Fast direct methods for molecular electrostatics

Kenneth L. Ho

Program in Computational Biology, NYU

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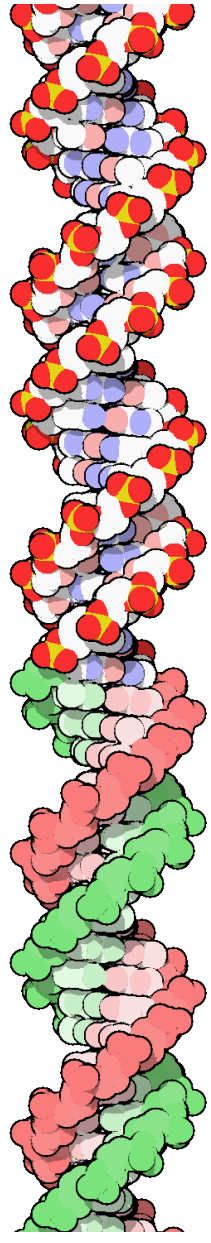
Suppose I give you a structure.

What can you tell me about its function?



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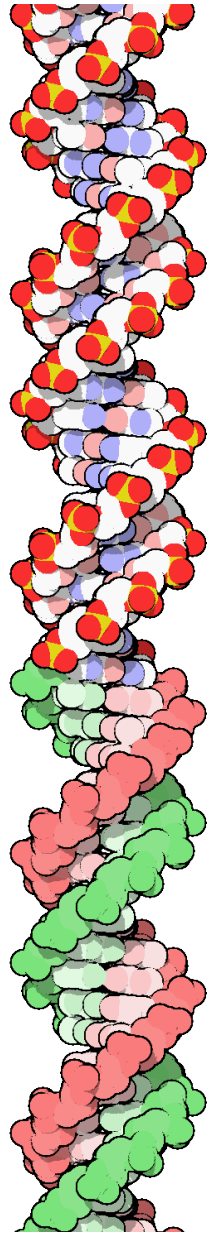
(What are the physics acting on it?)



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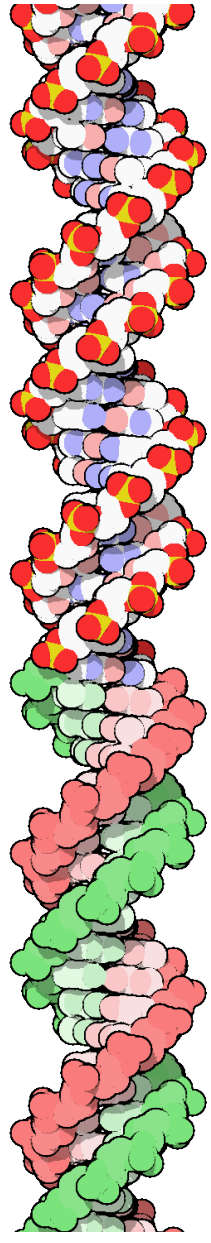
- Charge complementarity
- Conformation and dynamics
- Long-range steering
- Polarization and ionization



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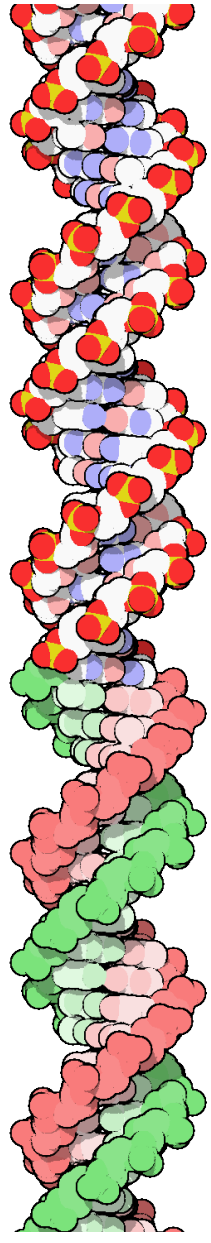
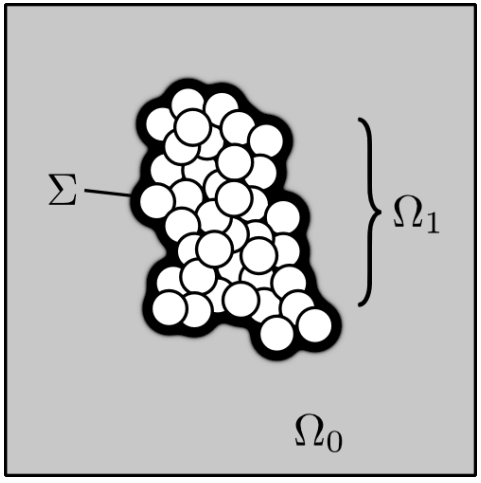
In this talk, we focus on electrostatics.





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

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

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

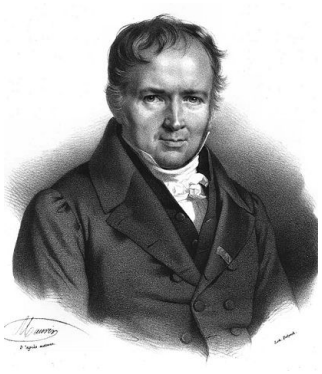
In the solvent:

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

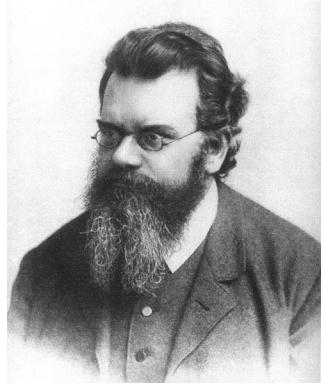
$$= \frac{1}{\varepsilon_0} \sum_i q_i c_i^\infty \exp\left(-\frac{q_i \varphi}{k_B T}\right)$$

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

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



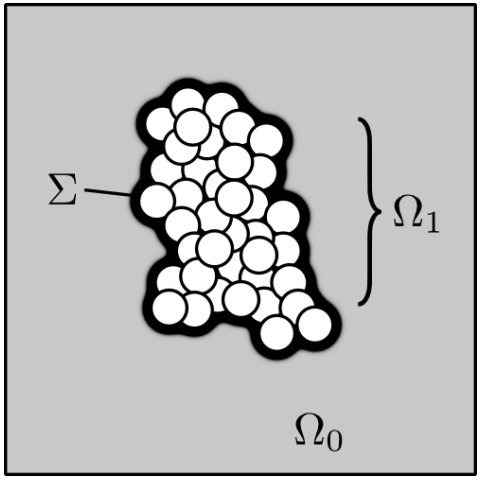
linearized Poisson-Boltzmann equation



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

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

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

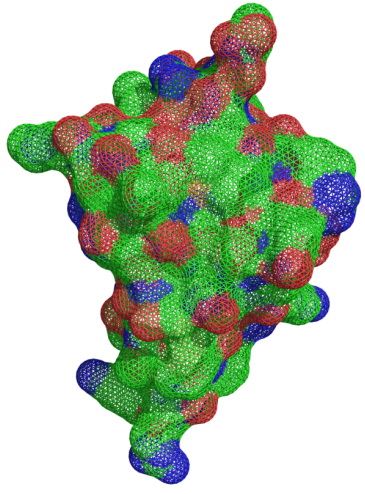


Many ways to solve: finite differences, finite elements

- Can be ill-conditioned
- Artificial domain truncation

We use instead boundary integral equation methods:

- Provably well-conditioned
- Exact boundary conditions
- Dimensional reduction



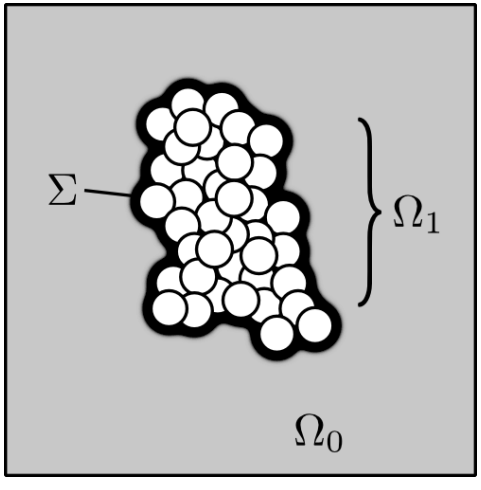
Integral equation basics

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

Jump relations as $\mathbf{r} \to \mathbf{s} \in \Sigma$:

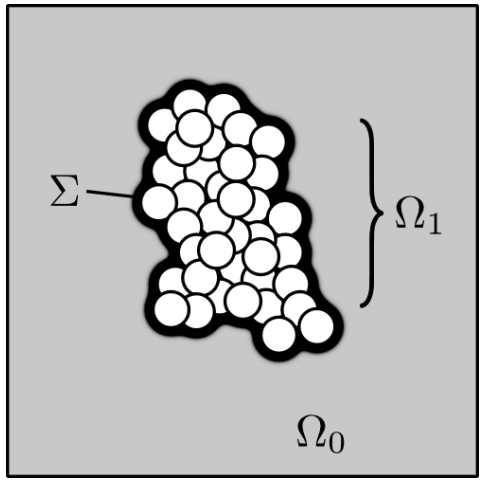


$$\left.\begin{aligned} S_k'[\sigma](\mathbf{r}) &\to \mp\frac{1}{2}\sigma(\mathbf{s}) + S_k'^{*}[\sigma](\mathbf{s}) \\ D_k[\mu](\mathbf{r}) &\to \pm\frac{1}{2}\mu(\mathbf{s}) + D_k^{*}[\mu](\mathbf{s}) \end{aligned}\right\} \quad \text{if } \mathbf{r} \in \Omega_{0,1}$$

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

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

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



Solution representation:

