Overview of the SAMPLing challenge results

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The SAMPLing challenge moves the focus from accuracy to convergence properties of statistical methods

	Target	Reference	Cost
Host-guest	Model + method	Experiments	/
SAMPLing	Method	Converged free energy calculation	Computational cost

Main questions that the SAMPLing challenge attempts to answer

- Do different methods converge to the same answer?
- How quickly do calculations converge?

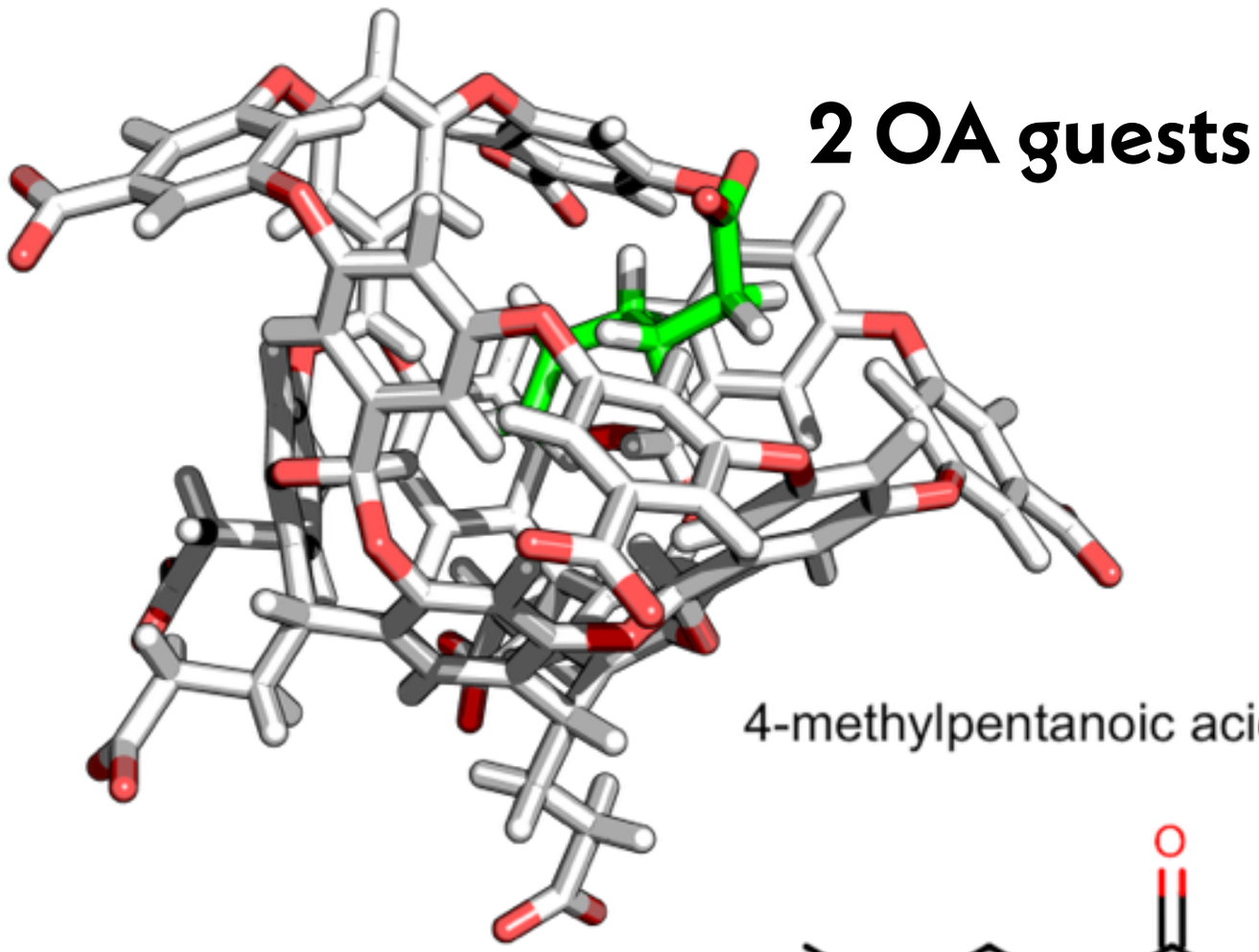
Outline

- Challenge description
- Reference calculations
- Overview of results

Measuring the "cost" of a *method* is not trivial

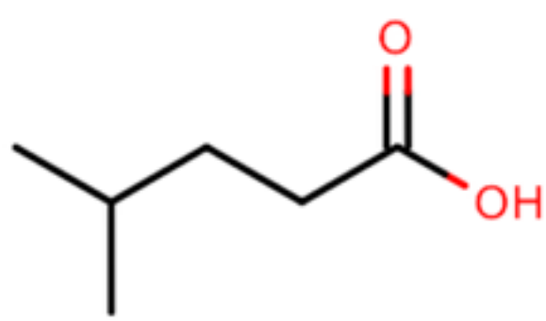
- **CPU/GPU time** affected by hardware/implementation
- Total ns/μs of MD depends on time step and lose meaning with MC
- **Number of energy evaluations**
  - Depend on system size (solvent complex)
  - Energy can often be just updated (MC on a subset of atoms, multiple time scale MD, switch Hamiltonian)

Few targets selected from host-guest challenge mixing fragment-like and drug-like molecules

