



# **Current limits of binding free energy calculations**

**Julien Michel**

**EaStCHEM School of Chemistry,  
University of Edinburgh**

**Workshop on Free Energy Methods in Drug Design, Boston  
– 17/05/16**



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# Acknowledgments



## Group members

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Lisa Patrick

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George Gerogiokas

Kevin Pinto-Gill

## Sponsors



European Research Council  
Established by the European Commission



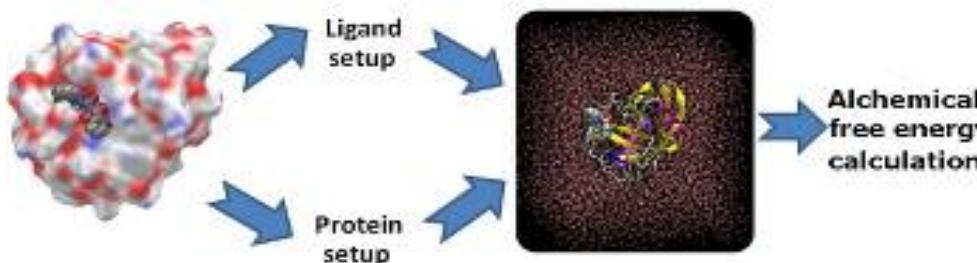
**UCB** Inspired by patients.  
Driven by science.





# Our alchemical free energy calculations workflow

- FESetup: workflow for automated setup



<http://www.hecbiosim.ac.uk/fesetup>

Sire

AMBER

Gromacs

CHARMM

Loeffler, Michel &  
Woods *JCIM 2015*

- SOMD: alchemical free energy calculation engine

Woods

**Sire:** MC &  
Free Energy

Eastman  
et al.

**OpenMM:**  
MD & GPUs

**Sire/OpenMM  
(SOMD)**

<http://www.siremol.org>



Gaetano Calabro



Antonia Mey

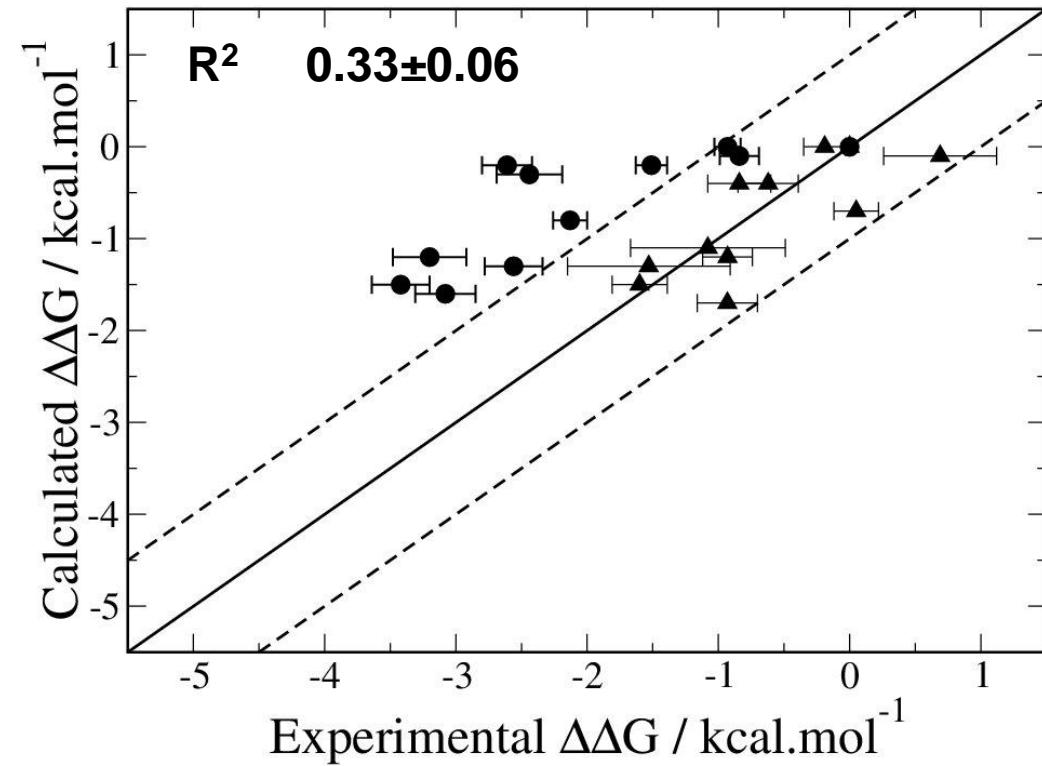
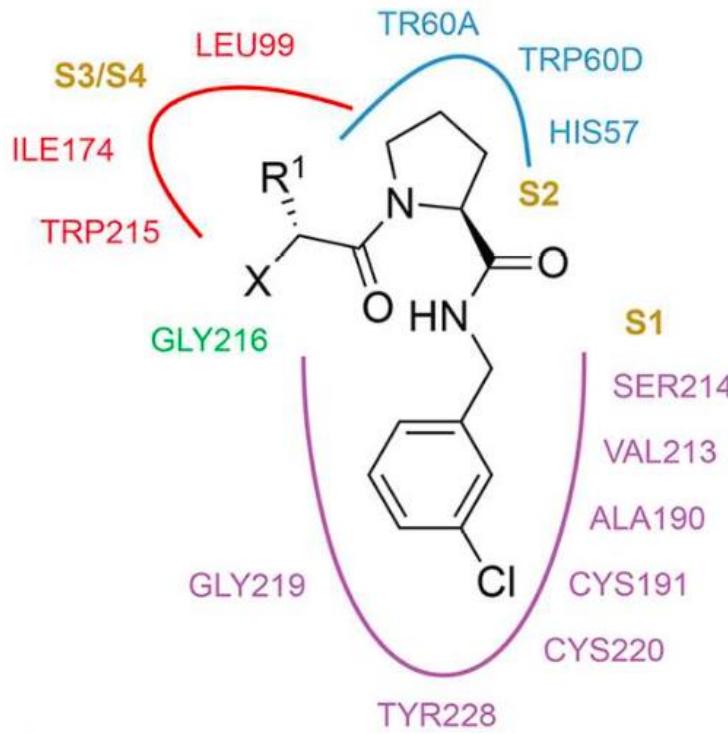
- Automate as much as possible...

