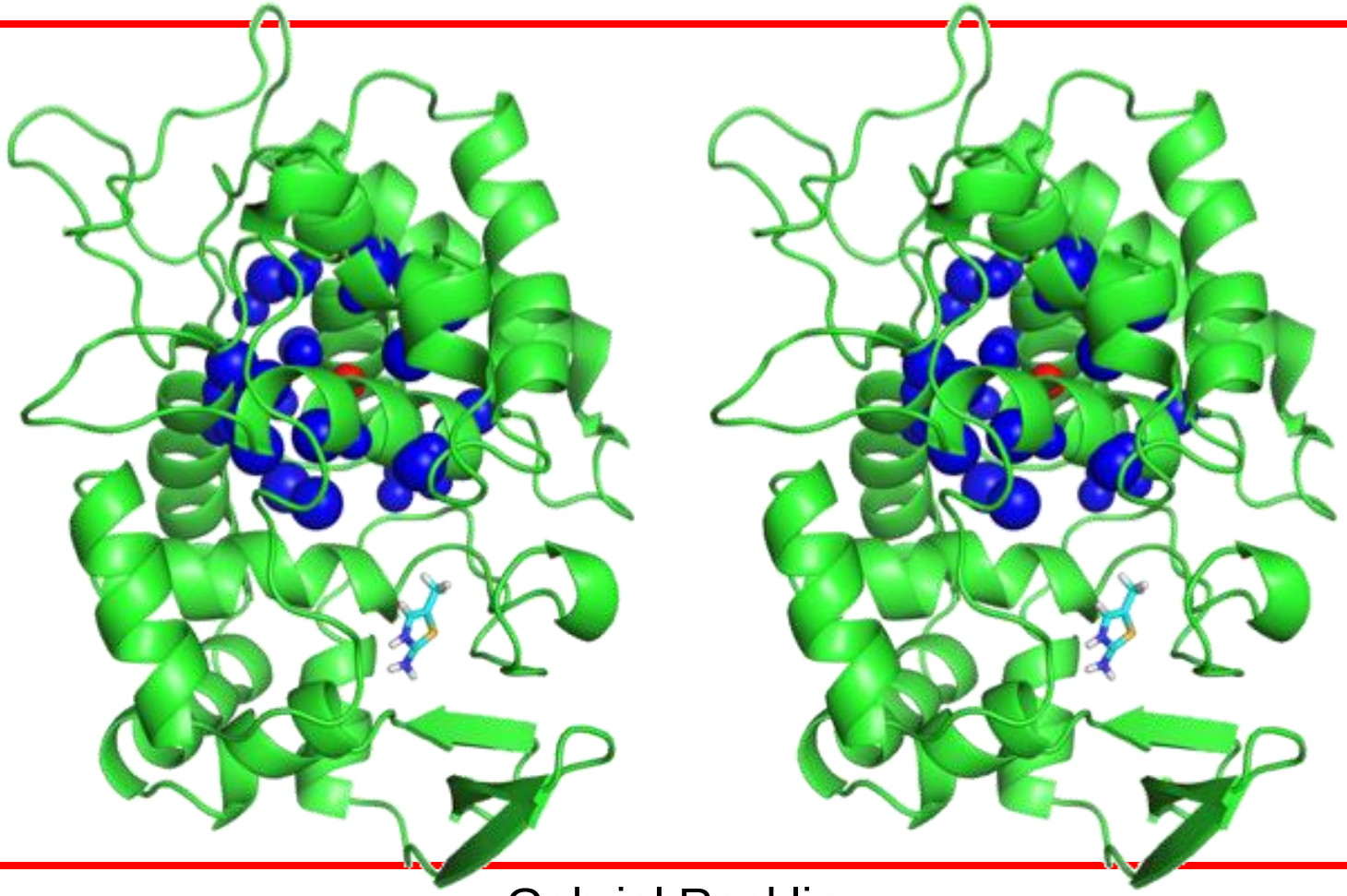
Analytical corrections for charged compound binding affinities computed from periodic simulations



