Begins with the numerics of BIEs and PDEs, and mathematics of the computation,
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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
NSF CIG Rep
NSF CIG EC
Rush Medical Center
Simula Research, NO
Széchenyi István, HU
GUCAS, CN

What is PETSc?

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

I have been a principal architect since 2001, and 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?

A freely available and supported research code for the parallel solution of nonlinear algebraic equations

Free
- Download from http://www.mcs.anl.gov/petsc
- Free for everyone, including industrial users

Supported
- Hyperlinked manual, examples, and manual pages for all routines
- Hundreds of tutorial-style examples
- Support via email: petsc-maint@mcs.anl.gov

Usable from C, C++, Fortran 77/90, Matlab, Julia, and Python
What is PETSc?

- Portable to any parallel system supporting MPI, including:
  - Tightly coupled systems
    - Cray XT6, BG/Q, NVIDIA Fermi, K Computer
  - Loosely coupled systems, such as networks of workstations
    - IBM, Mac, iPad/iPhone, PCs running Linux or Windows

PETSc History

- Begun September 1991
- Over 60,000 downloads since 1995 (version 2)
- Currently 400 per month

PETSc Funding and Support

- Department of Energy
  - SciDAC, MICS Program, AMR Program, INL Reactor Program
- National Science Foundation
  - CIG, CISE, Multidisciplinary Challenge Program
PETSc Citations, **2783** Total

![Bar chart showing PETSc citations per year from 2003 to 2014.](chart.png)
Outline

1. Bioelectrostatics
2. Approximate Operators
3. Approximate Boundary Conditions
4. Future Directions
Induced Surface Charge on Lysozyme
Electrostatic Potential $\phi$

\[
\nabla^2 \varphi_{\text{protein}}(r) = - \sum_i \frac{q_i \delta(r - r_i)}{\epsilon_0 \epsilon_{\text{protein}}}
\]

Region I: protein

Region II: solvent

Surface $\Gamma$

\[
\nabla^2 \varphi_{\text{solvent}}(r) = 0
\]
We can write a Boundary Integral Equation (BIE) for the induced surface charge $\sigma$,

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

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

where we define

$$\hat{\epsilon} = 2 \frac{\epsilon_I - \epsilon_{II}}{\epsilon_I + \epsilon_{II}} < 0$$
Boundary element discretizations of the solvation problem:

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

1. Bioelectrostatics
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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

\[ \Delta G_{es} = \frac{1}{2} \left\langle q, \phi^R \right\rangle \]

\[ = \frac{1}{2} \left\langle q, Lq \right\rangle \]

\[ = \frac{1}{2} \left\langle q, CA^{-1} Bq \right\rangle \]

where

\[ Bq = -\hat{\epsilon} \int_{\Omega} \frac{\partial}{\partial n(\vec{r})} \frac{q(\vec{r}')d^3\vec{r}'}{4\pi||\vec{r} - \vec{r}'||} \]

\[ A\sigma = I + \hat{\epsilon}D^* \]
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

\[
\left(1 + \frac{\hat{\epsilon}}{2}\right) \sigma_{LB} = Bq
\]
**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
Theorem: The electrostatic solvation energy $\Delta G_{es}$ has upper and lower bounds given by

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

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

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

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 $S$ for step 1,

$$S_{\tau}(\vec{r}) = \int \frac{\tau(\vec{r}') d^2\vec{r}'}{4\pi ||\vec{r} - \vec{r}'||}$$
The potential at the boundary $\Gamma$ given by

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

can also be obtained by solving an exterior Neumann problem for $\tau$,

$$\phi^{Coulomb}(\vec{r}) = S \tau$$

$$= S(\mathcal{I} - 2\mathcal{D}^*)^{-1}(\frac{2}{\hat{\epsilon}} B q)$$

$$= \frac{2}{\hat{\epsilon}} S(\mathcal{I} - 2\mathcal{D}^*)^{-1} B q$$

so that the solvation energy is given by

$$\frac{1}{2} \left\langle q, CA^{-1} B q \right\rangle = \frac{1}{\hat{\epsilon}} \left\langle S(\mathcal{I} - 2\mathcal{D}^*)^{-1} B q, (\mathcal{I} + \hat{\epsilon}\mathcal{D}^*)^{-1} B q \right\rangle$$
Plemelj’s symmetrization principle holds that

$$SD^* = DS$$

and we have

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

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

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

leading to an energy

$$\frac{1}{2} \left\langle q, CA^{-1} Bq \right\rangle = \frac{1}{\hat{\epsilon}} \left\langle Bq, S^{1/2} (I - 2H)^{-1} (I + \hat{\epsilon}H)^{-1} S^{1/2} Bq \right\rangle$$
The spectrum of $\mathcal{D}^*$ is in $[-\frac{1}{2}, \frac{1}{2})$, and the energy is

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

where

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

and

$$\tilde{x} = V^T S^{1/2} Bq$$
The BIBEE approximations yield the following bounds

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

\[
\frac{1}{2} \left\langle q, CA_P^{-1} Bq \right\rangle = \sum_i \frac{1}{\hat{\epsilon}} (1 - 2\lambda_i)^{-1} x_i^2
\]