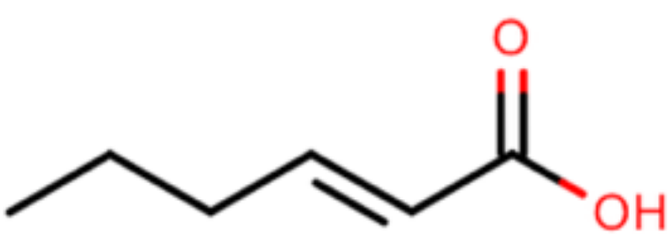


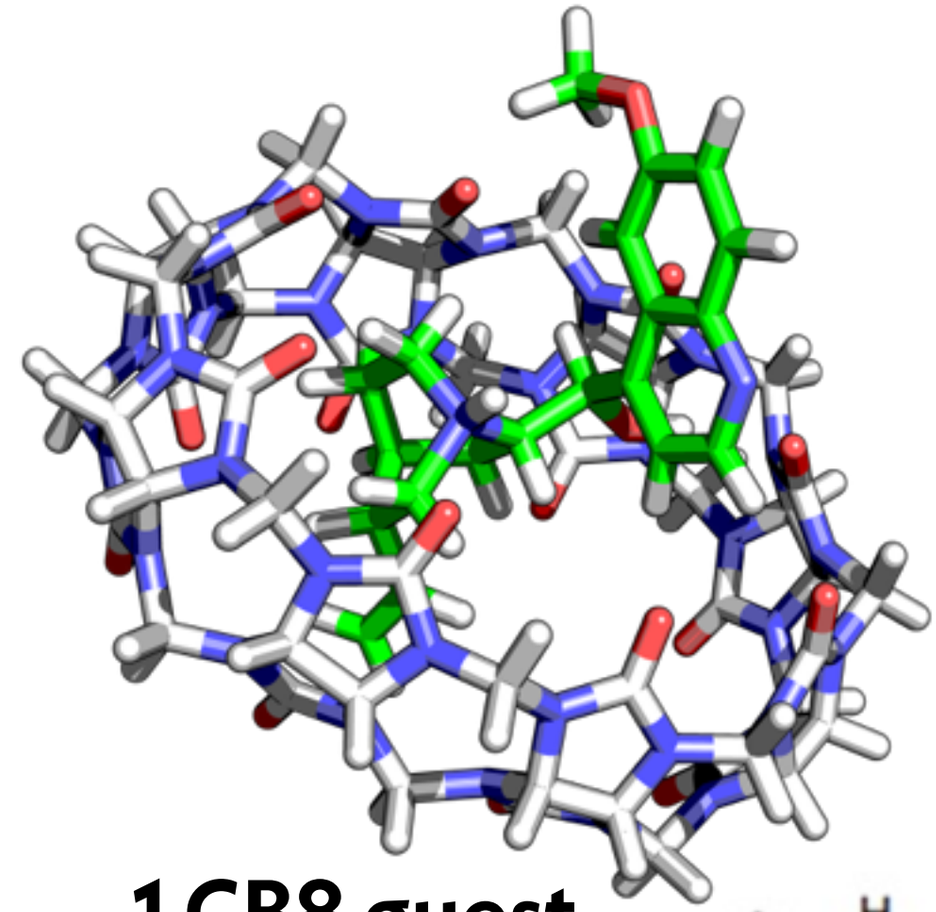
2 OA guests

4-methylpentanoic acid

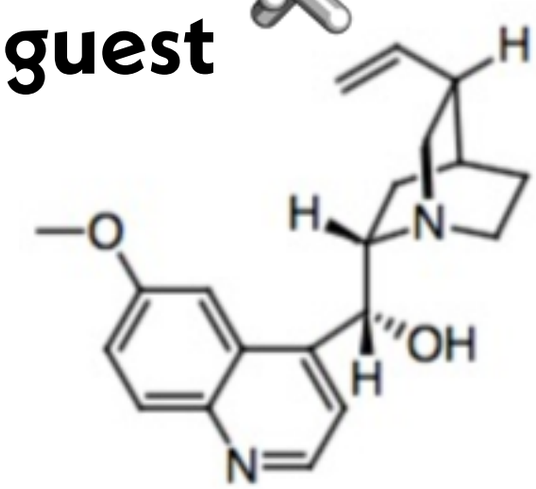


trans-2-hexenoic acid



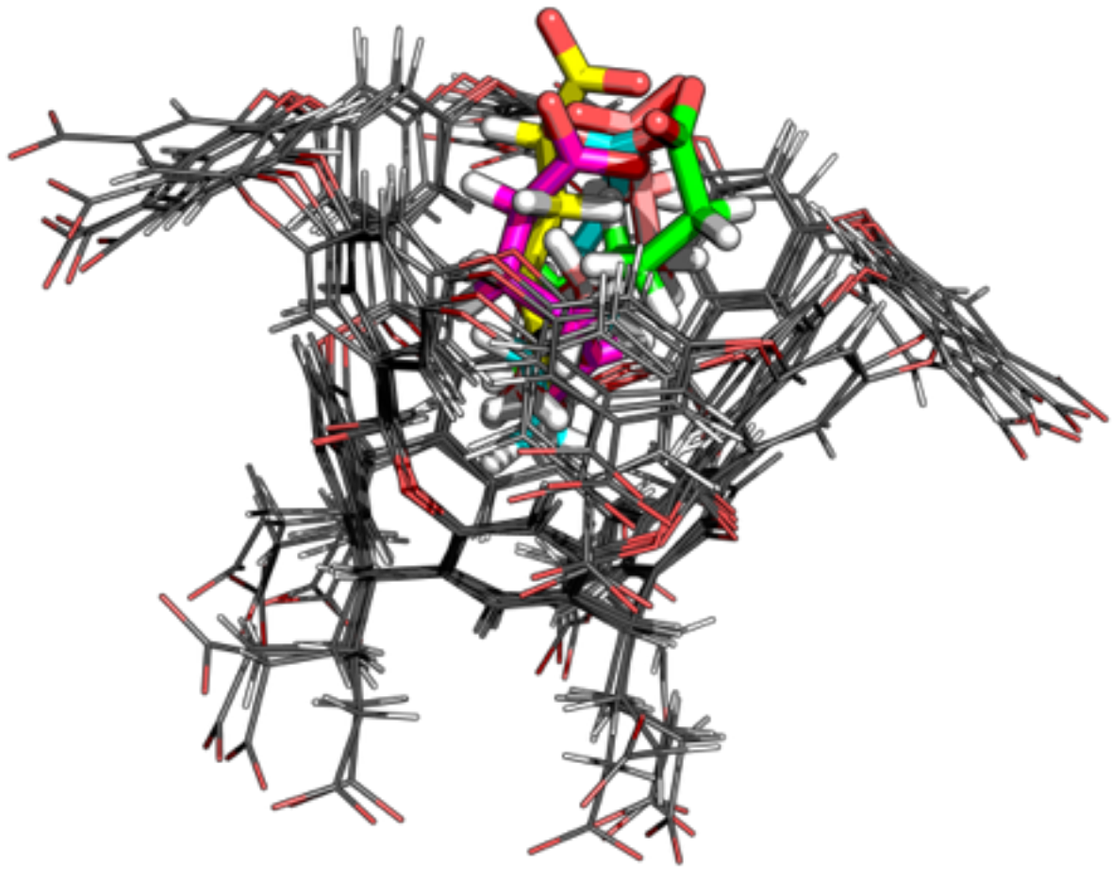


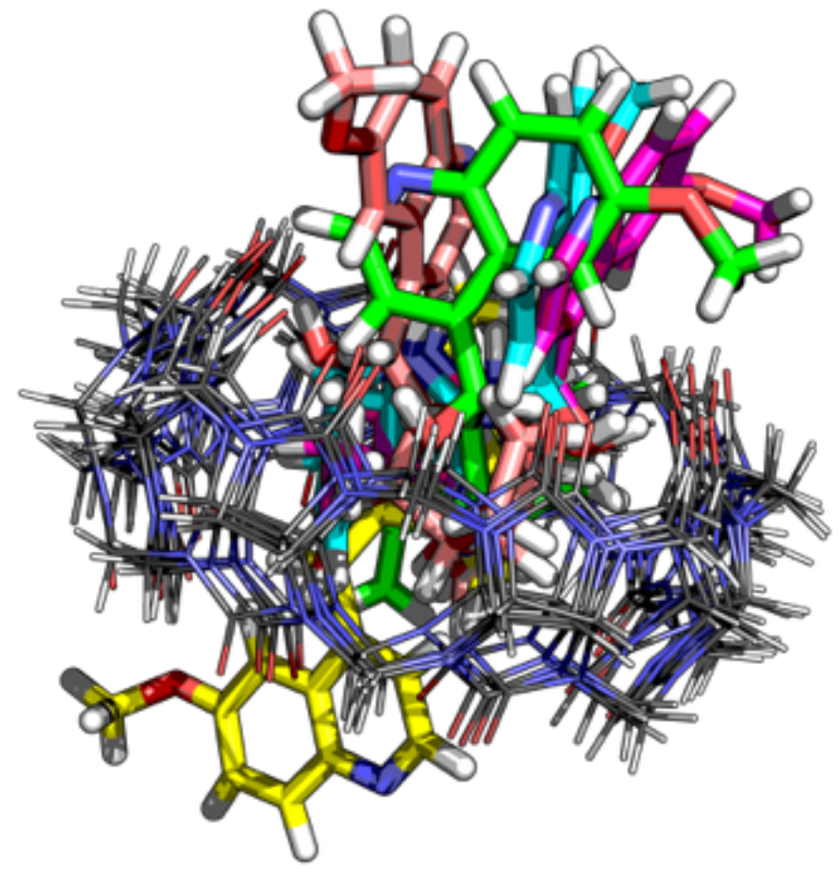
1 CB8 guest



Quinine
CAS 130-95-0
OakWood Chemical

Initial configurations and parameters are shared among all participants



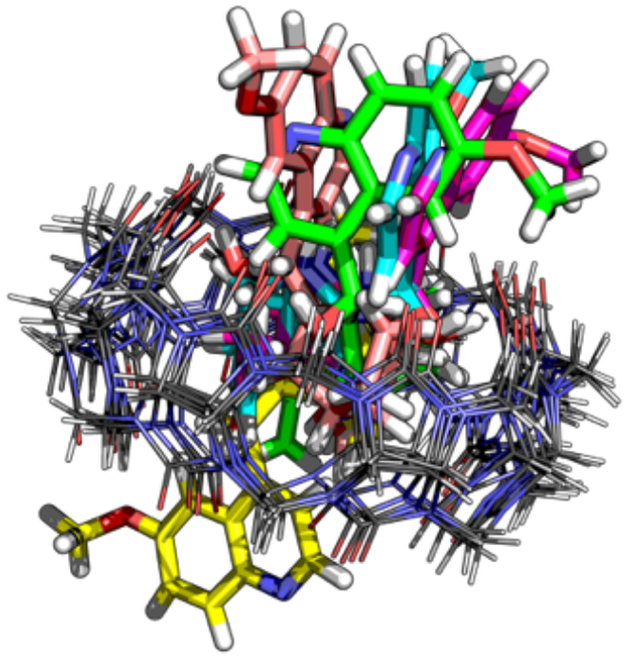


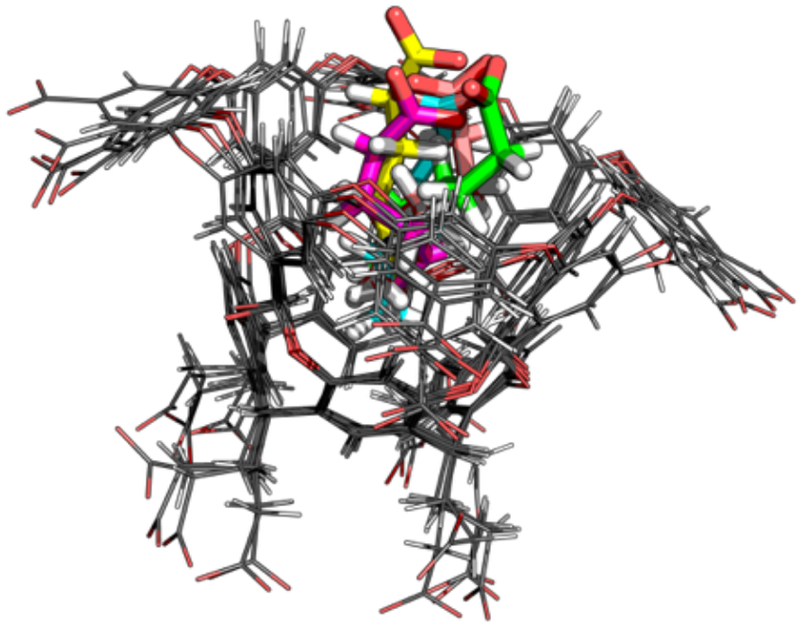
- A “common” setup: AM1-BCC charges / GAFF / TIP3P cubic water box + neutralizing and buffer Cl- Na+ ions

- Files converted in many formats (Michael Shirts)

Long-range treatment parameters can only be suggested

- Long-range treatment is not encoded in parameter file (although important part of the model)
- Reference calculations
  - PME
  - Cutoff electrostatics and VdW at 10Å
  - Switching function for VdW at 9Å





Free energy estimates of replicates at multiple time points allow us to observe the estimate variance in time

- Free energy estimates after 1, 2, ..., 100% of calculation
- Total cost in energy evaluations and time
- Replicates that belong to the same system must have same total cost

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YANK: A GPU-accelerated Python platform for absolute free energy calculations

