Novel Stochastic Methods in Biochemical Electrostatics

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Motivation

- Experimental Data: Folding, stability & binding behavior of biomolecules can be modulated by changes in salt concentration
- Physical Model: Implicit solvent-based Poisson-Boltzmann model can provide accurate predictions of salt dependent behavior of biomolecules
- Mathematical Model: Elliptic boundary-value problems

Specific Problems

- Electrostatic free energy for linear case: only finite number of electrostatic potential point values
- Dependence of energy on geometry: needs accurate treatment
- Singularities in solution: have to be taken into account analytically
- Behavior at infinity: must be exactly enforced
- Functional dependence on salt concentration: needs accurate estimate

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Monte Carlo Methods: Properties

- Monte Carlo methods for solving Poisson and linearized Poisson-Boltzmann equations (PBEs)
- Analytical treatment of geometry, singularities, behavior at infinity
- Capability to compute point values of solution (energies) and its spatial derivatives (forces)
- New methods for the flux boundary conditions (exact integral formulation)
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Mathematical Model: Molecular Geometry

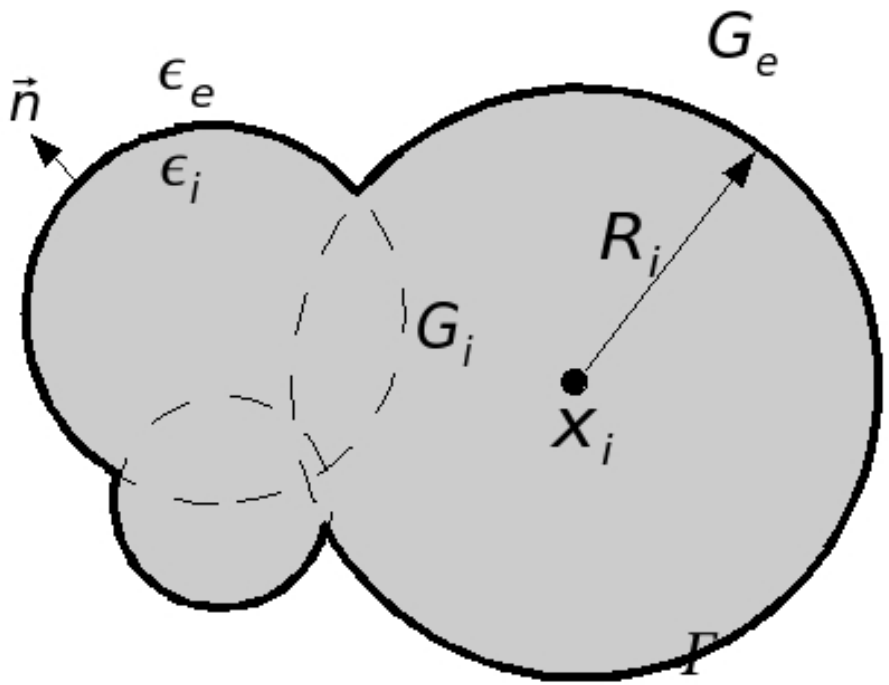

Figure: Biomolecule with dielectric ϵ_i and region region G_i is in solution with dielectric ϵ_e and region G_e. On the boundary of the biomolecule, electrostatic potential and normal component of dielectric displacement continue

Mathematical Model: Partial Differential Equations

- Poisson equation for the electrostatic potential, Φ_i, and point charges, Q_m, inside a molecule (in CGS units):

$$\epsilon_i \Delta \Phi_i(x) + 4\pi \sum_{m=1}^{M} Q_m \delta(x - x^{(m)}) = 0 \ , \ x \in G_i$$

- For 1-1 salt (such as *NaCl*): linearized PBE outside:

$$\Delta \Phi_e(x) - \kappa^2 \Phi_e(x) = 0 \ , \ x \in G_e$$

- For one-surface model: continuity condition on the dielectric boundary

$$\Phi_i = \Phi_e \ , \ \epsilon_i \frac{\partial \Phi_i}{\partial n(y)} = \epsilon_e \frac{\partial \Phi_e}{\partial n(y)} \ , \ y \in \Gamma$$

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Mathematical Model: Debye-Hückle Parameter

Dependence on salt in the Debye-Hückle parameter:

$$\kappa^2 = \frac{8\pi N_A e^2 C_s}{\epsilon_e 1000 k_B T}, \text{ where}$$

- C_s – concentration of ions (in moles)
- N_A – Avogadro's number
- e – elementary protonic charge
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- ϵ_e – dielectric permittivity outside the molecule

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Electrostatic Potential and Energy

- Point values of the potential: $\Phi(x) = \Phi_{rf}(x) + \Phi^c(x)$
  Here, singular part of Φ:

$$\Phi^c(x) = \sum_{m=1}^{M} \frac{Q_m}{|x - x^{(m)}|}$$

- Reaction field electrostatic free energy of a molecule is linear combination of point values of the regular part of the electrostatic potential:

$$W_{rf} = \frac{1}{2} \sum_{m=1}^{M} \Phi_{rf}(x^{(m)}) Q_m \ ,$$

- Electrostatic solvation free energy = difference between the energy for a molecule in solvent with a given salt concentration and the energy for the same molecule in vacuum:

$$\Delta G_{solv}^{elec} = W_{rf}(\epsilon_i, \epsilon_e, \kappa) - W_{rf}(\epsilon_i, 1, 0)$$