- Consistency & reproducibility
- Scalability

- ...but allow troubleshooting

- Log everything
- Enable manual interventions

# Thrombin: docking is the null model of molecular simulations

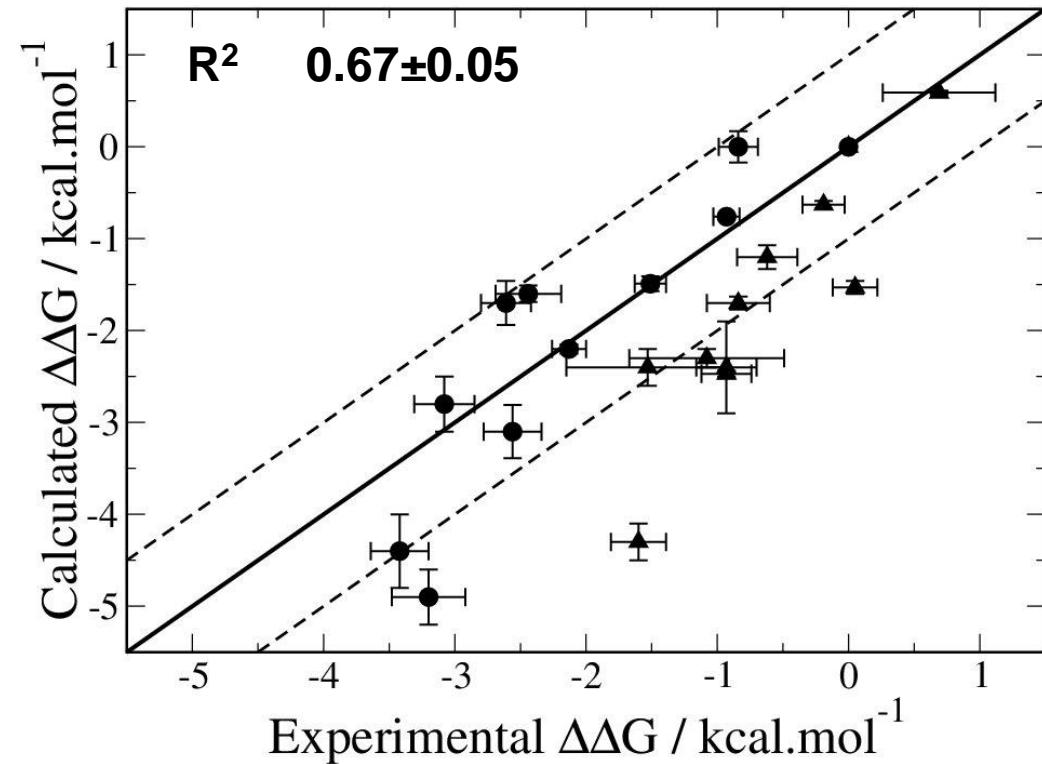
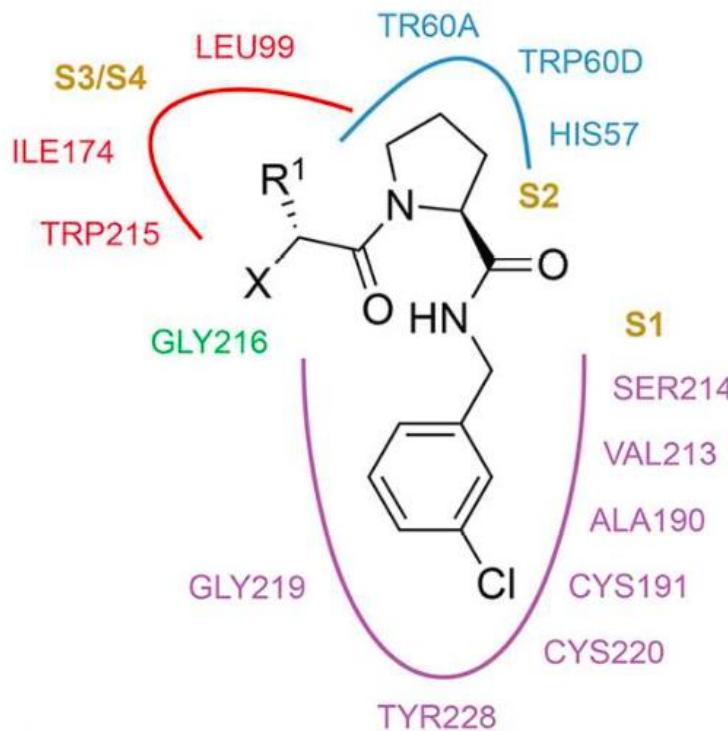