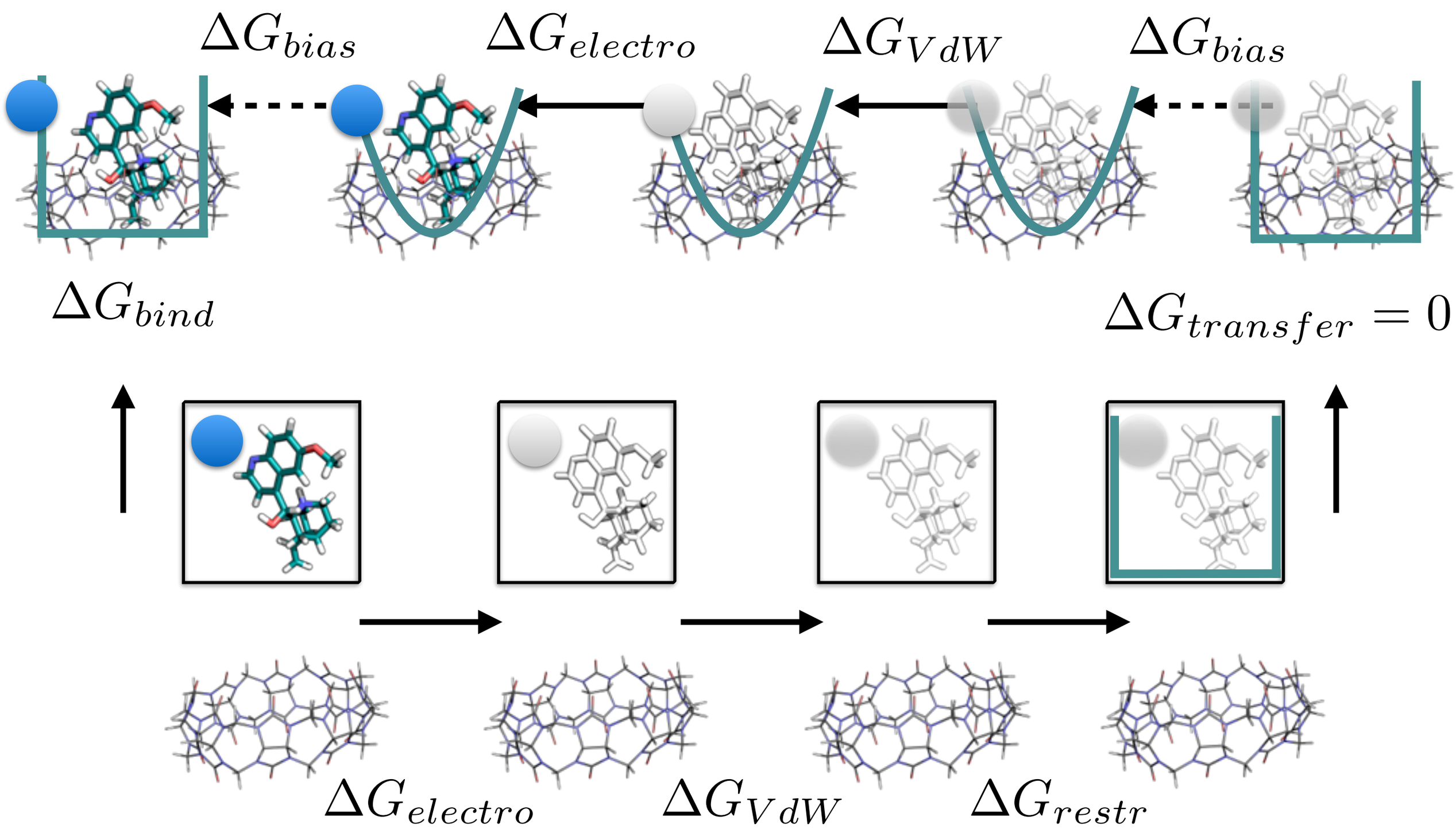
Docs: http://getyank.org/latest/

Built on:

- OpenMMTools
- OpenMM
- AmberTools
- Parmed
- MDTraj
- ...

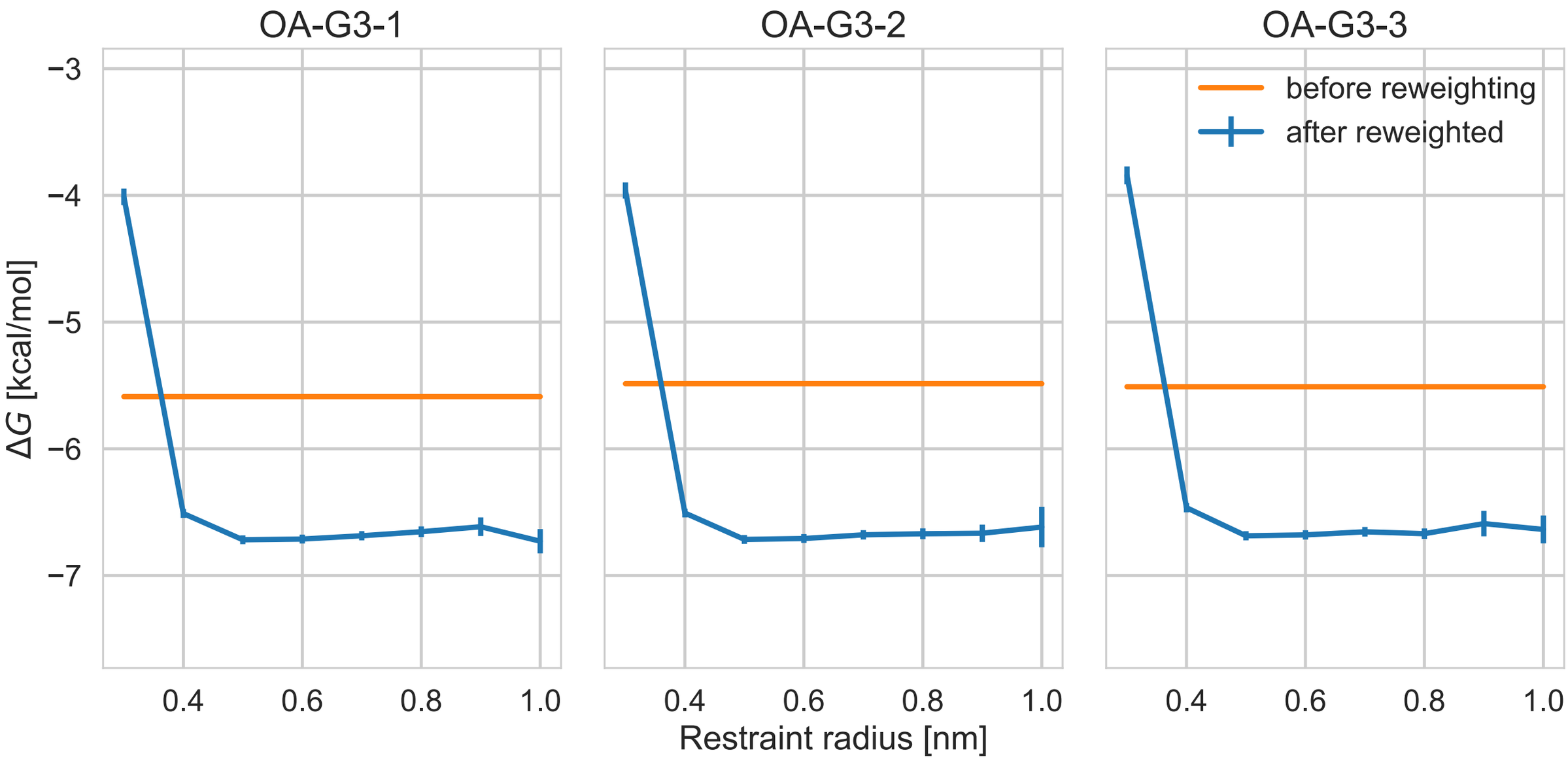
Levi Naden

Thermodynamic cycle



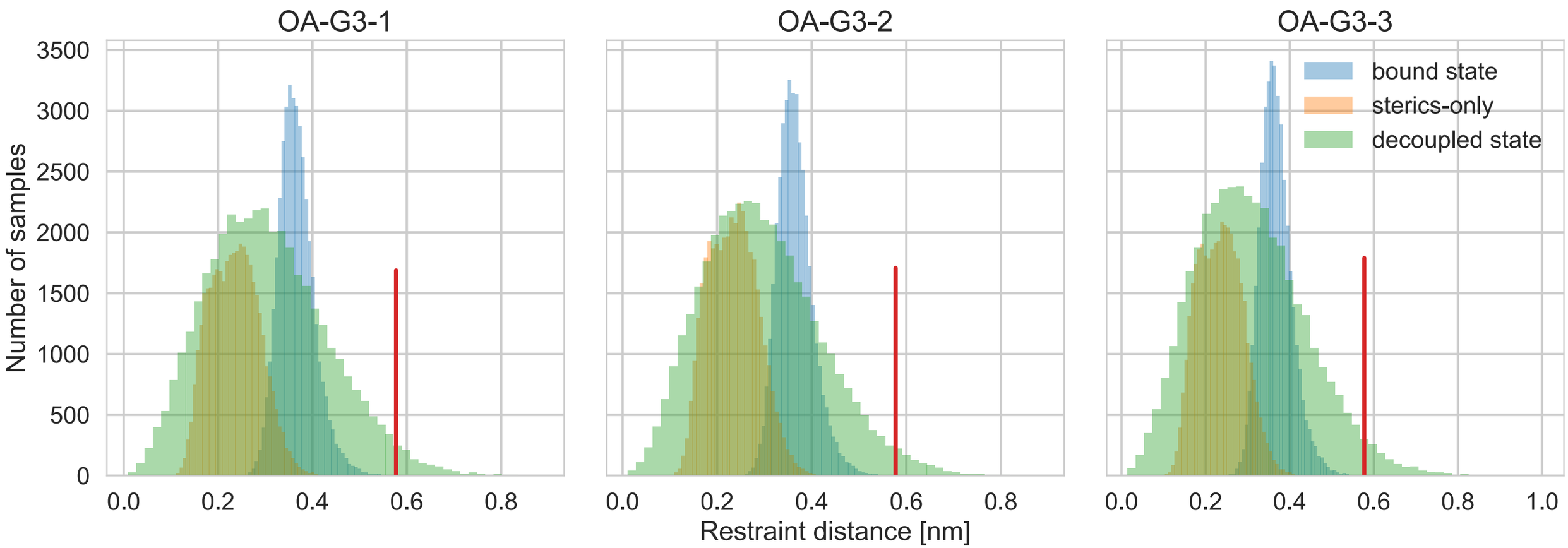
Gilson MK, Given JA, Bush BL, McCammon JA. *Biophysical Journal*. 1997 Mar 72:1047-69.

