

# Tackling Alchemical Free Energy Calculations with Sire/OpenMM-SOMD

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## Relative Alchemical Free Energy Calculation

Computing **free energies of binding** or **hydration** of small molecules is an important task in computer aided drug design. Using molecular dynamics simulations for computing binding free energies can be prohibitively long due to the **timescale problem**. However, it is possible to use an artificial alchemical transformation that allows to compute **relative free energy differences** making use of thermodynamic cycles. (See Fig.1)

The free energy difference of an alchemical transformation can for example be computed using **thermodynamic integration** or **MBAR**:

$$\Delta F = \int_0^1 \frac{\partial F}{\partial \lambda} d\lambda = \int_0^1 \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle d\lambda$$

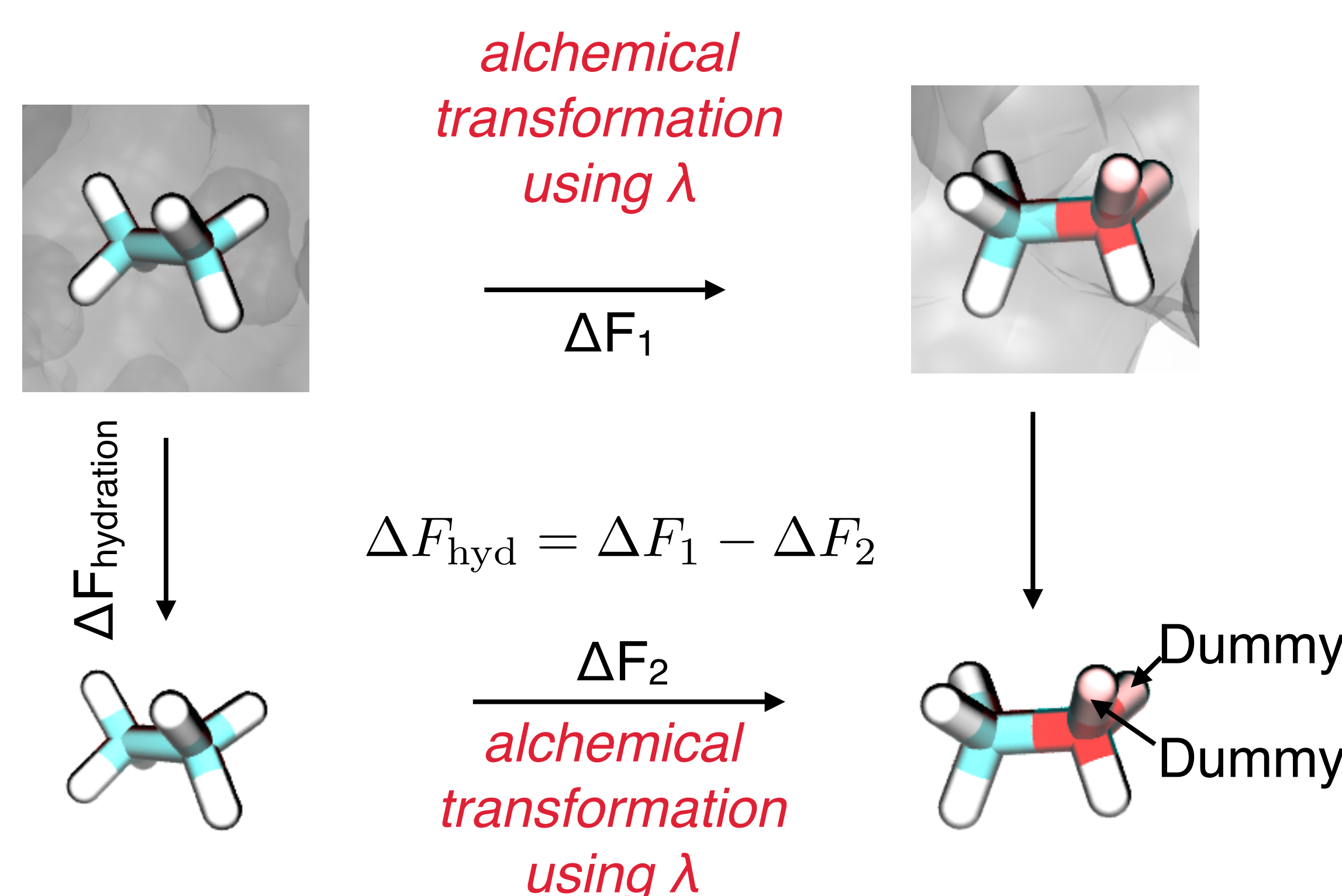


Figure 1: Illustrative thermodynamic cycle for the relative free energy of hydration of ethane and methanol.

## Relative Alchemical Free Energy Calculation

**SOMD** allows to compute relative free energy differences.

**Sire/OpenMM SOMD structure:**

Command line tools

pymbar<sup>1</sup>

somd,  
waterswap,  
analysis..., etc

Python wrapper exposing the C++ API

Sire Molecular Library  
in C++:  
coordinates,  
topology,  
dynamics ...

OpenMM<sup>2</sup>

GPU support

Support for AMBER  
topology files and  
compatibility with  
FESetup<sup>3</sup> to run free  
energy simulations.

**Sire development strategies**



Stable master on github  
with development branch  