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The Feynman-Kac Formula

- Consider the Dirichlet problem for the Poisson equation in the domain $\Omega \in \mathbb{R}^d$

$$-\frac{1}{2}\Delta u(x) = g(x), \quad x \in \Omega, \qquad u(x) = f(x), \quad x \in \partial\Omega$$

- If we assume $g(x) = 0$, then we have the Laplace equation, and the solution at the point $y \in \Omega$ is given as the following Brownian motion expectation:

$$u(y) = \mathbb{E}[f(\beta_y(\tau_{\partial\Omega}))],$$

where $\beta_y(\cdot)$ is Brownian motion starting at the point y, and $\tau_{\partial\Omega}$ is the first-passage time of this Brownian motion,
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- If we set $f(x) = 0$ and have $g(x) \neq 0$, the solution is

$$u(y) = \mathbb{E}\left[\int_0^{\tau_{\partial\Omega}} g(\beta_y(s))\, ds\right]$$

- By linear superposition, the solution to Poisson equation is given probabilistically as

$$u(y) = \mathbb{E}\left[\int_0^{\tau_{\partial\Omega}} g(\beta_y(s))\, ds + f(\beta_y(\tau_{\partial\Omega}))\right]$$

- The linearized Poisson-Boltzmann equation is given by

$$\Delta u(x) - \kappa^2 u(x) = 0, \;\; x \in \Omega, \;\; u(x) = f(x), \;\; x \in \partial\Omega, \;\; u \to 0 \text{ as } |x| \to \infty$$

and has Wiener integral representation:

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'Walk-on-Spheres' Algorithm

Walk-on-spheres (WOS) algorithm for general domains with regular boundary:
Define a Markov chain $\{x_i,\ i = 1, 2, \ldots\}$
Set $x_0 = x^{(m)}$ for some m.

$$x_i = x_{i-1} + d_i \omega_i\ ,\quad i = 1, 2, \ldots\ .$$

$d_i = d(x_{i-1})$ – distance from x_{i-1} to the boundary
$\{\omega_i\}$ – sequence of independent unit isotropic vectors
x_i – exit point from the ball, $B(x_{i-1}, d(x_{i-1}))$, for Brownian motion starting at x_{i-1}

Outside the molecule:
On every step, walk-on-spheres terminates with probability $1 - q(\kappa, d_i)$, where $q(\kappa, d_i) = \dfrac{\kappa d_i}{\sinh(\kappa d_i)}$

'Walk-on-Spheres' and 'Walk-in-Subdomains'

For general domains:
Efficient way to simulate exit points – combination of 'walk in subdomains' approach and 'walk on spheres' algorithm
The whole domain, G_i, is represented as a union of intersecting subdomains:

$$G_i = \bigcup_{m=1}^{M} G^m$$

Simulate exit point separately in every G^m
$x_0 = x, x_1, \ldots, x_N$ – Markov chain, every x_{i+1} is an exit point from the corresponding subdomain for Brownian motion starting at x_i
For spherical subdomains, $B(x_i^m, R_i^m)$, exit points are distributed in accordance with the Poisson kernel

$$\frac{1}{4\pi R_i^m} \frac{|x_i - x_i^m|^2 - (R_i^m)^2}{|x_i - x_{i+1}|^3}$$

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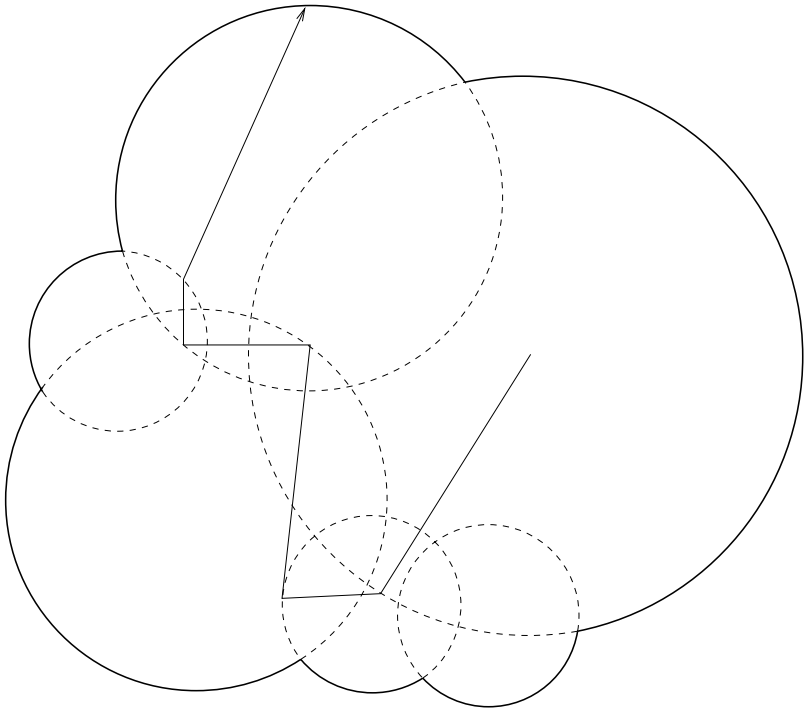