- Binding energies from VINA

22 congeneric thrombin ligands

Baum et al. *J. Mol. Biol.* 2010 , 397, 1042-1054

# Thrombin: free energy methods are more accurate than docking...



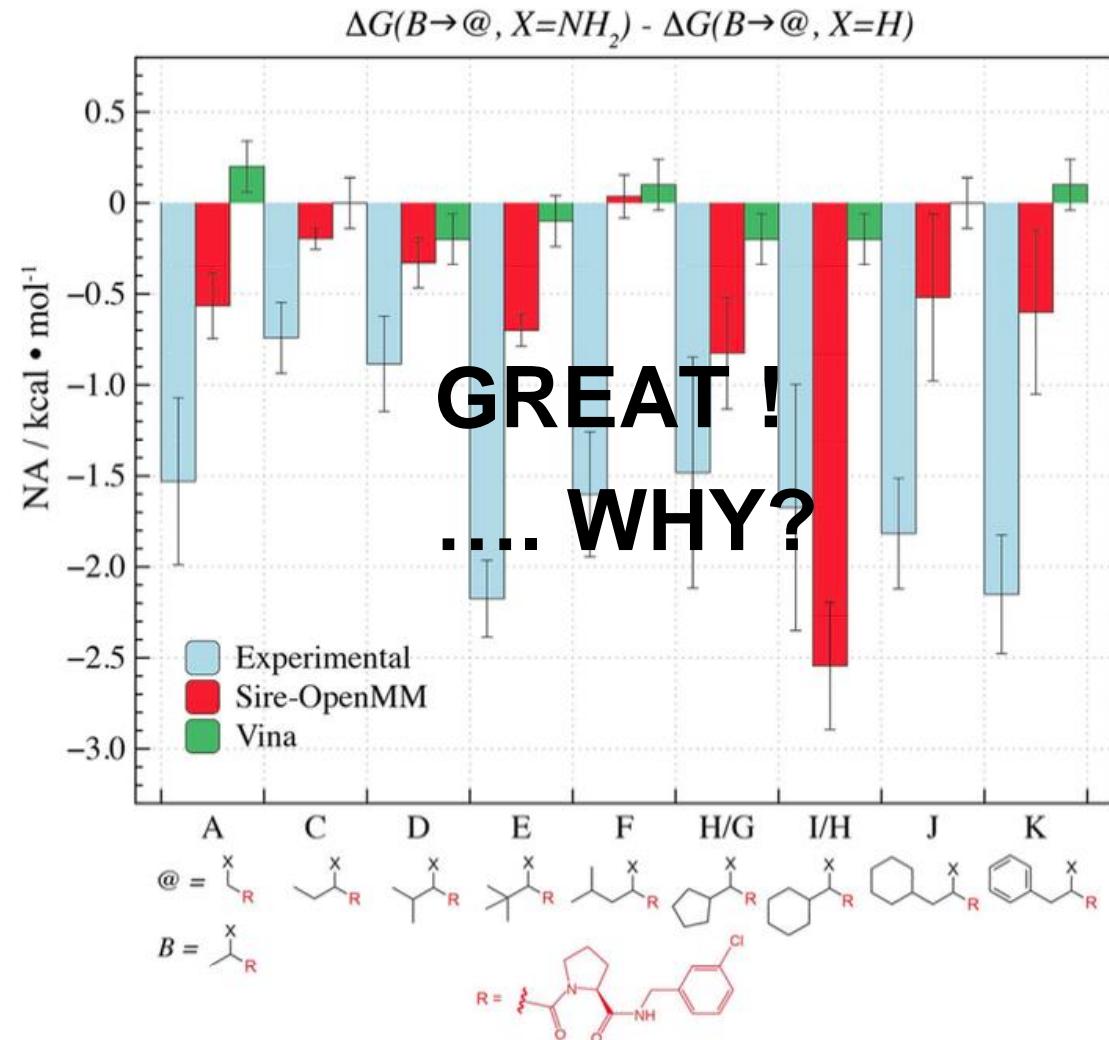
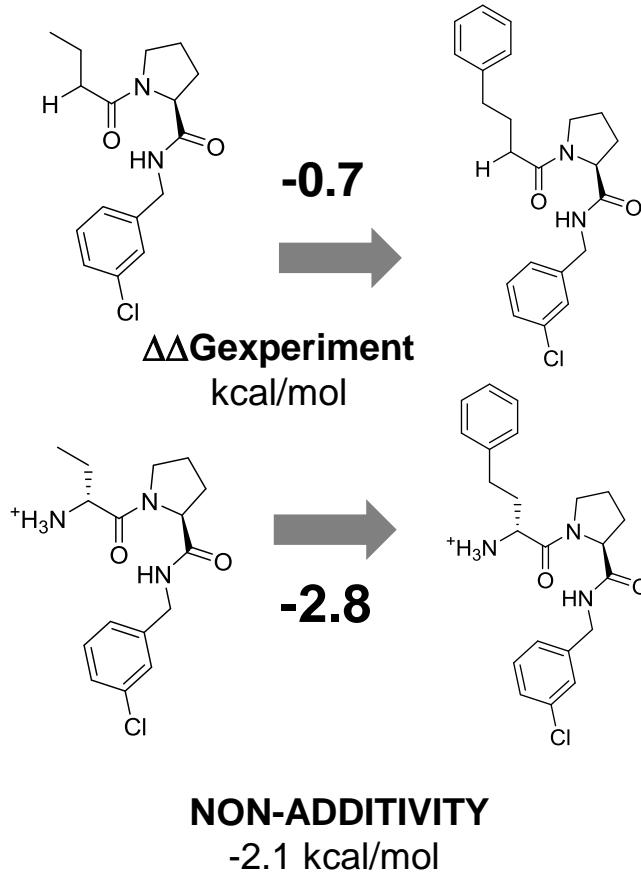
Gaetano Calabro

Calabro et al.  
J. Phys. Chem. B  
Article ASAP

- Binding energies from SOMD
  - GAFF/AM1-BCC + Amber99sb + TIP3P
  - Thermodynamic integration

22 congeneric thrombin ligands

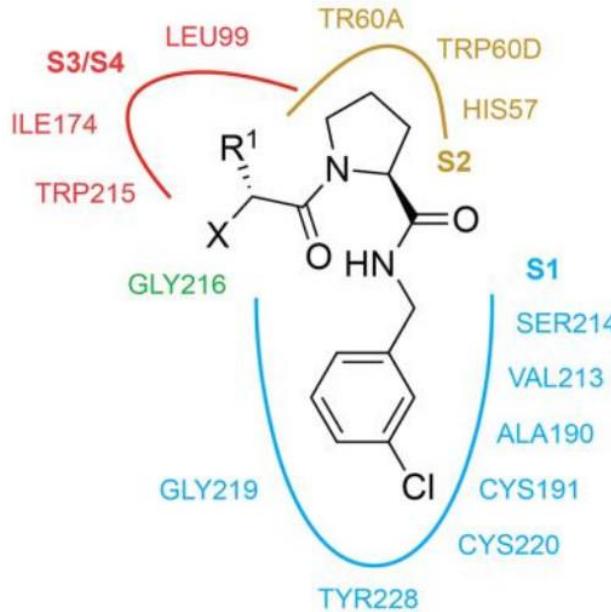
... and also capture non-additivity of structure-activity relationships\*



