Fast direct methods for molecular electrostatics

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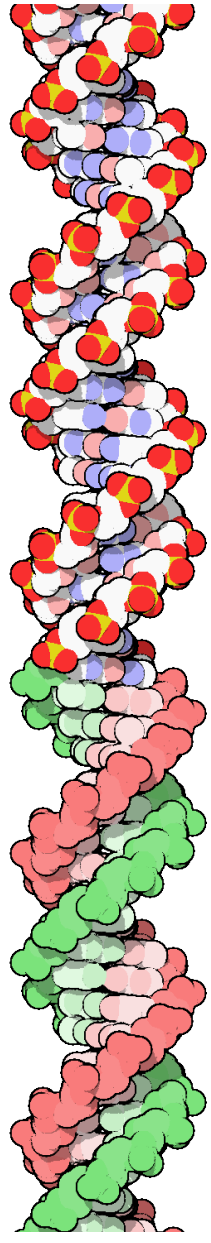
1. Boundary integral methods for molecular electrostatics
2. Application: protein pK_a calculations
3. A fast direct solver for integral equations
4. Results and conclusions

Suppose I give you a structure.

What can you tell me about its function?



Suppose I give you a structure.

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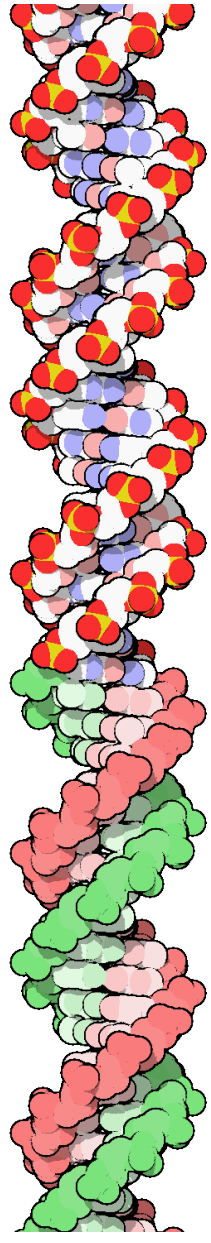
(What are the physics acting on it?)



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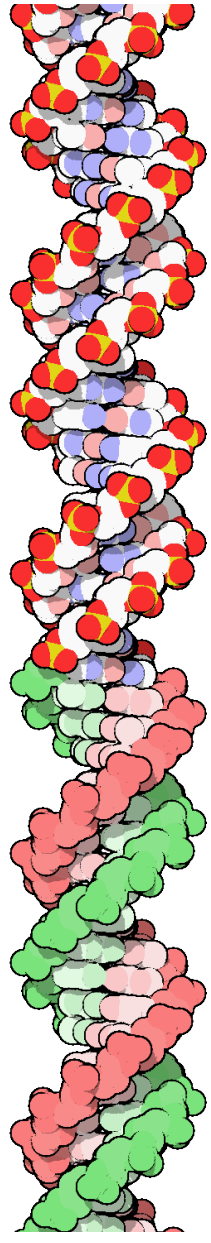
- Charge complementarity
- Conformation and dynamics
- Long-range steering
- Polarization and ionization



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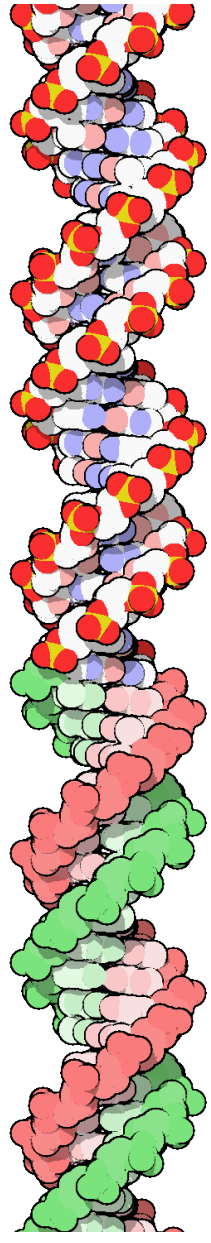
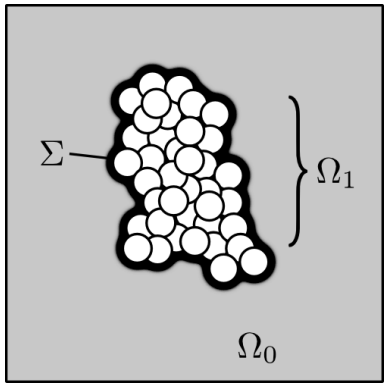
In this talk, we focus on electrostatics.



Molecular electrostatics



Molecule: discrete collection of charged atoms

Ω_0: solvent

Ω_1: (solvent-excluded) molecular volume

Σ: molecular surface

Explicit solvent:

- Discretize Ω_0
- Coulomb's law:

$$\varphi(\mathbf{r}) = k_e \sum_i \frac{q_i}{|\mathbf{r} - \mathbf{r}_i|}$$

- Can be expensive!

Implicit solvent:

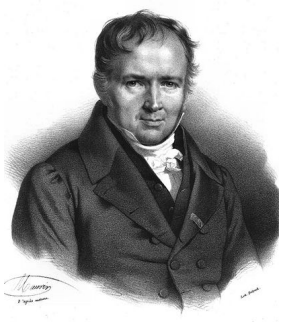
- Continuum dielectric
- Poisson equation:

$$-\nabla \cdot (\varepsilon \nabla \varphi) = \rho$$

For many applications, implicit solvation provides a good balance of physical realism and computational efficiency.

Poisson-Boltzmann equation

Poisson equation: $-\nabla \cdot (\varepsilon \nabla \varphi) = \rho$



Poisson-Boltzmann equation

Poisson equation: $-\nabla \cdot (\varepsilon \nabla \varphi) = \rho$

In the molecule: $-\Delta \varphi = \frac{1}{\varepsilon_1} \sum_i q_i \delta (\mathbf{r} - \mathbf{r}_i)$

Poisson-Boltzmann equation

Poisson equation: $-\nabla \cdot (\varepsilon \nabla \varphi) = \rho$

In the molecule: $-\Delta\varphi = \frac{1}{\varepsilon_1} \sum_i q_i \delta(\mathbf{r} - \mathbf{r}_i)$

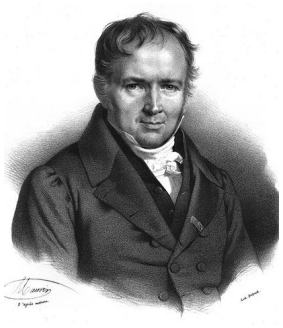
In the solvent:

$$-\Delta\varphi = \frac{1}{\varepsilon_0} \sum_i q_i c_i$$

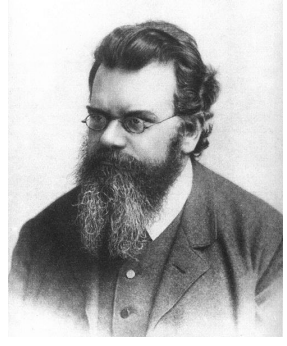
$$= \frac{1}{\varepsilon_0} \sum_i q_i c_i^\infty \exp\left(-\frac{q_i \varphi}{k_B T}\right)$$

$$\approx \frac{1}{\varepsilon_0} \left(\sum_i q_i c_i^\infty - \sum_i \frac{q_i^2 c_i^\infty}{k_B T} \varphi \right)$$

$$-\Delta\varphi \equiv -\kappa^2 \varphi$$



linearized Poisson-Boltzmann equation

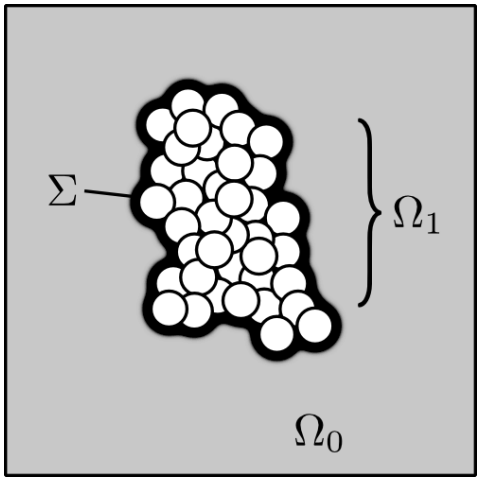


Electrostatic system

$$-\left(\Delta - \kappa^2\right)\varphi = 0 \qquad \text{in } \Omega_0$$

$$-\Delta\varphi = \frac{1}{\varepsilon_1}\sum_i q_i \delta\left(\mathbf{r} - \mathbf{r}_i\right) \qquad \text{in } \Omega_1$$

$$[\varphi] = \left[\varepsilon \frac{\partial \varphi}{\partial \nu}\right] = 0 \qquad \text{on } \Sigma$$