Figure: Walk in subdomains example

Monte Carlo Treatment of Boundary Conditions

- Randomization of finite-difference approximation with step, h. $u(y) = \mathbb{E}u(x) + O(h^2)$
- Exact treatment of boundary conditions (mean-value theorem) for boundary point, y, in the ball $B(y, a)$ with surface $S(y, a)$:

$$\begin{aligned} u(y) &= \frac{\epsilon_e}{\epsilon_e + \epsilon_i} \int_{S_e(y,a)} \frac{1}{2\pi a^2} \frac{\kappa a}{\sinh(\kappa a)} u_e \\ &+ \frac{\epsilon_i}{\epsilon_e + \epsilon_i} \int_{S_i(y,a)} \frac{1}{2\pi a^2} \frac{\kappa a}{\sinh(\kappa a)} u_i \\ &- \frac{\epsilon_e - \epsilon_i}{\epsilon_e + \epsilon_i} \int_{\Gamma \cap B(y,a) \setminus \{y\}} \frac{\cos \varphi_{yx}}{2\pi |y - x|^2} Q_{\kappa,a} u \\ &+ \frac{\epsilon_i}{\epsilon_e + \epsilon_i} \int_{B_i(y,a)} [-2\kappa^2 \Phi_\kappa] u_i \end{aligned} \tag{1}$$

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u(y) &= \frac{\epsilon_e}{\epsilon_e + \epsilon_i} \int_{S_e(y,a)} \frac{1}{2\pi a^2} \frac{\kappa a}{\sinh(\kappa a)} u_e \\
&+ \frac{\epsilon_i}{\epsilon_e + \epsilon_i} \int_{S_i(y,a)} \frac{1}{2\pi a^2} \frac{\kappa a}{\sinh(\kappa a)} u_i \qquad (1) \\
&- \frac{\epsilon_e - \epsilon_i}{\epsilon_e + \epsilon_i} \int_{\Gamma \bigcap B(y,a)\setminus\{y\}} \frac{\cos\varphi_{yx}}{2\pi|y-x|^2} Q_{\kappa,a} u \\
&+ \frac{\epsilon_i}{\epsilon_e + \epsilon_i} \int_{B_i(y,a)} [-2\kappa^2 \Phi_\kappa] u_i
\end{aligned}
$$

Monte Carlo Estimates

Estimate for the reaction-field potential point value:

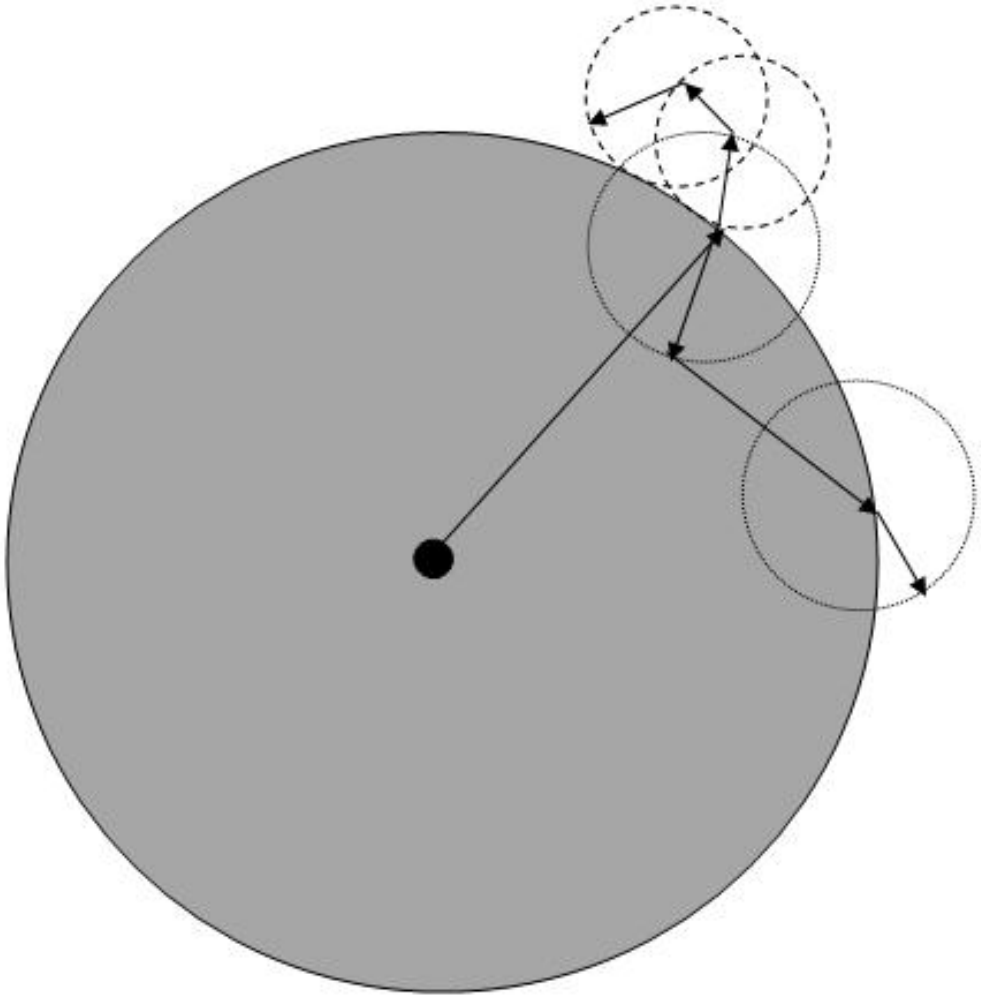
$$\begin{aligned}\xi[\Phi_{rf}](x^{(m)}) &= -\Phi^c(x_1^*) \\ &+ \sum_{j=2}^{N_{ins}} F_j(\kappa)\left(\Phi^c(x_j^{ins}) - \Phi^c(x_{j,ins}^*)\right), \end{aligned} \tag{2}$$

where $\{x_{j,ins}^*\}$ is a sequence of such boundary hits, after which the random walker jumps inside the domain, G_i, to a point, x_j^{ins}.