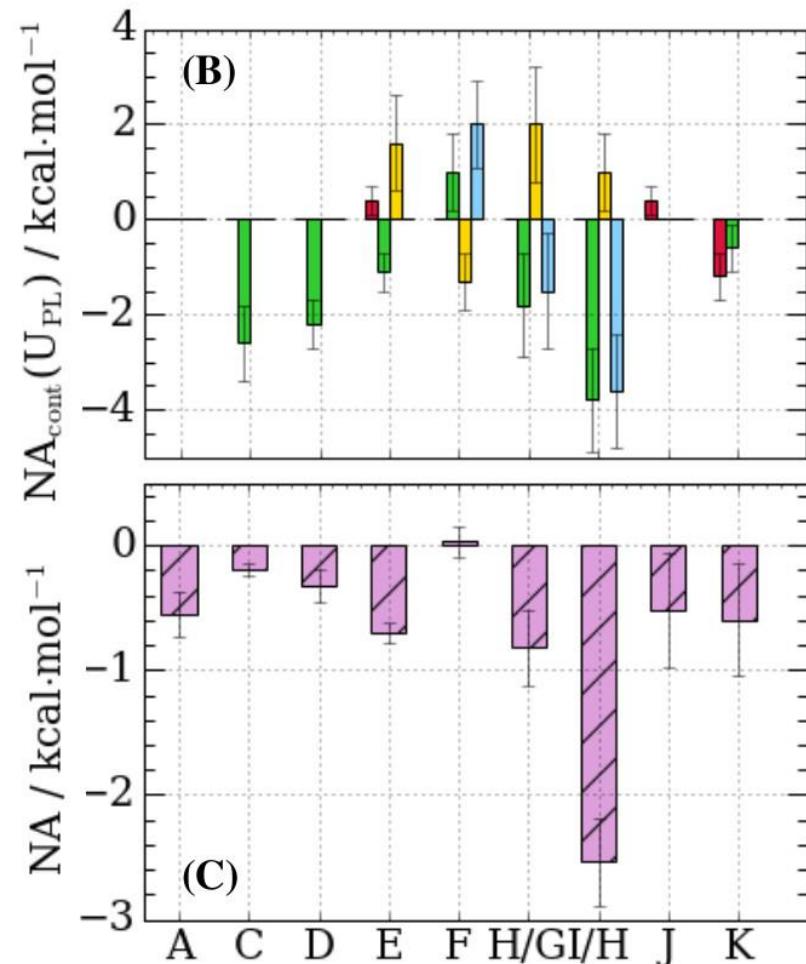
\* But not systematically  
and effect weaker than  
in experimental data

# The basis for positive coupling between X & R<sup>1</sup>

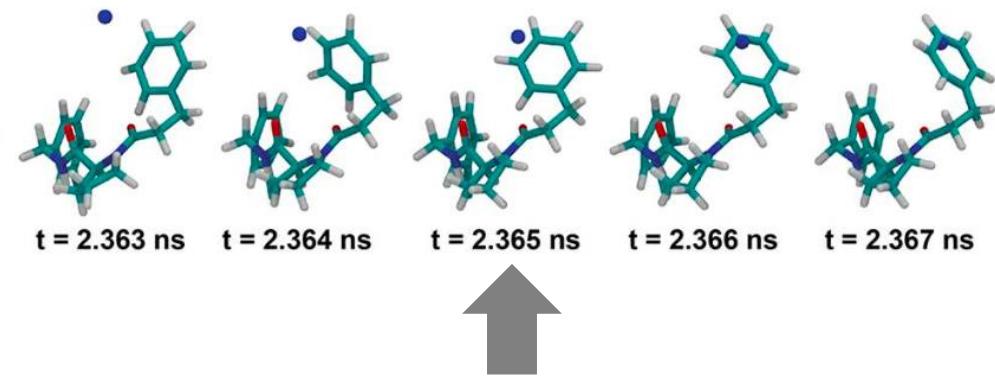
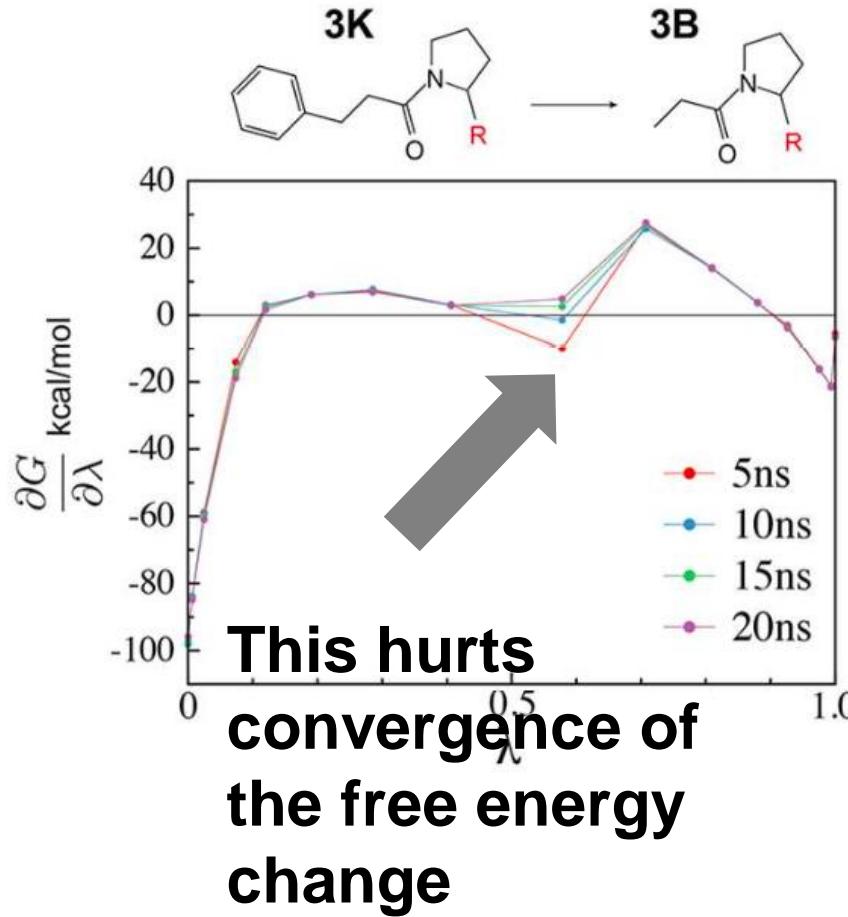
(A)