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

Boundary integral equation on Σ:

$$\frac{1}{2}\left(1+\alpha\right)\mu+\left(S_\kappa-S_0\right)\sigma+\left(D_\kappa-\alpha D_0\right)\mu=\varphi_s,$$

$$-\frac{1}{2}\left(1+\alpha\right)\sigma+\left(\alpha S'_\kappa-S'_0\right)\sigma+\alpha\left(D'_\kappa-D'_0\right)\mu=\frac{\partial\varphi_s}{\partial\nu}$$

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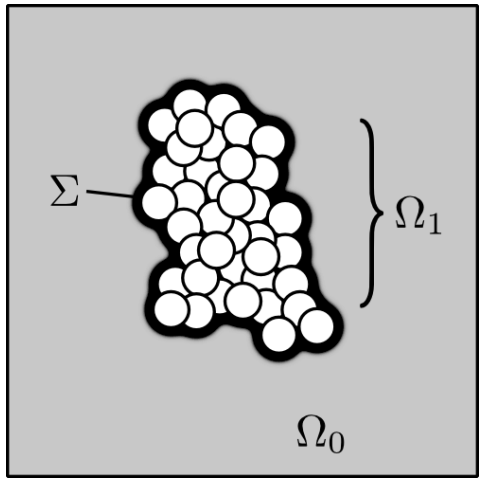

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$$\left(I+\lambda K\right)\begin{bmatrix}\mu\\ \sigma\end{bmatrix}=\lambda\begin{bmatrix}\varphi_s\\ -\partial\varphi_s/\partial\nu\end{bmatrix}$$

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.

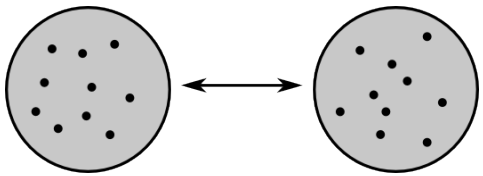
- Cost of applying A: $\mathcal{O}(N^2)$
- Cost of inverting A: $\mathcal{O}(N^3)$

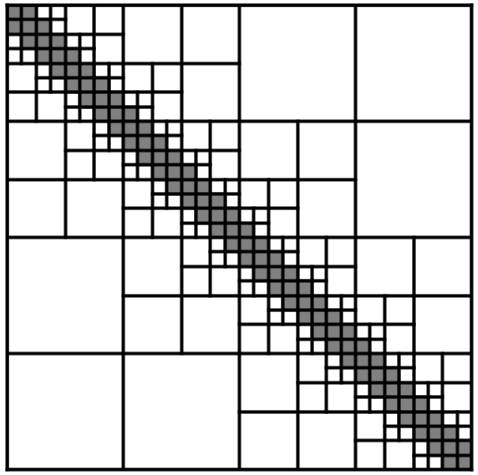
Fast iterative solvers:

- Krylov subspace methods (GMRES, BiCG, CGR)
- Fast matrix-vector product algorithms (treecode, FMM, panel clustering)
- Cost: $\mathcal{O}(N)$ or $\mathcal{O}(N \log N)$

Basic idea:

- Non-oscillatory Green's functions have smooth far fields
- Exploit smoothness with a hierarchical decomposition of space





Fast iterative solvers have been very successful, but they remain inefficient in certain important regimes:

- When A is ill-conditioned (multiphysics, singular geometries)
- When $Ax = b$ must be solved with many right-hand sides b or many perturbations of a base matrix A (optimization, design, time marching)
- Biological context: $\mathrm{p}K_\mathrm{a}$ calculation, structure prediction, docking

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One solution: direct solvers (construct A^{-1}).

- Robust: insensitive to conditioning, always works
- Fast solves and inverse updates following initial factorization

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Can we accelerate direct solvers to the same extent?

The answer is yes (more or less).

The same basic ideas apply, though some numerical machinery is required.

Related work:

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

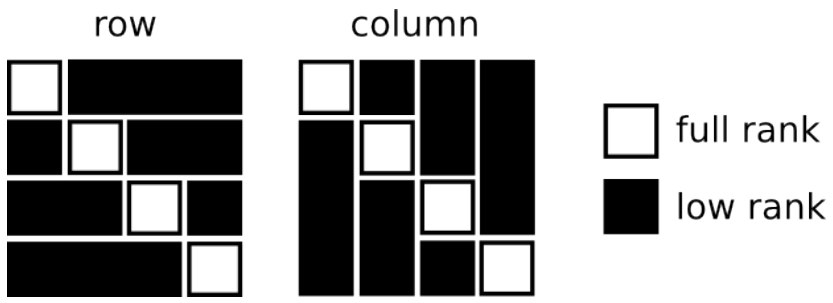
Here, we present a multilevel fast direct solver in general dimension. For BIEs:

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

Each solve is very fast, often beating the FMM by several orders of magnitude.

A block matrix A is block separable if

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



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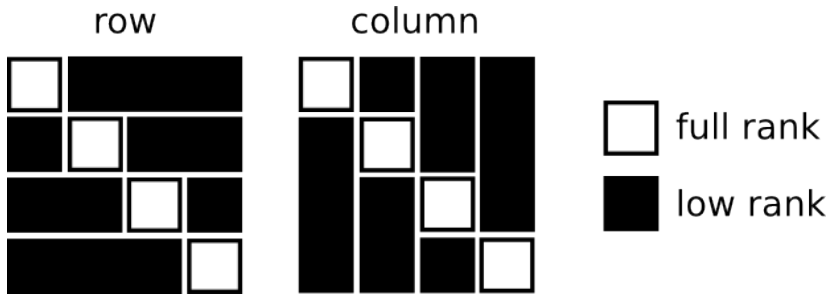
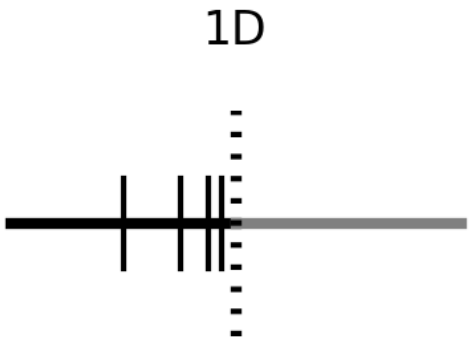
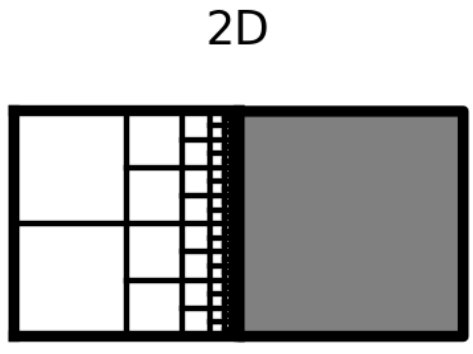


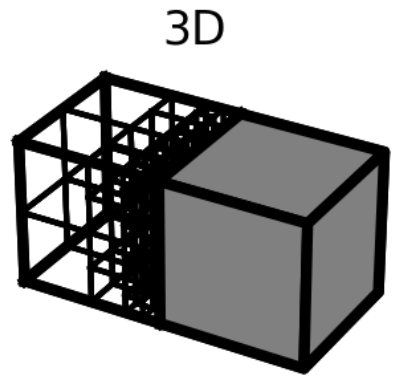
Integral equation matrices are block separable.



$\mathcal{O}(\log n)$

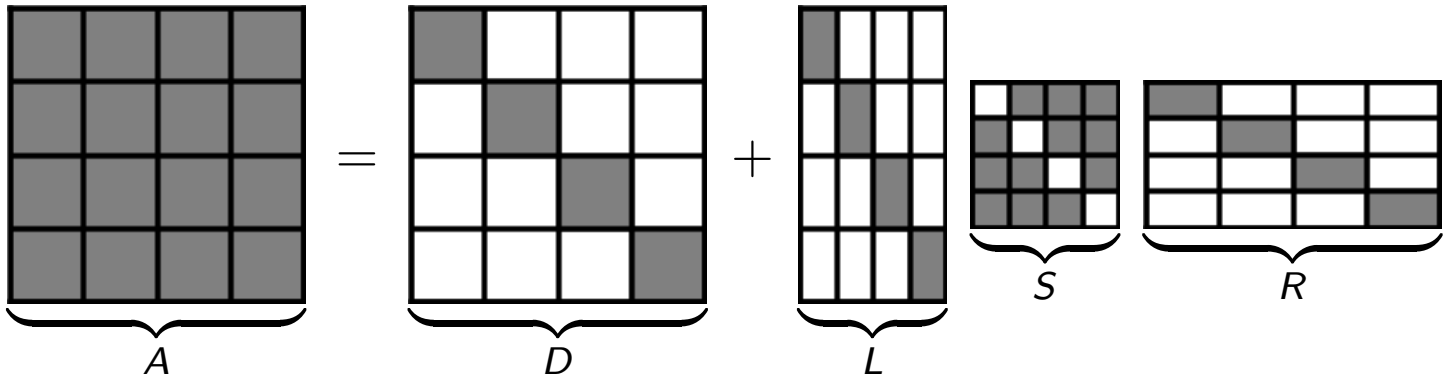


$\mathcal{O}(n^{1/2})$



$\mathcal{O}(n^{2/3})$

If A is block separable, then



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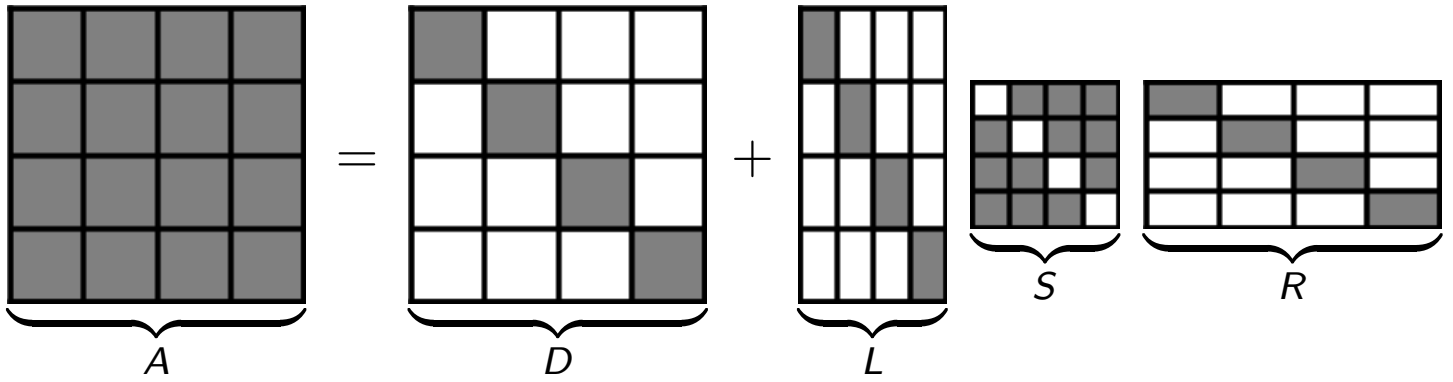