and features



Travis CI

Continuous integration using  
Travis, with automated build  
testing of every commit.

**Deployment: [siremol.org](http://siremol.org)**

- Developer documentation
- User documentation



## SOMD

**Example usage:**

somd-freenrg -C **sim.cfg** -t **SYSTEM.top** -c **SYSTEM.crd** -m **MORPH.pert** -p CUDA

|                      |   |                                       |           |  |          |
|----------------------|---|---------------------------------------|-----------|--|----------|
| Name of the Sire app | Configuration file:<br>set integrator,<br>thermostat<br>barostat,<br>etc. | Simulation<br>topology:<br>e.g. AMBER | Positions | Defines the<br>morphing<br>between<br>structures | Platform |
|----------------------|---|---------------------------------------|-----------|--|----------|

## HSP90 target from D3R Grand Challenge 2015

**Goal: automated pipeline**

input files

FESetup<sup>3</sup>

SOMD

MBAR

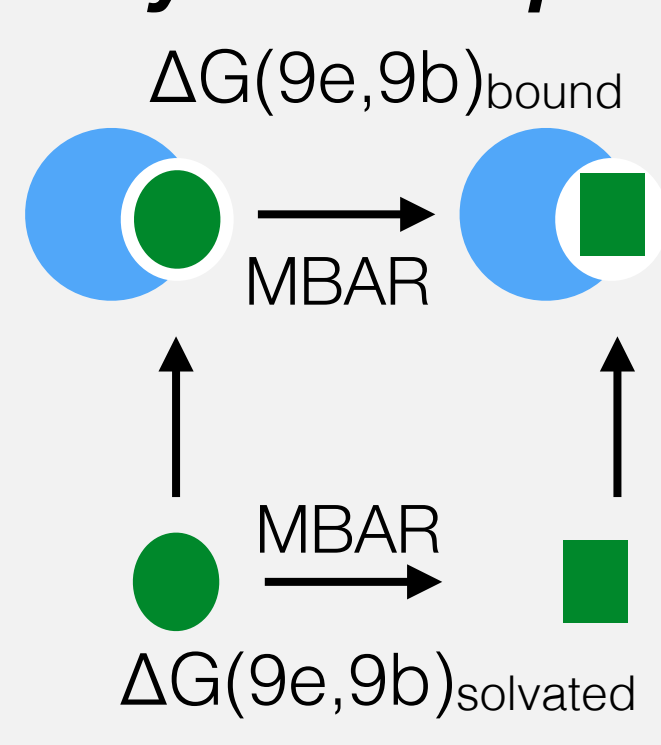
Network X

### Experimental

| ID | IC50 [ $\mu$ M] |
|----|-----------------|
| 9b | 2.32            |
| 9c | 0.22            |
| 9d | 34.9            |
| 9e | 0.054           |
| 9f | 2.53            |

taken from<sup>4</sup>

### Cycle example



### Simulation protocol

- NPT simulation, with 4 fs time step at 298K using hydrogen mass repartitioning
- Single topology.
- 17 equally spaced  $\lambda$  windows.
- 2 independent 8 ns production run.
- MBAR analysis after drawing uncorrelated data from simulated dataset using the time series analysis module in pymbar<sup>1</sup>.
- PDB ID: 3OWD taken from<sup>4</sup>.