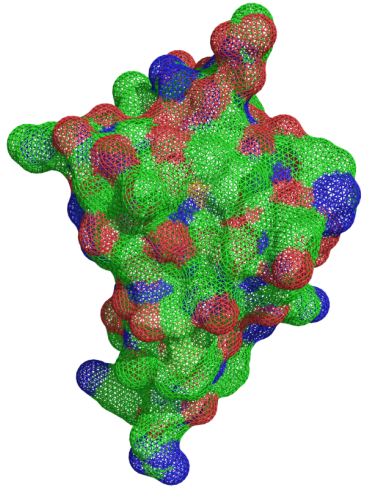


Many ways to solve: finite differences, finite elements

- Can be ill-conditioned
- Artificial domain truncation

We use instead boundary integral equation methods:

- Satisfies PDE exactly
- Provably well-conditioned
- Dimensional reduction



Boundary integral formulation

Green's function: $$G_k(\mathbf{r},\mathbf{s}) = \frac{e^{-k|\mathbf{r}-\mathbf{s}|}}{4\pi|\mathbf{r}-\mathbf{s}|}$$

Single-layer potential: $$S_k[\sigma](\mathbf{r}) = \int_\Sigma G_k(\mathbf{r},\mathbf{s})\,\sigma(\mathbf{s})\,dA_\mathbf{s} \qquad \text{in } \Omega_{0,1}$$

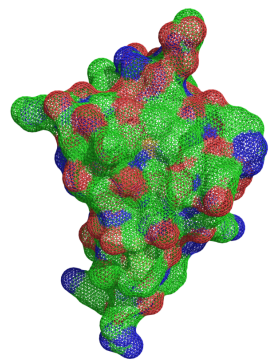
Double-layer potential: $$D_k[\mu](\mathbf{r}) = \int_\Sigma \frac{\partial G_k}{\partial \nu_\mathbf{s}}(\mathbf{r},\mathbf{s})\,\mu(\mathbf{s})\,dA_\mathbf{s} \qquad \text{in } \Omega_{0,1}$$

Solution representation:

$$\varphi \equiv \begin{cases} S_\kappa\sigma + D_\kappa\mu & \text{in } \Omega_0, \\ S_0\sigma + \alpha D_0\mu + \varphi_s & \text{in } \Omega_1, \end{cases} \qquad \alpha \equiv \frac{\varepsilon_0}{\varepsilon_1}, \quad \varphi_s(\mathbf{r}) \equiv \frac{1}{\varepsilon_1}\sum_i q_i G_0(\mathbf{r},\mathbf{r}_i)$$

Boundary integral equation on Σ:

$$\frac{1}{2}(1+\alpha)\mu + (S_\kappa - S_0)\sigma + (D_\kappa - \alpha D_0)\mu = \varphi_s,$$
$$-\frac{1}{2}(1+\alpha)\sigma + (\alpha S'_\kappa - S'_0)\sigma + \alpha(D'_\kappa - D'_0)\mu = \frac{\partial\varphi_s}{\partial\nu}$$



Rewrite in block form: $$(I+\lambda K)\begin{bmatrix}\mu\\ \sigma\end{bmatrix} = \lambda\begin{bmatrix}\varphi_s\\ -\varphi'_s\end{bmatrix} \xrightarrow{\text{discretize}} A(\Sigma)\,x = b(q)$$

Numerical considerations

Let $A \in \mathbb{C}^{N \times N}$ be a matrix discretization of some non-oscillatory Green's function integral operator. Note that A is **dense**.

- Cost of applying A: $\mathcal{O}(N^2)$
- Cost of inverting A: $\mathcal{O}(N^3)$

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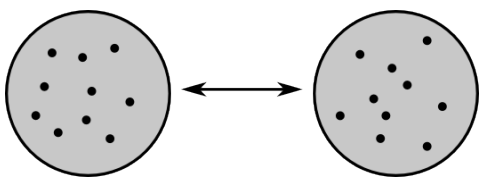
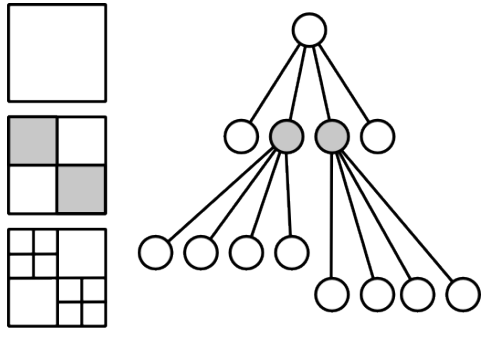
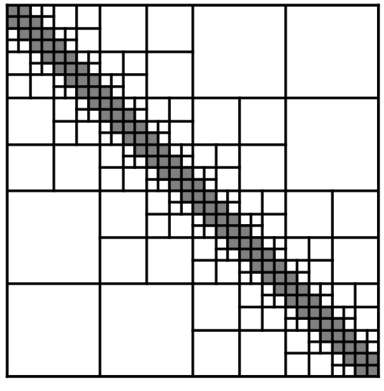
- Cost of applying A: $\mathcal{O}(N^2)$
- Cost of inverting A: $\mathcal{O}(N^3)$

But Green's function equation matrices are often structured.

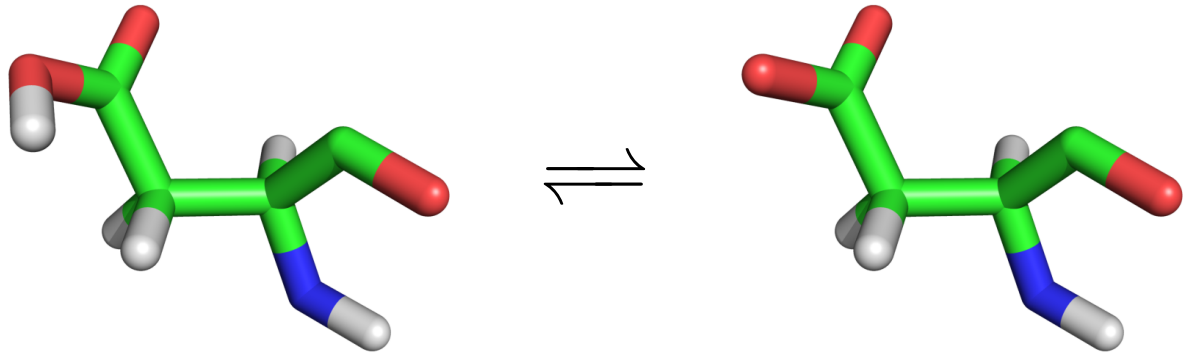
- Hierarchical low-rank approximation of far-field interactions
- Matrix-vector multiplication in $\mathcal{O}(N \log N)$ operations
  - Treecode, FMM, panel clustering, pFFT, FFTSVD
- Fast iterative solvers when combined with GMRES, BiCG, CGR, etc.







Protein pK_a calculations



$$\mathrm{p}K_\mathrm{a} \equiv -\log_{10}\frac{[\mathrm{A}]\,[\mathrm{H}]}{[\mathrm{AH}]} = \log_{10}\frac{[\mathrm{AH}]}{[\mathrm{A}]} + \mathrm{pH}$$

Ionization behavior is important for many biomolecular phenomena

- Binding affinities
- Enzymatic activities
- Structural properties

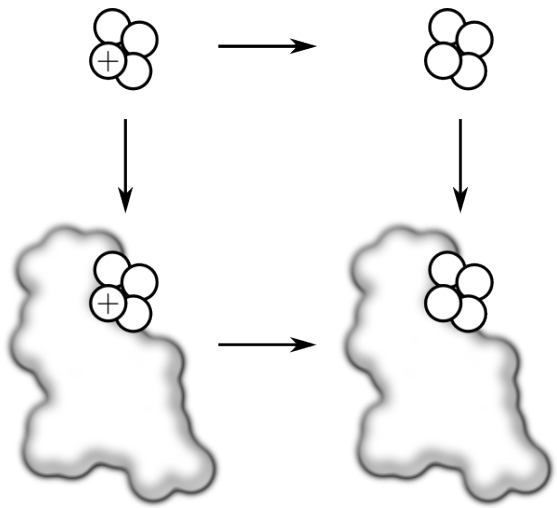
Theoretical interest: Bashford and Karplus, Juffer et al., Alexov et al.