The inverse can be written in essentially the same form:

$$A^{-1} = \mathcal{D} + \mathcal{L}\mathcal{S}^{-1}\mathcal{R},$$

where

$$\mathcal{D} = D^{-1} - D^{-1}L\Lambda RD^{-1}, \quad \mathcal{L} = D^{-1}L\Lambda, \quad \mathcal{R} = \Lambda RD^{-1}, \quad \mathcal{S} = \Lambda + S,$$

with $\Lambda = \left(RD^{-1}L\right)^{-1}$. If A has $p \times p$ blocks and each $S_{ij} \in \mathbb{C}^{k\times k}$, then A^{-1} can be computed in $\mathcal{O}(p(N/p)^3 + (pk)^3)$ operations.

We can also adopt a sparse matrix perspective. For

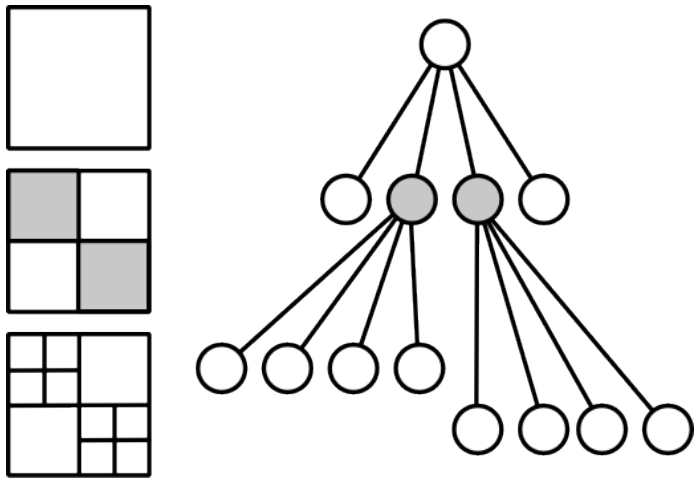
$$Ax = (D + LSR)\, x = b,$$

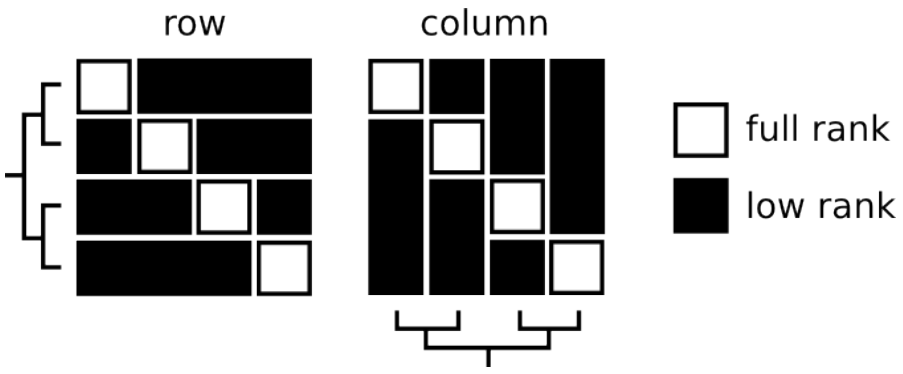
let $z \equiv Rx$ and $y \equiv Sz$. Then this is equivalent to the structured sparse system

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

Factor using UMFPACK, SuperLU, MUMPS, Pardiso, etc.

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.

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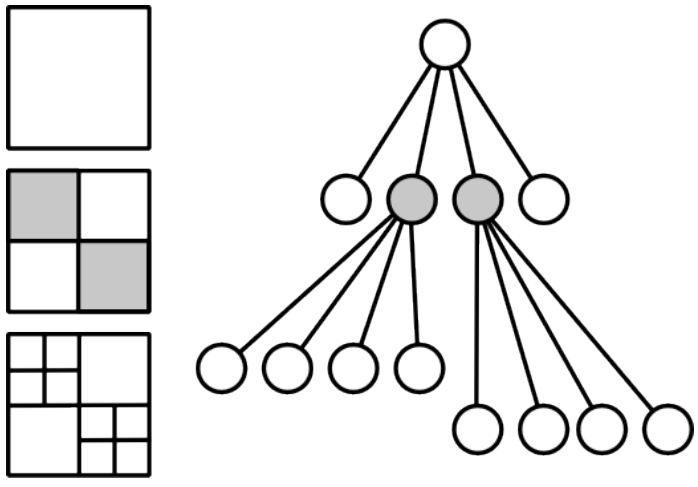
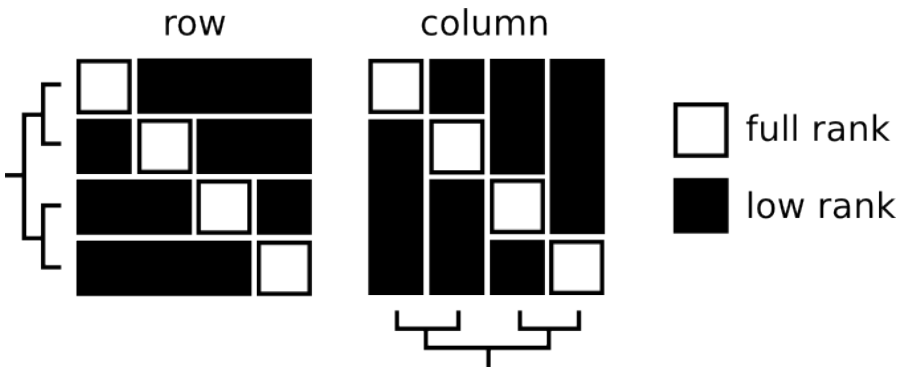




In this setting, much more powerful algorithms can be developed.

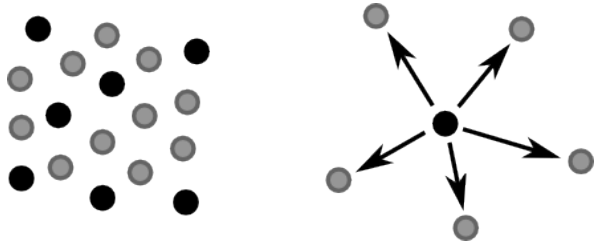
How to compress to block separable form?

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

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

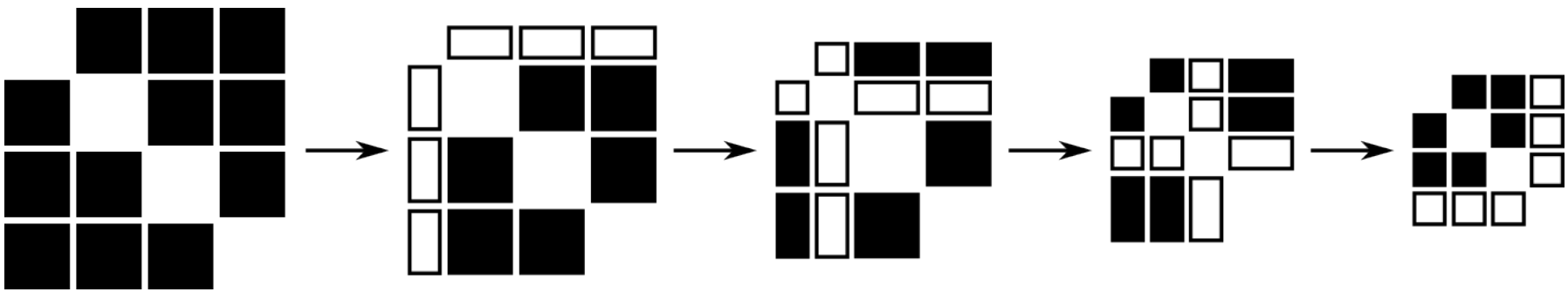
where B is a column-submatrix of A (with $\|P\|$ small).

- 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 $\epsilon > 0$.