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2014 Workshop on Free Energy Methods in Drug Design
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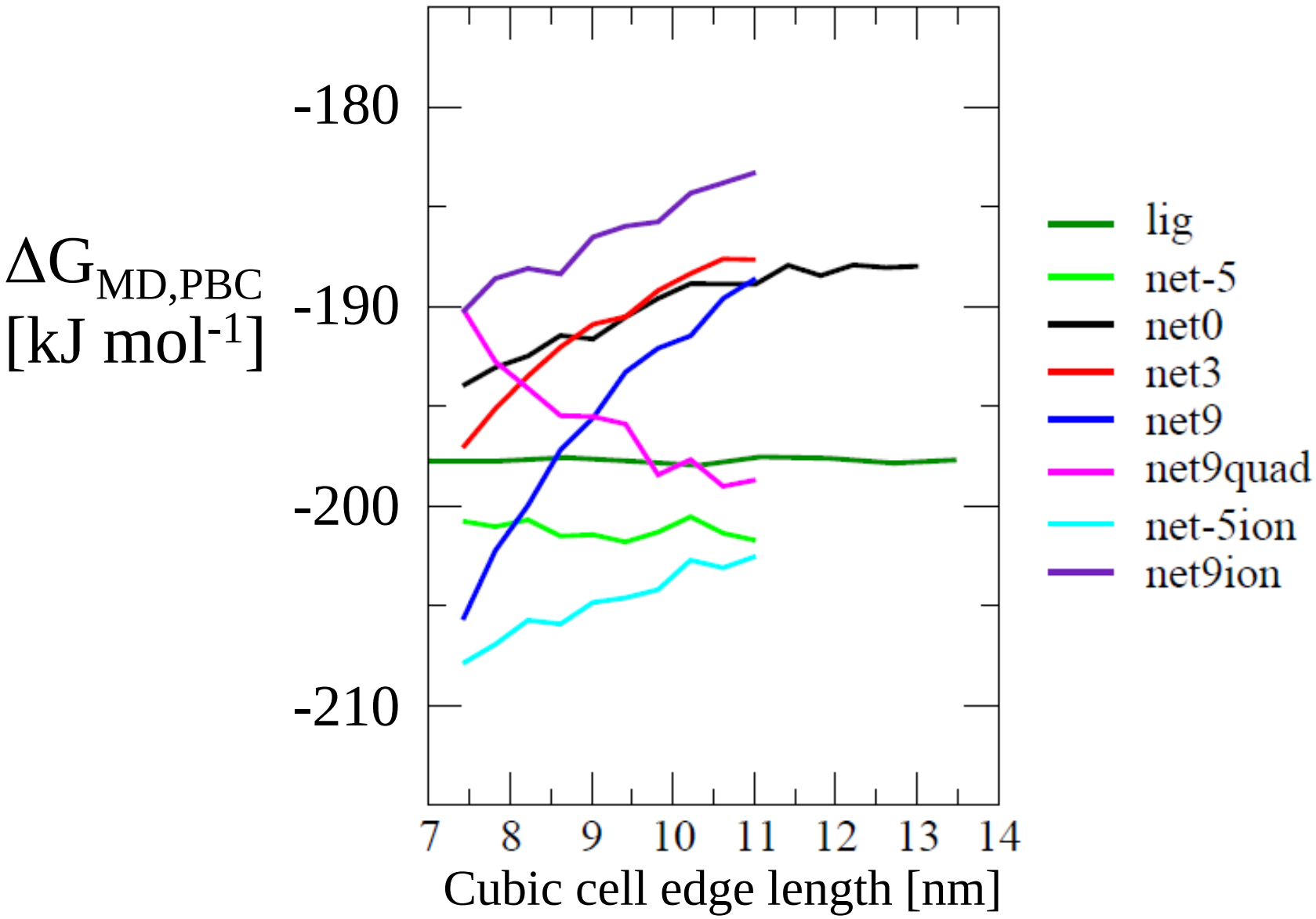
Alchemical charging free energies for a charged ligand highly depend on the box size



Finite size artifacts affect binding calculations because…

1. Simulations of the protein and free ligand may use different box sizes
2. Simulations of the protein and free ligand have different number-densities of water
3. A protein's charge distribution and excluded volume create unique finite size effects
4. Even a one-box PMF calculation effectively causes a change in ionic radius, meaning bound and unbound states have different magnitude artifacts **in the same box**

Why correct finite size artifacts? (even if they are small?)

1. It should improve your comparisons to experimental results

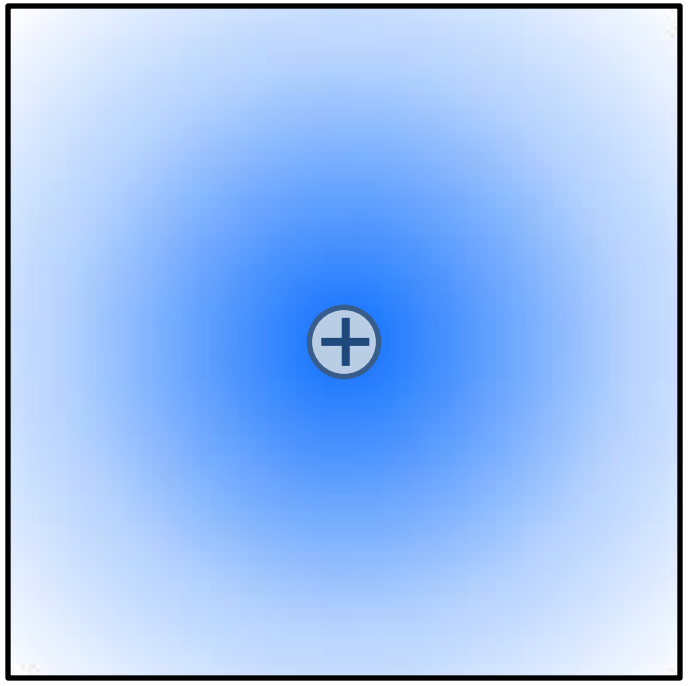
2. It is the only way to compare precise converged results between methods