A single titrating site

$$\mathrm{p}K_\mathrm{a} = \frac{\beta}{\ln 10}\Delta G^\mathrm{p}_{\mathrm{AH}\to\mathrm{A}+\mathrm{H}}$$

$$\begin{aligned}\Delta G^\mathrm{p}_{\mathrm{AH}\to\mathrm{A}+\mathrm{H}} &= \Delta G^\mathrm{s}_{\mathrm{AH}\to\mathrm{A}+\mathrm{H}} + \Delta G^{\mathrm{s}\to\mathrm{p}}_\mathrm{A} - \Delta G^{\mathrm{s}\to\mathrm{p}}_\mathrm{AH} \\ &= \underbrace{\Delta G^\mathrm{s}_{\mathrm{AH}\to\mathrm{A}+\mathrm{H}}}_{\text{experiment}} + \underbrace{\Delta G^\mathrm{s}_{\mathrm{A}\to\mathrm{AH}} - \Delta G^\mathrm{p}_{\mathrm{A}\to\mathrm{AH}}}_{\text{electrostatic only}}\end{aligned}$$

$$\begin{array}{ccc} \mathrm{A_sH} & \xrightarrow{\Delta G^\mathrm{s}_{\mathrm{AH}\to\mathrm{A}+\mathrm{H}}} & \mathrm{A_s} + \mathrm{H} \\ \Big\downarrow{\scriptstyle \Delta G^{\mathrm{s}\to\mathrm{p}}_\mathrm{AH}} & & \Big\downarrow{\scriptstyle \Delta G^{\mathrm{s}\to\mathrm{p}}_\mathrm{A}} \\ \mathrm{A_pH} & \xrightarrow{\Delta G^\mathrm{p}_{\mathrm{AH}\to\mathrm{A}+\mathrm{H}}} & \mathrm{A_p} + \mathrm{H} \end{array}$$



$$\mathrm{p}K_\mathrm{a} = \underbrace{\mathrm{p}K^\mathrm{model}_\mathrm{a}}_{\text{experiment}} - \frac{\beta}{\ln 10}\underbrace{\Delta\Delta G^{\mathrm{s}\to\mathrm{p}}_{\mathrm{A}\to\mathrm{AH}}}_{\text{electrostatic}}$$

Multiple titrating sites

Let $\theta_i \in \{0, 1\}$ denote the protonation state of each site $i = 1, \ldots, M$.

$$\mathrm{p}K_i^{\mathrm{intr}} \equiv \mathrm{p}K_i^{\mathrm{model}} - \frac{\beta}{\ln 10} \Delta\Delta G^{\mathrm{s}\to\mathrm{p}}_{\mathrm{A}\to\mathrm{A}(e_i)}$$

$$\Delta G_{\mathrm{A}\to\mathrm{A}(e_i)}\,(\mathrm{pH}) = -RT \ln 10 \left(\mathrm{p}K_i^{\mathrm{intr}} - \mathrm{pH}\right)$$

$$\Delta G_{\mathrm{A}\to\mathrm{A}(\theta)}\,(\mathrm{pH}) = -RT \ln 10 \sum_i \theta_i \left(\mathrm{p}K_i^{\mathrm{intr}} - \mathrm{pH}\right) + \frac{1}{2} \sum_i \theta_i \sum_{j\neq i} \theta_j \Delta G_{ij}$$

Sample mean site protonation using Markov chain Monte Carlo:

$$\langle \theta_i \rangle\,(\mathrm{pH}) = \frac{1}{Z} \sum_\theta \theta_i e^{-\beta \Delta G_{\mathrm{A}\to\mathrm{A}(\theta)}(\mathrm{pH})}, \quad \mathrm{p}K_i = \arg\underset{\mathrm{pH}}{} \langle \theta_i \rangle\,(\mathrm{pH}) = \frac{1}{2}$$

Bottleneck: interaction energies in protein

- Calculate φ_j for each j: solve $A(\Sigma)x = b(q_j)$
- Compute $\Delta G_{ij} = q_i^{\mathsf{T}} \varphi_j$ for each i
- Requires M solves with the same matrix

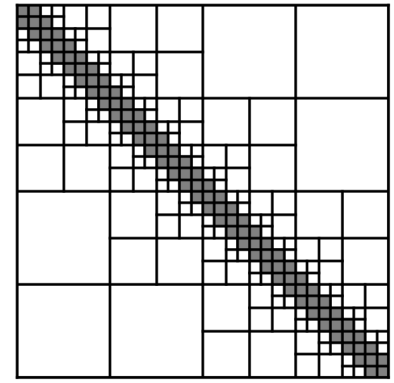
Solving systems with multiple right-hand sides

Standard iterative solvers for $Ax = b$:

- Sequence of operations depends on b
- Can be inefficient for multiple right-hand sides
- cf. blocking, projection, deflation, subspace recycling

An alternative: direct solvers

- Compute A^{-1} (factor A)
- Reuse factors for each solve
- Robust, always works
- Accelerate using similar low-rank ideas



Various approaches in recent years:

- $\mathscr{H}$-matrices (Hackbusch, Börm, Grasedyck, Bebendorf et al.)
- HSS matrices (Chandrasekaran, Gu, Xia, Li et al.)
- Skeletonization (Martinsson, Rokhlin, Greengard, Gillman et al.)
  - BIEs in 2D
  - One-level BIEs in 3D

A fast direct solver for integral equations

Here, we present a multilevel skeletonization-based fast direct solver in general dimension. For BIEs:

	2D	3D
precomp	$\mathcal{O}(N)$	$\mathcal{O}(N^{3/2})$
solve	$\mathcal{O}(N)$	$\mathcal{O}(N \log N)$

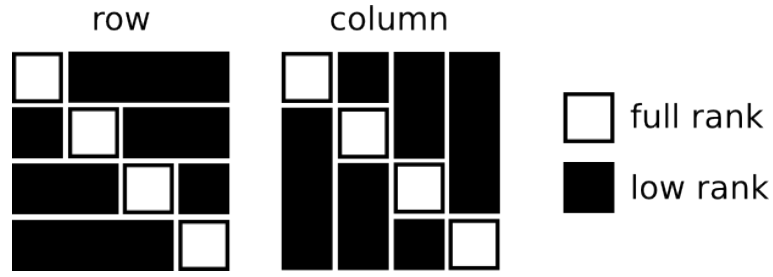
Main ideas/take-home messages :

- Kernel-independent: Laplace, Stokes, Yukawa, low-frequency Helmholtz, etc.
- Robust to geometry (e.g., boundary vs. volume, dimensionality)
- User-specified precision: trade accuracy for speed
- Naturally exposes the data-sparsity of integral equation matrices
- Very fast solve times, beating the FMM by factors of 100–1000
- Simple framework: easy to analyze, implement, and optimize
- Somewhat similar in flavor to nested dissection
- Can also apply to PDE formulations (Xia, Gillman et al.)