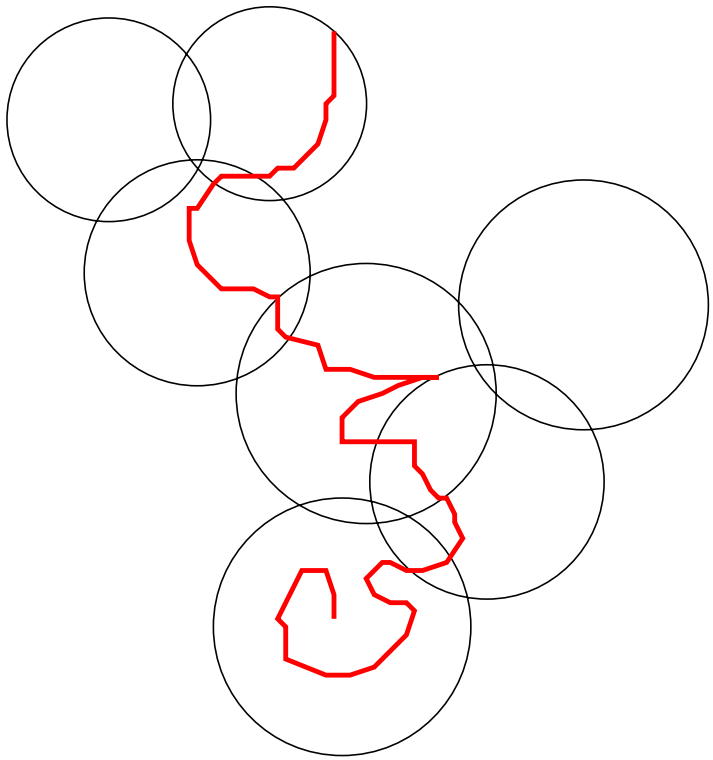
Estimate for the reaction-field energy:

$$\xi[W_{rf}] = \frac{1}{2}\sum_{m=1}^{M} Q_m\, \xi[\Phi_{rf}](x^{(m)}) . \tag{3}$$

A Picture: The Algorithm for a Single Spherical Atom



The Algorithm in Pictures: Walk Inside



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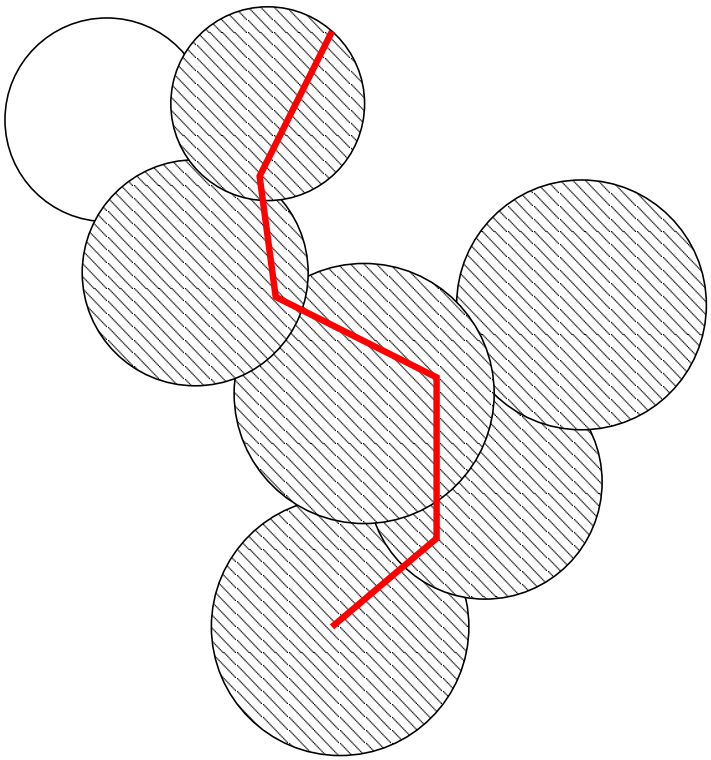
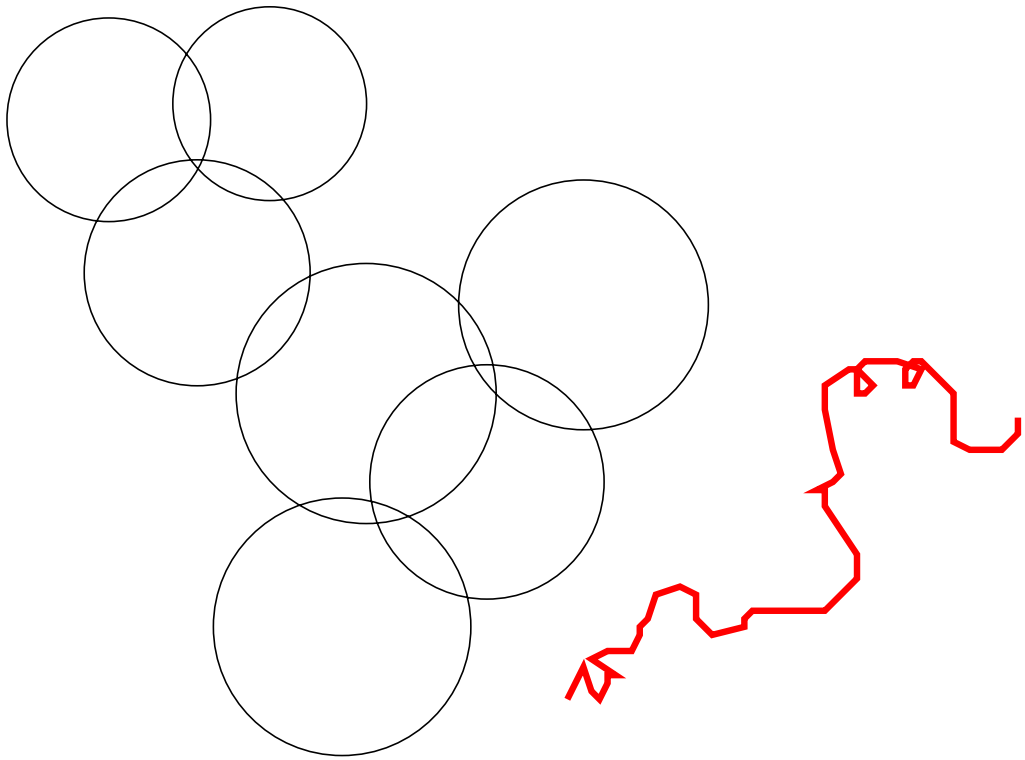