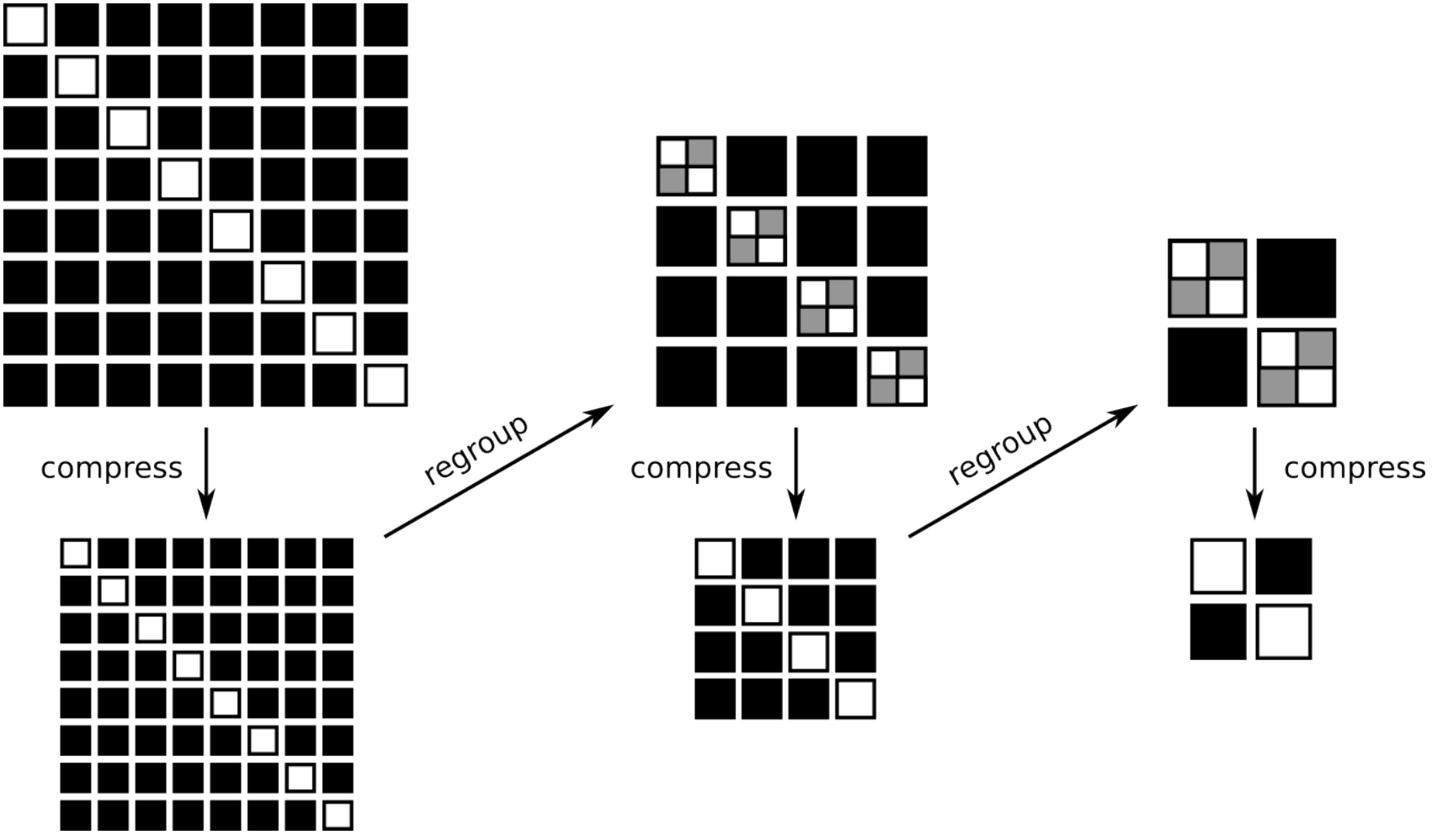
One-level matrix compression

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



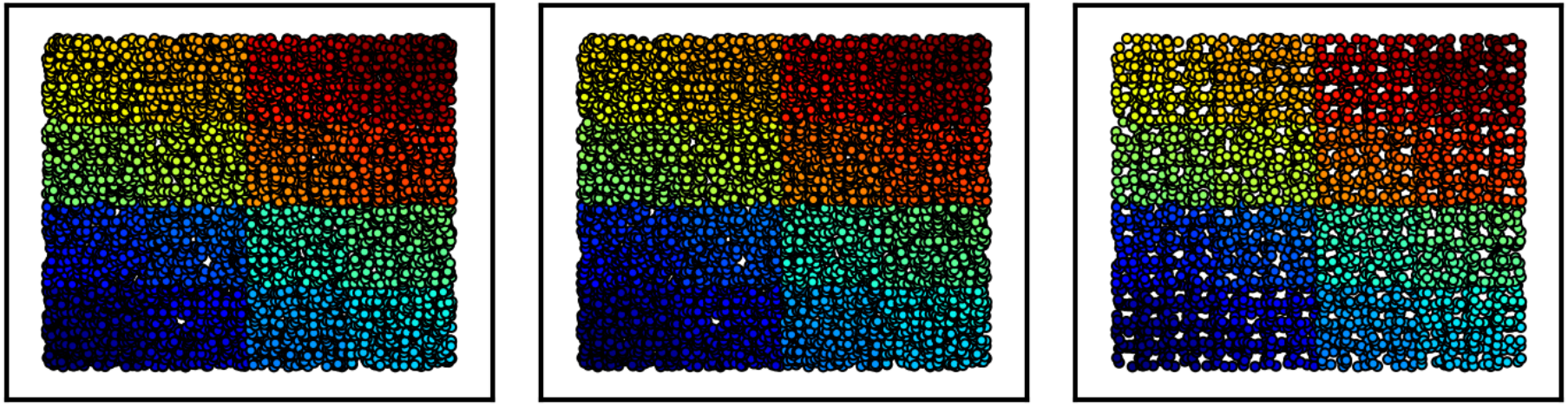
Skeletonization

Multilevel matrix compression

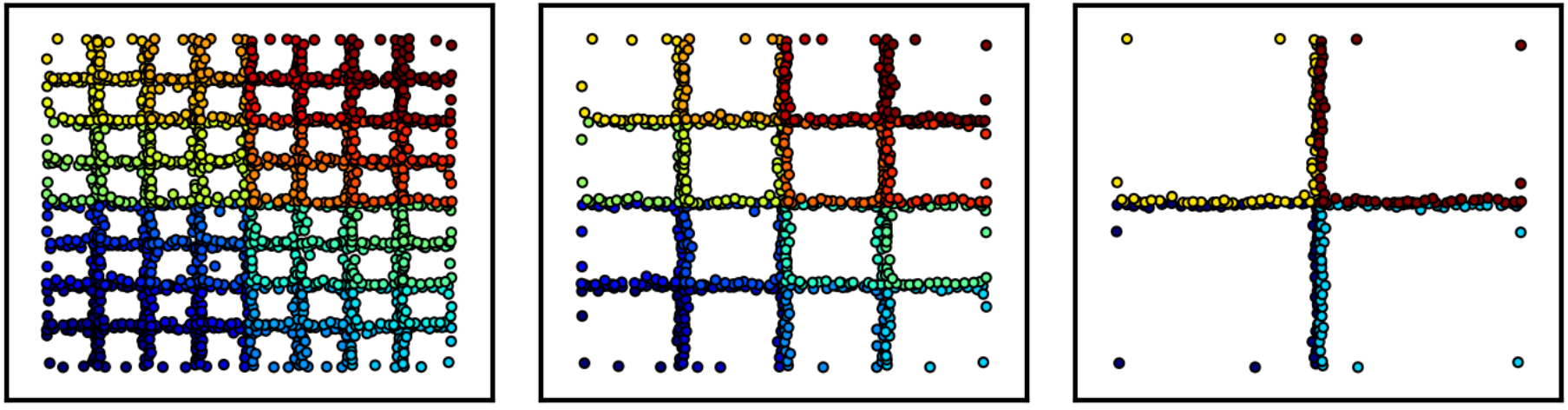


Recursive skeletonization

$N_0 = 8192$ $N_1 = 7134$ $N_2 = 4138$



$N_3 = 1849$ $N_4 = 776$ $N_5 = 265$

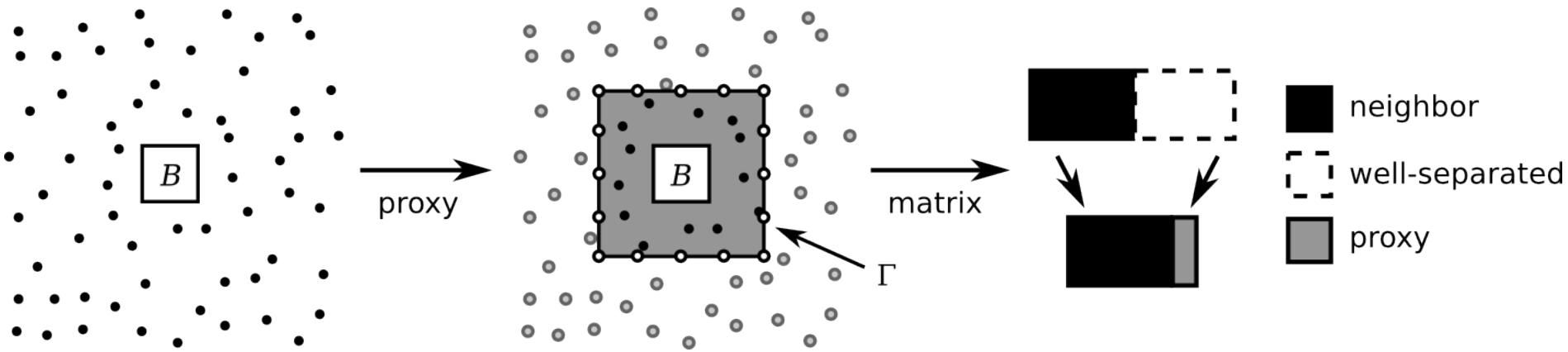


$$G(x,y) = -\frac{1}{2\pi}\log|x-y| \ , \quad \epsilon = 10^{-3}$$

- General compression algorithm is global and so at least $\mathcal{O}(N^2)$
- For potential fields, use Green's theorem to accelerate:

$$u(\mathbf{r}) = \int_\Gamma \left[u(\mathbf{s}) \frac{\partial G}{\partial \nu_\mathbf{s}}(\mathbf{r}, \mathbf{s}) - G(\mathbf{r}, \mathbf{s}) \frac{\partial u}{\partial \nu}(\mathbf{s}) \right] dA_\mathbf{s}$$

- Represent well-separated points with a local proxy surface



Compressed telescoping matrix representation:

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

- Efficient storage (data-sparse)

N	uncomp	comp
8192	537 MB	9.7 MB
131072	137 GB	184 MB

- Fast matrix-vector multiplication (generalized FMM)
- Fast matrix factorization and inverse application

Recursively expand in sparse form:

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

This can be treated efficiently using any standard sparse direct solver.