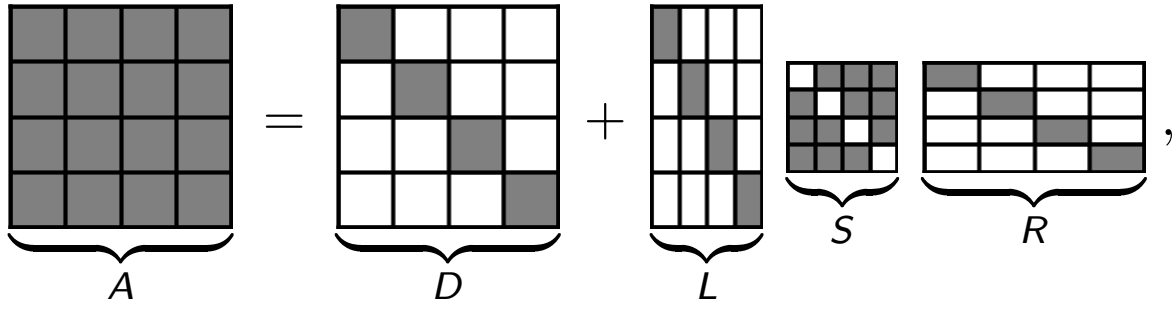
Block separable matrices

A block matrix A is block separable if

$$\underbrace{\begin{bmatrix} \times & \times \\ \times & \times \end{bmatrix}}_{A_{ij}} = \underbrace{\begin{bmatrix} \times \\ \times \end{bmatrix}}_{L_i} \underbrace{\begin{bmatrix} \times \end{bmatrix}}_{S_{ij}} \underbrace{\begin{bmatrix} \times & \times \end{bmatrix}}_{R_j}, \quad i \neq j.$$



Then



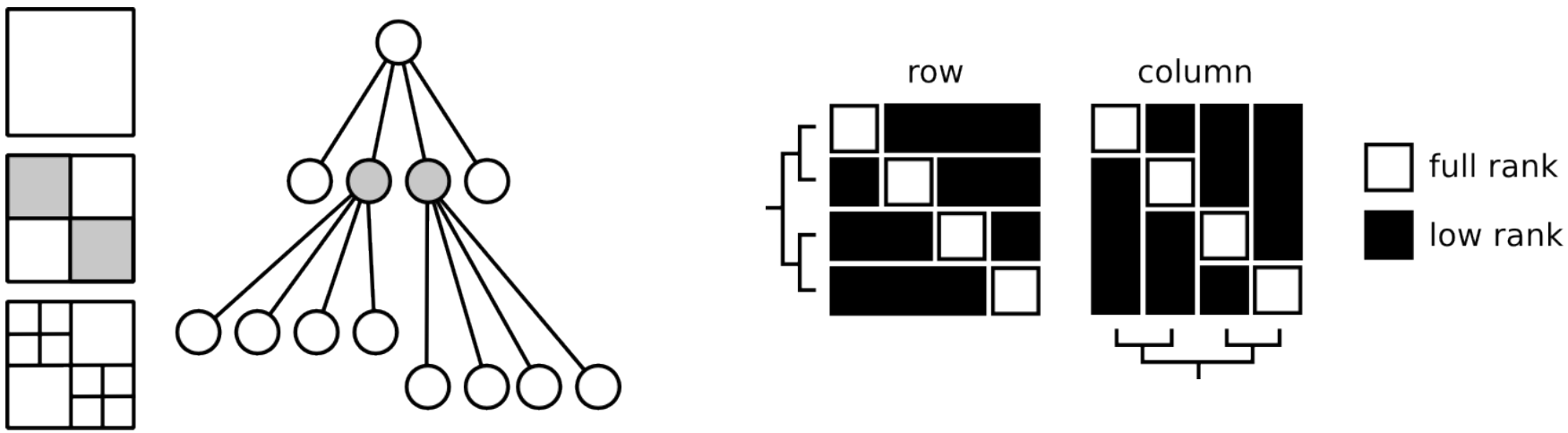
so $Ax = b$ is equivalent to the structured sparse system

$$\begin{bmatrix} D & L & \\ R & & -I \\ & -I & S \end{bmatrix} \begin{bmatrix} x \\ y \\ z \end{bmatrix} = \begin{bmatrix} b \\ 0 \\ 0 \end{bmatrix}$$

with $z \equiv Rx$ and $y \equiv Sz$. Factor using UMFPACK, SuperLU, WSMP, etc.

Hierarchically block separable matrices

Integral equation matrices are, in fact, hierarchically block separable, i.e., they are block separable at every level of an octree-type ordering.



In this setting, much more powerful algorithms can be developed.

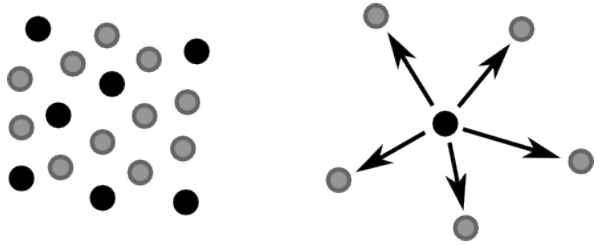
Interpolative decomposition

An interpolative decomposition of a rank-k matrix is a factorization

$$\underbrace{A}_{m\times n} = \underbrace{B}_{m\times k}\,\underbrace{P}_{k\times n},$$

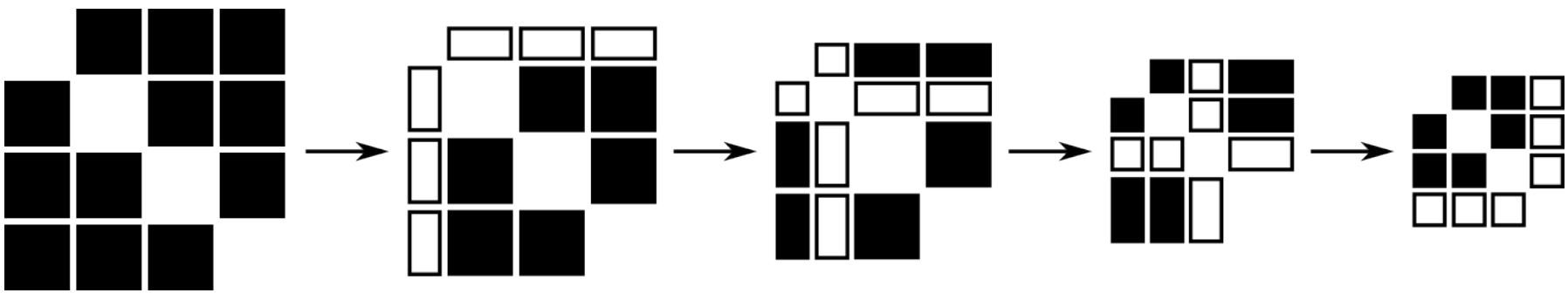
where B is a column-submatrix of A (with $\|P\|$ small).

- The ID compresses the column space; to compress the row space, apply the ID to A^{T}. We call the retained rows and columns skeletons.
- Adaptive algorithms can compute the ID to any specified precision $\epsilon > 0$.
- Related factorizations: SVD, RRQR, pseudoskeleton (CUR), ACA