The Algorithm in Pictures: Walk Outside



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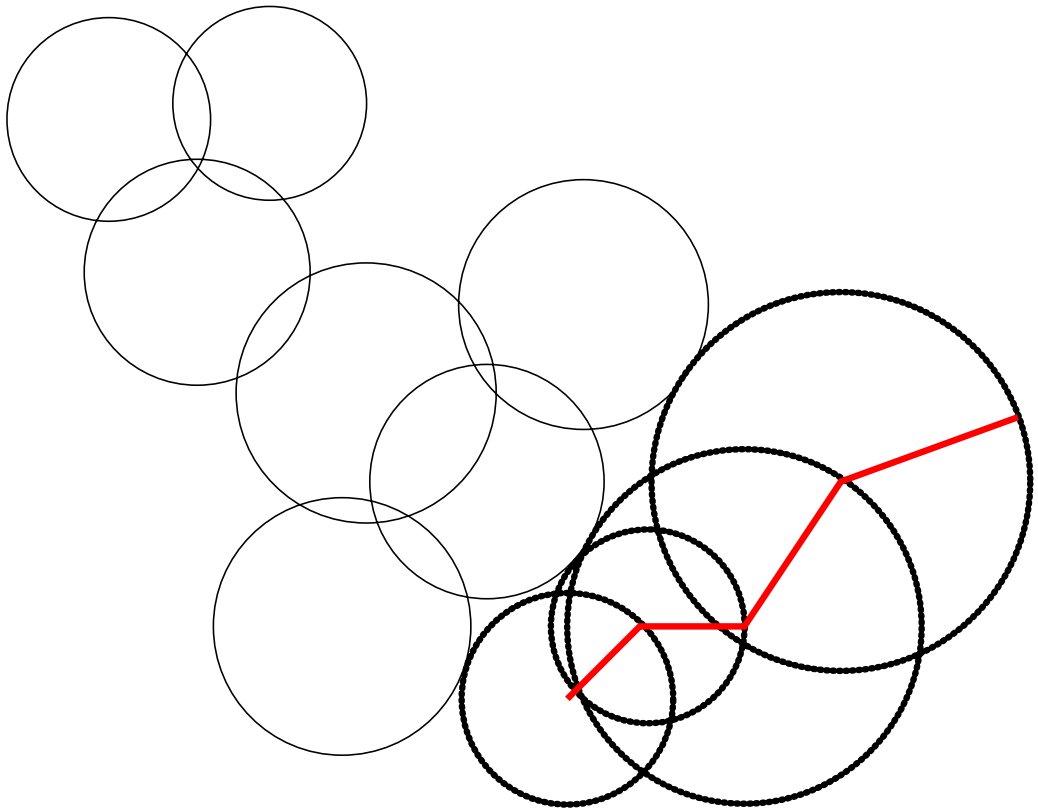