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

where we note that

\[|\hat{\epsilon}| < \frac{1}{2}\]
Electrostatic solvation free energies of met-enkephalin structures

Snapshots taken from a 500-ps MD simulation at 10-ps intervals.
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
Yokota, Bardhan, Knepley, Barba, Hamada, CPC, 2011.
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Electrostatic Potential $\phi$

Region I: protein

Region II: solvent

Surface $\Gamma$

$\nabla^2 \phi_{\text{protein}}(r) = - \sum_i \frac{q_i \delta(r - r_i)}{\epsilon_0 \epsilon_{\text{protein}}}$

$\nabla^2 \phi_{\text{solvent}}(r) = 0$

$q_1, q_2$
Kirkwood’s Solution (1934)

The potential inside Region I is given by

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

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 $\psi$ 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

$$\sum_{k=1}^{Q} \frac{q_k}{\epsilon_1 |\vec{r} - \vec{r}_k|} = \sum_{n=0}^{\infty} \sum_{m=-n}^{n} \frac{E_{nm}}{\epsilon_1 r^{n+1}} P_n^m(\cos \theta) e^{im\phi}.$$
By applying the boundary conditions, letting the sphere have radius \( b \),

\[
\Phi_I|_{r=b} = \Phi_{II}|_{r=b} \\
\epsilon_I \frac{\partial \Phi_I}{\partial r}|_{r=b} = \epsilon_{II} \frac{\partial \Phi_{II}}{\partial r}|_{r=b}
\]

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

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

\[ \epsilon_l \Delta \Phi_{CFA,P} = \sum_{k=1}^{Q} q_k \delta(\vec{r} - \vec{r}_k) \]

\[ \epsilon_{ll} \Delta \Phi_{CFA,P} = 0 \]

\[ \Phi_I|_{r=b} = \Phi_{II}|_{r=b} \]

\[ \frac{\epsilon_l \partial \Phi_C^I}{\epsilon_{ll} \partial r}|_{r=b} = \frac{\partial \Phi_{II}}{\partial r} - \frac{\partial \psi_{CFA}}{\partial r}|_{r=b} \]

or

\[ \frac{3\epsilon_l - \epsilon_{ll} \partial \Phi_C^I}{\epsilon_l + \epsilon_{ll} \partial r}|_{r=b} = \frac{\partial \Phi_{II}}{\partial r} - \frac{\partial \psi_P}{\partial r}|_{r=b} \]

where \( \Phi_C^I \) is the Coulomb field due to interior charges.
**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**: 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

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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.
Approximate Boundary Conditions

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The result does not hold for general boundaries.
Series Solutions

Note that the approximate solutions are *separable*:

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

\[
B_{nm}^{CFA} = \frac{1}{\epsilon_2} \frac{1}{2n + 1} \gamma_{nm}
\]

\[
B_{nm}^P = \frac{1}{\epsilon_1 + \epsilon_2} \frac{1}{n + \frac{1}{2}} \gamma_{nm}.
\]

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

\[
B_{nm} = B_{nm}^{CFA} = B_{nm}^P = \frac{1}{\epsilon (2n + 1)} \gamma_{nm}.
\]
Approximate Boundary Conditions

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B_{nm} = B_{nm}^{CFA} = B_{nm}^P = \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 $n \to \infty$:

$$\lim_{n \to \infty} B_{nm} = \lim_{n \to \infty} B_{nm}^P = \frac{1}{(\epsilon_1 + \epsilon_2)n} \gamma_{nm}.$$
BIBEE/CFA is exact for the $n = 0$ mode,

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

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$$\lim_{n \to \infty} B_{nm} = \lim_{n \to \infty} B_{nm}^P = \frac{1}{(\epsilon_1 + \epsilon_2)n} \gamma_{nm}.$$
In the limit $\epsilon_1/\epsilon_2 \to 0$,

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

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

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

so that the approximation ratios are given by

$$
\frac{B_{nm}^{CFA}}{B_{nm}} = \frac{n + 1}{2n + 1}, \quad \frac{B_{nm}^{P}}{B_{nm}} = \frac{n + 1}{n + \frac{1}{2}}.
$$
Improved Accuracy

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

Bardhan, Knepley, JCP, 2011.
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.
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.
For ellipses, we add a few low order multipole moments, up to the octopole, to recover 5% accuracy for all synthetic proteins tested.
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
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More Physics

New Phenomena:

New Model:
More Physics

New Phenomena:
  Dielectric Saturation

New Model:
More Physics

New Phenomena:
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New Model:
  Nonlocal Dielectric
Future Directions

More Physics

New Phenomena:
- Dielectric Saturation
- Charge–Hydration Asymmetry

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More Physics

New Phenomena:
- Dielectric Saturation
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- Solute–Solvent Interface Potential

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More Physics

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New Model:
- Nonlocal Dielectric
- Nonlinear Boundary Condition
- Static Solvation Potential
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Future Directions

Impact of Mathematics on Science

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Enabling Scientific Discovery
Thank You!

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