The harmonic restraint introduces a non-negligible bias



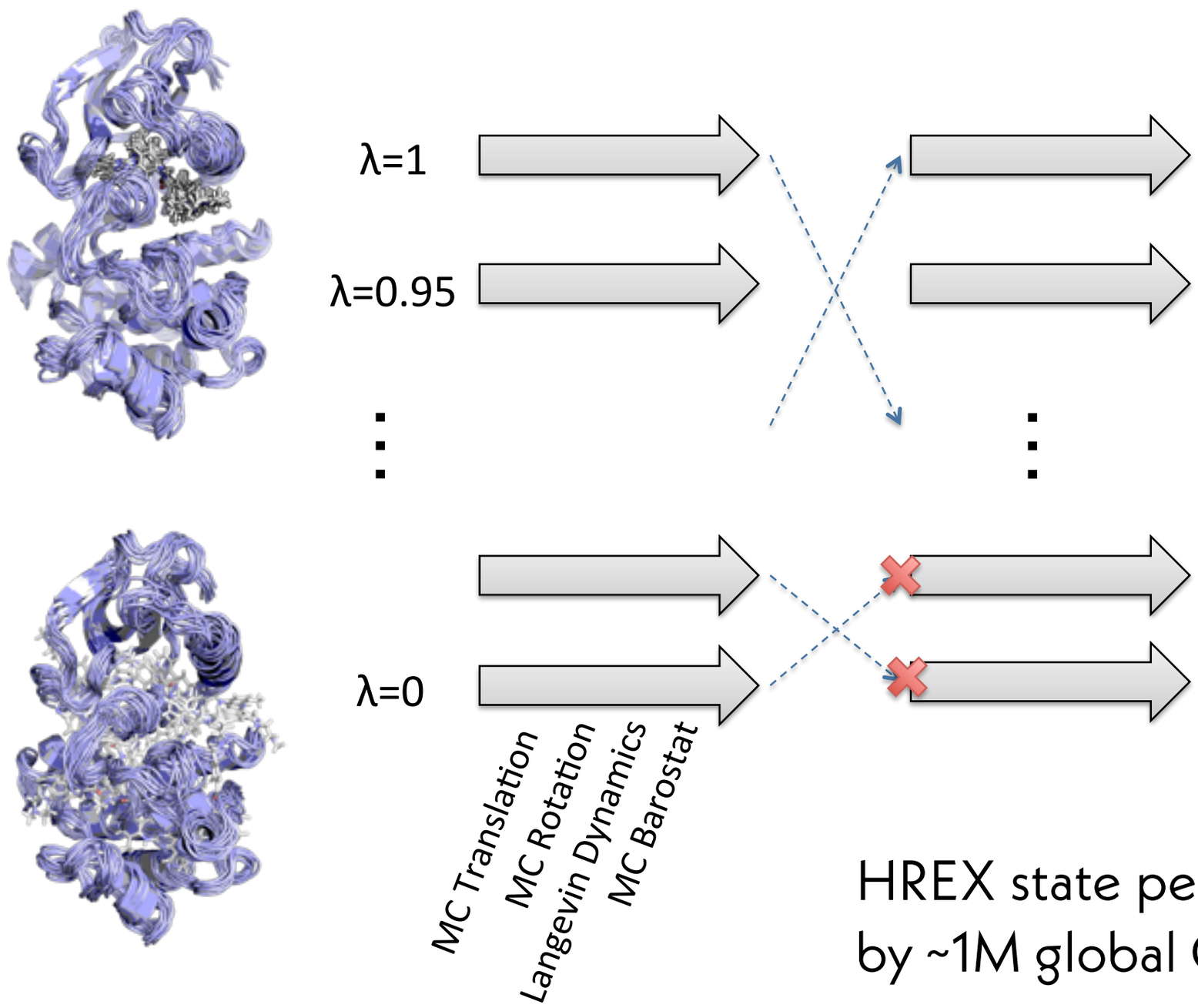
Restraint spring constant ~0.17 kcal/(mol Å^2)

Let the simulation define the binding site and integration volume



Radius of the square well distance determined as 99.99-percentile of bound state harmonic restraint distance distribution.

We mix HREX, MD and Monte Carlo moves to decrease correlation times



HREX state permutation obtained by ~1M global Gibbs swaps.

Chodera JD, Shirts MR. The Journal of chemical physics. 2011 Nov 21;135(19):194110.

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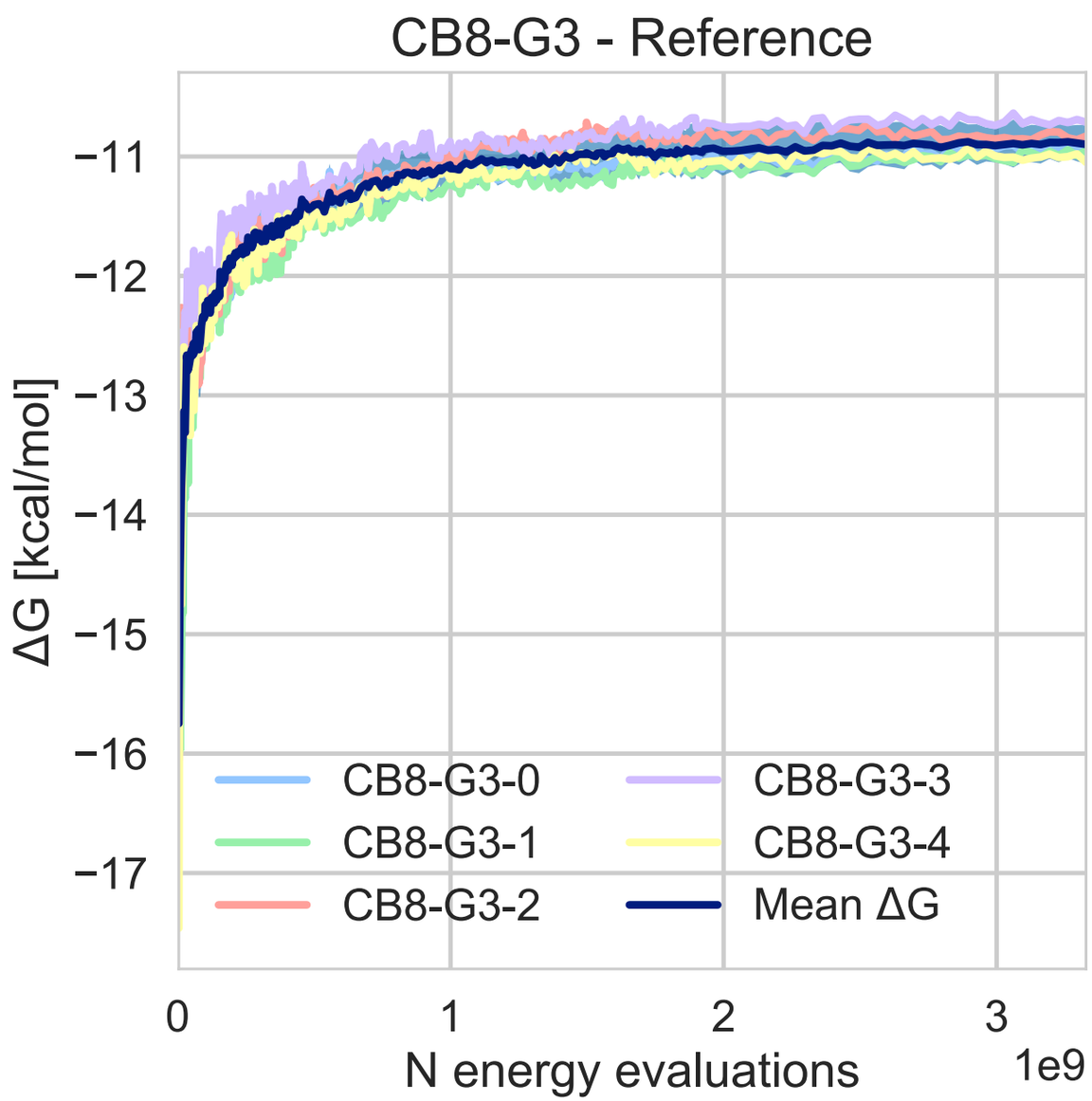
The 5 replicates converged to the same value