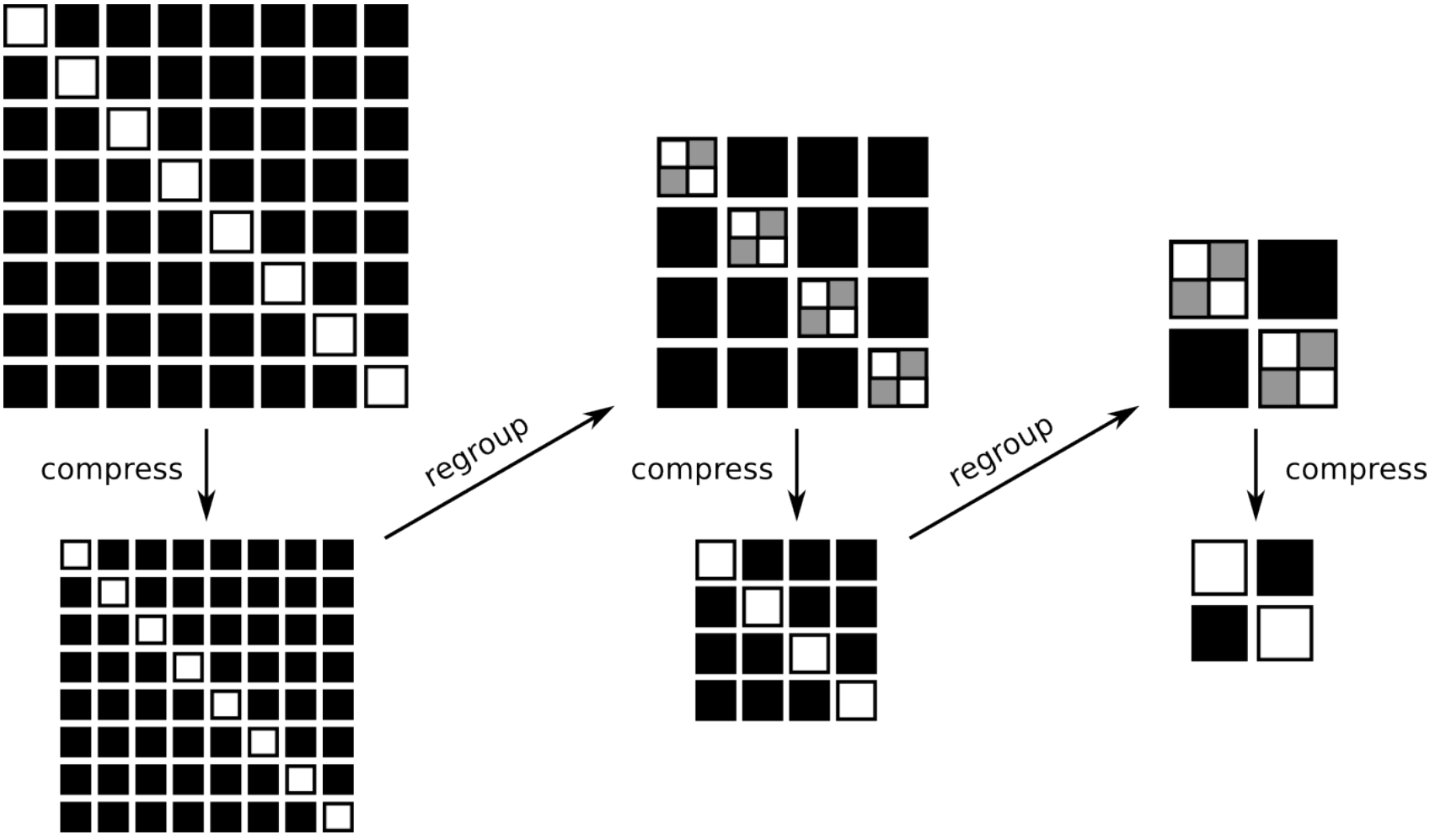
One-level matrix compression

- Compress the row space of each off-diagonal block row.
  Let the L_i be the corresponding row interpolation matrices.
- Compress the column space of each off-diagonal block column.
  Let the R_j be the corresponding column interpolation matrices.
- Approximate the off-diagonal blocks by $A_{ij} \approx L_i S_{ij} R_j$ for $i \neq j$.
- S is a skeleton submatrix of A