The Algorithm in Pictures: Walk to ∞ in One Step

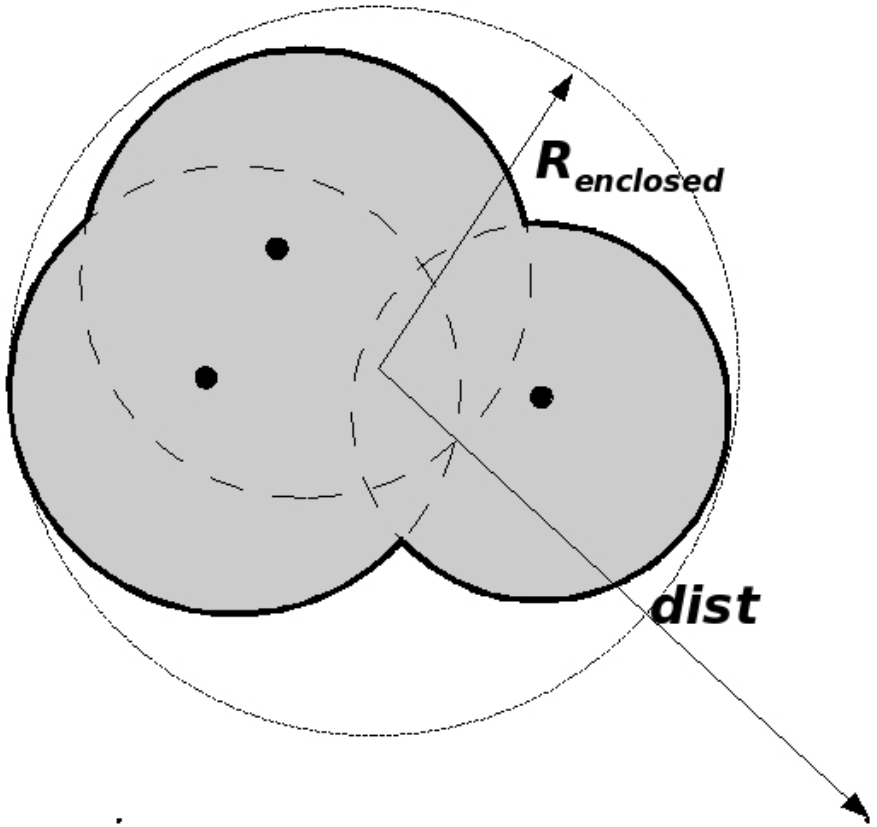

Figure: $\kappa = 0$, $p_\infty = 1 - R_{Enclosed}/dist$

Monte Carlo Algorithm's Computational Complexity

Cost of a single trajectory

- Number of steps is random walk is not dependent on M, the number of atoms
- The cost of finding the nearest sphere is $M \log_2(M)$ due to optimizations

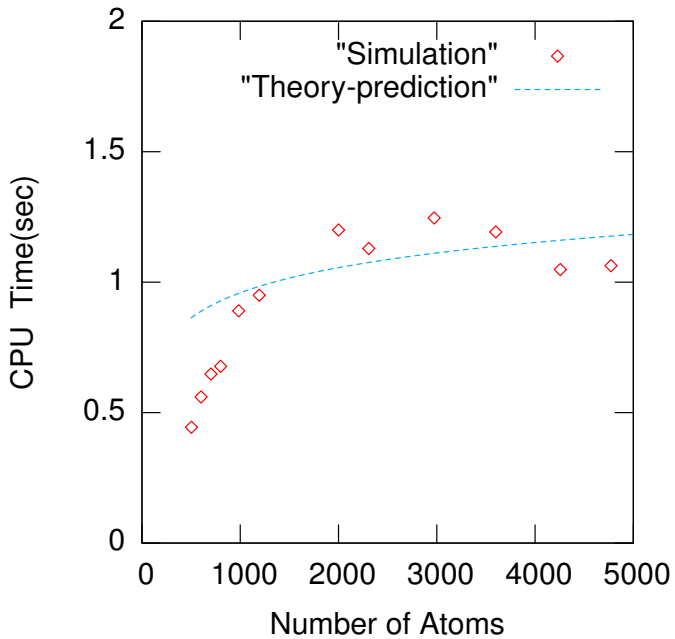

Figure: The CPU time per atom per trajectory is plotted as function of number of atoms. For small number of atoms the CPU time scales linearly and for large number of atoms it asymptotically scales logarithmically

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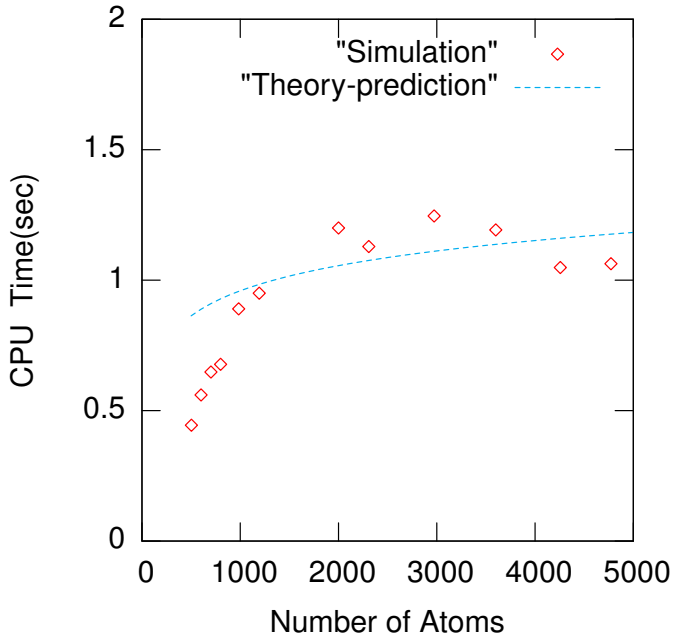

Figure: The CPU time per atom per trajectory is plotted as function of number of atoms. For small number of atoms the CPU time scales linearly and for large number of atoms it asymptotically scales logarithmically

Dependence on Salt Concentration

Dependence on salt

For κ used in simulations, $F_j(\kappa) = 1$.