Multilevel inversion formula (for analysis):

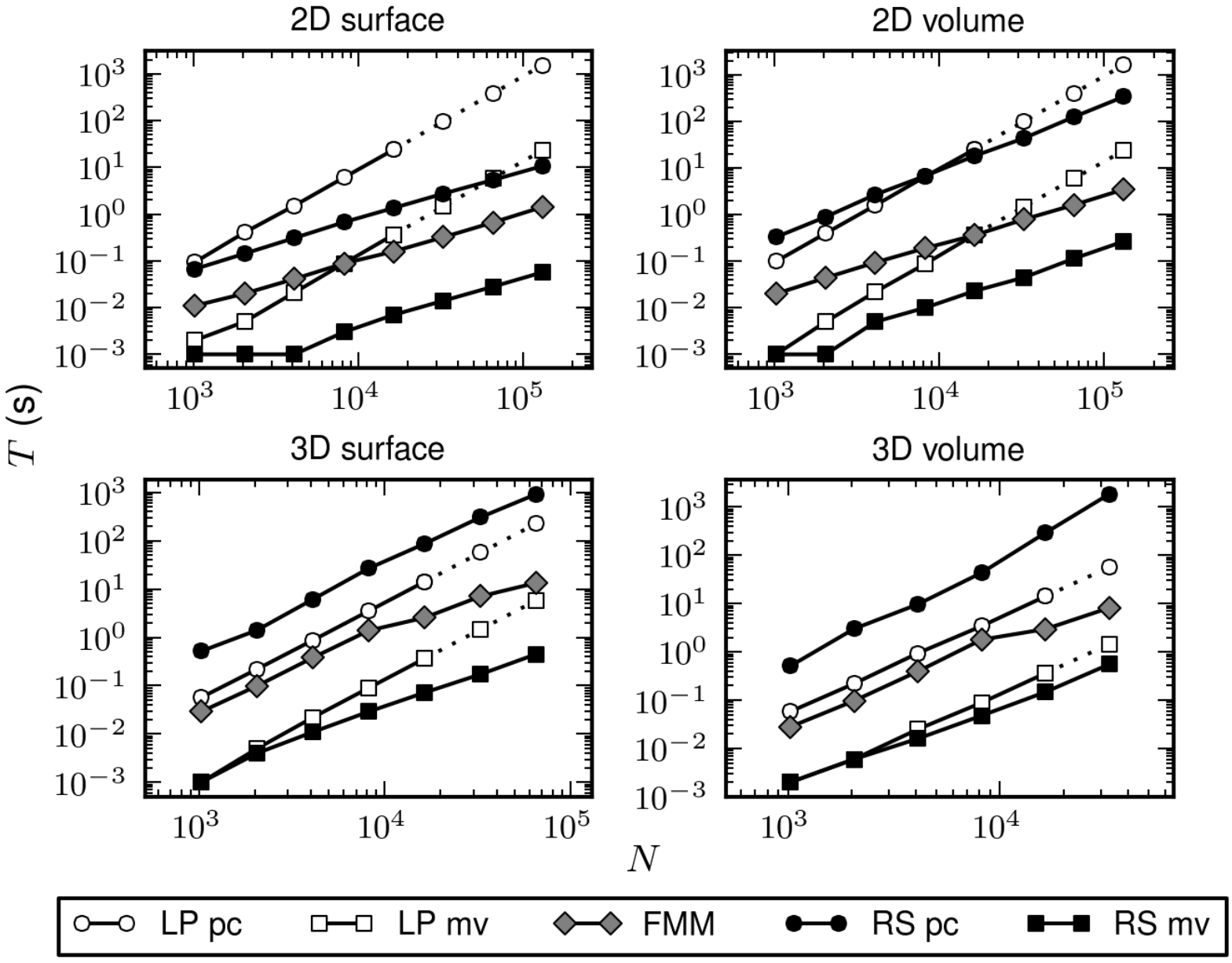
$$A^{-1} \approx \mathcal{D}^{(1)} + \mathcal{L}^{(1)} \left[\mathcal{D}^{(2)} + \mathcal{L}^{(2)} \left(\cdots D^{(\lambda)} + \mathcal{L}^{(\lambda)} \mathcal{S}^{-1} \mathcal{R}^{(\lambda)} \cdots \right) \mathcal{R}^{(2)} \right] \mathcal{R}^{(1)}$$

Complexities in d dimensions (BIEs in $d+1$ dimensions):

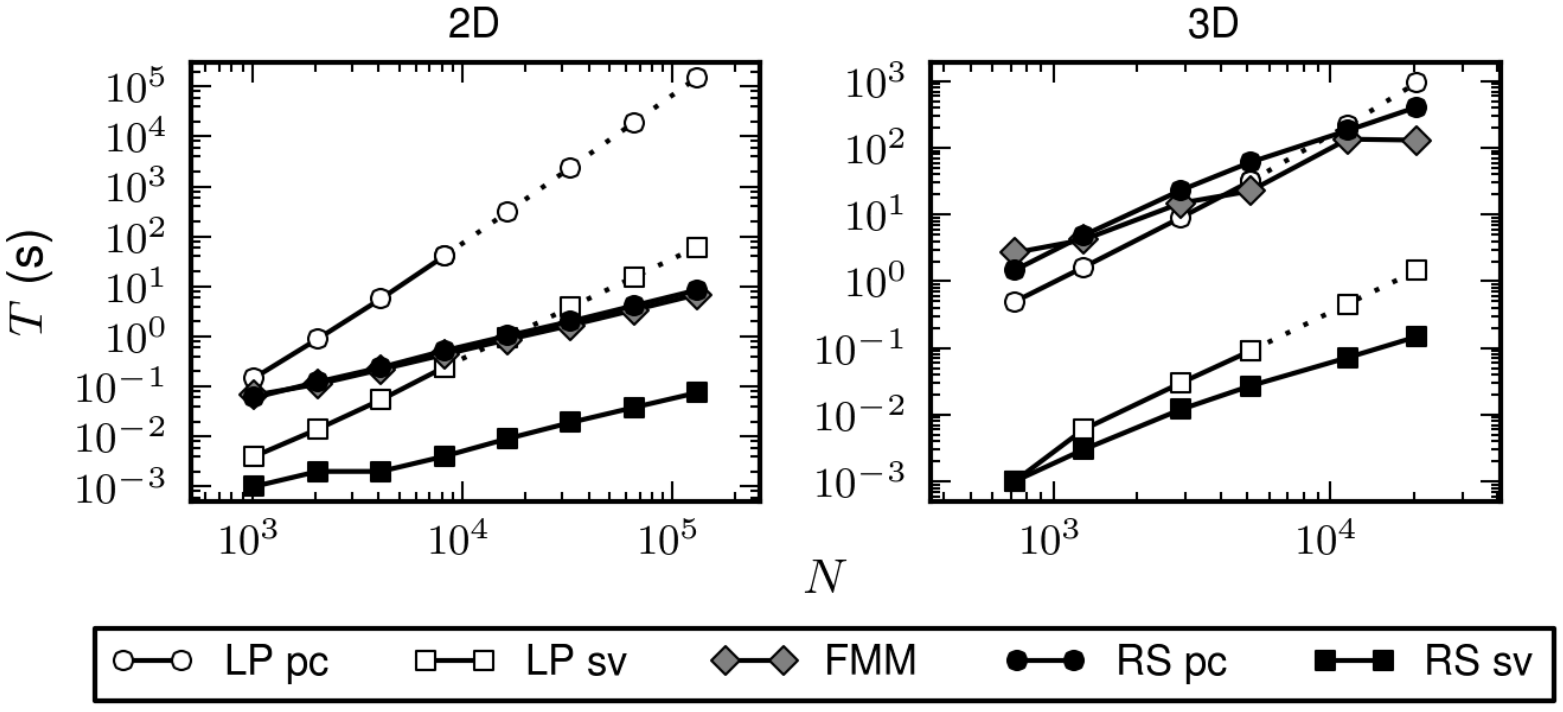
$$\text{precomp} \sim \begin{cases} N & \text{if } d = 1, \\ N^{3(1-1/d)} & \text{if } d > 1, \end{cases} \qquad \text{solve} \sim \begin{cases} N & \text{if } d = 1, \\ N \log N & \text{if } d = 2, \\ N^{2(1-1/d)} & \text{if } d > 2 \end{cases}$$

- Mild assumptions: low-rank off-diagonal blocks, Green's theorem
- Based on numerical linear algebra rather than analytic expansions
- Kernel-independent: Laplace, Stokes, Yukawa, low-frequency Helmholtz, etc.
- Compressed ranks are optimal for the problem at hand
- Like the FMM but with some near-field compression
- Trade accuracy for speed: user-specified precision
- Naturally parallelizable via block-sweep structure

Laplace FMM


2D surface
2D volume
3D surface
3D volume
T (s)
N
10^3
10^2
10^1
10^0
10^{-1}
10^{-2}
10^{-3}
10^4
10^5
LP pc
LP mv
FMM
RS pc
RS mv

