin. Inv.	$\backslash$	$\vec{y} = \vec{J}(\vec{x})^{-1}\vec{r}(\vec{x}) = \mathrm{K}(\vec{J}(\vec{x}), \vec{y}_0, \vec{b})$	$\mathcal{N} \backslash \mathrm{K}$

As a principal architect since 2001, I developed

- unstructured meshes (model, algorithms, implementation),
- nonlinear preconditioning (model, algorithms),
- FEM discretizations (data structures, solvers optimization),
- optimizations for multicore and GPU architectures.

What is PETSc?

Aagaard, Knepley, and Williams, J. of Geophysical Research, 2013.

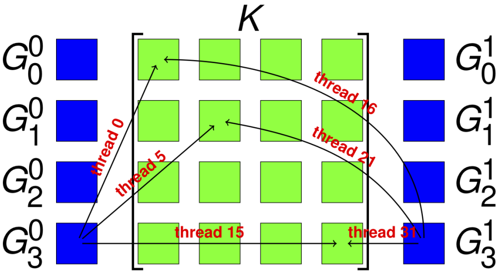


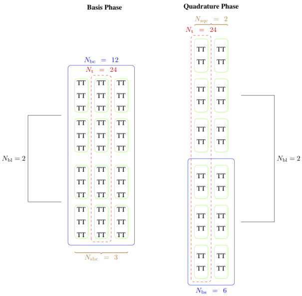
As a principal architect since 2001, I developed

- unstructured meshes (model, algorithms, implementation),
- nonlinear preconditioning (model, algorithms),
- FEM discretizations (data structures, solvers optimization),
- optimizations for multicore and GPU architectures.

What is PETSc?

Knepley and Terrel, Transactions on Mathematical Software, 2012.





As a principal architect since 2001, I developed

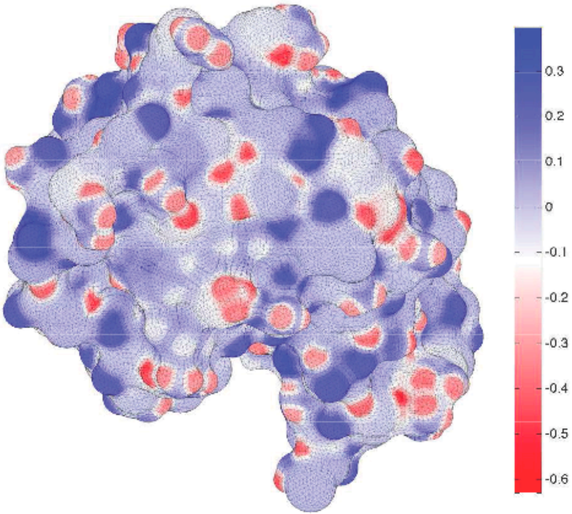
- unstructured meshes (model, algorithms, implementation),
- nonlinear preconditioning (model, algorithms),
- FEM discretizations (data structures, solvers optimization),
- optimizations for multicore and GPU architectures.

Outline

1. Bioelectrostatics
2. Approximate Operators
3. Approximate Boundary Conditions
4. Future Directions

Bioelectrostatics

The Natural World

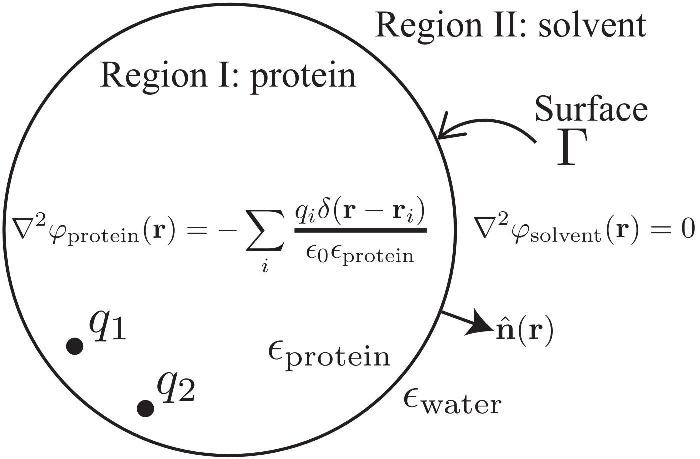


Induced Surface Charge on Lysozyme

Bioelectrostatics

Physical Model

Electrostatic Potential ϕ



Bioelectrostatics

Mathematical Model

We can write a Boundary Integral Equation (BIE) for the induced surface charge σ,

$$\sigma(\vec{r}) + \hat{\epsilon} \int_{\Gamma} \frac{\partial}{\partial n(\vec{r})} \frac{\sigma(\vec{r}')d^2\vec{r}'}{4\pi||\vec{r} - \vec{r}'||} = -\hat{\epsilon} \sum_{k=1}^{Q} \frac{\partial}{\partial n(\vec{r})} \frac{q_k}{4\pi||\vec{r} - \vec{r}_k||}$$

$$\left(\mathcal{I} + \hat{\epsilon}\mathcal{D}^*\right) \sigma(\vec{r}) =$$

where we define

$$\hat{\epsilon} = 2\frac{\epsilon_I - \epsilon_{II}}{\epsilon_I + \epsilon_{II}} < 0$$

Problem

Boundary element discretizations of the solvation problem:

- can be expensive to solve
- are more accurate than required by intermediate design iterations