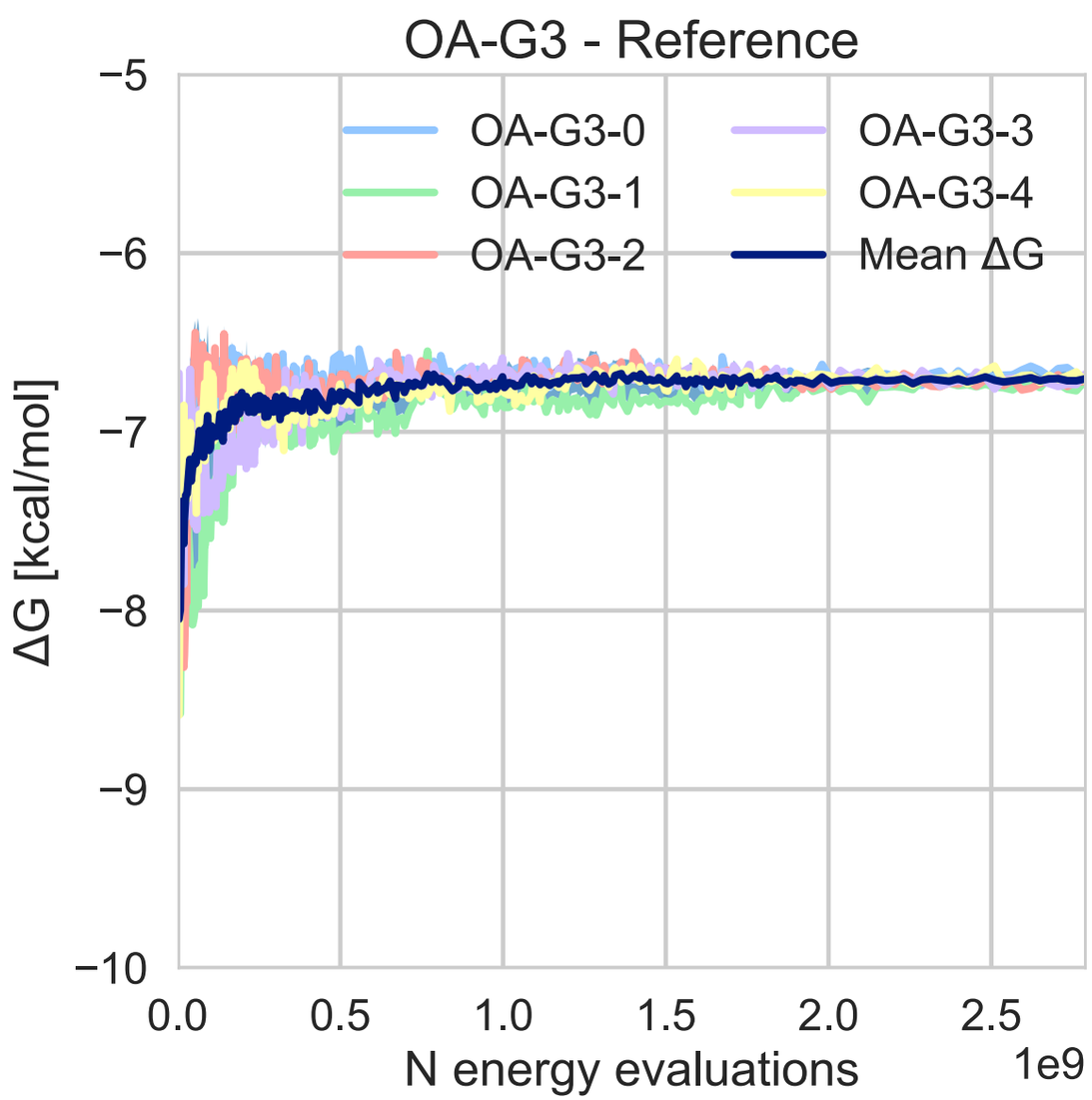


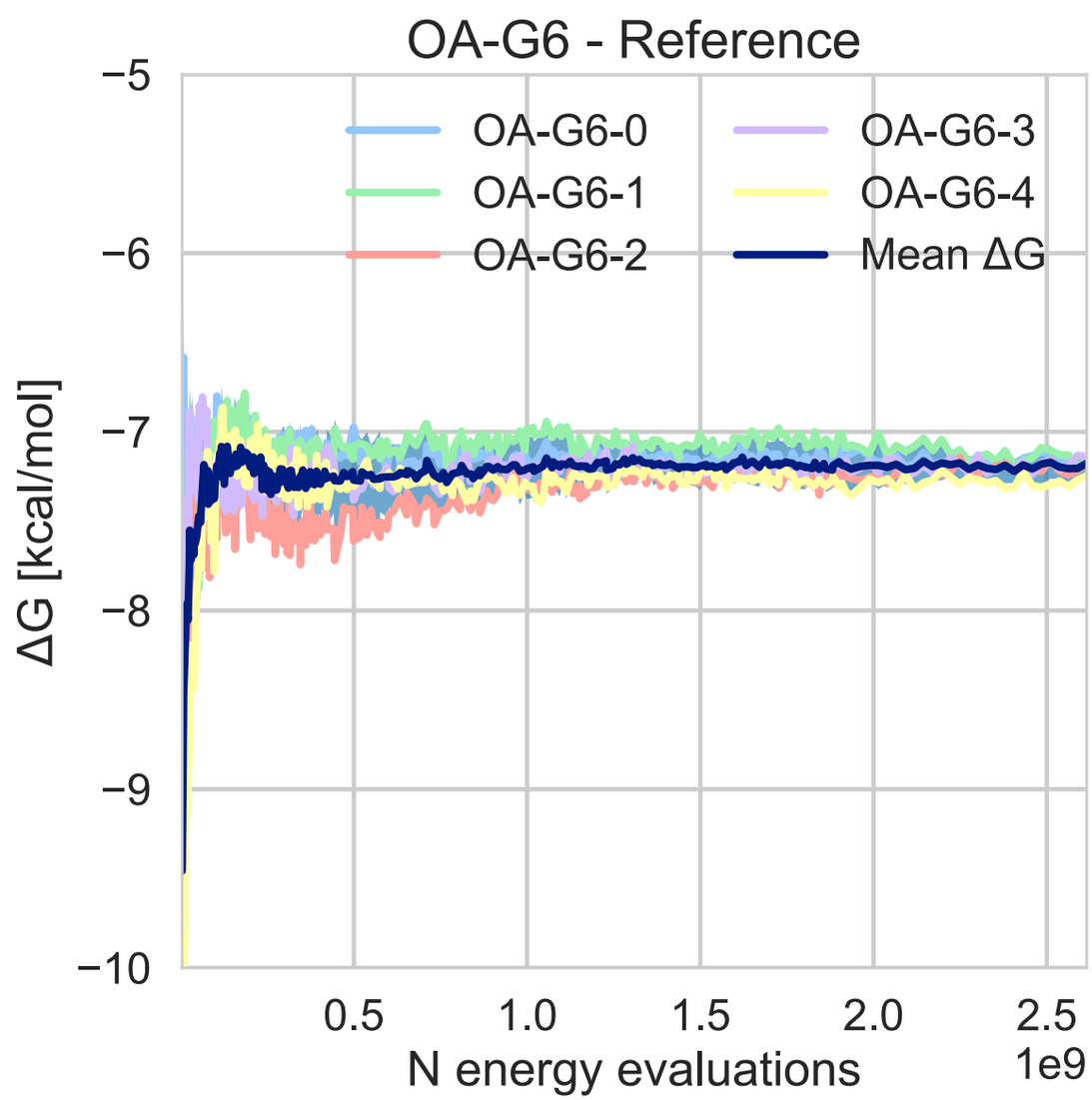
$$\Delta G_{mean} = -10.9 \pm 0.1 \ kcal/mol$$

(t-based 95% confidence interval)

N energy evaluations include calculation of (#states × #states) energy matrix for MBAR and Gibbs sampling.