- Enhanced interactions of X with Gly216 is one factor...
- ... but not systematically, and changes in other interactions are also detected across the entire binding site.



# Technical point: your softcore can kill you



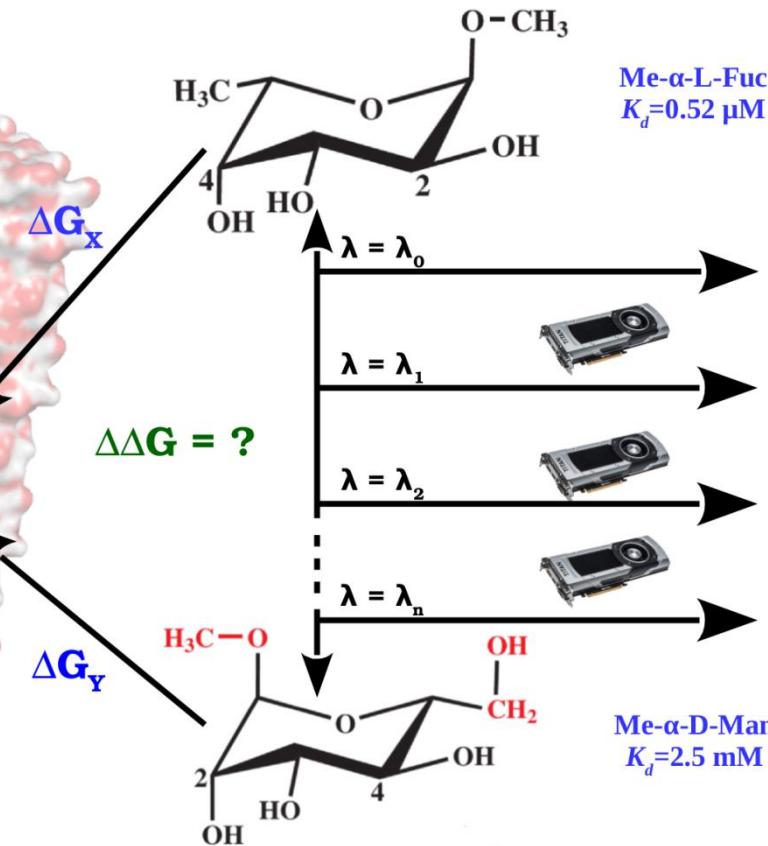
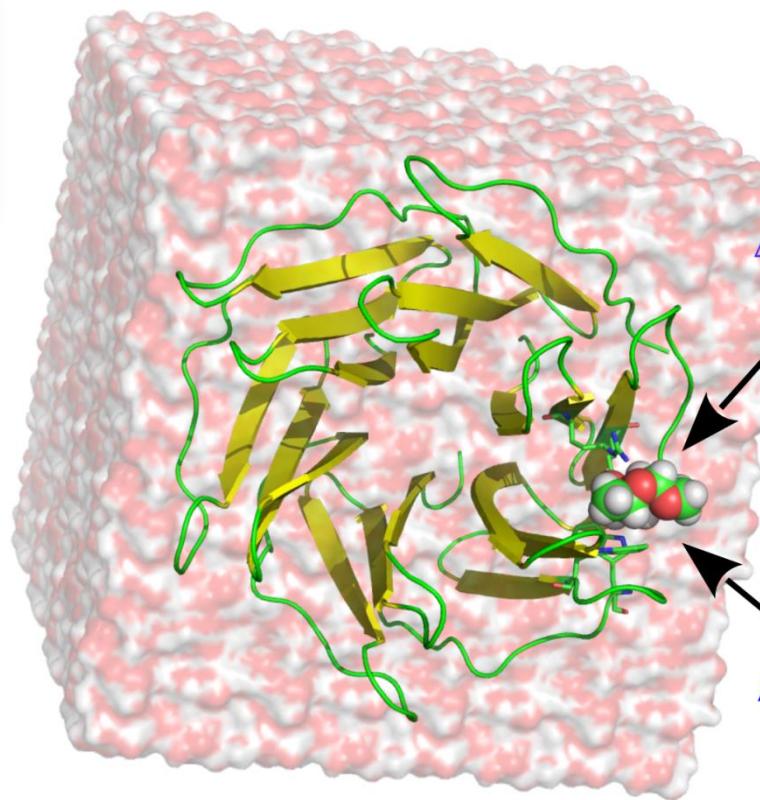
**This happens because we did simultaneous softening of Coulombic and LJ terms**

- **Solutions:** Adjust default soft-core parameters or perturb non-bonded terms sequentially