Outline

1. Bioelectrostatics
2. Approximate Operators
3. Approximate Boundary Conditions
4. Future Directions

Bioelectrostatics

Mathematical Model

The *reaction* potential is given by

$$\phi^R(\vec{r}) = \int_\Gamma \frac{\sigma(\vec{r}')d^2\vec{r}'}{4\pi\epsilon_1||\vec{r}-\vec{r}'||} = C\sigma$$

which defines G_{es}, the electrostatic part of the solvation free energy

$$\begin{aligned}\Delta G_{es} &= \frac{1}{2}\left\langle q, \phi^R \right\rangle \\ &= \frac{1}{2}\langle q, Lq \rangle \\ &= \frac{1}{2}\left\langle q, CA^{-1}Bq \right\rangle\end{aligned}$$

where

$$\begin{aligned} Bq &= -\hat{\epsilon}\int_\Omega \frac{\partial}{\partial n(\vec{r})} \frac{q(\vec{r}')d^3\vec{r}'}{4\pi||\vec{r}-\vec{r}'||} \\ A\sigma &= \mathcal{I} + \hat{\epsilon}\mathcal{D}^* \end{aligned}$$

BIBEE

Approximate $\mathcal{D}^*$ by a diagonal operator

Boundary Integral-Based Electrostatics Estimation

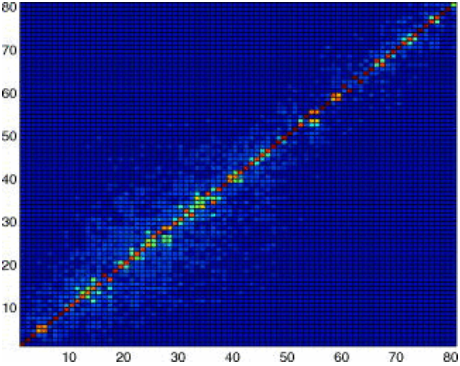
Coulomb Field Approximation:
uniform normal field

$$\left(1 - \frac{\hat{\epsilon}}{2}\right) \sigma_{CFA} = Bq$$

Lower Bound:
no good physical motivation

$$\left(1 + \frac{\hat{\epsilon}}{2}\right) \sigma_{LB} = Bq$$

Eigenvectors: BEM $e_i \cdot e_j$ BIBEE/P



BIBEE

Approximate $\mathcal{D}^*$ by a diagonal operator

Boundary Integral-Based Electrostatics Estimation

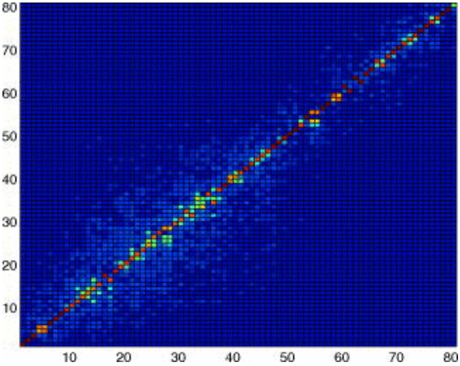
Coulomb Field Approximation: uniform normal field

$$\left(1 - \frac{\hat{\epsilon}}{2}\right) \sigma_{CFA} = Bq$$

Preconditioning: consider only local effects

$$\sigma_P = Bq$$

Eigenvectors: BEM $e_i \cdot e_j$ BIBEE/P



BIBEE Bounds on Solvation Energy

Theorem: The electrostatic solvation energy ΔG_{es} has upper and lower bounds given by

$$\frac{1}{2}\left(1+\frac{\hat{\epsilon}}{2}\right)^{-1}\langle q, CBq\rangle \leq \frac{1}{2}\left\langle q, CA^{-1}Bq\right\rangle \leq \frac{1}{2}\left(1-\frac{\hat{\epsilon}}{2}\right)^{-1}\langle q, CBq\rangle,$$

and for spheres and prolate spheroids, we have the improved lower bound,

$$\frac{1}{2}\langle q, CBq\rangle \leq \frac{1}{2}\left\langle q, CA^{-1}Bq\right\rangle,$$

and we note that

$$|\hat{\epsilon}| < \frac{1}{2}.$$

Energy Bounds:

Proof: Bardhan, Knepley, Anitescu, JCP, **130**(10), 2008

I will break the proof into three steps,

- Replace C with B
- Symmetrization
- Eigendecomposition

shown in the following slides.

We will need the single layer operator $\mathcal{S}$ for step 1,

$$\mathcal{S}\tau(\vec{r}) = \int \frac{\tau(\vec{r}')d^2\vec{r}'}{4\pi||\vec{r} - \vec{r}'||}$$

Energy Bounds: First Step

Replace C with B

The potential at the boundary Γ given by

$$\phi^{Coulomb}(\vec{r}) = C^T q$$

can also be obtained by solving an exterior Neumann problem for τ,

$$\begin{aligned}\phi^{Coulomb}(\vec{r}) &= \mathcal{S}\tau \\ &= \mathcal{S}(\mathcal{I} - 2\mathcal{D}^*)^{-1}(\frac{2}{\hat{\epsilon}}Bq) \\ &= \frac{2}{\hat{\epsilon}}\mathcal{S}(\mathcal{I} - 2\mathcal{D}^*)^{-1}Bq\end{aligned}$$

so that the solvation energy is given by

$$\frac{1}{2}\left\langle q, CA^{-1}Bq\right\rangle = \frac{1}{\hat{\epsilon}}\left\langle \mathcal{S}(\mathcal{I} - 2\mathcal{D}^*)^{-1}Bq, (\mathcal{I} + \hat{\epsilon}\mathcal{D}^*)^{-1}Bq\right\rangle$$