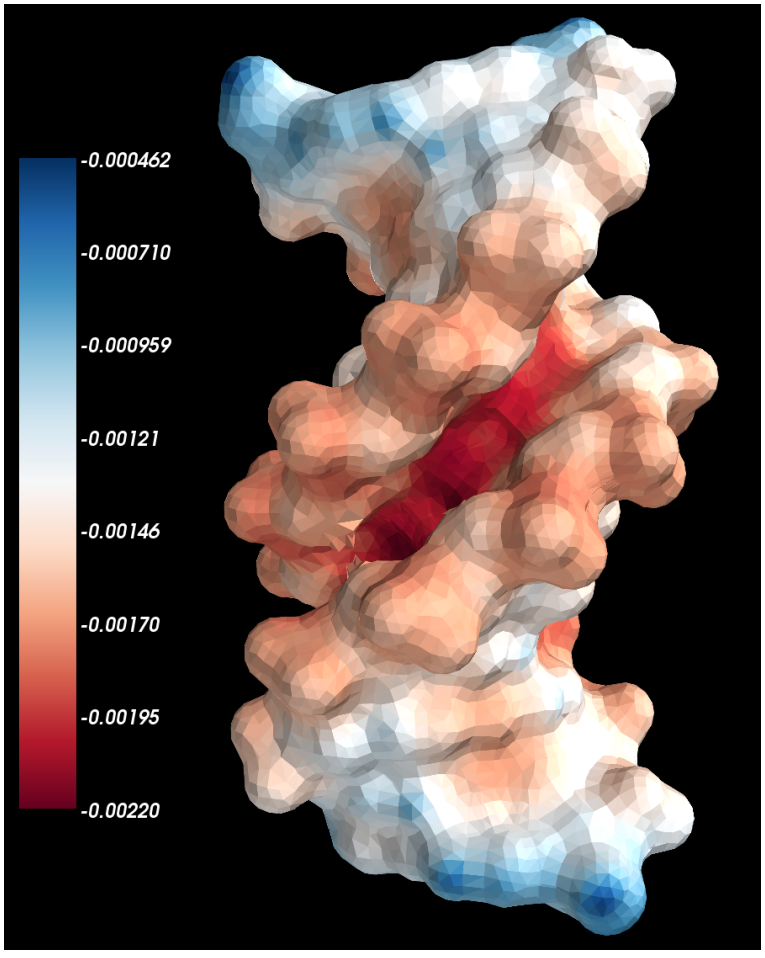
Laplace BIE solver



- 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



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

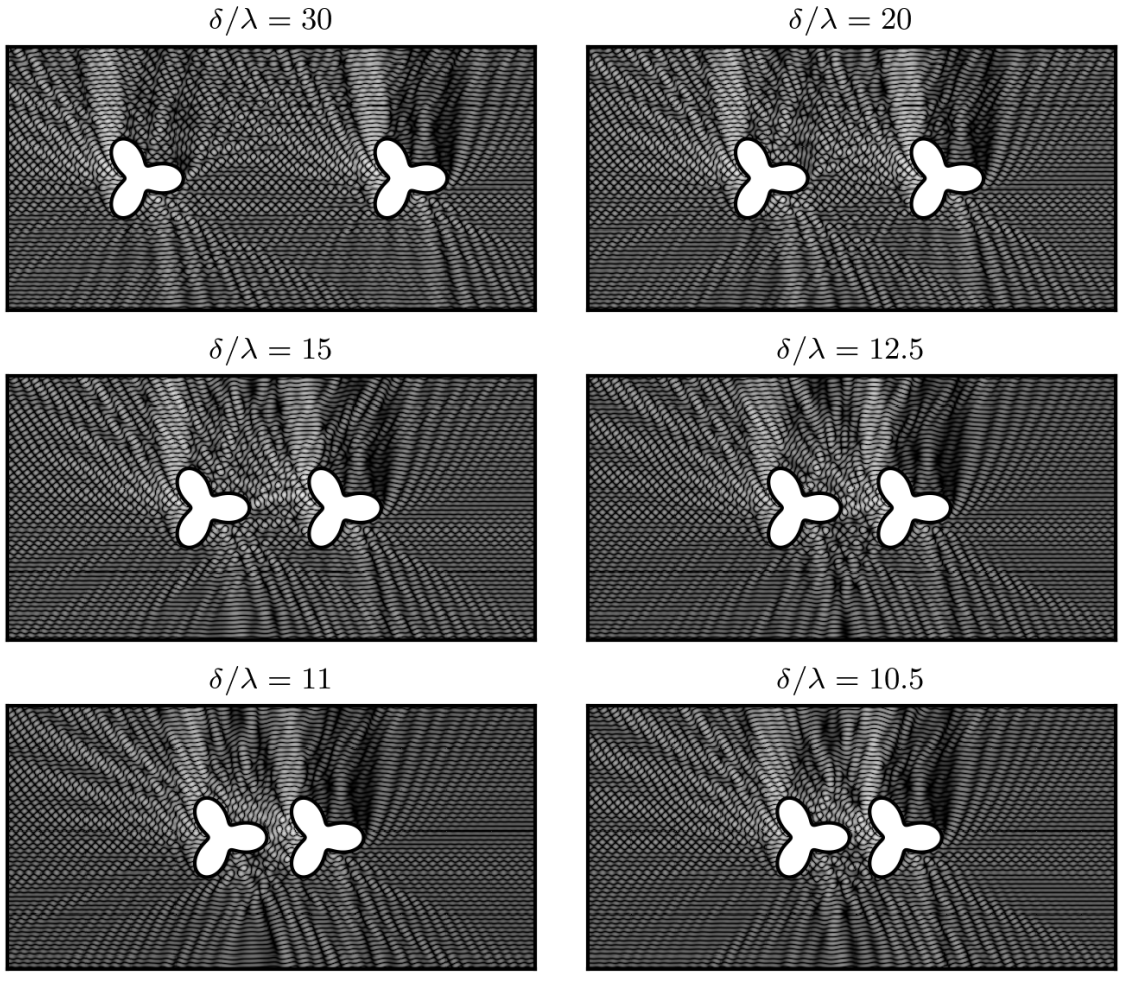
$$-\Delta\varphi = \frac{1}{\varepsilon_1}\sum_i q_i \delta\left(\mathbf{r} - \mathbf{r}_i\right) \qquad \text{in } \Omega_1$$

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

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

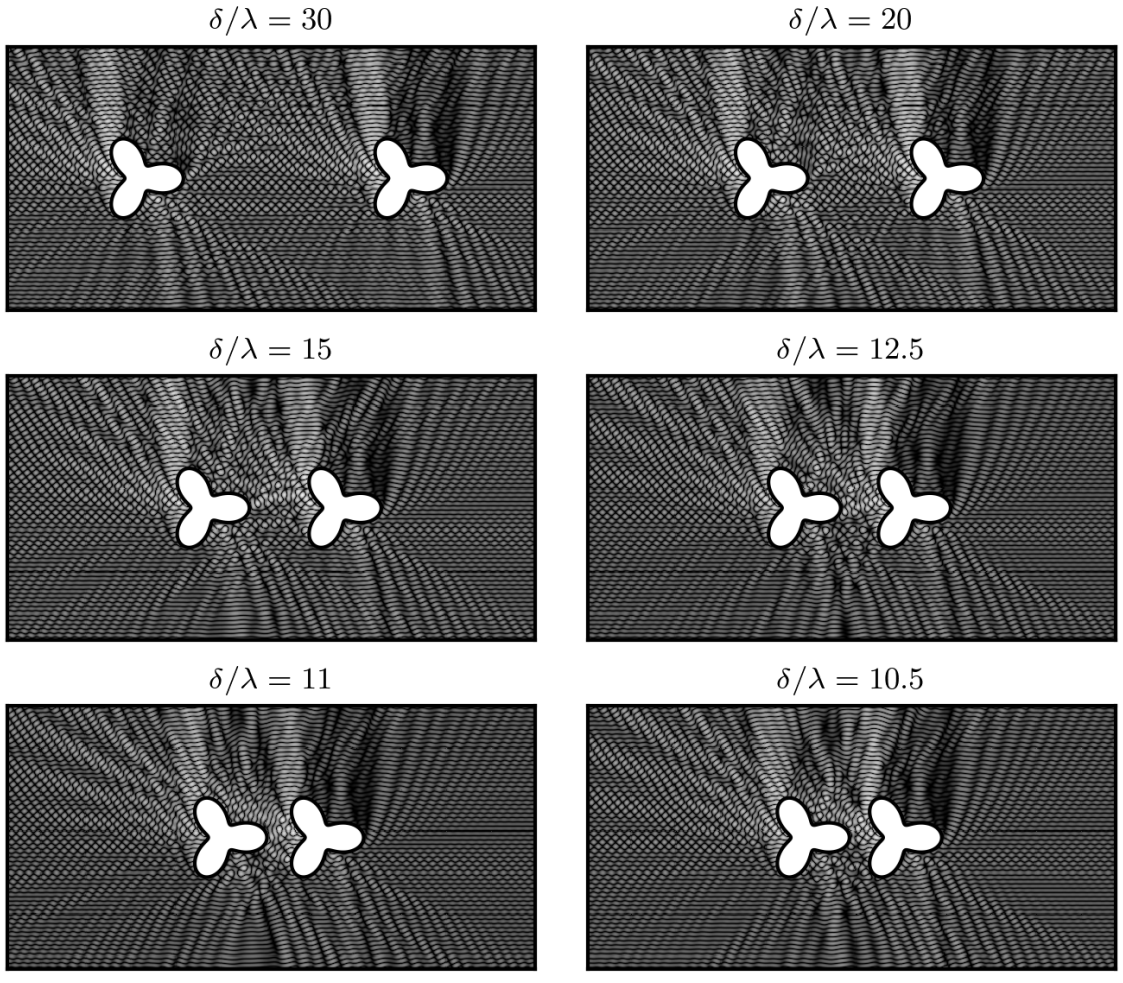
$$\begin{bmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} b_1 \\ b_2 \end{bmatrix}$$