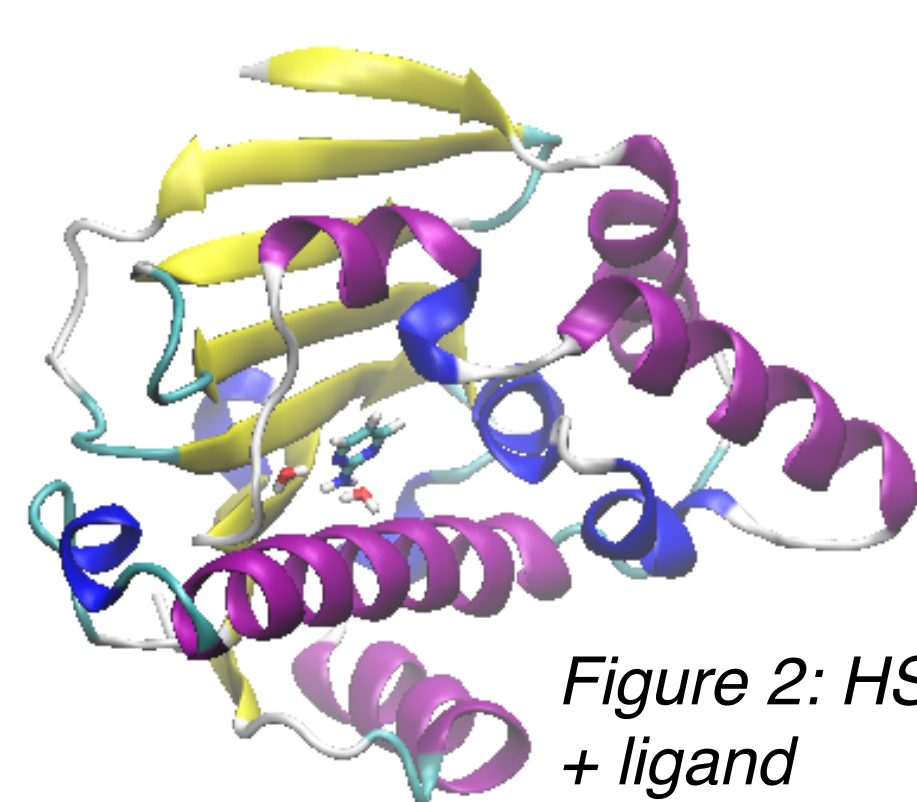


Figure 2: HSP90 + ligand

- HSP90 is a chaperone protein
- Part of many oncological drug programs
- Difficult drug target, due to:
  - a) open and closed conformations
  - b) water mediate ligand binding