Energy Bounds: Second Step

Quasi-Hermiticity

Plemelj's symmetrization principle holds that

$$\mathcal{S}\mathcal{D}^* = \mathcal{D}\mathcal{S}$$

and we have

$$\mathcal{S} = \mathcal{S}^{1/2}\mathcal{S}^{1/2}$$

which means that we can define a Hermitian operator H similar to $\mathcal{D}^*$

$$H = \mathcal{S}^{1/2}\mathcal{D}^*\mathcal{S}^{-1/2}$$

leading to an energy

$$\frac{1}{2}\left\langle q, CA^{-1}Bq\right\rangle = \frac{1}{\hat{\epsilon}}\left\langle Bq, \mathcal{S}^{1/2}(\mathcal{I} - 2H)^{-1}(\mathcal{I} + \hat{\epsilon}H)^{-1}\mathcal{S}^{1/2}Bq\right\rangle$$

Energy Bounds: Third Step

Eigendecomposition

The spectrum of $\mathcal{D}^*$ is in $[-\frac{1}{2}, \frac{1}{2})$, and the energy is

$$\frac{1}{2}\left\langle q, CA^{-1}Bq \right\rangle = \sum_i \frac{1}{\hat{\epsilon}} \left(1 - 2\lambda_i\right)^{-1} \left(1 + \hat{\epsilon}\lambda_i\right)^{-1} x_i^2$$

where

$$H = V\Lambda V^T$$

and

$$\vec{x} = V^T \mathcal{S}^{1/2} Bq$$

Energy Bounds: Diagonal Approximations

The BIBEE approximations yield the following bounds

$$\frac{1}{2}\left\langle q, CA_{CFA}^{-1}Bq\right\rangle = \sum_i \frac{1}{\hat{\epsilon}}\left(1-2\lambda_i\right)^{-1}\left(1-\frac{\hat{\epsilon}}{2}\right)^{-1} x_i^2$$

$$\frac{1}{2}\left\langle q, CA_{P}^{-1}Bq\right\rangle = \sum_i \frac{1}{\hat{\epsilon}}\left(1-2\lambda_i\right)^{-1} x_i^2$$

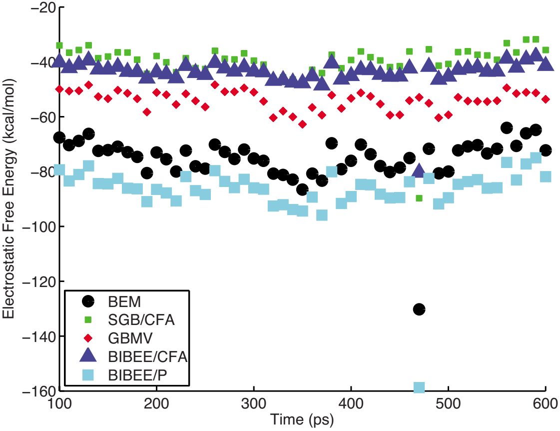
$$\frac{1}{2}\left\langle q, CA_{LB}^{-1}Bq\right\rangle = \sum_i \frac{1}{\hat{\epsilon}}\left(1-2\lambda_i\right)^{-1}\left(1+\frac{\hat{\epsilon}}{2}\right)^{-1} x_i^2$$

where we note that

$$|\hat{\epsilon}| < \frac{1}{2}$$

BIBEE Accuracy

Electrostatic solvation free energies of met-enkephalin structures



Snapshots taken from a 500-ps MD simulation at 10-ps intervals.
Bardhan, Knepley, Anitescu, JCP, 2009.

Generalized Born Approximation

The pairwise energy between charges is defined by the *Still equation*:

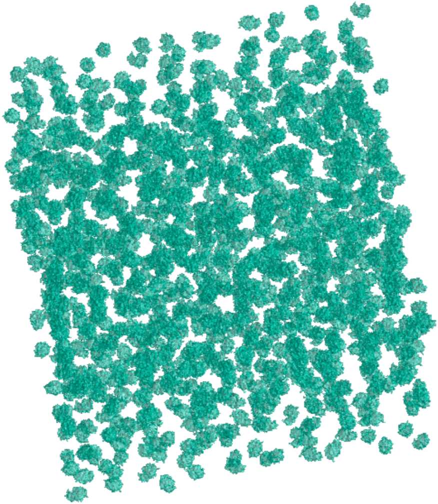
$$G_{es}^{ij} = \frac{1}{8\pi}\left(\frac{1}{\epsilon_{II}} - \frac{1}{\epsilon_{I}}\right)\sum_{i,j}^{N}\frac{q_i q_j}{r_{ij}^2 + R_i R_j e^{-r_{ij}^2/4R_i R_j}}$$

where the *effective Born radius* is

$$R_i = \frac{1}{8\pi}\left(\frac{1}{\epsilon_{II}} - \frac{1}{\epsilon_{I}}\right)\frac{1}{E_i}$$

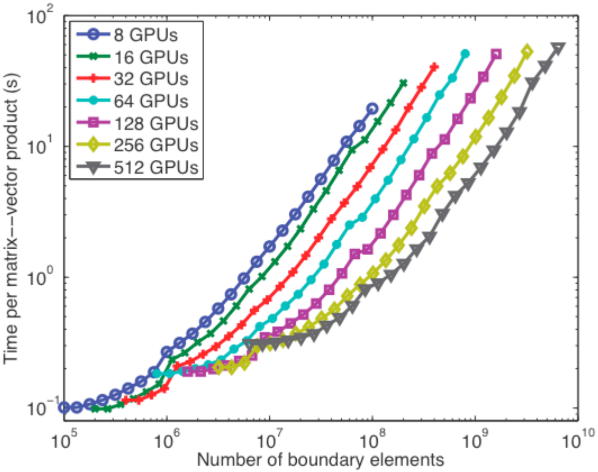
where E_i is the *self-energy* of the charge q_i, the electrostatic energy when atom i has unit charge and all others are neutral.