3. It's easy!

Most finite size corrections are caused by different definitions of zero potential

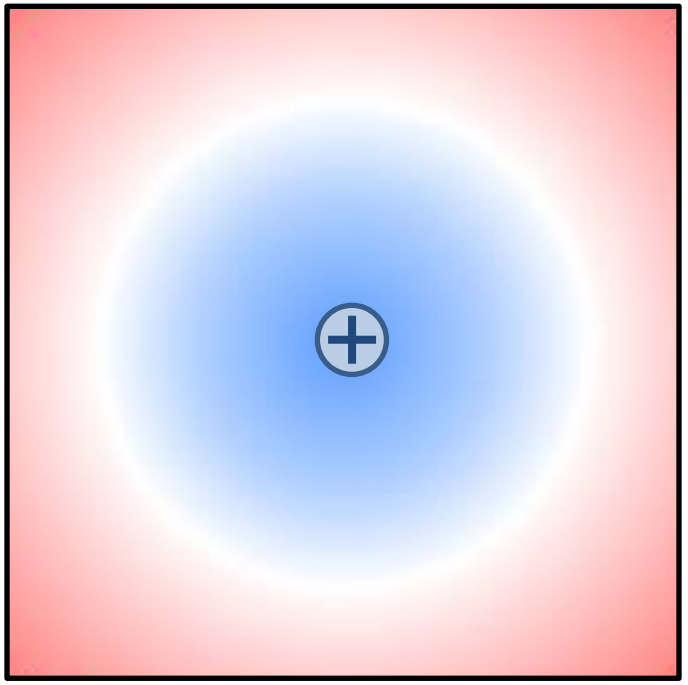
Nonperiodic

$\Phi(\infty)=0$



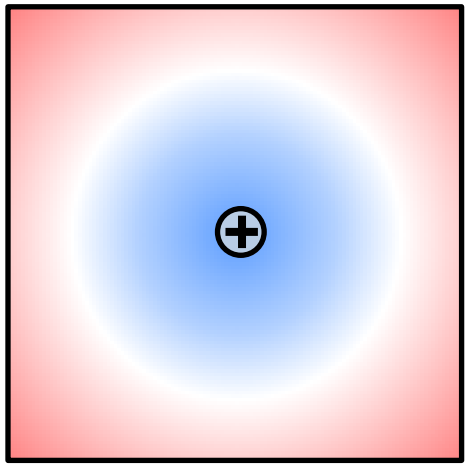
Periodic

$\langle\Phi\rangle=0$



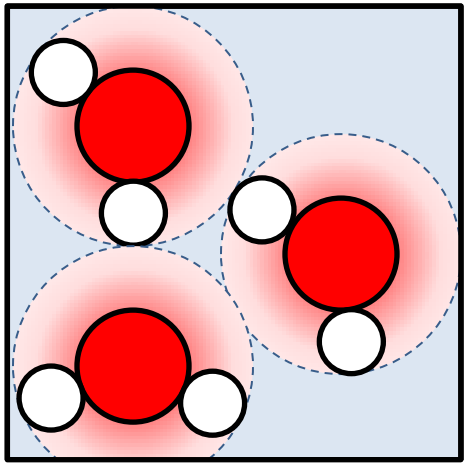
Three things perturb ⟨Φ⟩ in a periodic box

Net charges



ΔG NET

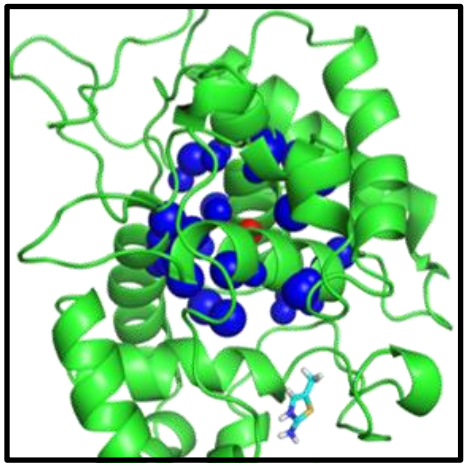
Solvent internal potentials



ΔG DSC

(Discrete Solvent Correction)