# Scoring monosaccharides binding to RSL lectin

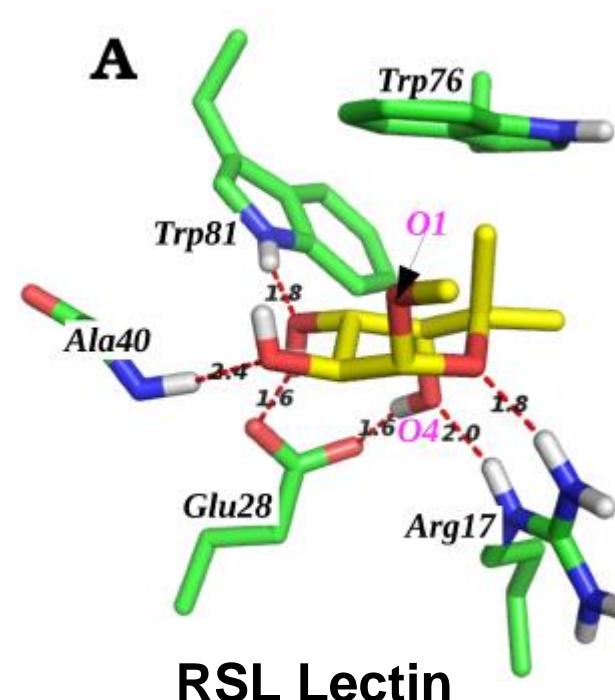
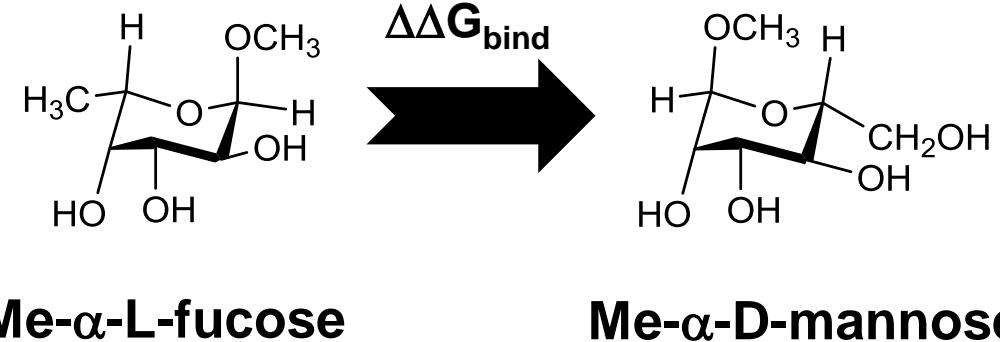


Sushil Kumar  
Mishra

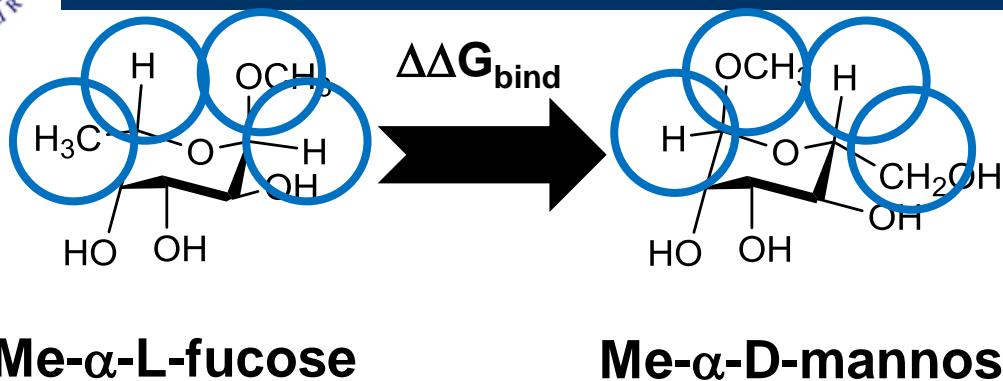


- Dataset of 9 monosaccharides ligands of RSL Lectin
- Evaluated with 12 scoring methodologies