Crowded Protein Solution



Important for drug design of antibody therapies

BIBEE Scalability



Yokota, Bardhan, Knepley, Barba, Hamada, CPC, 2011.

Outline

1 Bioelectrostatics

2 Approximate Operators

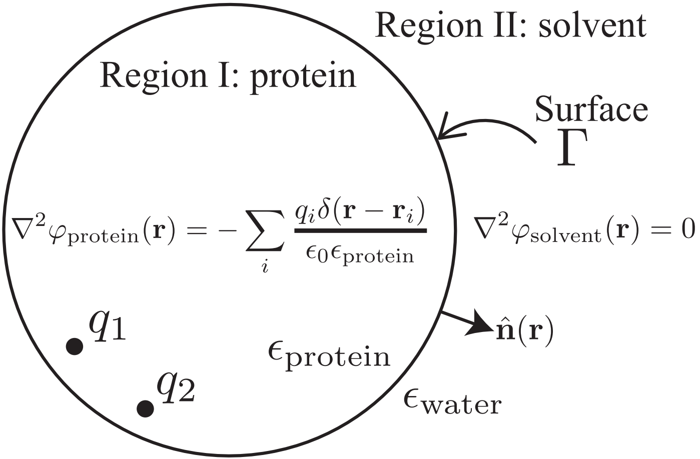
3 Approximate Boundary Conditions

4 Future Directions

Bioelectrostatics

Physical Model

Electrostatic Potential ϕ



Kirkwood's Solution (1934)

The potential inside Region I is given by

$$\Phi_I = \sum_{k=1}^{Q} \frac{q_k}{\epsilon_1 \left|\vec{r} - \vec{r}_k\right|} + \psi,$$

and the potential in Region II is given by

$$\Phi_{II} = \sum_{n=0}^{\infty} \sum_{m=-n}^{n} \frac{C_{nm}}{r^{n+1}} P_n^m(\cos\theta) e^{im\phi}.$$

Kirkwood's Solution (1934)

The reaction potential ψ is expanded in a series

$$\psi = \sum_{n=0}^{\infty} \sum_{m=-n}^{n} B_{nm} r^n P_n^m(\cos\theta) e^{im\phi}.$$

and the source distribution is also expanded

$$\sum_{k=1}^{Q} \frac{q_k}{\epsilon_1 \left|\vec{r} - \vec{r}_k\right|} = \sum_{n=0}^{\infty} \sum_{m=-n}^{n} \frac{E_{nm}}{\epsilon_1 r^{n+1}} P_n^m(\cos\theta) e^{im\phi}.$$

Kirkwood's Solution (1934)

By applying the boundary conditions, letting the sphere have radius b,

$$\Phi_I\big|_{r=b} = \Phi_{II}\big|_{r=b}$$
$$\epsilon_I \frac{\partial \Phi_I}{\partial r}\Big|_{r=b} = \epsilon_{II} \frac{\partial \Phi_{II}}{\partial r}\Big|_{r=b}$$

we can eliminate C_{nm}, and determine the reaction potential coefficients in terms of the source distribution,

$$B_{nm} = \frac{1}{\epsilon_I b^{2n+1}} \frac{(\epsilon_I - \epsilon_{II})(n+1)}{\epsilon_I n + \epsilon_{II}(n+1)} E_{nm}.$$

Approximate Boundary Conditions

Theorem: The BIBEE boundary integral operator approximations

$$A_{CFA} = \mathcal{I}\left(1 + \frac{\hat{\epsilon}}{2}\right)$$
$$A_{P} = \mathcal{I}$$

have an equivalent PDE formulation,

$$\epsilon_I \Delta \Phi_{CFA,P} = \sum_{k=1}^{Q} q_k \delta(\vec{r} - \vec{r}_k)$$
$$\epsilon_{II} \Delta \Phi_{CFA,P} = 0$$
$$\Phi_I|_{r=b} = \Phi_{II}|_{r=b}$$

$$\frac{\epsilon_I}{\epsilon_{II}} \frac{\partial \Phi_I^C}{\partial r}|_{r=b} = \frac{\partial \Phi_{II}}{\partial r} - \frac{\partial \psi_{CFA}}{\partial r}|_{r=b}$$

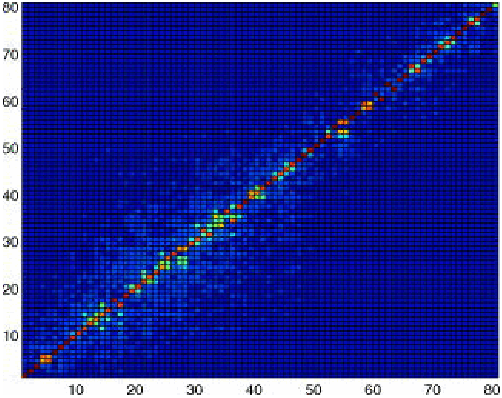
or

$$\frac{3\epsilon_I - \epsilon_{II}}{\epsilon_I + \epsilon_{II}} \frac{\partial \Phi_I^C}{\partial r}|_{r=b} = \frac{\partial \Phi_{II}}{\partial r} - \frac{\partial \psi_{P}}{\partial r}|_{r=b},$$

where Φ_1^C is the Coulomb field due to interior charges.