The 5 replicates converged to the same value

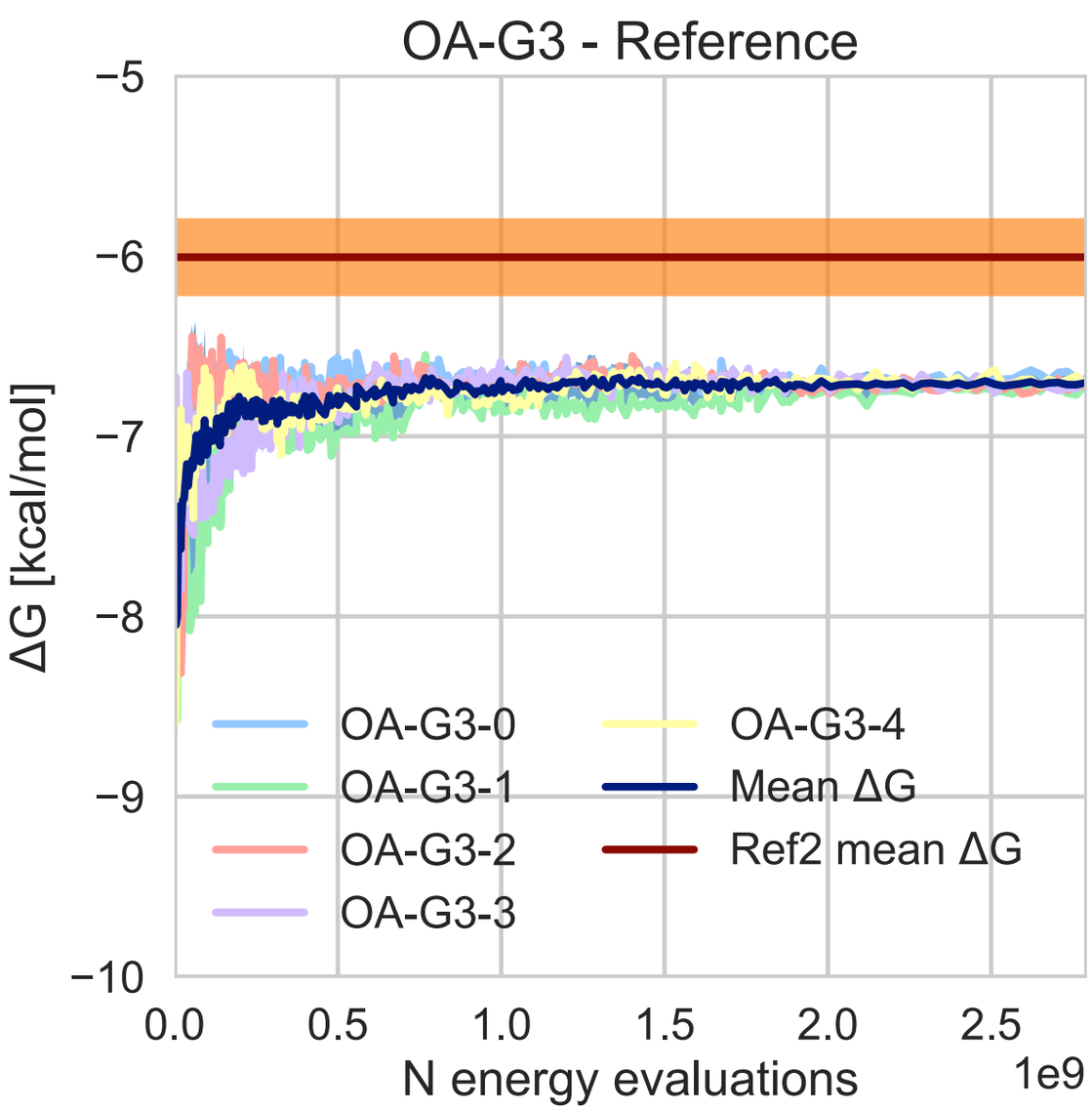


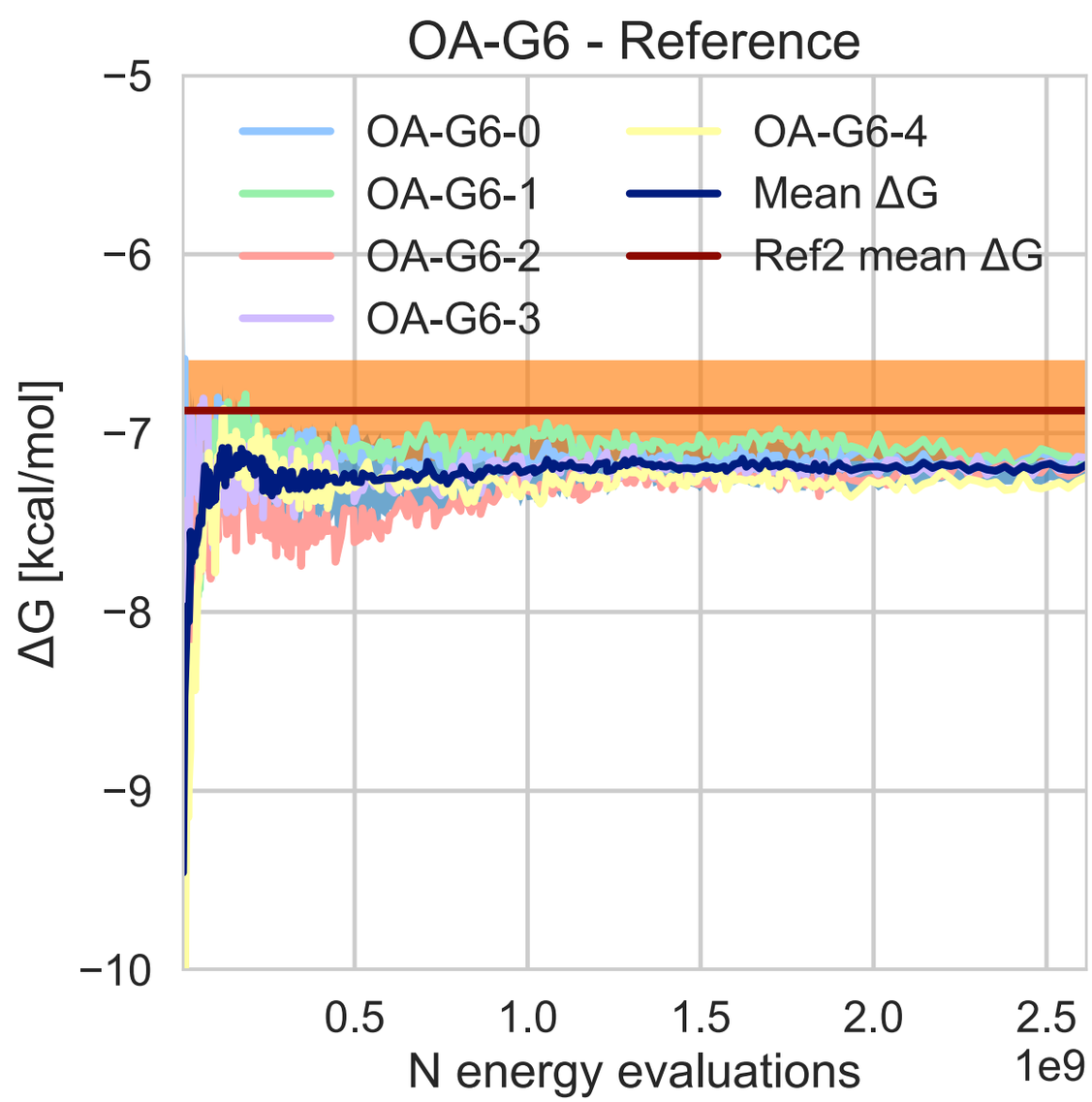


$$\Delta G_{mean} = -6.70 \pm 0.02 \ kcal/mol$$

$$\Delta G_{mean} = -7.17 \pm 0.05 \ kcal/mol$$

There are discrepancies between the two sets of reference calculations on the order of 1kcal/mol





$$\Delta G_{mean} = -6.70 \pm 0.02\ kcal/mol$$

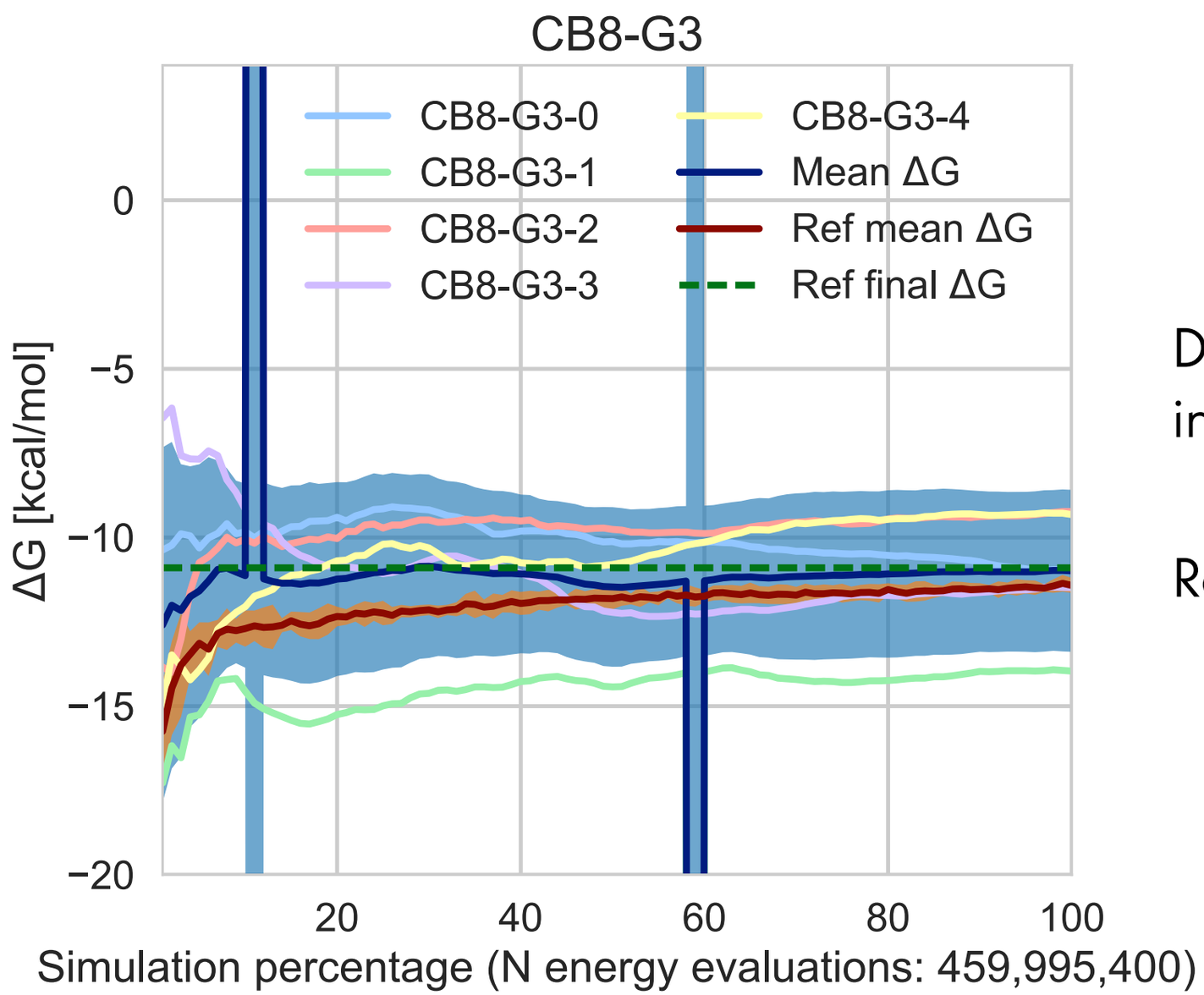
$$\Delta G_{mean\ ref2} = -6.0 \pm 0.2\ kcal/mol$$