Protein internal potentials

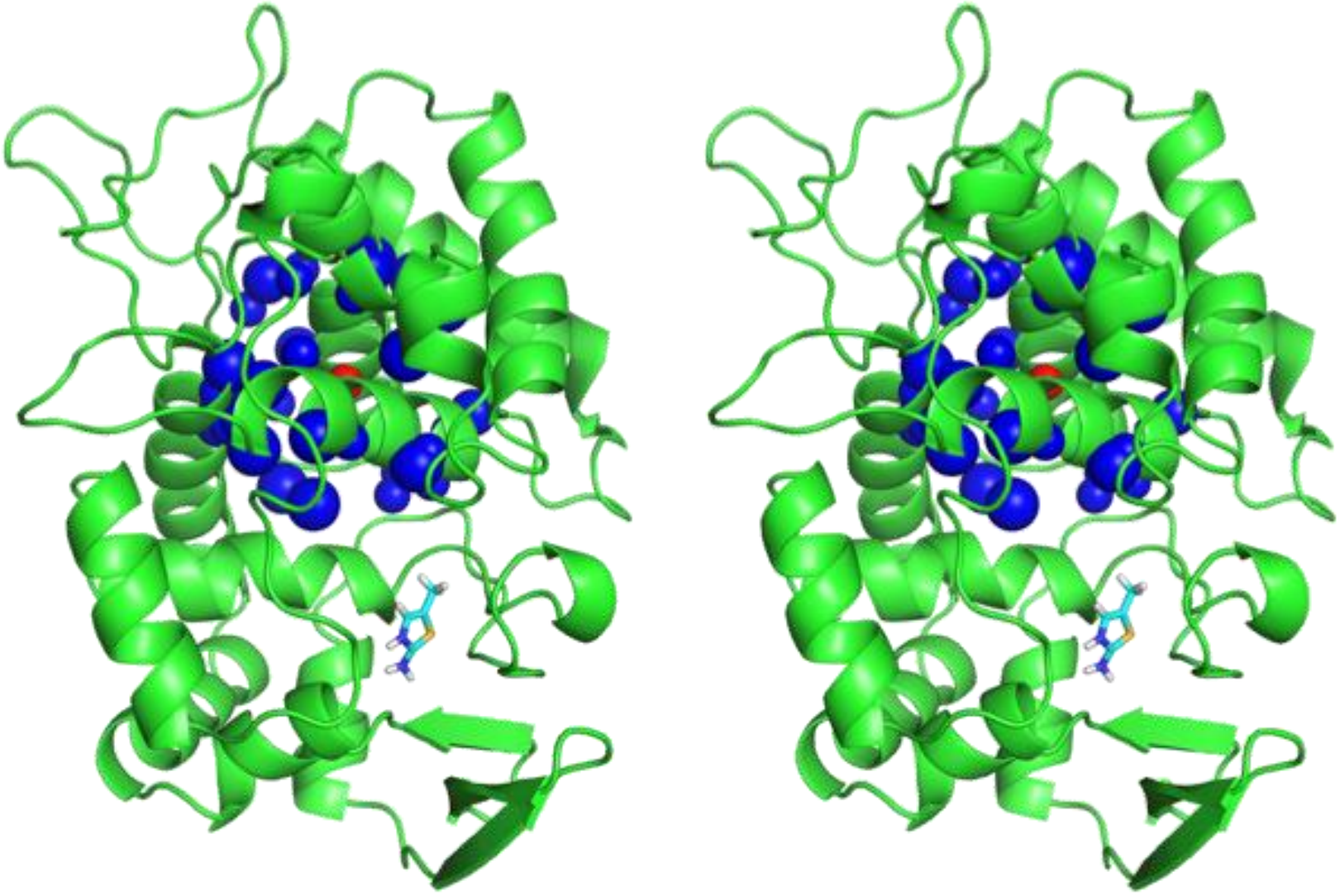


ΔG RIP

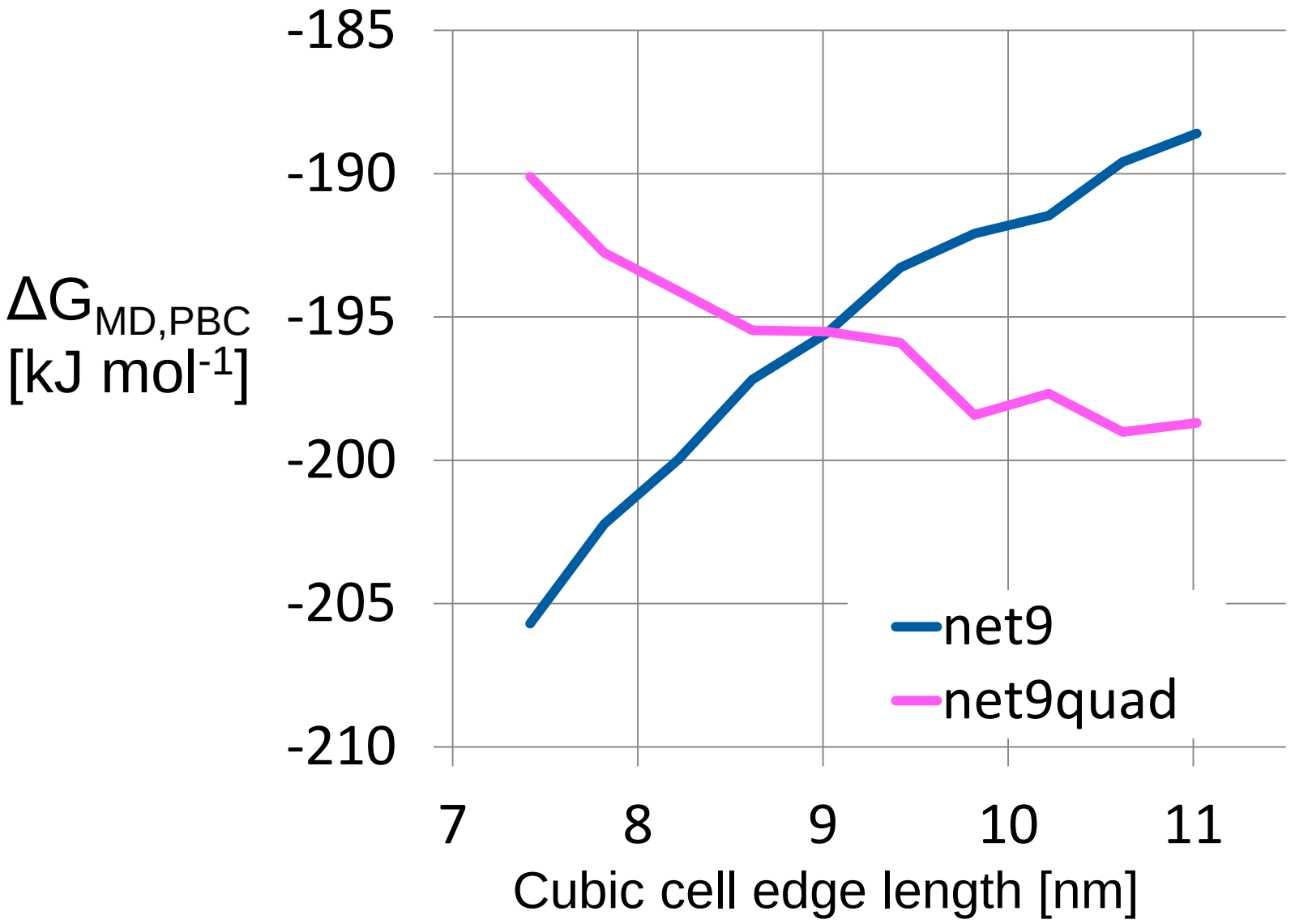
(Residual Integrated Potential)

Nonperiodic PB Required

An artificial quadrupole on the protein demonstrates the importance of the RIP term