Skeletonization

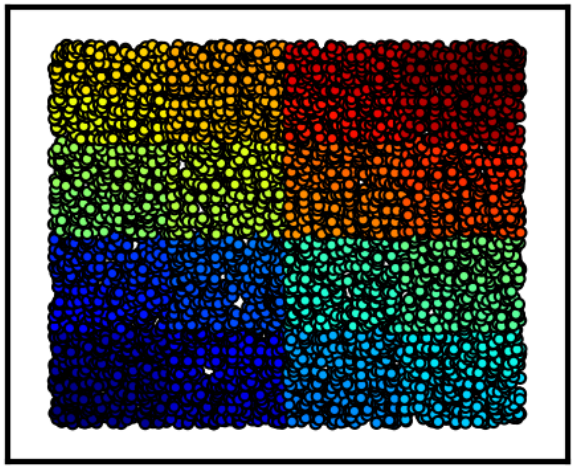
Multilevel matrix compression



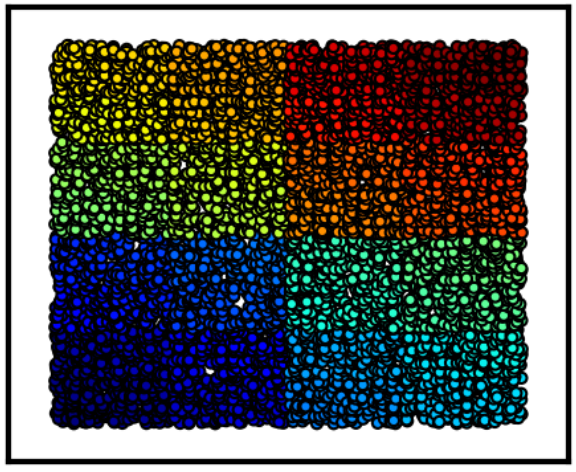
Recursive skeletonization

Data sparsification

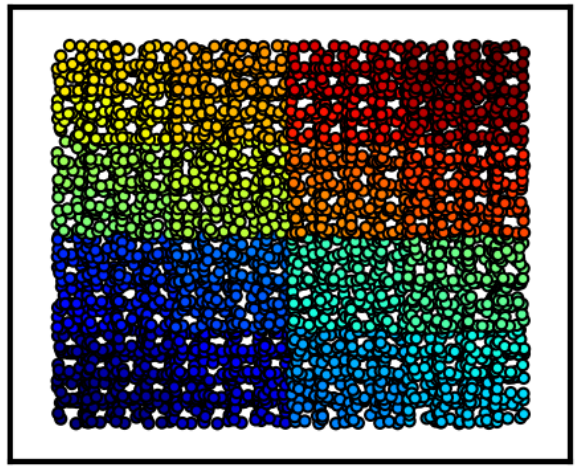
$N_0 = 8192$



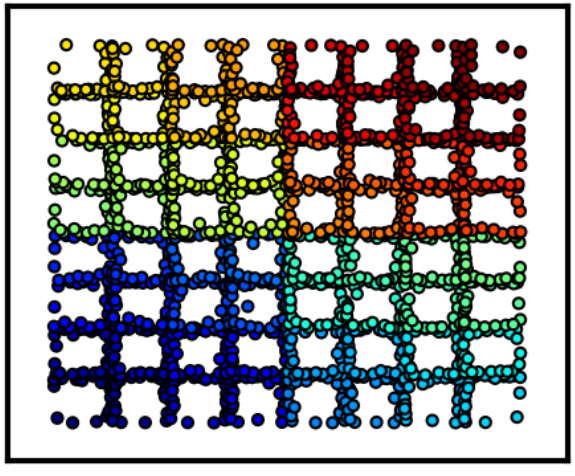
$N_1 = 7134$



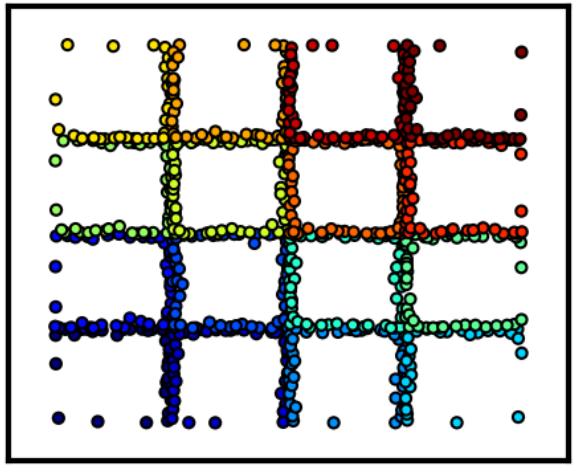
$N_2 = 4138$



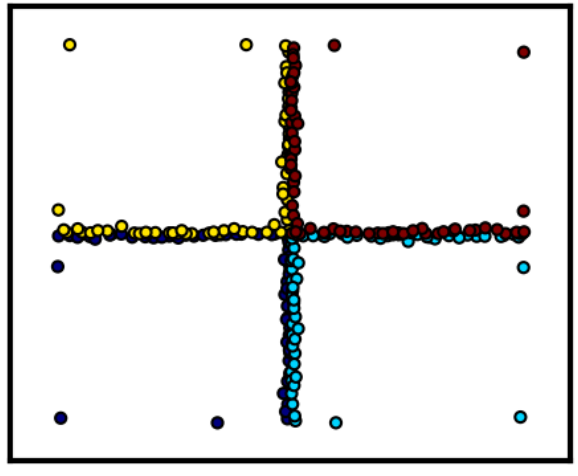
$N_3 = 1849$



$N_4 = 776$



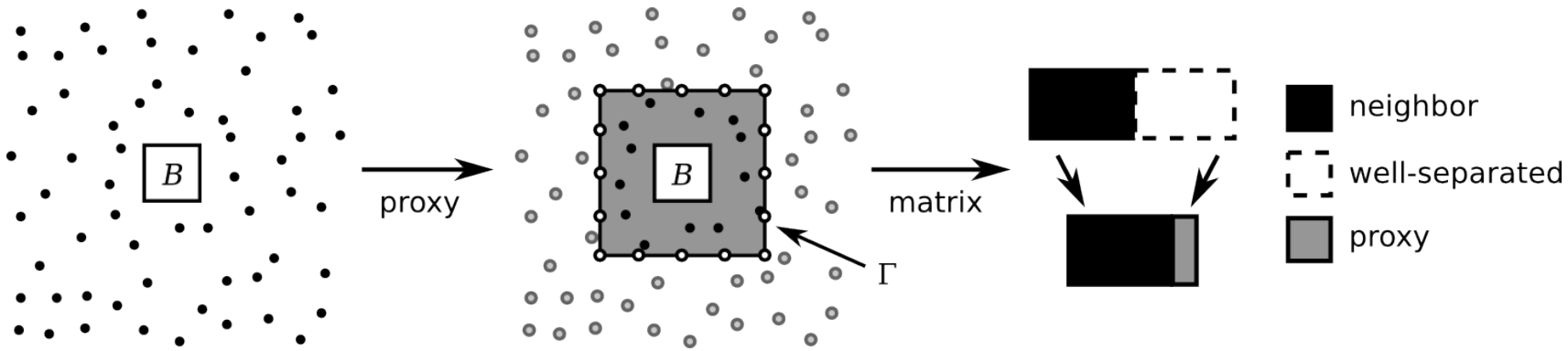
$N_5 = 265$



$$G(\mathbf{r},\mathbf{s}) = -\frac{1}{2\pi}\log|\mathbf{r}-\mathbf{s}|\ , \quad \epsilon = 10^{-3}$$

Accelerated compression for PDEs

- General compression algorithm is global and so at least $\mathcal{O}(N^2)$
- For potential fields, use Green's theorem to accelerate
- Represent well-separated interactions via a local proxy surface
- Can be generalized to non-PDE kernels using sparse grids



Compressed matrix representation

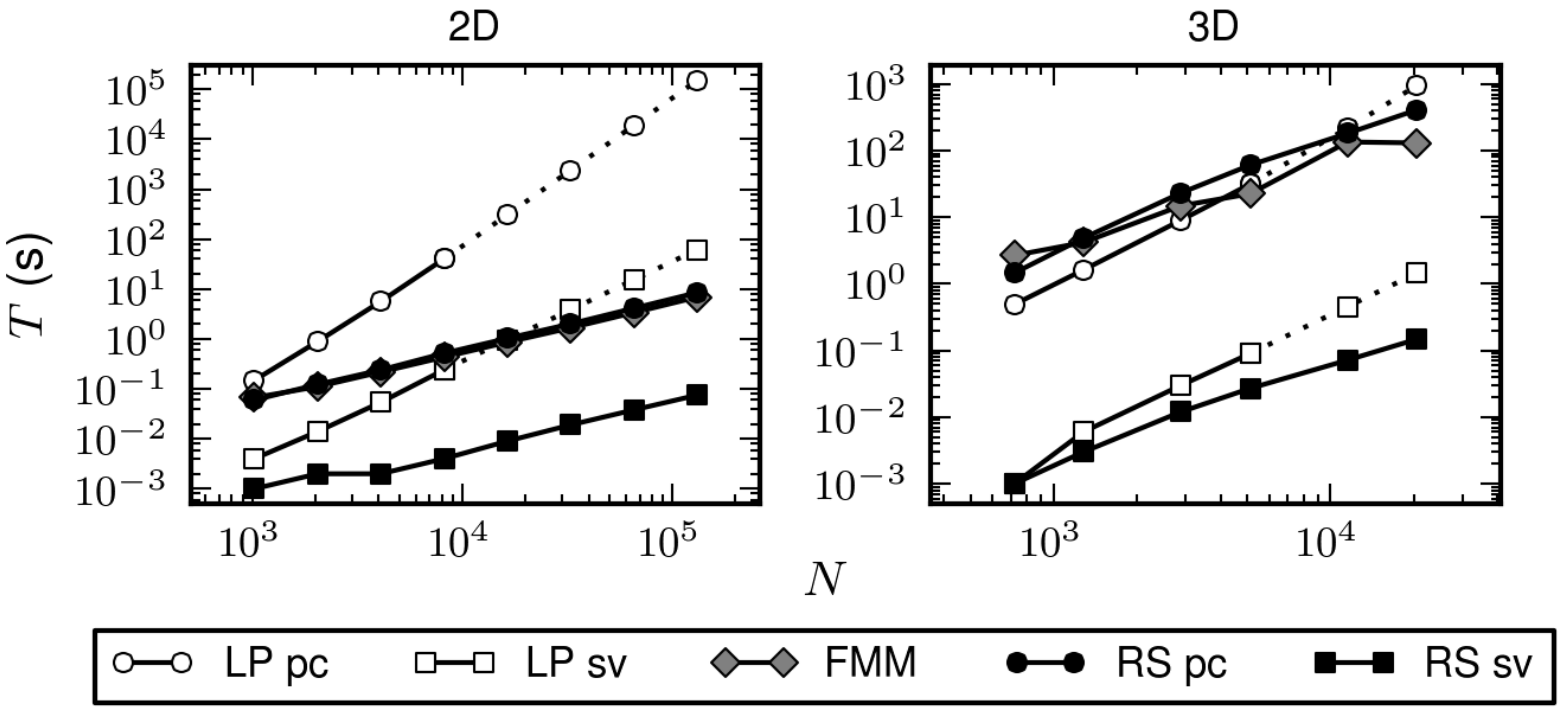
- Telescoping formula:

$$A \approx D^{(1)} + L^{(1)} \left[D^{(2)} + L^{(2)} \left(\cdots D^{(\lambda)} + L^{(\lambda)} S R^{(\lambda)} \cdots \right) R^{(2)} \right] R^{(1)}$$

- Efficient storage, fast matrix-vector multiplication (generalized FMM)
- Structured sparse inversion:

$$\begin{bmatrix}
D^{(1)} & L^{(1)} & & & & & \\
R^{(1)} & & -I & & & & \\
 & -I & D^{(2)} & L^{(2)} & & & \\
 & & R^{(2)} & \ddots & \ddots & & \\
 & & & \ddots & D^{(\lambda)} & L^{(\lambda)} & \\
 & & & & R^{(\lambda)} & & -I \\
 & & & & & -I & S
\end{bmatrix}
\begin{bmatrix} x \\ y^{(1)} \\ z^{(1)} \\ \vdots \\ \vdots \\ y^{(\lambda)} \\ z^{(\lambda)} \end{bmatrix}
=
\begin{bmatrix} b \\ 0 \\ 0 \\ \vdots \\ \vdots \\ 0 \\ 0 \end{bmatrix}$$

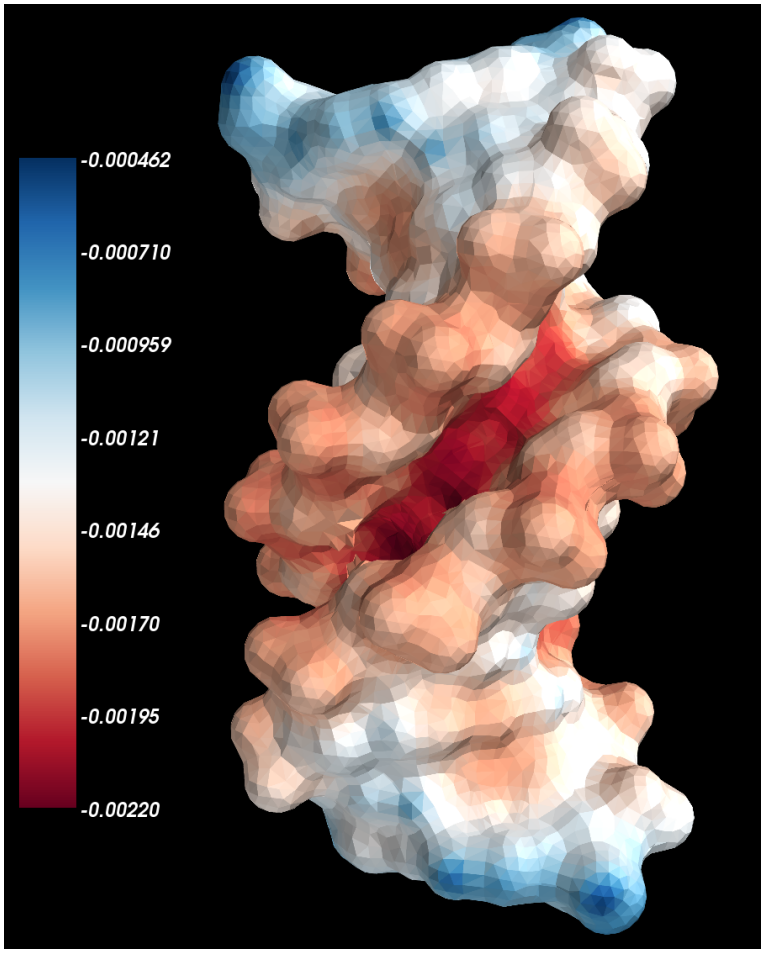
Laplace BIE solver



- Less memory-efficient than FMM/GMRES
- Each solve is extremely fast (in elements/sec)