$$\Delta G_{mean} = -7.17 \pm 0.05\ kcal/mol$$

$$\Delta G_{mean\ ref2} = -6.9 \pm 0.2\ kcal/mol$$

Travis Jensen, Michael Shirts

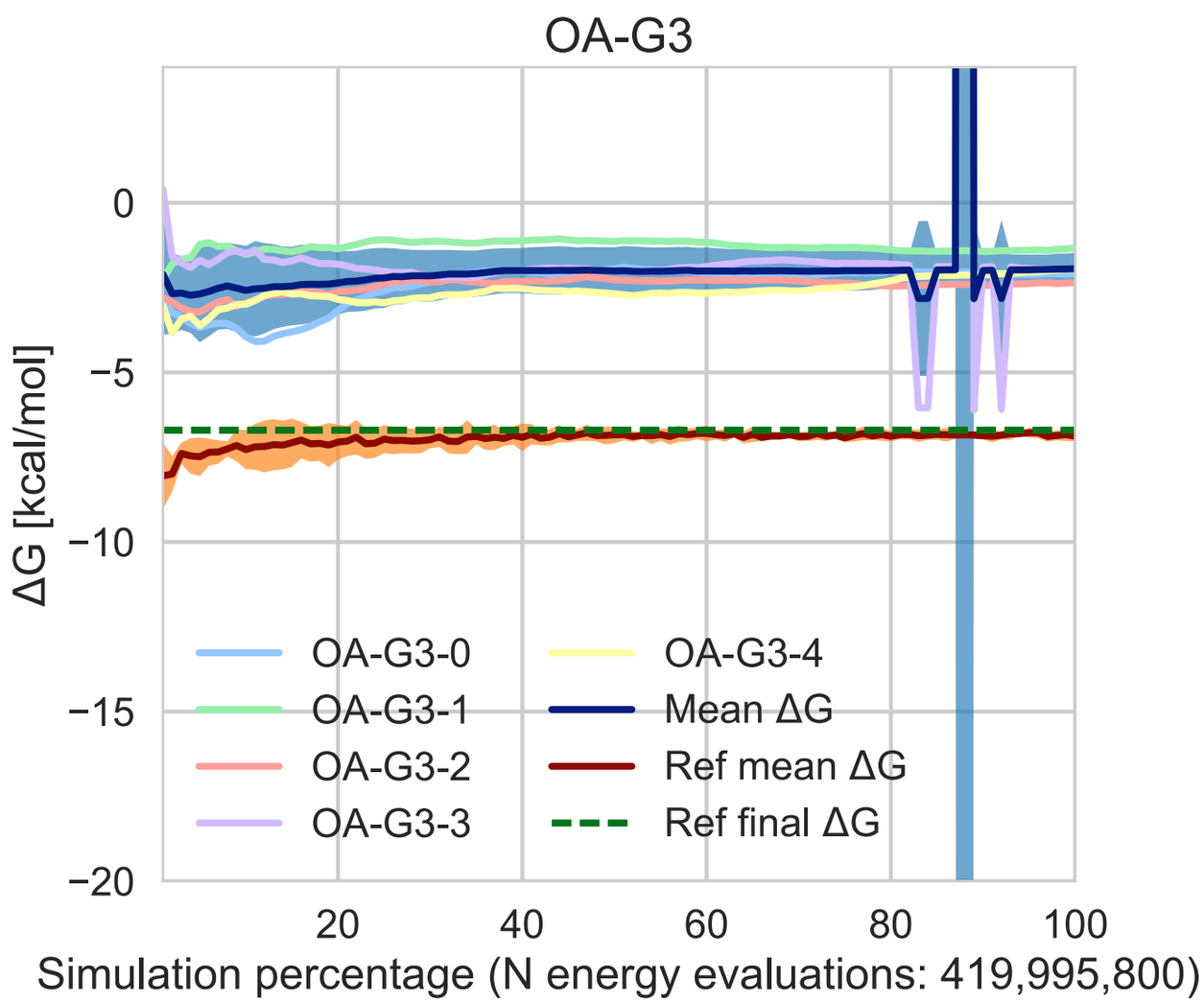
Despite starting from same input files, getting different methods to agree is non-trivial

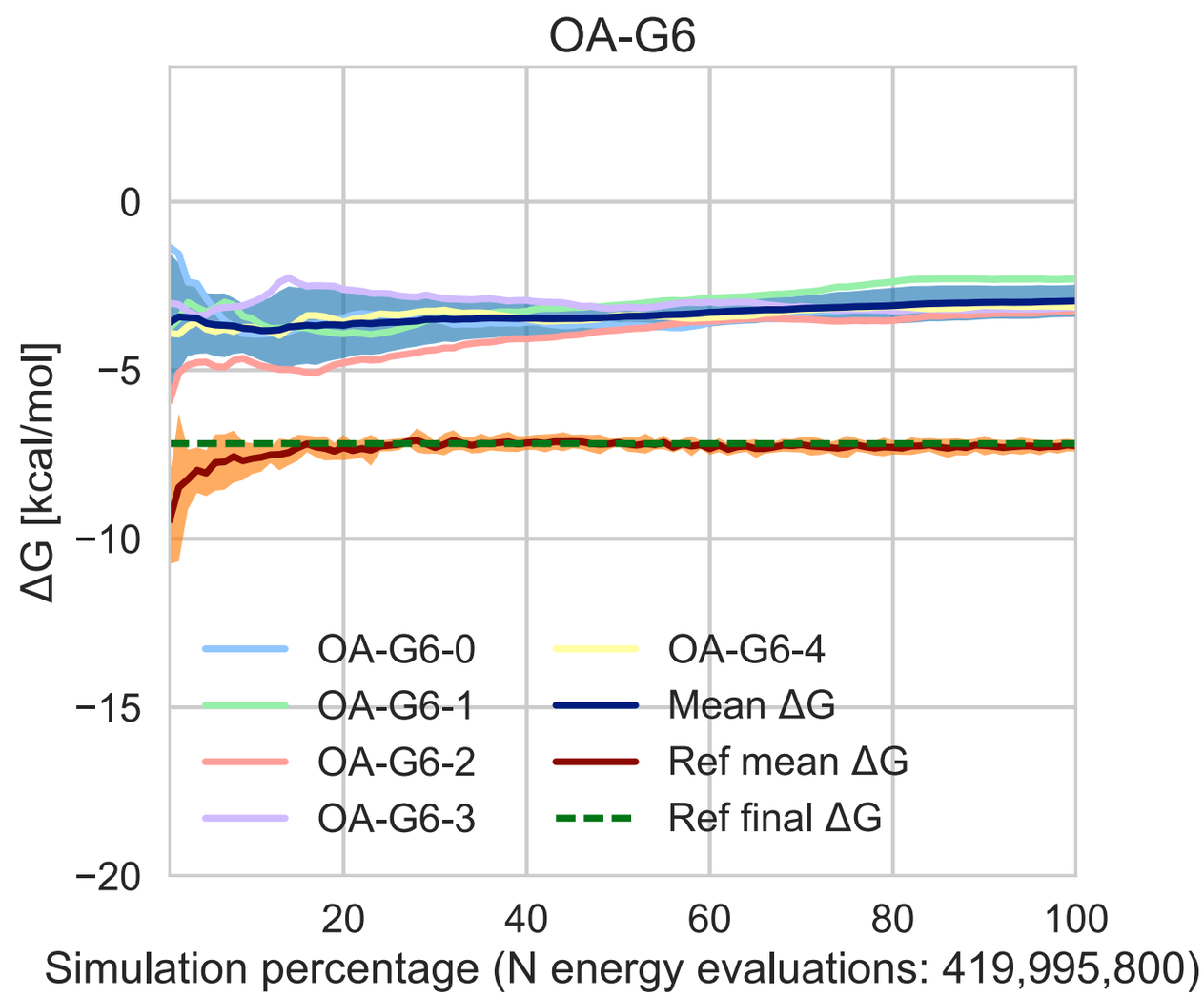


Double annihilation method, independent replicas, 20ns/replica

Reaction Field and 12Å cutoff

Despite starting from same input files, getting different methods to agree is non-trivial