Approximate Boundary Conditions

Theorem: For spherical solute, the BIBEE boundary integral operator approximations have eigenspaces are identical to that of the original operator.



BEM eigenvector $e_i \cdot e_j$ BIBEE/P eigenvector

Proof of PDE Equivalence

Proof: Bardhan and Knepley, JCP, **135**(12), 2011.

In order to show that these PDEs are equivalent to the original BIEs,

- Start with the fundamental solution to Laplace's equation $G(r, r')$
- Note that $\int_\Gamma G(r, r')\sigma(r')d\Gamma$ satisfies the bulk equation and decay at infinity
- Insertion into the approximate BC gives the BIBEE boundary integral approximation

Proof of PDE Equivalence

Proof: Bardhan and Knepley, JCP, **135**(12), 2011.

In order to show that these PDEs are equivalent to the original BIEs,

- Start with the fundamental solution to Laplace's equation $G(r, r')$
- Note that $\int_\Gamma G(r, r')\sigma(r')d\Gamma$ satisfies the bulk equation and decay at infinity
- Insertion into the approximate BC gives the BIBEE boundary integral approximation

Proof of PDE Equivalence

Proof: Bardhan and Knepley, JCP, **135**(12), 2011.

In order to show that these PDEs are equivalent to the original BIEs,

- Start with the fundamental solution to Laplace's equation $G(r, r')$
- Note that $\int_\Gamma G(r, r')\sigma(r')d\Gamma$ satisfies the bulk equation and decay at infinity
- Insertion into the approximate BC gives the BIBEE boundary integral approximation

Proof of PDE Equivalence

Proof: Bardhan and Knepley, JCP, **135**(12), 2011.

In order to show that these PDEs are equivalent to the original BIEs,

- Start with the fundamental solution to Laplace's equation $G(r, r')$
- Note that $\int_\Gamma G(r, r')\sigma(r')d\Gamma$ satisfies the bulk equation and decay at infinity
- Insertion into the approximate BC gives the BIBEE boundary integral approximation

Proof of Eigenspace Equivalence

Proof: Bardhan and Knepley, JCP, **135**(12), 2011.

In order to show that these integral operators
share a common eigenbasis,

- Note that, for a spherical boundary, $\mathcal{D}^*$ is compact and has a pure point spectrum
- Examine the effect of the operator on a unit spherical harmonic charge distribution
- Use completeness of the spherical harmonic basis

Proof of Eigenspace Equivalence

Proof: Bardhan and Knepley, JCP, **135**(12), 2011.

In order to show that these integral operators
share a common eigenbasis,

- Note that, for a spherical boundary,
  $\mathcal{D}^*$ is compact and has a pure point spectrum
- Examine the effect of the operator on a
  unit spherical harmonic charge distribution
- Use completeness of the spherical harmonic basis

Proof of Eigenspace Equivalence

Proof: Bardhan and Knepley, JCP, **135**(12), 2011.

In order to show that these integral operators
share a common eigenbasis,

- Note that, for a spherical boundary,
  $\mathcal{D}^*$ is compact and has a pure point spectrum
- Examine the effect of the operator on a
  unit spherical harmonic charge distribution
- Use completeness of the spherical harmonic basis

Proof of Eigenspace Equivalence

Proof: Bardhan and Knepley, JCP, **135**(12), 2011.

In order to show that these integral operators
share a common eigenbasis,

- Note that, for a spherical boundary,
  $\mathcal{D}^*$ is compact and has a pure point spectrum
- Examine the effect of the operator on a
  unit spherical harmonic charge distribution
- Use completeness of the spherical harmonic basis

Proof of Eigenspace Equivalence

Proof: Bardhan and Knepley, JCP, **135**(12), 2011.

In order to show that these integral operators
share a common eigenbasis,

- Note that, for a spherical boundary,
  $\mathcal{D}^*$ is compact and has a pure point spectrum
- Examine the effect of the operator on a
  unit spherical harmonic charge distribution
- Use completeness of the spherical harmonic basis

The result does not hold for general boundaries.

Series Solutions

Note that the approximate solutions are *separable*:

$$
\begin{aligned}
B_{nm} &= \frac{1}{\epsilon_1 n + \epsilon_2 (n+1)} \gamma_{nm} \\
B^{CFA}_{nm} &= \frac{1}{\epsilon_2} \frac{1}{2n+1} \gamma_{nm} \\
B^{P}_{nm} &= \frac{1}{\epsilon_1 + \epsilon_2} \frac{1}{n + \frac{1}{2}} \gamma_{nm}.
\end{aligned}
$$

If $\epsilon_I = \epsilon_{II} = \epsilon$, both approximations are exact:

$$
B_{nm} = B^{CFA}_{nm} = B^{P}_{nm} = \frac{1}{\epsilon(2n+1)} \gamma_{nm}.
$$

Series Solutions

Note that the approximate solutions are *separable*:

$$B_{nm} = \frac{1}{\epsilon_1 n + \epsilon_2(n+1)}\gamma_{nm}$$

$$B^{CFA}_{nm} = \frac{1}{\epsilon_2}\frac{1}{2n+1}\gamma_{nm}$$

$$B^{P}_{nm} = \frac{1}{\epsilon_1 + \epsilon_2}\frac{1}{n+\frac{1}{2}}\gamma_{nm}.$$