- 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

Multiple scattering



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Rigid-body "docking"

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- After precomputation, very fast solves (sub-second)
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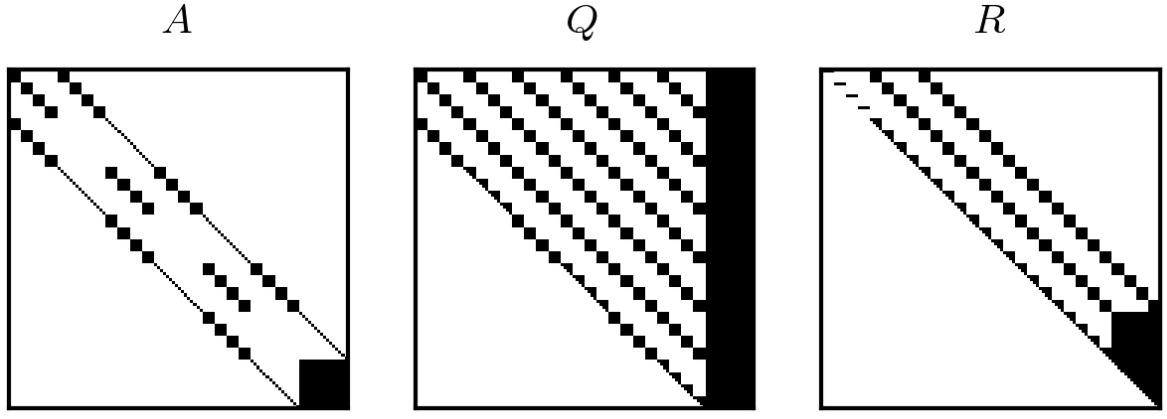
Extensions:

- Approximate inverse preconditioning
- Local geometric perturbations:

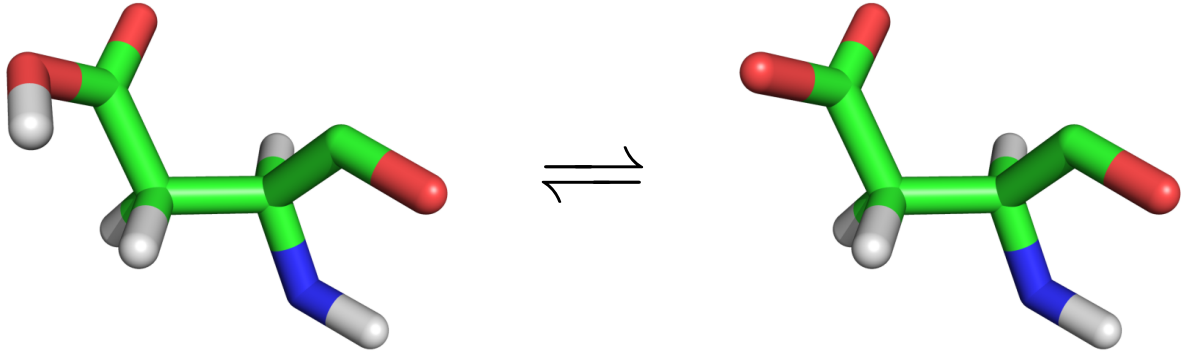
$$\begin{bmatrix} A & B_+ & B_- \\ C_+ & D_+ & D_* \\ C_- & & I \end{bmatrix} \begin{bmatrix} x \\ x_+ \\ x_- \end{bmatrix} = \begin{bmatrix} b \\ b_+ \\ 0 \end{bmatrix}$$

- Least squares (semi-direct QR)



- Compression-based FMM

Back to biophysics: protein pK_a calculations



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

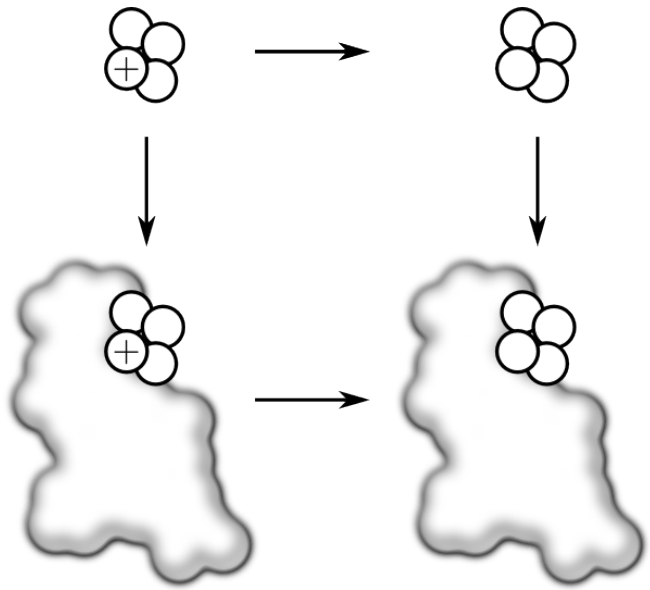
Ionization behavior is important for many biomolecular phenomena:

- Binding affinities
- Enzymatic activities
- Structural properties

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

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

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



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

For M titrating sites, let $\theta \in \{0,1\}^M$ denote the protonation state of each site.

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

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

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

Mean site protonation:

$$\langle \theta_i \rangle (\mathrm{pH}) = \frac{1}{Z}\sum_\theta \theta_i e^{-\beta \Delta G_{\mathrm{A}\to\mathrm{A}(\theta)}(\mathrm{pH})}$$

Sample using Markov chain Monte Carlo.

Find $\mathrm{p}K_i$ such that $\langle \theta_i \rangle (\mathrm{p}K_i) = 1/2$.

How to calculate the titrating site interaction energies $\Delta G_{ij} = q_i^{\mathsf{T}} \varphi_j$? Recall:

$$\varphi = \begin{cases} S_\kappa \sigma + D_\kappa \mu & \text{in } \Omega_0, \\ S_0 \sigma + \alpha D_0 \mu + \varphi_s & \text{in } \Omega_1, \end{cases} \qquad (I + \lambda K) \begin{bmatrix} \mu \\ \sigma \end{bmatrix} = \lambda \begin{bmatrix} \varphi_s \\ -\partial \varphi_s / \partial \nu \end{bmatrix}.$$

Therefore, $\varphi_j = (CA^{-1}B + D) q_j$, where

$$A = I + \lambda K, \quad B = \lambda \begin{bmatrix} \varphi_s \\ -\partial \varphi_s / \partial \nu \end{bmatrix},$$

$$C = \begin{bmatrix} D_0 & \alpha S_0 \end{bmatrix}, \quad D_{ij} = \begin{cases} 0 & \text{if } i = j, \\ \dfrac{1}{\varepsilon_1} G_0 (\mathbf{r}_i, \mathbf{r}_j) & \text{if } i \neq j. \end{cases}$$

- Calculate φ_j for each site j.
- Compute $\Delta G_{ij} = q_i^{\mathsf{T}} \varphi_j$ for each site i.
- Requires M solves in total.
- Compress matrices as direct solver or generalized FMM.

pK_a algorithm

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

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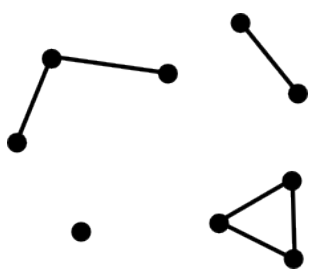

- Link sites by interaction energy
- Clusters: connected components
- Modify one cluster at random
- Pick move distance from geometric distribution

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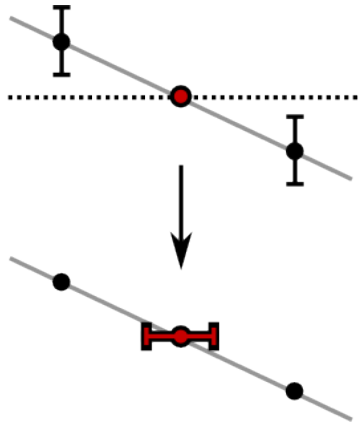
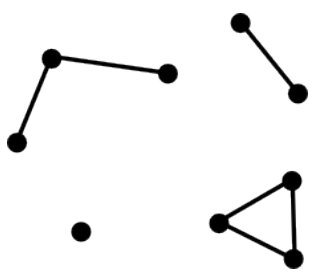


Apply delta method.