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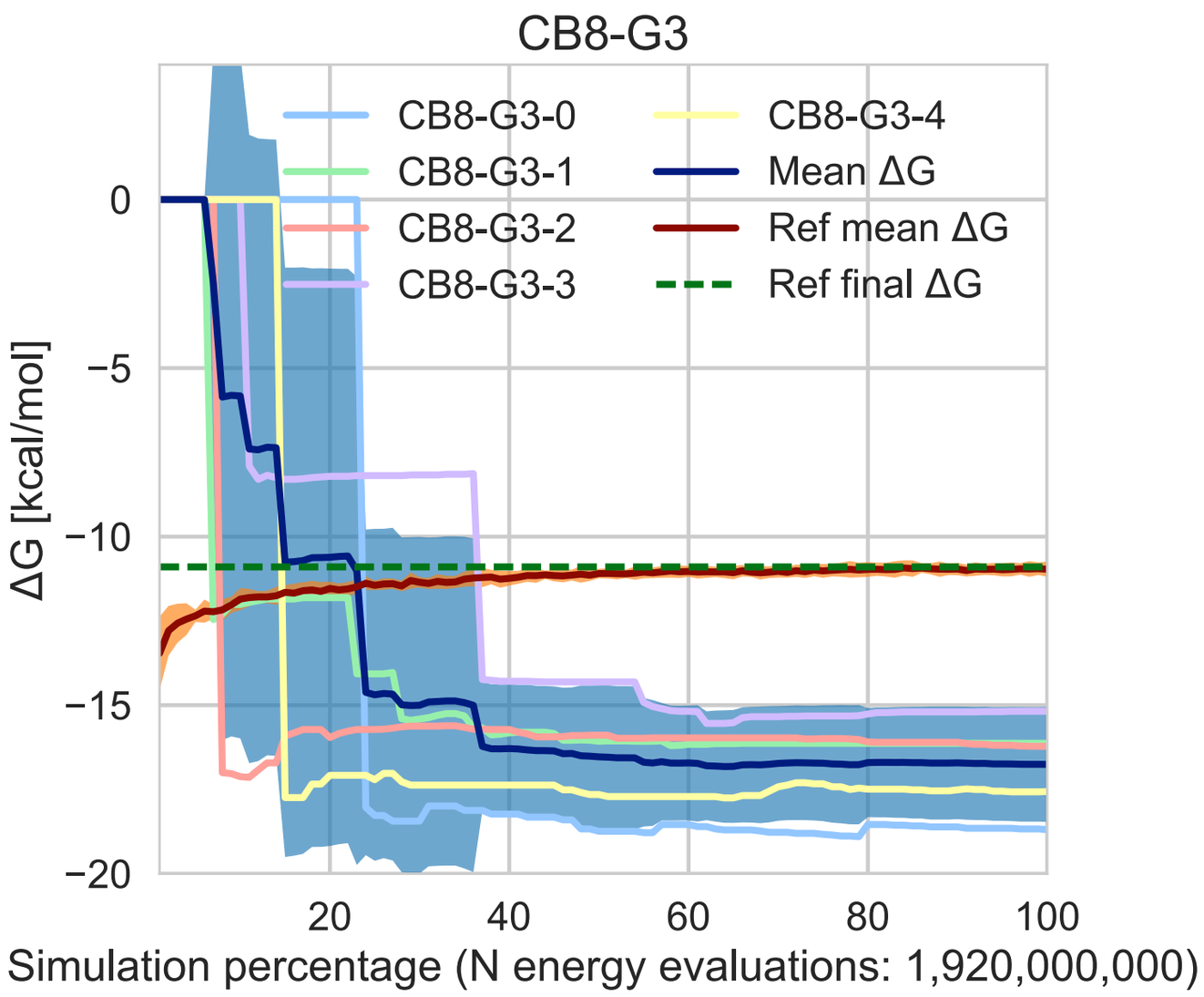
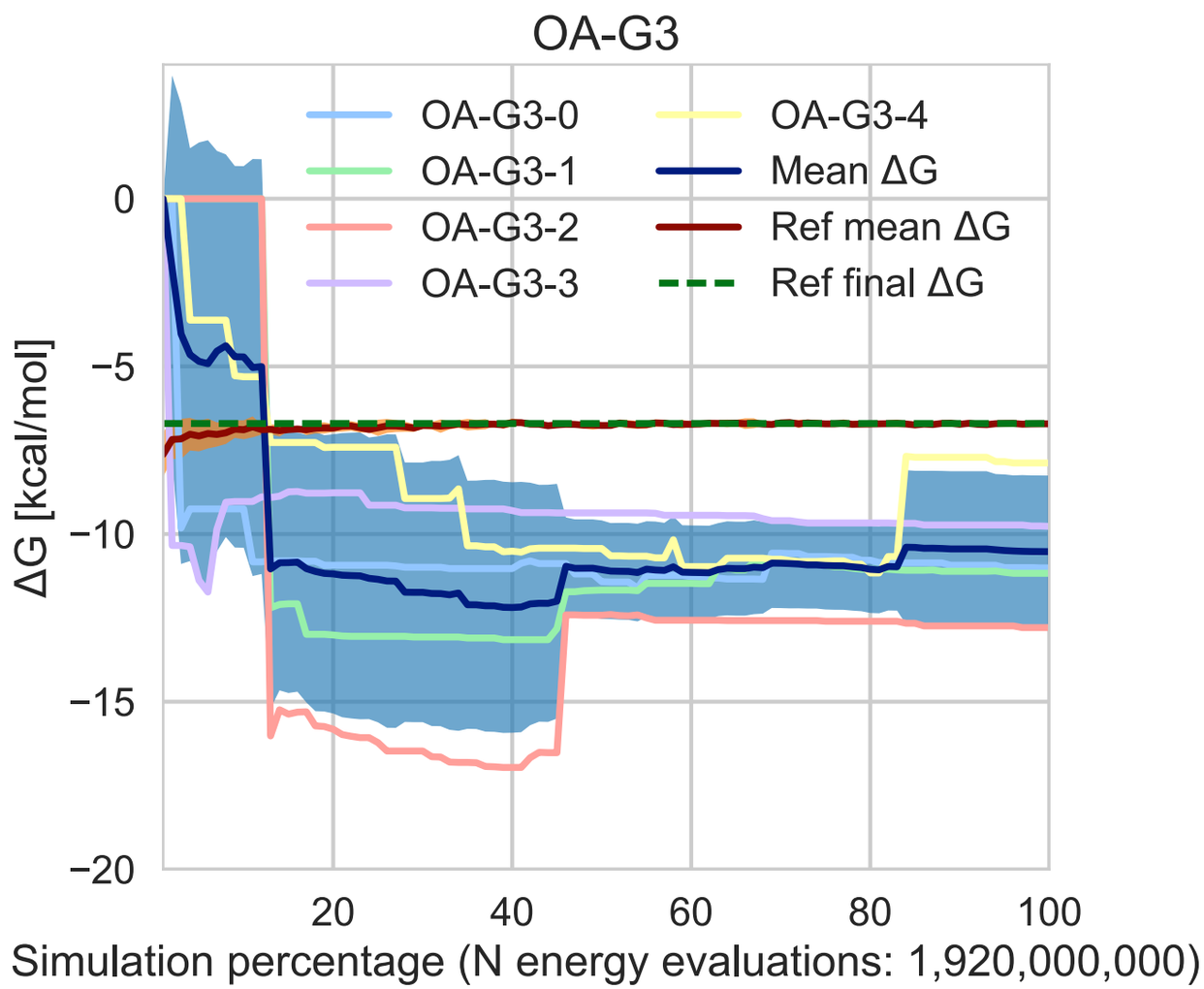
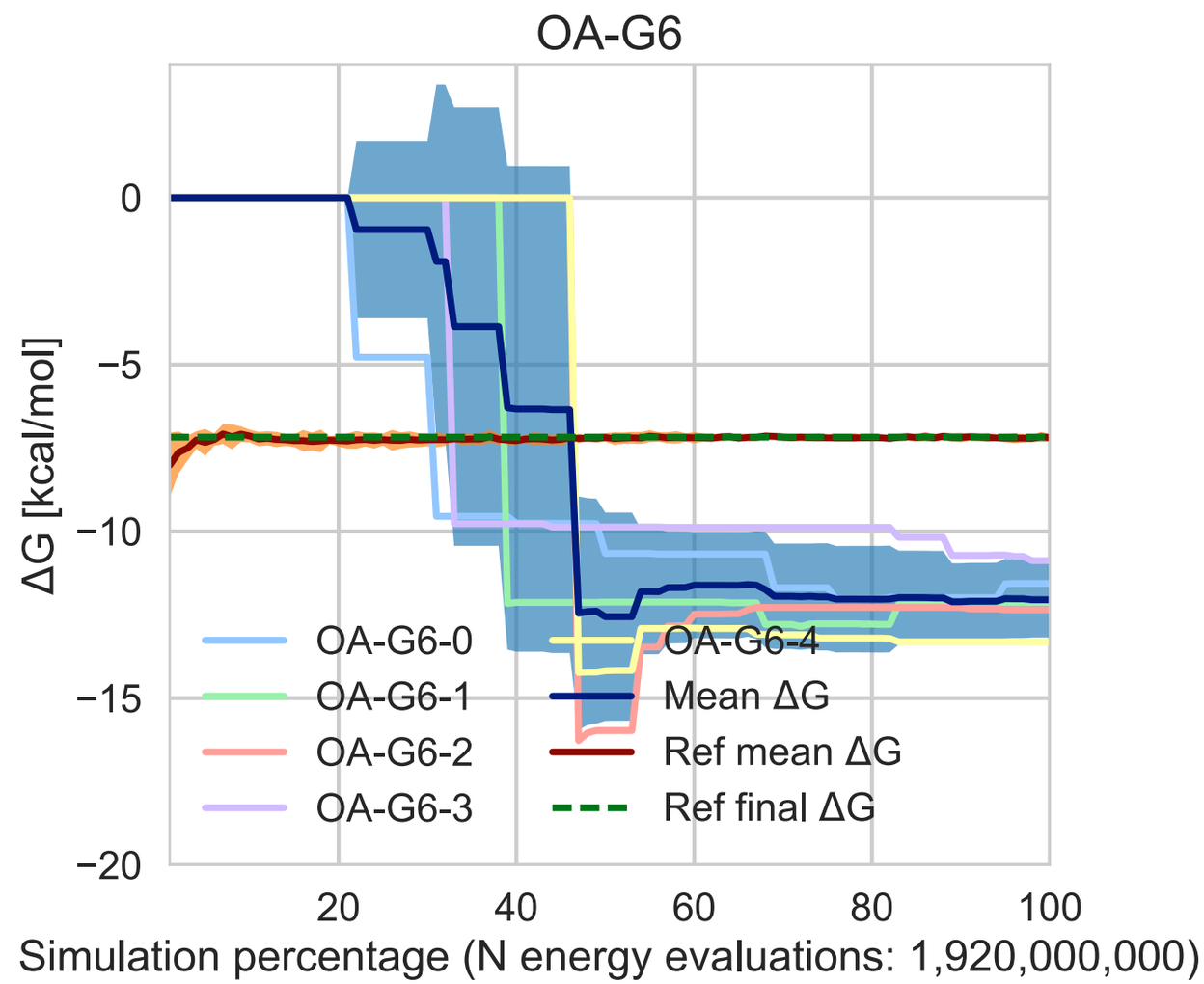


Estimate free energy from k_{on}/k_{off}

Despite starting from same input files, getting different methods to agree is non-trivial





Next steps

- Get reference calculations to agree
  - Restraint handling
  - Different barostat and PME parameters
  - Missing conformational space (water binding)
- Understand the causes of the discrepancies for the submissions

Conclusions and prospects

- Very different results even when starting from same input files!
  - It might be easier to zero-in on methodological issues.
- Lower the barrier to participate in this type of study. We'd love to hear your feedback!

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Participants

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Reference calculations

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John Chodera (MSKCC)

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Christina Leslie

Kathleen Pickering

Margie Hinonangan-Mendoza