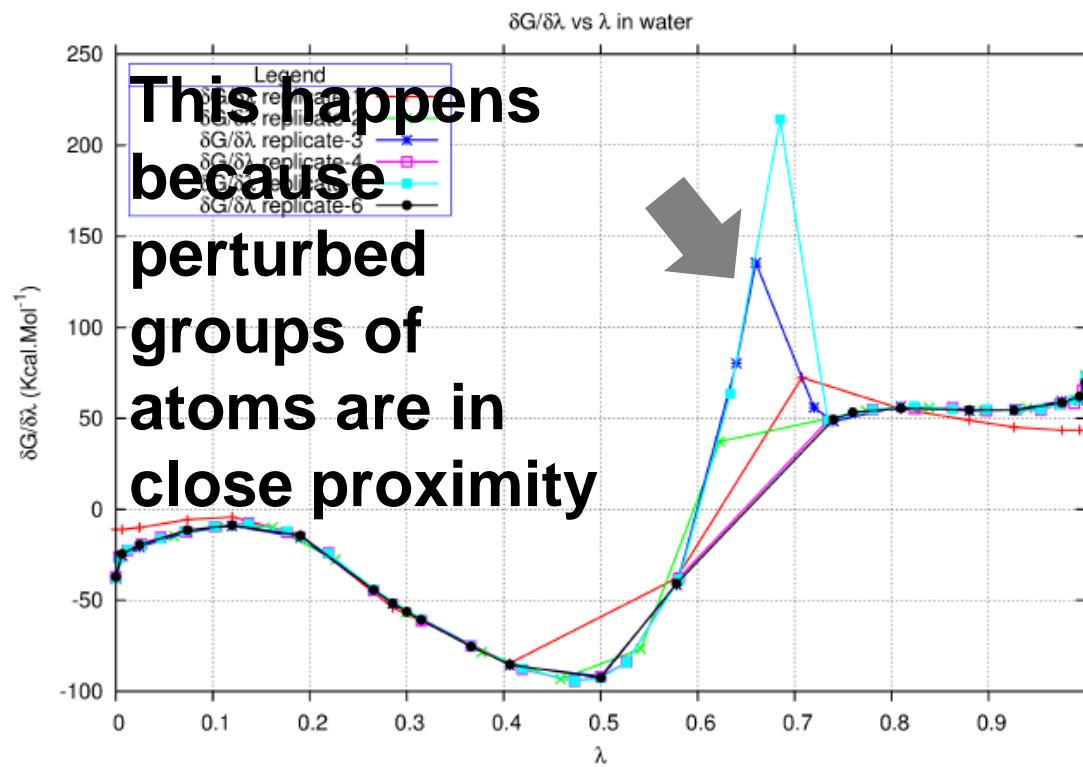
# Return of the killer softcore



# The direct path gives noisy gradients

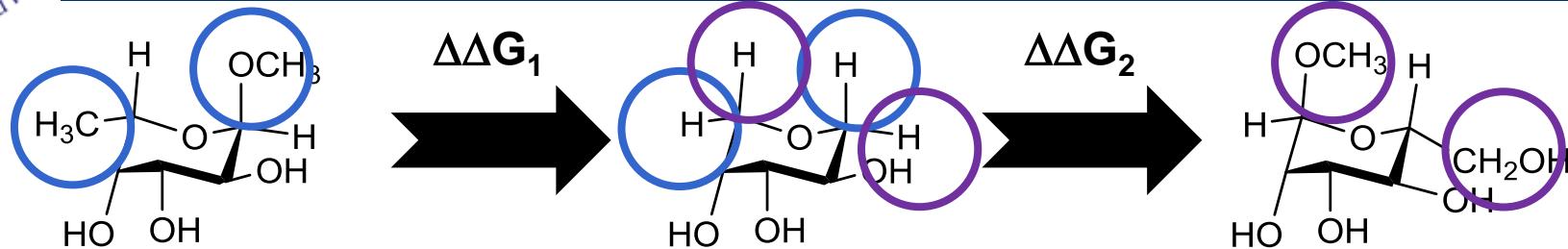


- Simultaneous softening of Coulombic and LJ terms

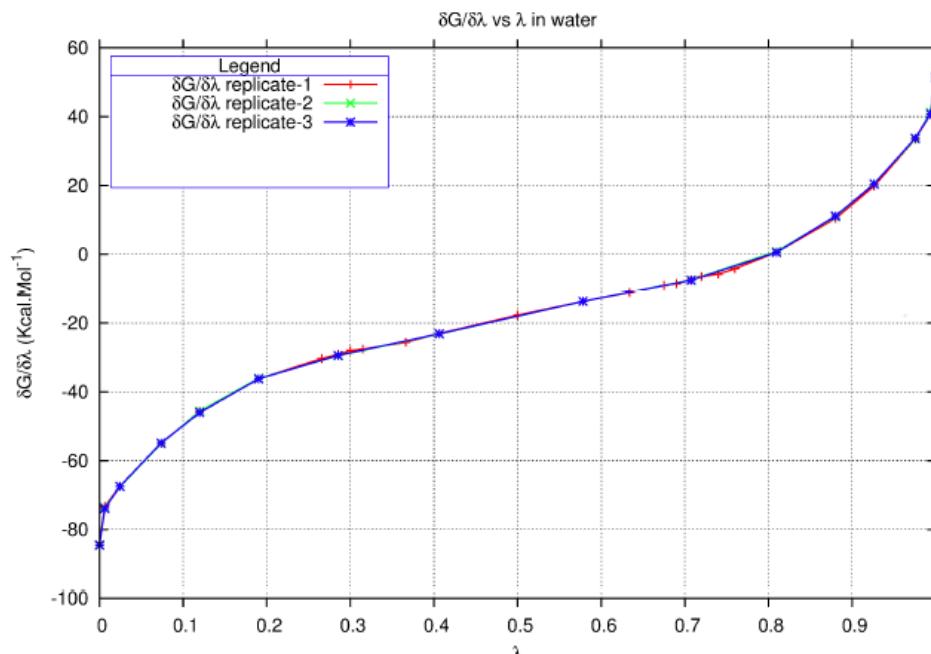


- Simpler setup
- Fewer windows
- High uncertainties

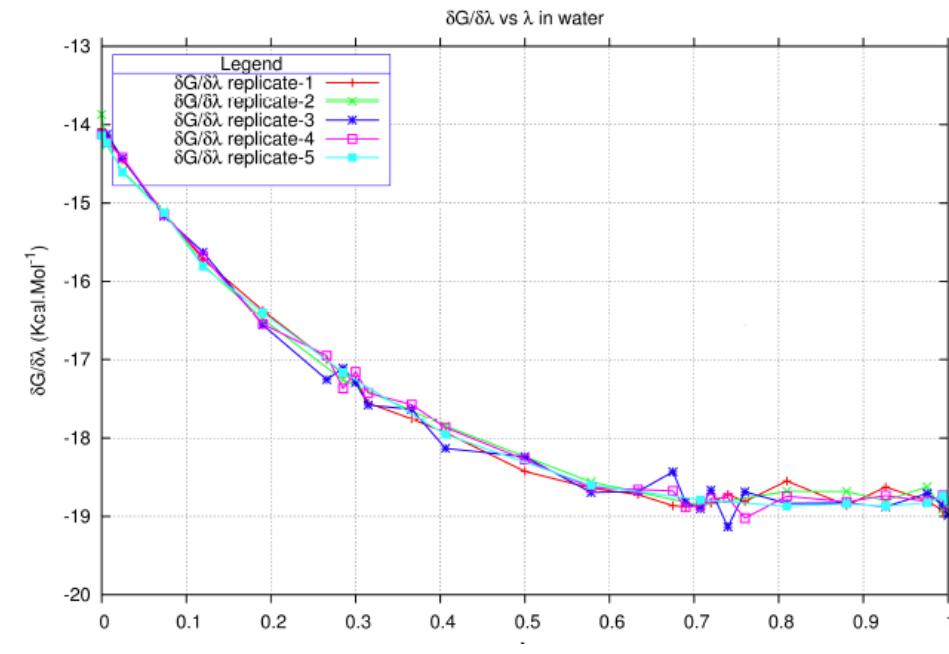
# A two-steps path gives smooth gradients