ϵ	10^{-3}	10^{-6}	10^{-9}
2D	3.3×10^6	2.0×10^6	1.7×10^6
3D	6.0×10^5	1.4×10^5	6.2×10^4

Poisson electrostatics



$$-\Delta\varphi = 0 \qquad \text{in } \Omega_0$$

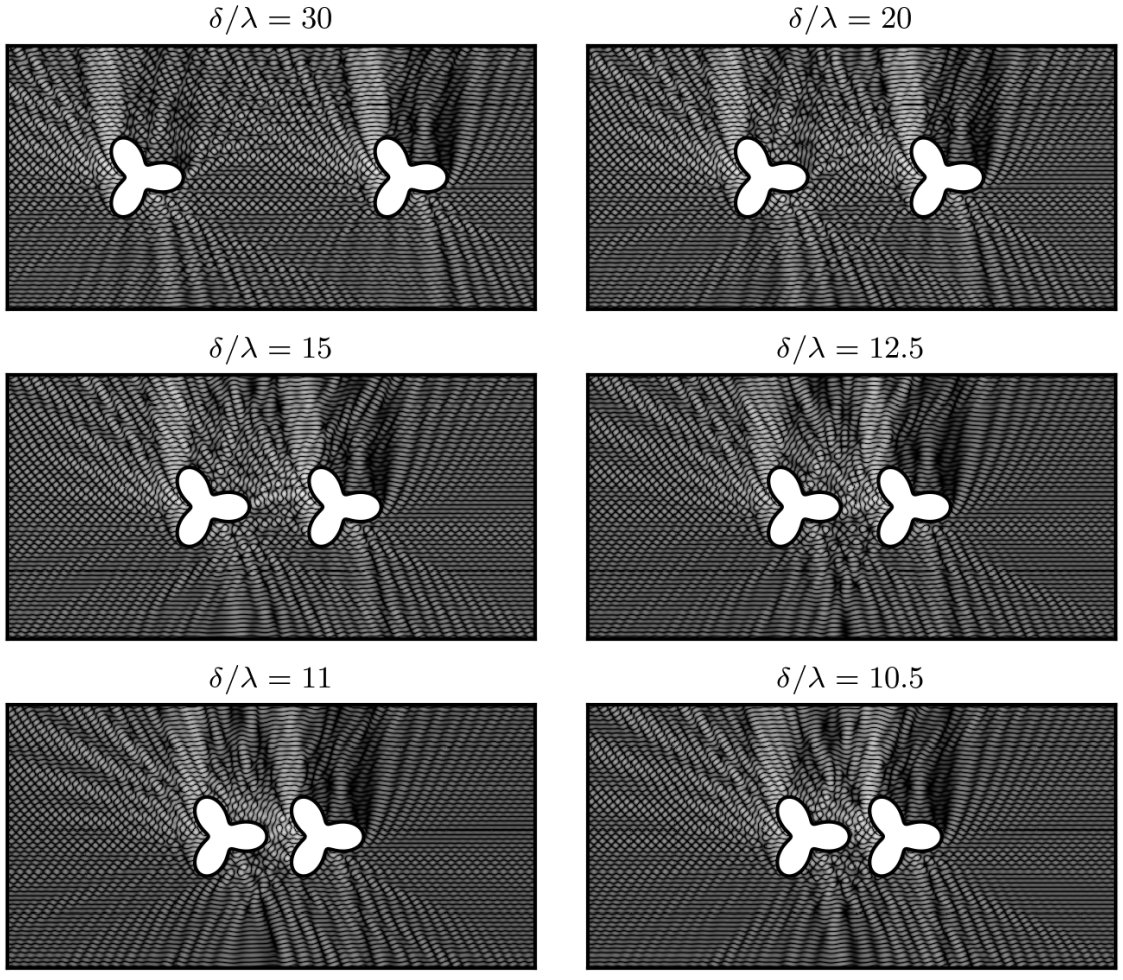
$$-\Delta\varphi = \frac{1}{\varepsilon_1}\sum_i q_i \delta\left(\mathbf{r} - \mathbf{r}_i\right) \qquad \text{in } \Omega_1$$

$$[\varphi] = \left[\varepsilon \frac{\partial\varphi}{\partial\nu}\right] = 0 \qquad \text{on } \Sigma$$

N	7612	19752
FMM/GMRES	12.6 s	26.9 s
RS precomp	151 s	592 s
RS solve	0.03 s	0.08 s

Break-even point: 10–25 solves

Multiple scattering



- Each object: 10λ

$$\begin{bmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} b_1 \\ b_2 \end{bmatrix}$$

- FMM/GMRES with block preconditioner via RS

$$\begin{bmatrix} A_{11}^{-1} & \\ & A_{22}^{-1} \end{bmatrix}$$

- Unprecon: 700 iterations
- Precon: 10 iterations
- $50\times$ speedup

Rigid-body "docking"

Summary

Main results:

- After precomputation, very fast solves (sub-second)
- Complexities in d dimensions (BIEs in $d+1$ dimensions):

$$\text{precomp} \sim \begin{cases} N & \text{if } d = 1, \\ N^{3(1-1/d)} & \text{if } d > 1, \end{cases} \qquad \text{solve} \sim \begin{cases} N & \text{if } d = 1, \\ N \log N & \text{if } d = 2, \\ N^{2(1-1/d)} & \text{if } d > 2 \end{cases}$$

- Useful for systems involving many right-hand sides

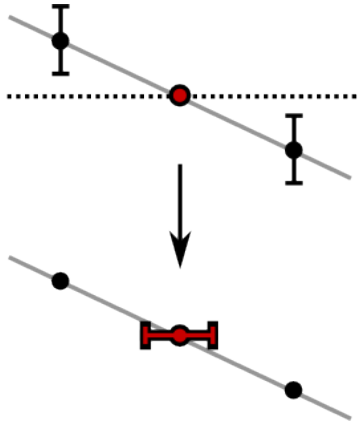
Extensions:

- Preconditioning, least squares
- Local geometric perturbations:

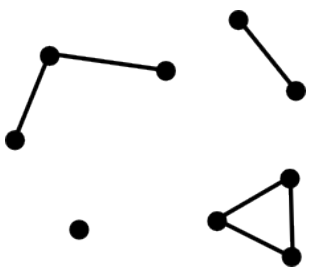
$$\begin{bmatrix} A & B_+ & B_- \\ C_+ & D_+ & D_* \\ C_- & & I \end{bmatrix} \begin{bmatrix} x \\ x_+ \\ x_- \end{bmatrix} = \begin{bmatrix} b \\ b_+ \\ 0 \end{bmatrix}$$

pK_a algorithm

- Protein preparation
- Matrix precomputation
  - Compress/factor
- Energy calculation
- Monte Carlo sampling
  - Reduced site approximation
  - Multi-site cluster moves
- Estimate pK_i
  - Error bars



Apply delta method.