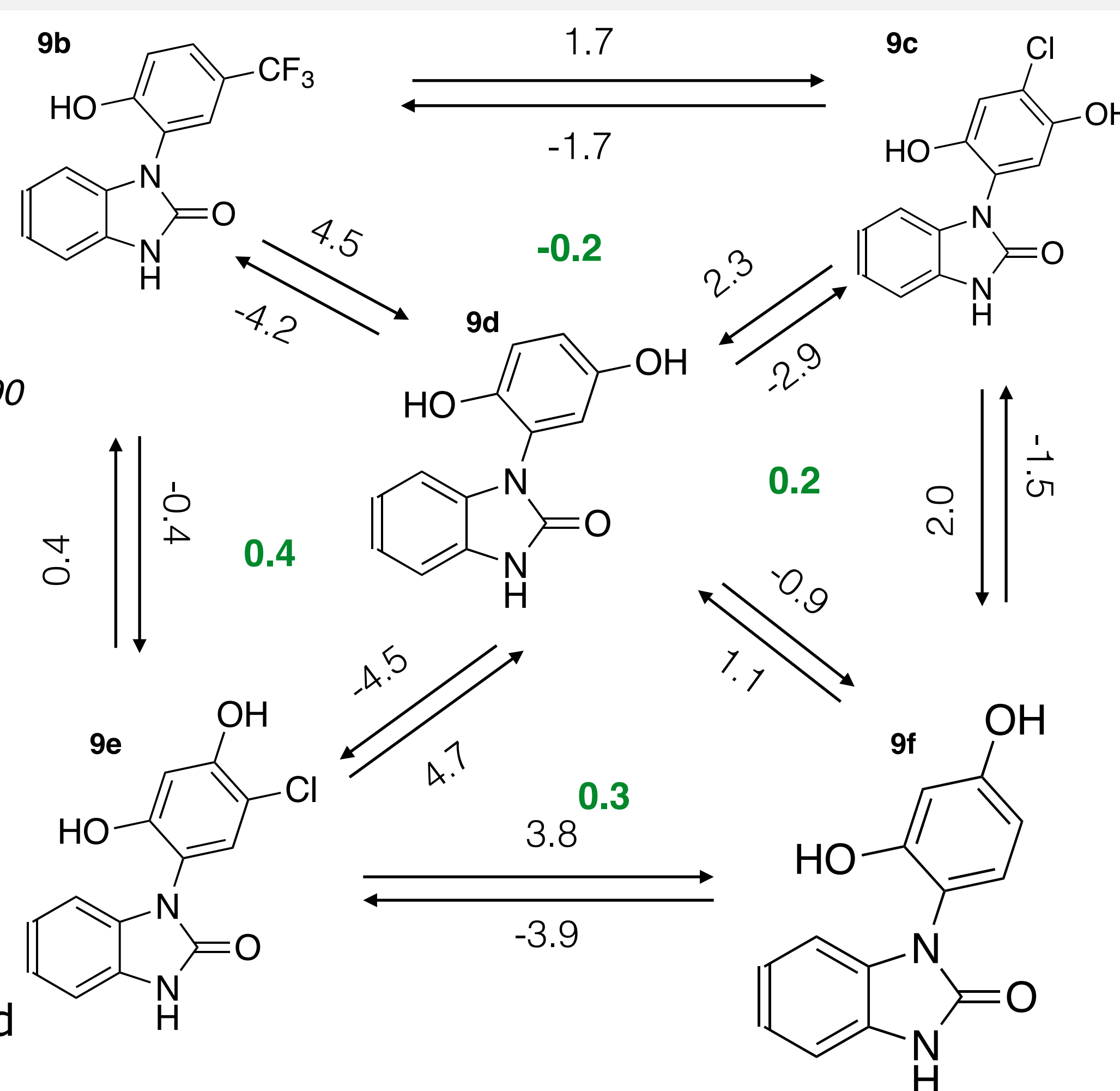


Figure 3: Perturbation network of HSP90 ligands

**Perturbation network (Fig. 3)** is constructed over averaged simulations with relative binding free energies shown in [kcal/mol]. Relative free energies with respect to a target structure are computed based on **sum over all possible paths between** two structures in the networks. Errors are given by the standard deviation.

$$\text{Experimental: } \Delta \Delta G_{A,B} = k_B T \ln \left( \frac{\text{IC}_{50_B}}{\text{IC}_{50_A}} \right)$$