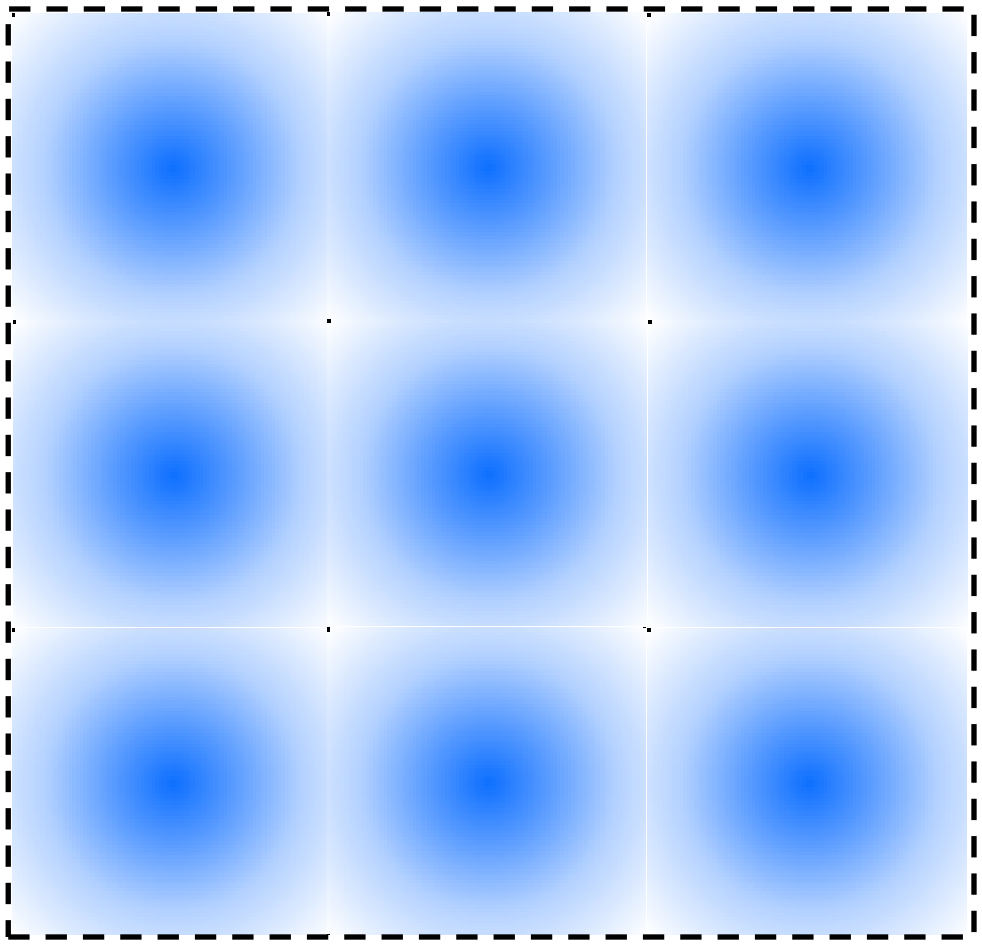


Protein residual integrated potentials can create large finite size effects in charged systems