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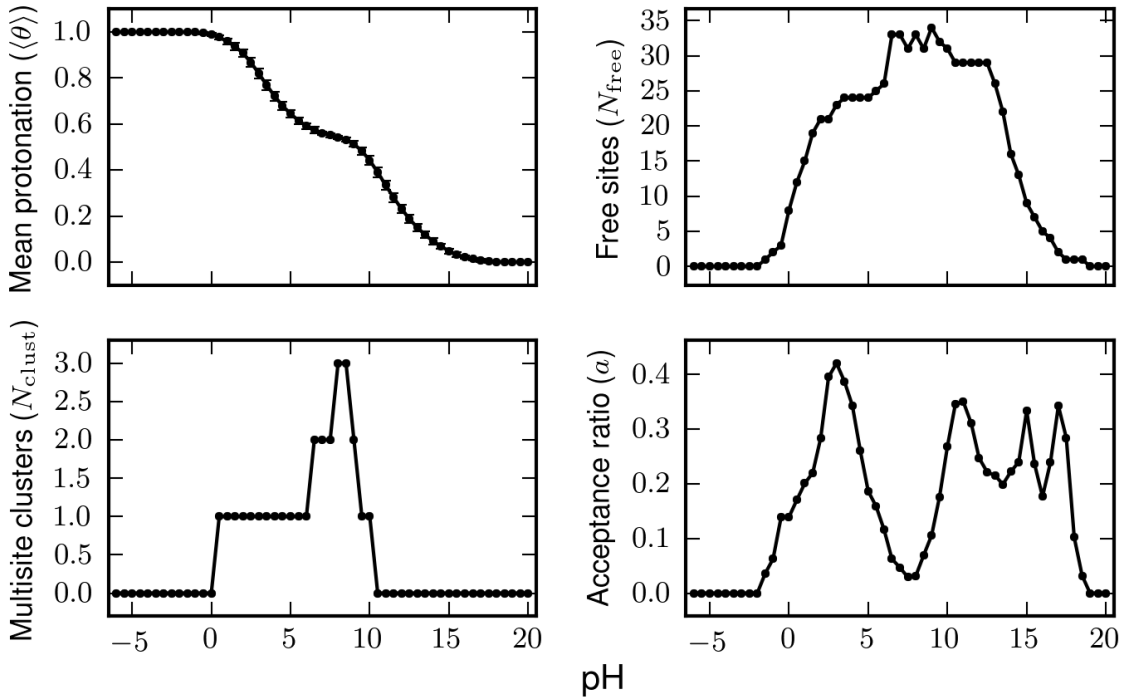
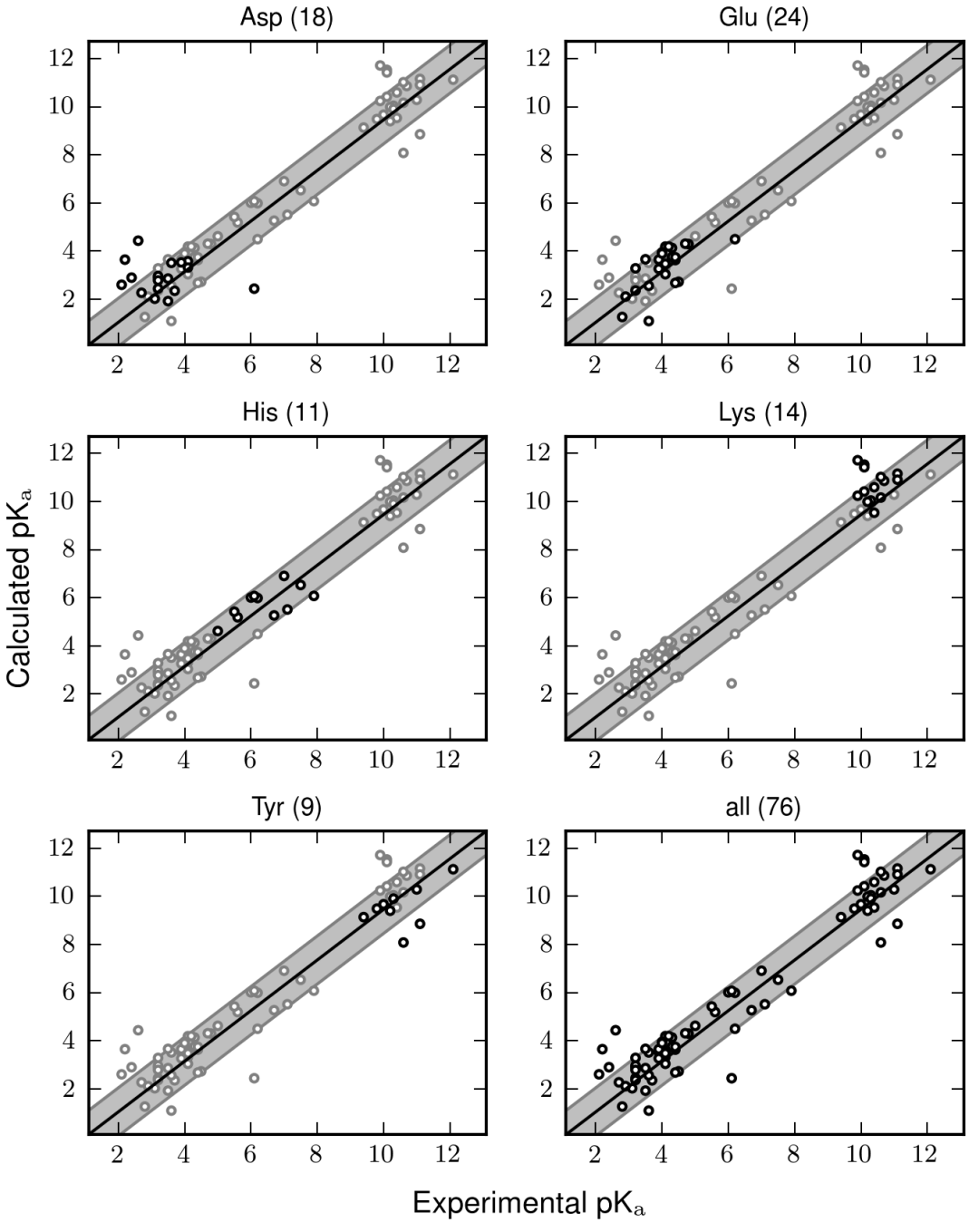
name	PDB ID	residues	atoms	sites
BPTI	4PTI	58	891	18
OMTKY3	2OVO	56	813	15
HEWL	2LZT	129	1965	30
RNase A	3RN3	124	1865	34
RNase H	2RN2	155	2474	53

- DoFs: 10,000–30,000
- Energy calc time: 10 s
- Much less memory than classical direct methods
- Much faster solves than iterative methods
- Precomputation is still somewhat expensive





RMSD	ε_1 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	number	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

How to improve our pK_a predictions?

- One possibility is to include conformational flexibility (Gunner et al.)
- Treat with perturbative techniques

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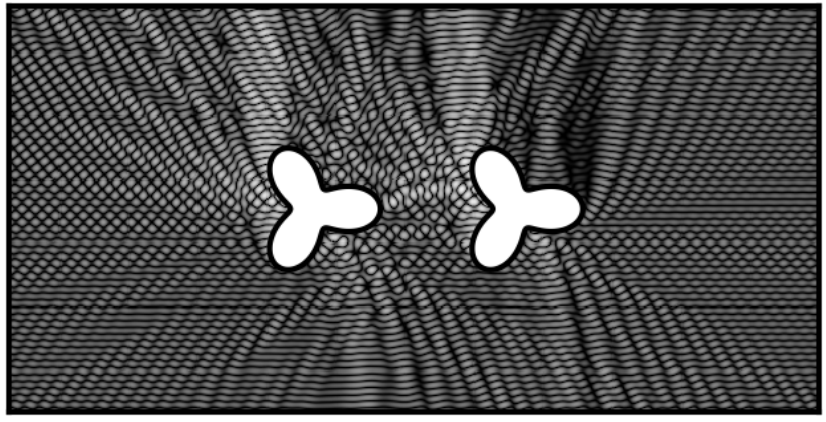


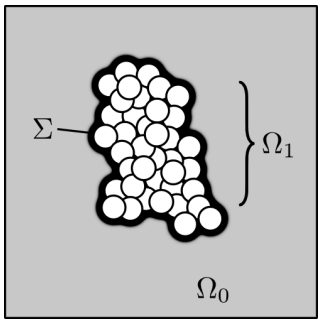
Similar ideas are also relevant for other biological problems.

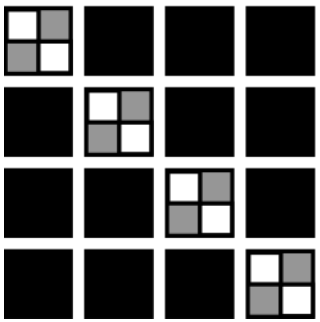
- Structure prediction: fixed backbone, rotamer optimization
- Rigid-body docking: like multiple scattering
- Flexible docking: combination of the above

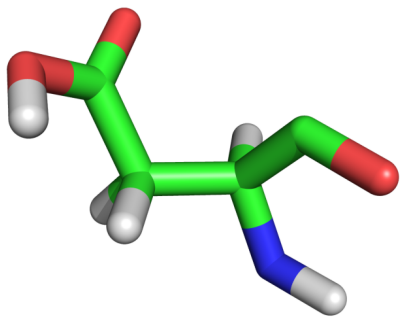
These are all characterized by much larger search spaces and hence enable more efficient amortization of the matrix precomputation costs.

Summary

- Molecular electrostatics: second-kind boundary integral equation
- Fast direct solver for non-oscillatory integral equations
  - Kernel-independent: Laplace, Stokes, Yukawa, low-frequency Helmholtz
  - Very fast solves following precomputation (~ 0.1 s)
- Application to protein pK_a calculations







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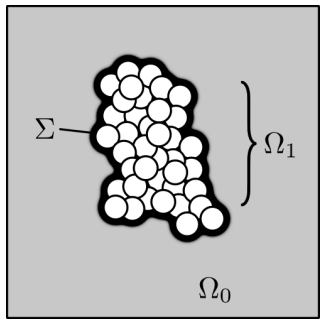

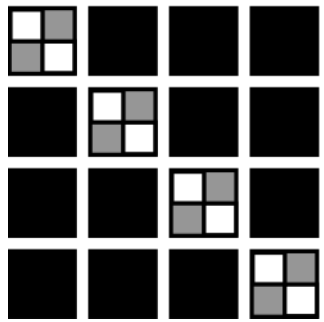

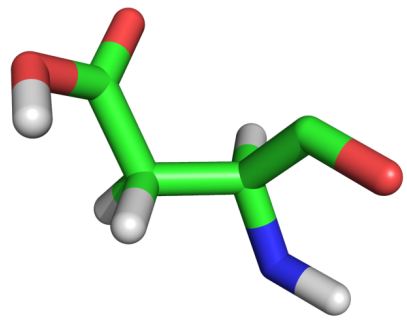

Next steps:

- Faster direct solvers: aim for $\mathcal{O}(N \log N)$
- Other compression-based numerical algorithms
- More realistic electrostatics: inhomogeneous dielectrics, solvent correlations
- Further biological applications: structure prediction, docking