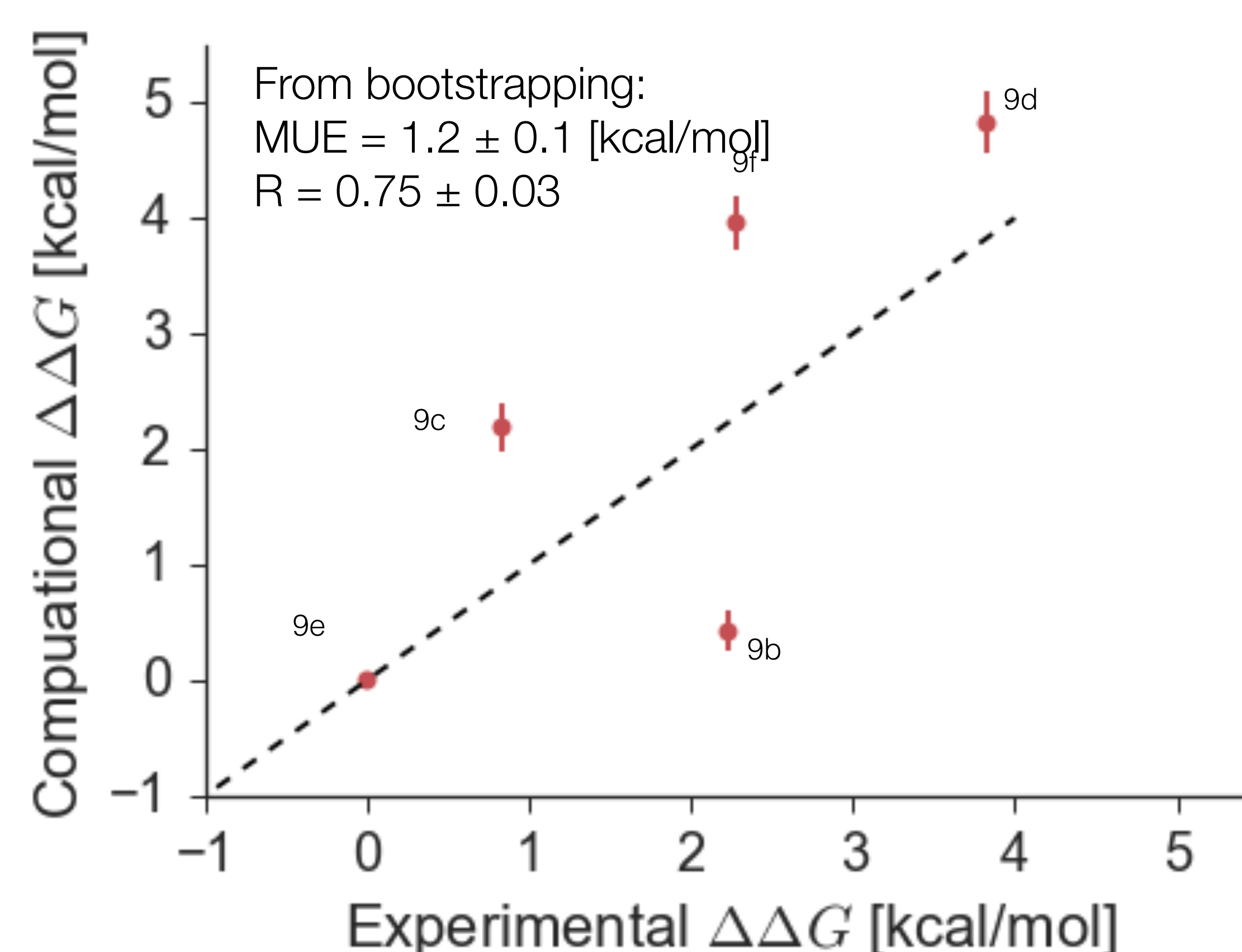


Figure 4: Comparison of experimental and computed free energy values.

## HSP90 Example Dataset

### References:

[1] Shirts, Michael R., and John D. Chodera. *JCP* (2008): 124105.

[2] Eastman, Peter, et al. *JCTC* (2012): 461-469.

[3] Löffler, Hannes, et al. *J. Chem. Inf. Model.*, 2015, 55 (12), pp 2485-2490

[4] Bioorg Med Chem Lett 20 (2010) 7503-7506

[5] A. Mey et al, *Bioorg. Med. Chem.*, in press (2016)