For an arbitrary $\kappa' > \kappa$:

$F_j(\kappa')$ is multiplied by the ratio $\dfrac{q(\kappa', d)}{q(\kappa, d)}$ on every step of the WOS in the exterior

The results obtained with the estimates (2) and (3) for different values of κ are **highly correlated**.

Correlated and Uncorrelated Sampling

Correlated sampling in Monte Carlo is essential to obtain

- Smooth curves with a minimum of sampling
- You need to difference your Monte Carlo results

With this correlated sampling sampling you can get a "smooth curve" with three orders of magnitude less sampling, note: you still have $O(N^{-1/2})$ errors, just in "curve space," not point by point

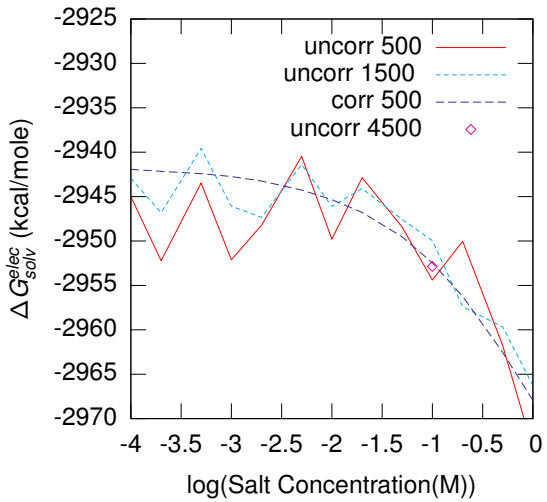

Figure: Electrostatic Solvation free Energy of `3icb` calculated with three four conditions: uncorrelated sampling with 500 number of trajectories per concentration, uncorrelated sampling with 1500 number of trajectories per concentration, uncorrelated sampling with 4500 number of iterations, and correlated sampling with 500 number of trajectories

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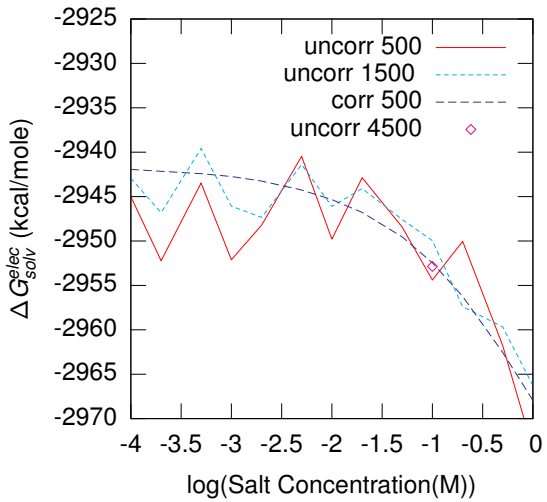

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Computational Results: 3 Truncated Arginine-Rich Peptides

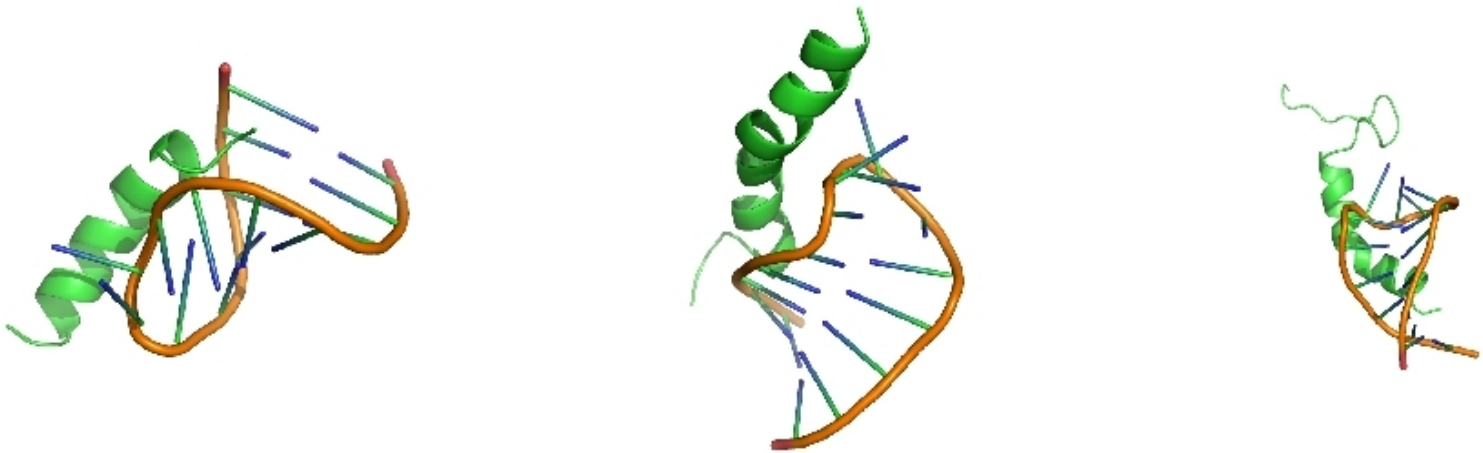

Figure: PDB IDs: 1a4t, 1hji, 1qfq

Computational Results

Computational Experiments

We take $\epsilon_i = 1$, therefore
$\Delta G^{elec}_{solv} = W_{rf}(\epsilon_i, \epsilon_e, \kappa)$
(Results are obtained in one computation)

Other parameters: $\epsilon_e = 78.5$, $T = 298.15\ K$
Boundary Γ – van der Waals surface (defined by the overlapping atomic spheres)

Parameters of Monte Carlo algorithm:
$a = 0.03$ Å, $\varepsilon = 10^{-4}$ Å, which provided a 1% order of bias. The number of simulated estimates, N_s was 10^4.