If $\epsilon_I = \epsilon_{II} = \epsilon$, both approximations are exact:

$$B_{nm} = B^{CFA}_{nm} = B^{P}_{nm} = \frac{1}{\epsilon(2n+1)}\gamma_{nm}.$$

Asymptotics

BIBEE/CFA is exact for the $n = 0$ mode,

$$B_{00} = B_{00}^{CFA} = \frac{\gamma_{00}}{\epsilon_2},$$

whereas BIBEE/P approaches the exact response in the limit $n \to \infty$:

$$\lim_{n\to\infty} B_{nm} = \lim_{n\to\infty} B_{nm}^{P} = \frac{1}{(\epsilon_1 + \epsilon_2)n}\gamma_{nm}.$$

Asymptotics

BIBEE/CFA is exact for the $n = 0$ mode,

$$B_{00} = B_{00}^{CFA} = \frac{\gamma_{00}}{\epsilon_2},$$

whereas BIBEE/P approaches the exact response in the limit $n \to \infty$:

$$\lim_{n\to\infty} B_{nm} = \lim_{n\to\infty} B_{nm}^{P} = \frac{1}{(\epsilon_1 + \epsilon_2)n}\gamma_{nm}.$$

Asymptotics

In the limit $\epsilon_1/\epsilon_2 \to 0$,

$$\lim_{\epsilon_1/\epsilon_2 \to 0} B_{nm} = \frac{\gamma_{nm}}{\epsilon_2(n+1)}$$

$$\lim_{\epsilon_1/\epsilon_2 \to 0} B^{CFA}_{nm} = \frac{\gamma_{nm}}{\epsilon_2(2n+1)},$$

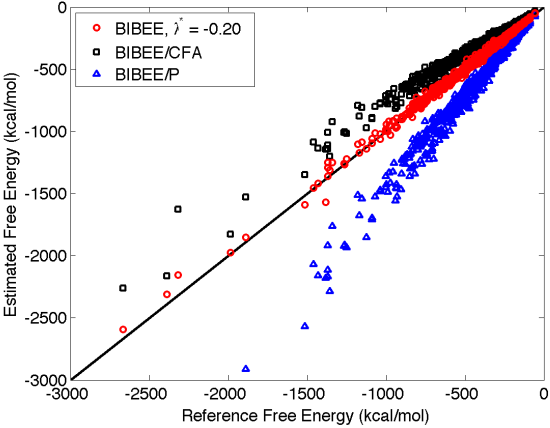
$$\lim_{\epsilon_1/\epsilon_2 \to 0} B^{P}_{nm} = \frac{\gamma_{nm}}{\epsilon_2\left(n+\frac{1}{2}\right)},$$

so that the approximation ratios are given by

$$\frac{B^{CFA}_{nm}}{B_{nm}} = \frac{n+1}{2n+1}, \qquad \frac{B^{P}_{nm}}{B_{nm}} = \frac{n+1}{n+\frac{1}{2}}.$$

Improved Accuracy

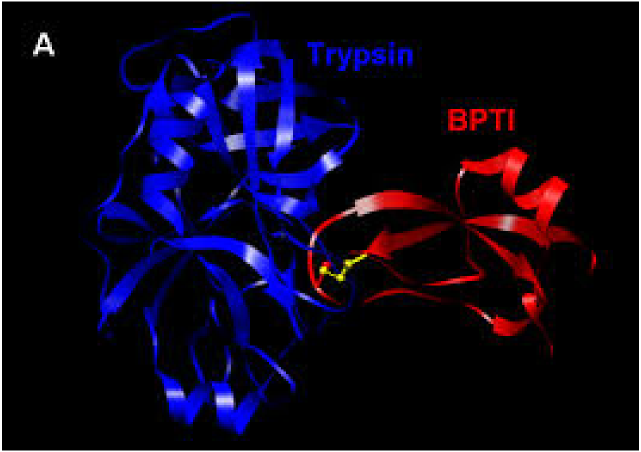
BIBEE/I interpolates between BIBEE/CFA and BIBEE/P



Bardhan, Knepley, JCP, 2011.

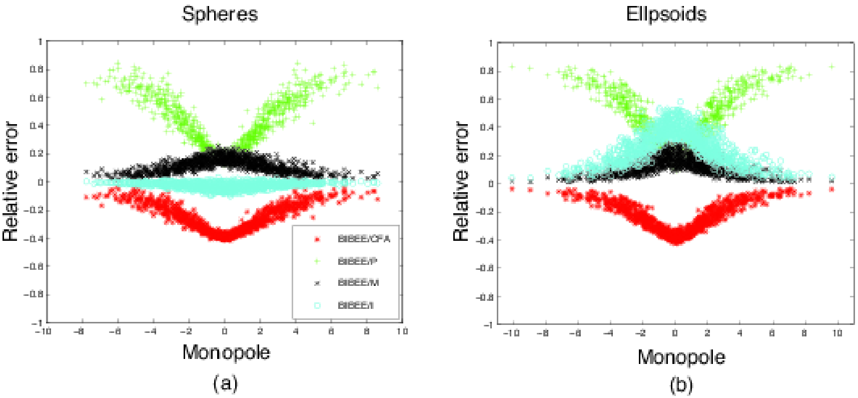
Basis Augmentation

We examined the more complex problem of protein-ligand binding using trypsin and bovine pancreatic trypsin inhibitor (BPTI), using *electrostatic component analysis* to identify residue contributions to binding and molecular recognition.