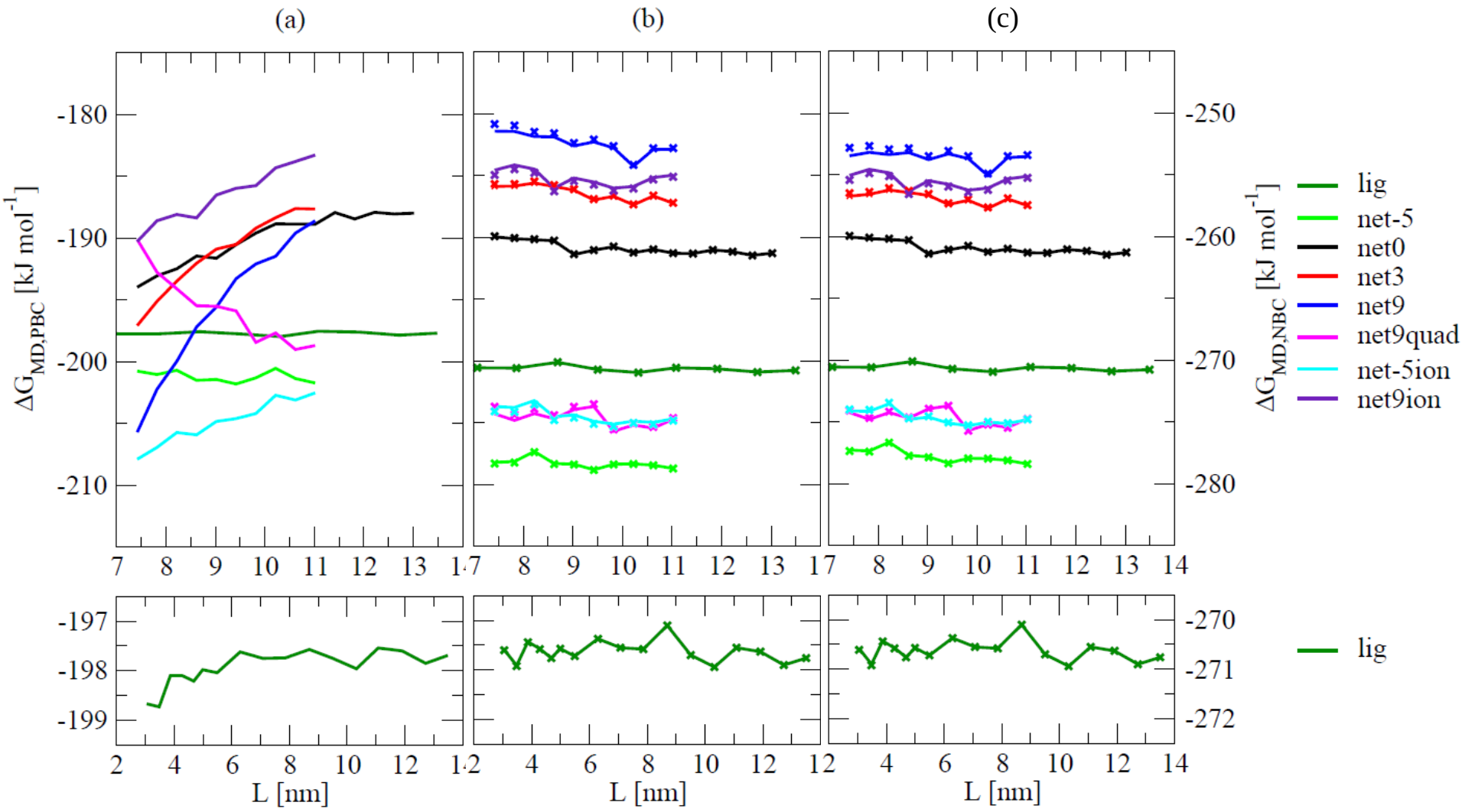


One last term corrects for the finite amount of solvent per ion in a periodic box