Computational Results: 1a4t

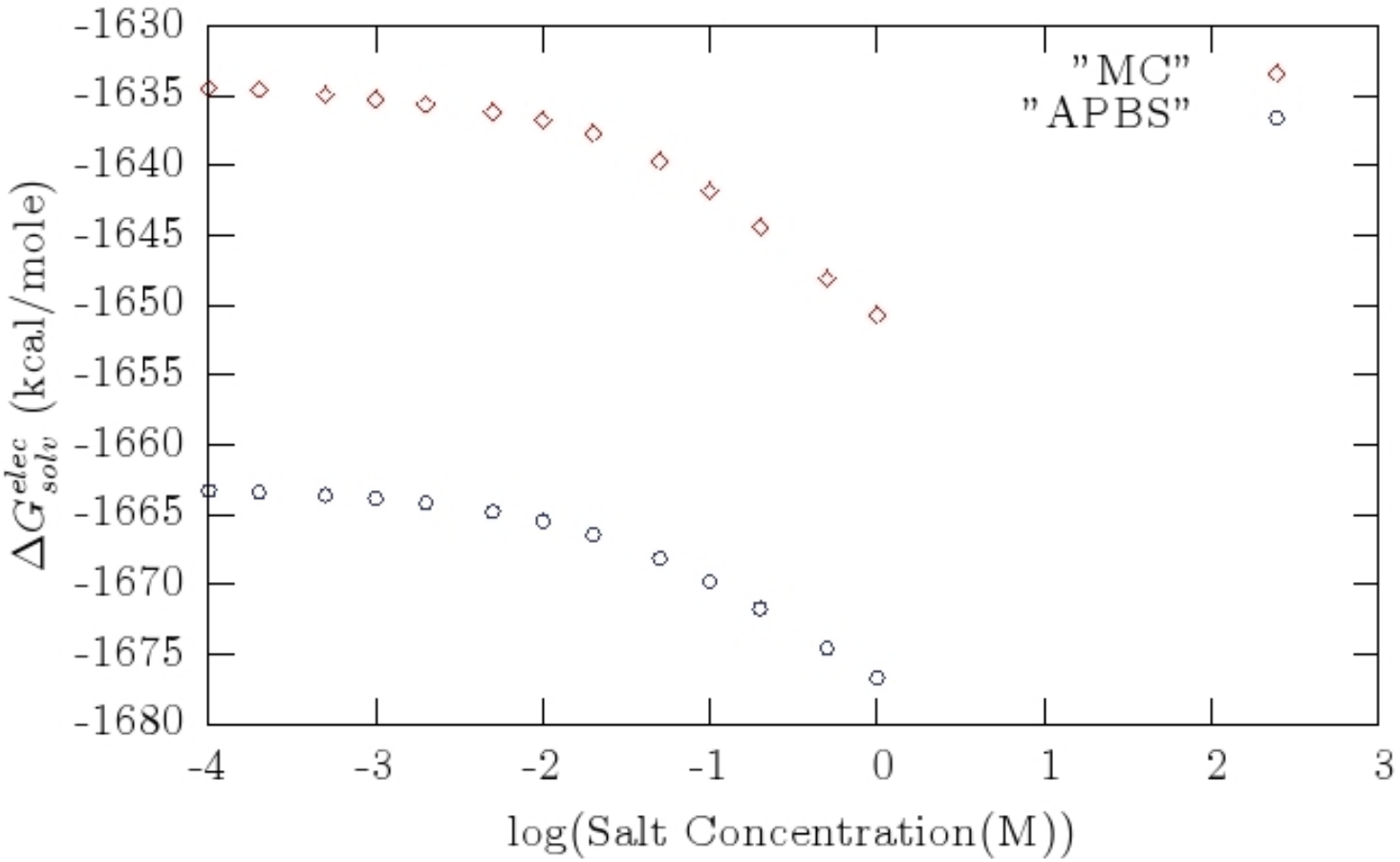

Figure: Number of atoms = 351, APBS: 225^3, 0.25 Å

Conclusions and Future Work

- We have developed a novel stochastic linear PBE solver that can provide highly accurate salt-dependent electrostatic properties of biomolecules in a single PBE calculation
- Advantages of the stochastic linear PBE solver over the more mature deterministic methods include: the subtle geometric features of the biomolecule can be treated with higher precision, the continuity and outer boundary conditions are accounted for exactly, a singularity free scheme is employed and straightforward implementation on parallel computer platform is possible
- We are currently benchmarking the stochastic linear PBE code against various deterministic codes in an effort to better understand the strengths and limitations of all existing numerical methods. These results should be of interest to the general biophysics community

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