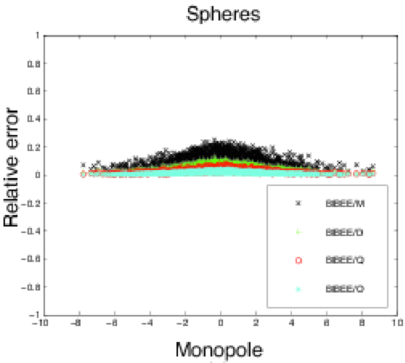
Basis Augmentation

Looking at an ensemble of synthetic proteins, we can see that BIBEE/CFA becomes more accurate as the monopole moment increases, and BIBEE/P more accurate as it decreases. BIBEE/I is accurate for spheres, but must be extended for ellipses.

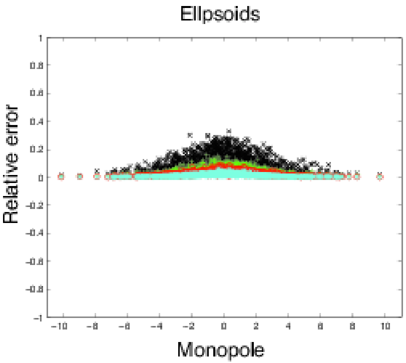


Basis Augmentation

For ellipses, we add a few low order multipole moments, up to the octopole, to recover 5% accuracy for all synthetic proteins tested.



(b)



(d)

Resolution

Boundary element discretizations of the solvation problem:

- can be expensive to solve
  - **Bounding the electrostatic free energies associated with linear continuum models of molecular solvation**, Bardhan, Knepley, Anitescu, JCP, 2009
- are more accurate than required by intermediate design iterations
  - **Analysis of fast boundary-integral approximations for modeling electrostatic contributions of molecular binding**, Kreienkamp, et al., Molecular-Based Mathematical Biology, 2013

Resolution

Boundary element discretizations of the solvation problem:

- can be expensive to solve
  - **Bounding the electrostatic free energies associated with linear continuum models of molecular solvation**, Bardhan, Knepley, Anitescu, JCP, 2009
- are more accurate than required by intermediate design iterations
  - **Analysis of fast boundary-integral approximations for modeling electrostatic contributions of molecular binding**, Kreienkamp, et al., Molecular-Based Mathematical Biology, 2013

Resolution

Boundary element discretizations of the solvation problem:

- can be expensive to solve
  - **Bounding the electrostatic free energies associated with linear continuum models of molecular solvation**, Bardhan, Knepley, Anitescu, JCP, 2009
- are more accurate than required by intermediate design iterations
  - **Analysis of fast boundary-integral approximations for modeling electrostatic contributions of molecular binding**, Kreienkamp, et al., Molecular-Based Mathematical Biology, 2013

Outline

1 Bioelectrostatics

2 Approximate Operators

3 Approximate Boundary Conditions

4 Future Directions

New Physics

Phenomenon:

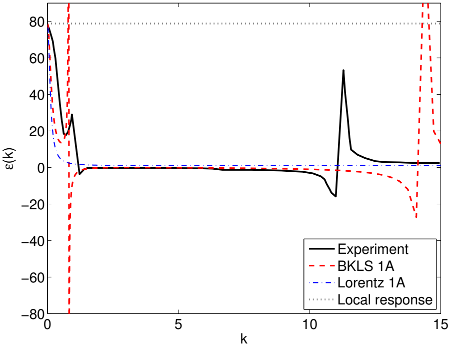
Model:

New Physics

Phenomenon:

Dielectric Saturation

Model:



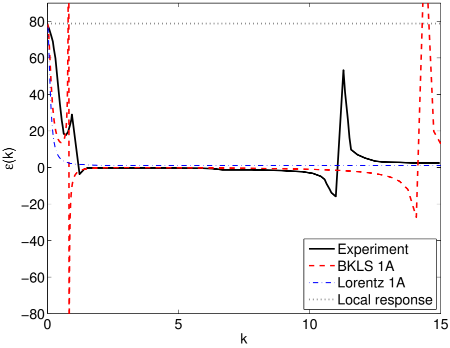
New Physics

Phenomenon:

Dielectric Saturation

Model:

Nonlocal Dielectric

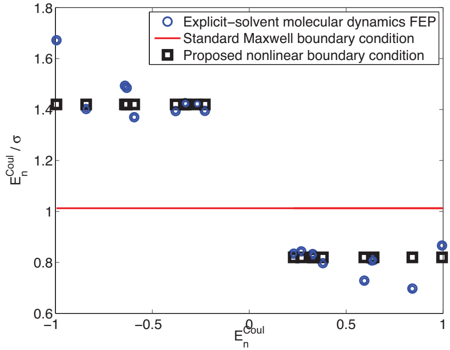


New Physics

Phenomenon:

Charge–Hydration Asymmetry

Model:



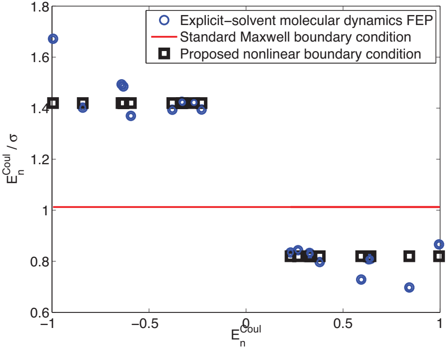
New Physics

Phenomenon:

Charge–Hydration Asymmetry

Model:

Nonlinear Boundary Condition

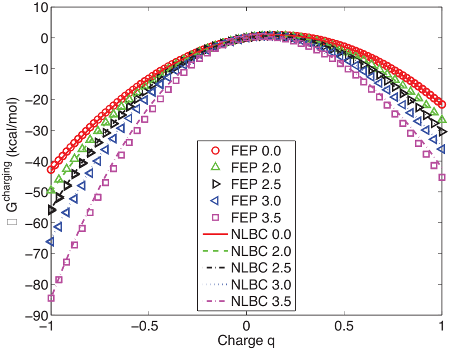


New Physics

Phenomenon:

Solute–Solvent Interface Potential

Model:



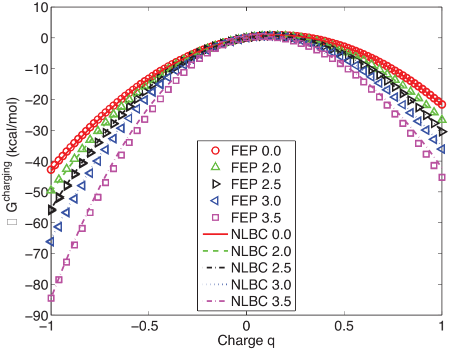
New Physics

Phenomenon:

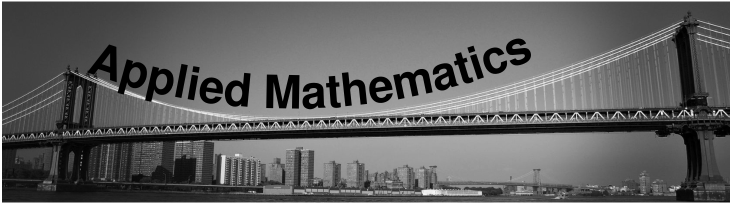
Solute–Solvent Interface Potential

Model:

Static Solvation Potential

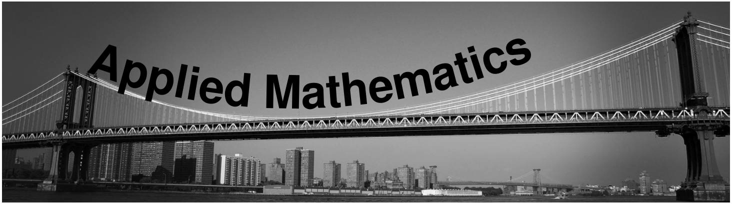


Impact of Mathematics on Science

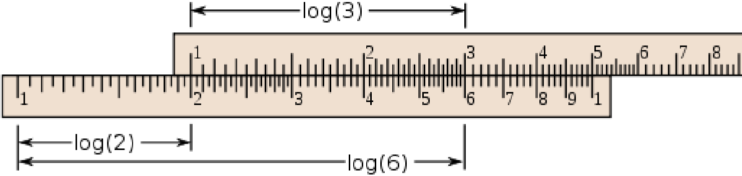


Computational Leaders have always
embraced the latest technology
and been inspired by physical problems,

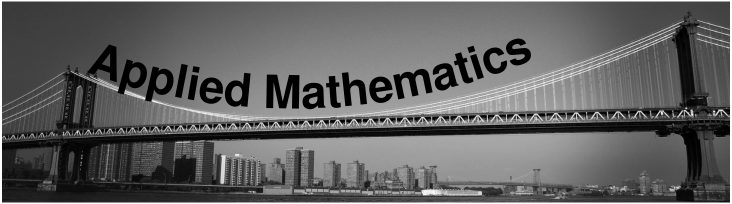
Impact of Mathematics on Science



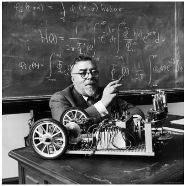
Computational Leaders have always
embraced the latest technology
and been inspired by physical problems,

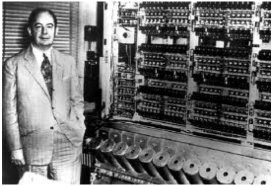


Impact of Mathematics on Science

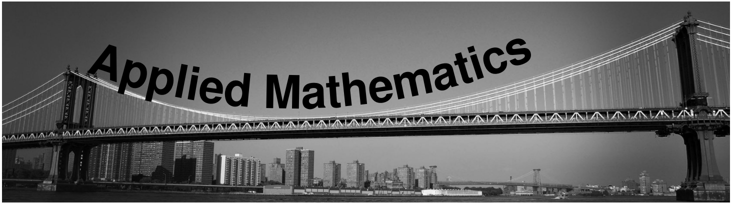


Computational Leaders have always
embraced the latest technology
and been inspired by physical problems,





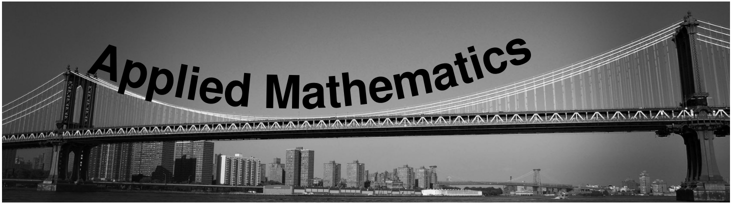
Impact of Mathematics on Science



Computational Leaders have always
embraced the latest technology
and been inspired by physical problems,

PETSc

Impact of Mathematics on Science



Computational Leaders have always
embraced the latest technology
and been inspired by physical problems,

Enabling Scientific Discovery

Thank You!

http://www.cs.uchicago.edu/~knepley