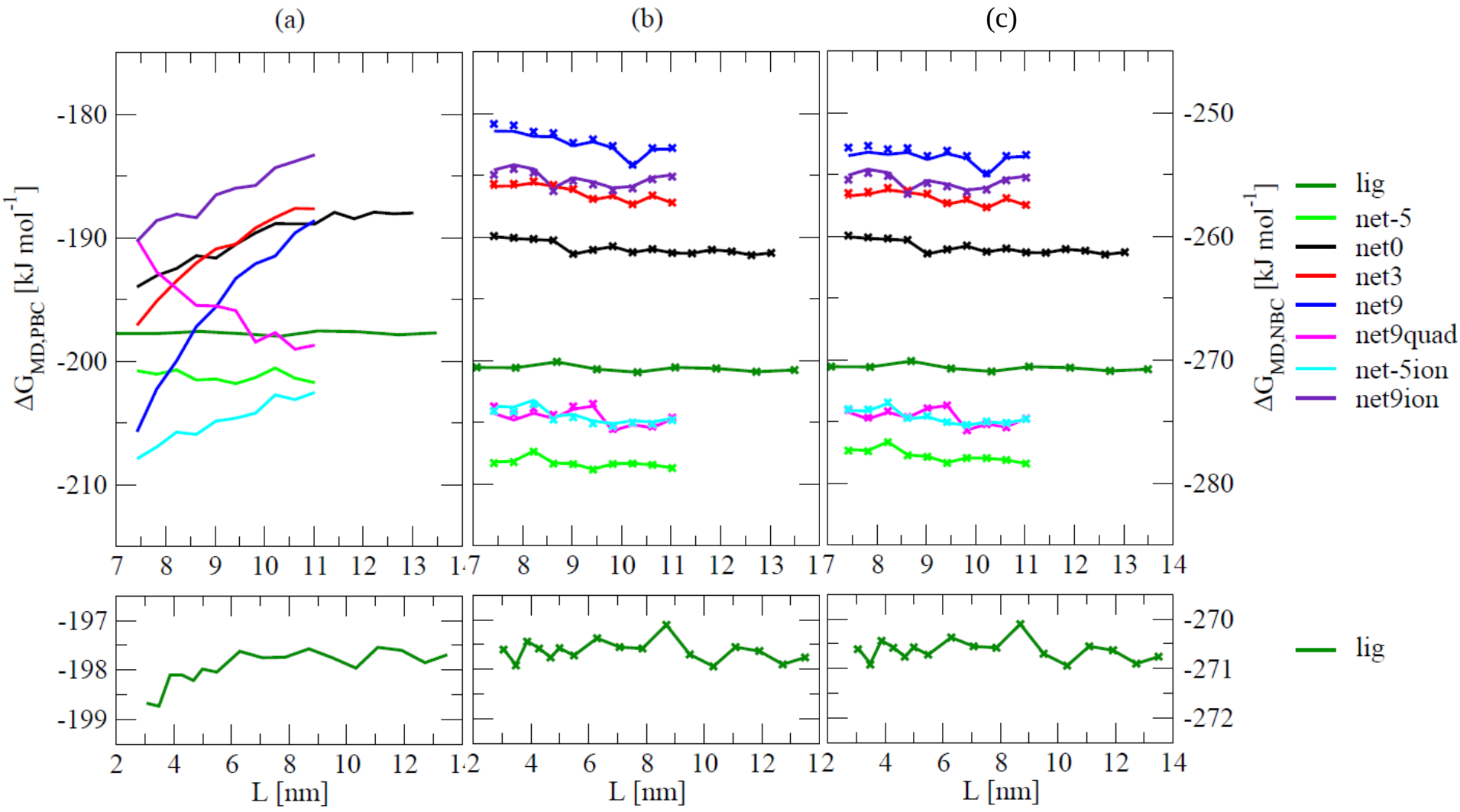
ΔG Finite Solvent



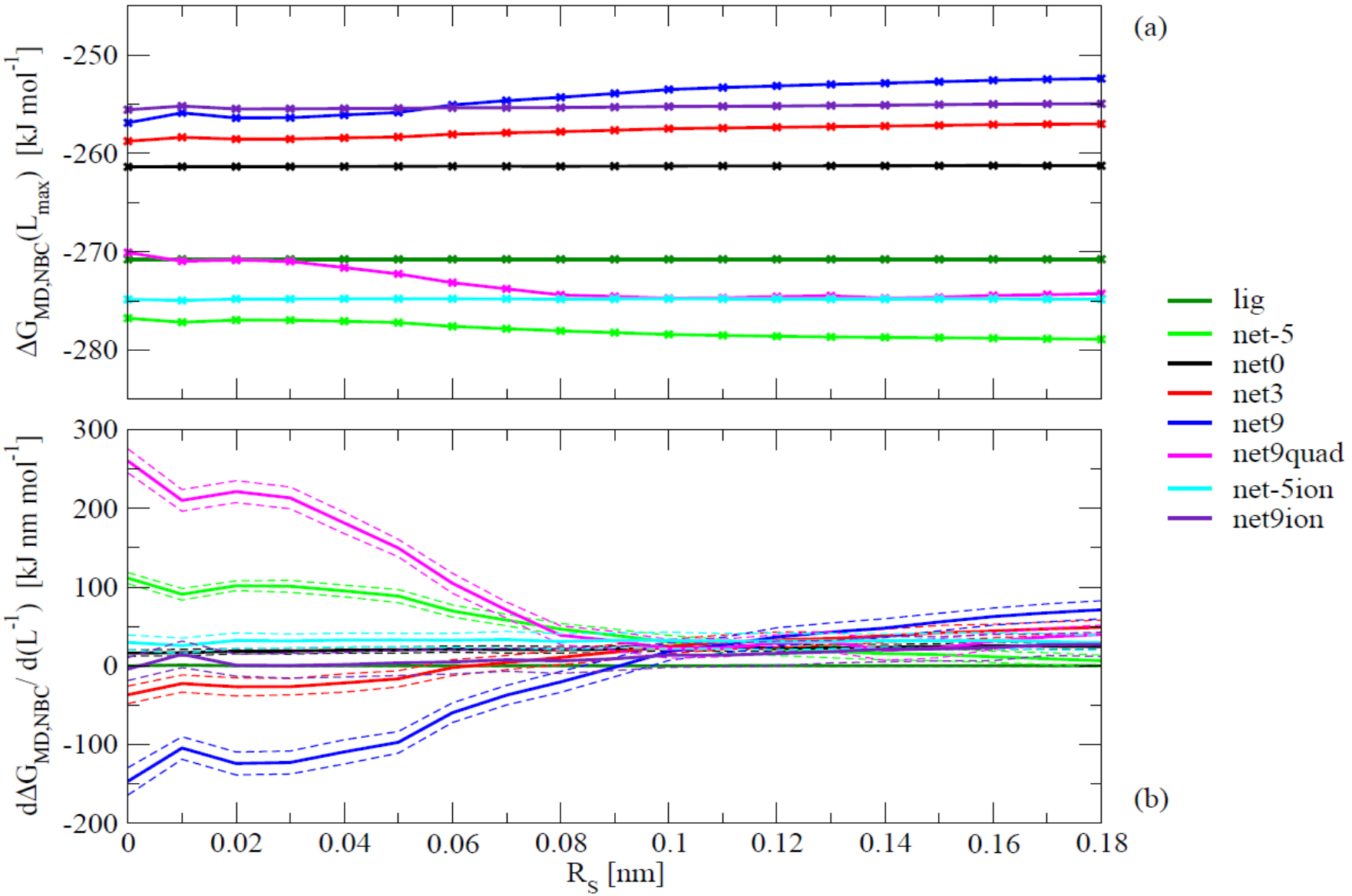
We tested corrections in two ways:
(1) Application to explicit solvent MD results



We tested corrections in two ways:
(2) Agreement with periodic boundary Poisson-Boltzmann



After correcting, remaining size dependence comes from artificial PB dielectric boundary



Takeaways

1. Charging calculations in periodic systems suffer from significant artifacts due to periodicity.
2. These artifacts can be corrected using analytical corrections, but a non-periodic PB calculation is also required.
   We provide a Python script for PB analysis.
3. Artifacts are largest when the system net charge is large, or ligand net charge is large.

What we all agree on
(Roux, Oostenbrink, Rocklin)

1. Periodic boundary Poisson-Boltzmann calculations provide a “gold standard” determination of periodicity artifacts
2. Internal water potential needs to be cancelled in boxes with different water number-densities
3. Even one-box PMF calculations still have artifacts, perhaps small

Acknowledgements

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