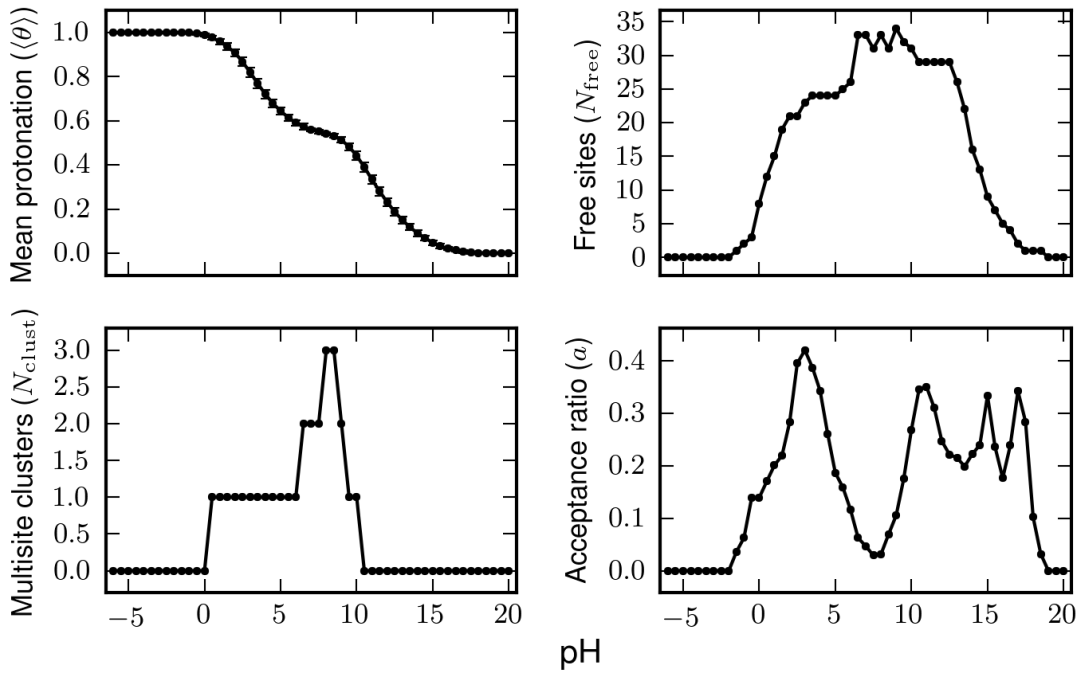


- Link sites by interaction energy
- Clusters: connected components
- Modify one cluster at random
- Pick move distance from geometric distribution

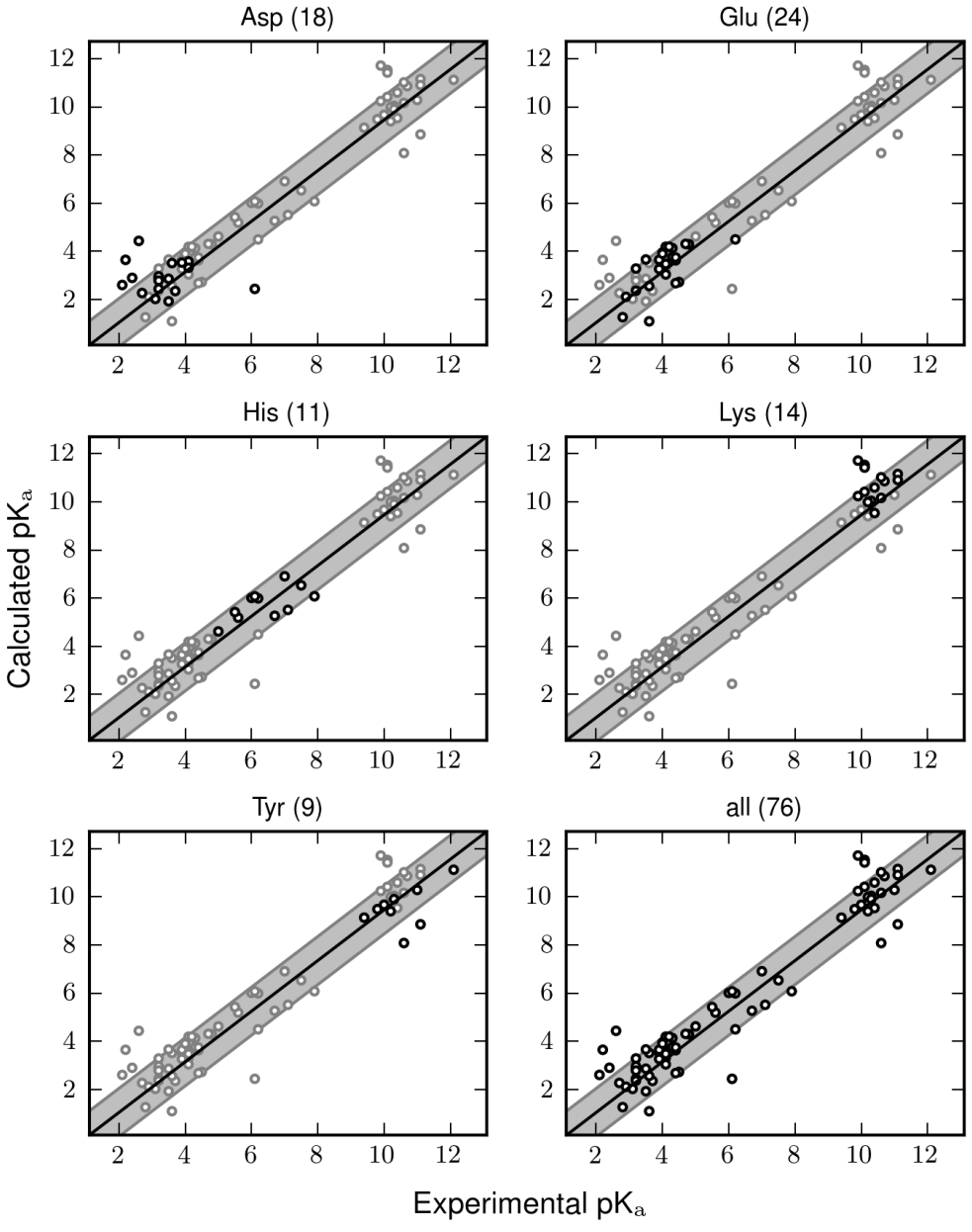
pK_a results: computational

name	PDB ID	residues	atoms	sites
BPTI	4PTI	58	891	18
OMTKY3	2OVO	56	813	15
HEWL	2LZT	129	1965	30
RNase A	3RN3	124	1865	34
RNase H	2RN2	155	2474	53

- DoFs: 10,000–30,000
- Precomp time: 1–2 hr
- Energy calc time: 10 s
- Much less memory than classical direct methods
- Much faster solves than iterative methods
- Precomp still expensive



pK_a results: biological



RMSD	protein dielectric 4	8	20
BPTI	1.47	0.96	0.82
OMTKY3	1.77	1.07	1.09
HEWL	2.52	1.49	0.79
RNase A	3.22	2.25	0.85
RNase H	4.53	2.53	1.36

type	err ≤ 1	RMSD
Arg	12 / 18	1.23
Glu	17 / 24	1.00
His	8 / 11	0.92
Lys	11 / 14	0.79
Tyr	7 / 9	1.24
all	55 / 76	1.05

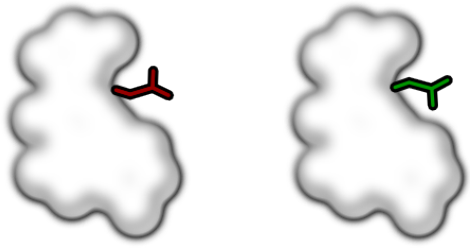
Conclusions

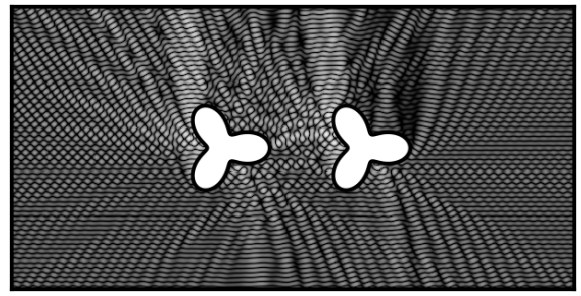
Main pK_a results:

- Can efficiently treat large numbers of titrating sites
- Similar accuracy as other Poisson-Boltzmann methods

Future work:

- Faster $\mathcal{O}(N \log N)$ direct solvers (forthcoming)
- Model conformational flexibility (Gunner et al.)
  - Treat with perturbative techniques





Generalizations:

- Structure prediction: fixed backbone, rotamer optimization
- Docking: like multiple scattering
- Charge optimization, molecular dynamics
- Inhomogeneous dielectrics, nonlocal electrostatics, etc.

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- Greengard L, Gueyffier D, Martinsson P-G, Rokhlin V (2009) Fast direct solvers for integral equations in complex three-dimensional domains. Acta Numer 18: 243–275.
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