**Me- $\alpha$ -L-fucose**



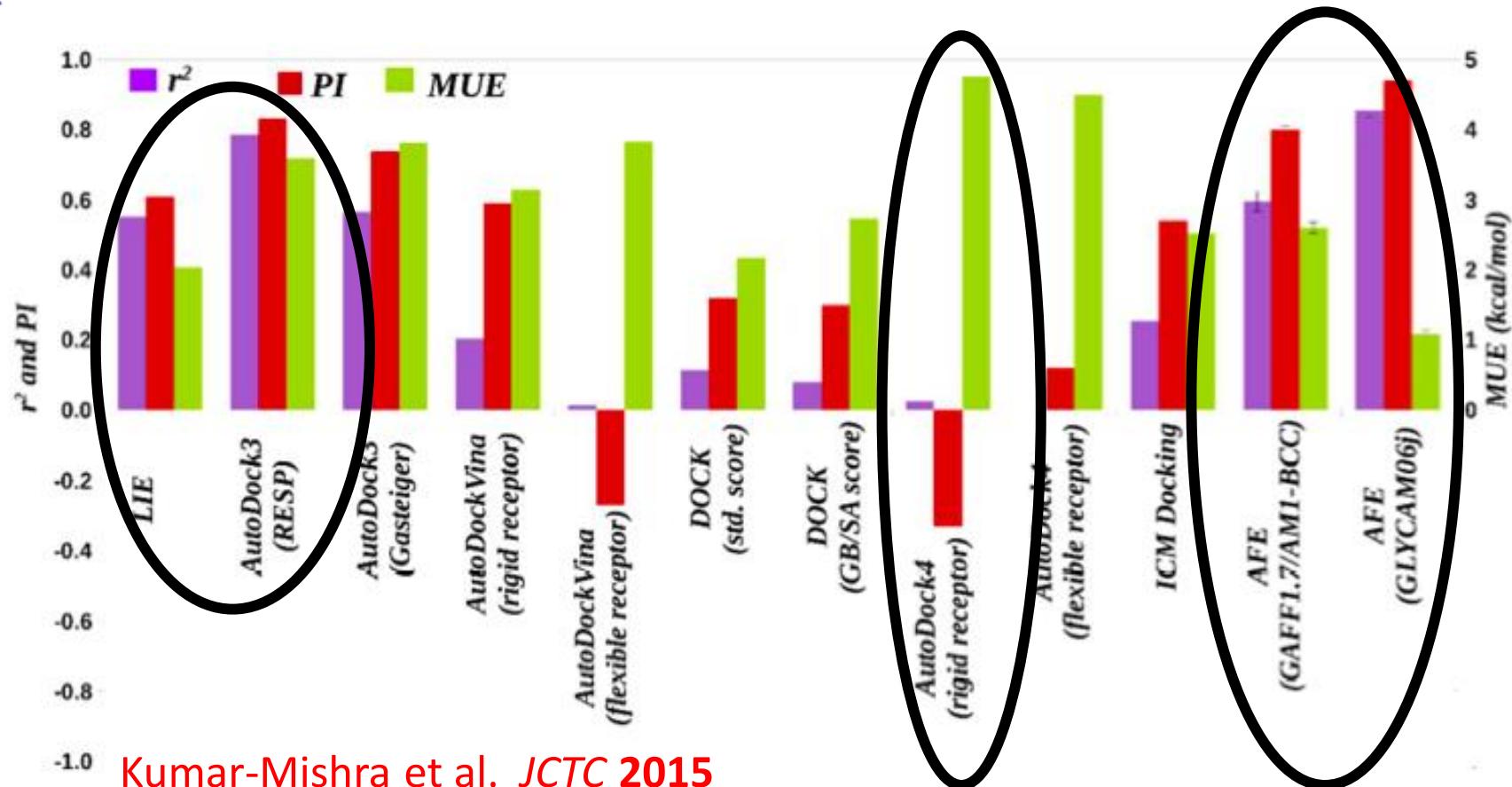
**Intermediate**



- More complex setup

- Less uncertainties

# RSL lectin/monosaccharides: dataset metrics

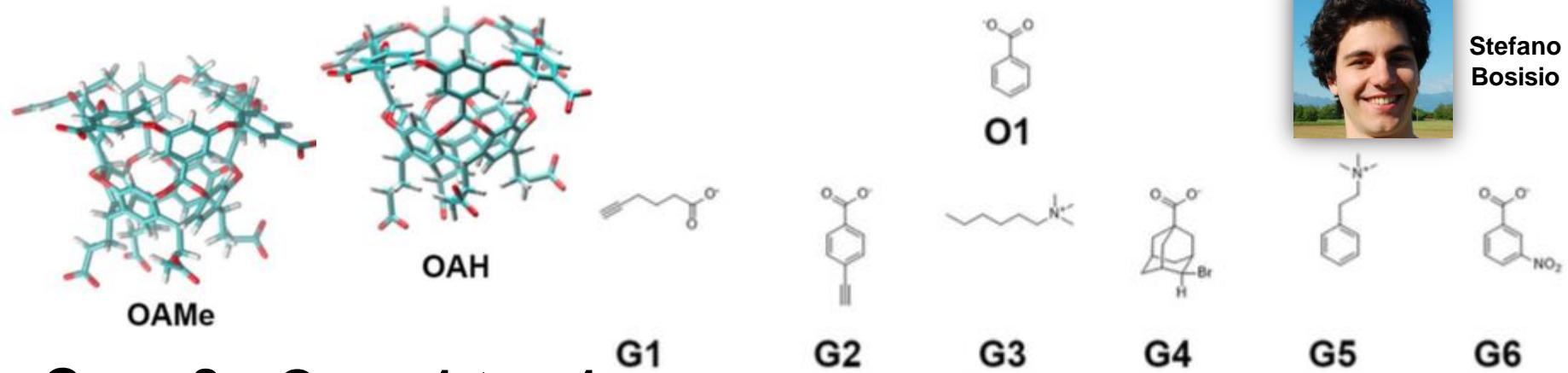


Kumar-Mishra et al. *JCTC* 2015

- Free energy protocol performs best but only with a specialized carbohydrate force field (GLYCAM06j)
- General force field (GAFF1.7) comparable to best alternative simulation methods (LIE) or docking protocols (Autodock 3)



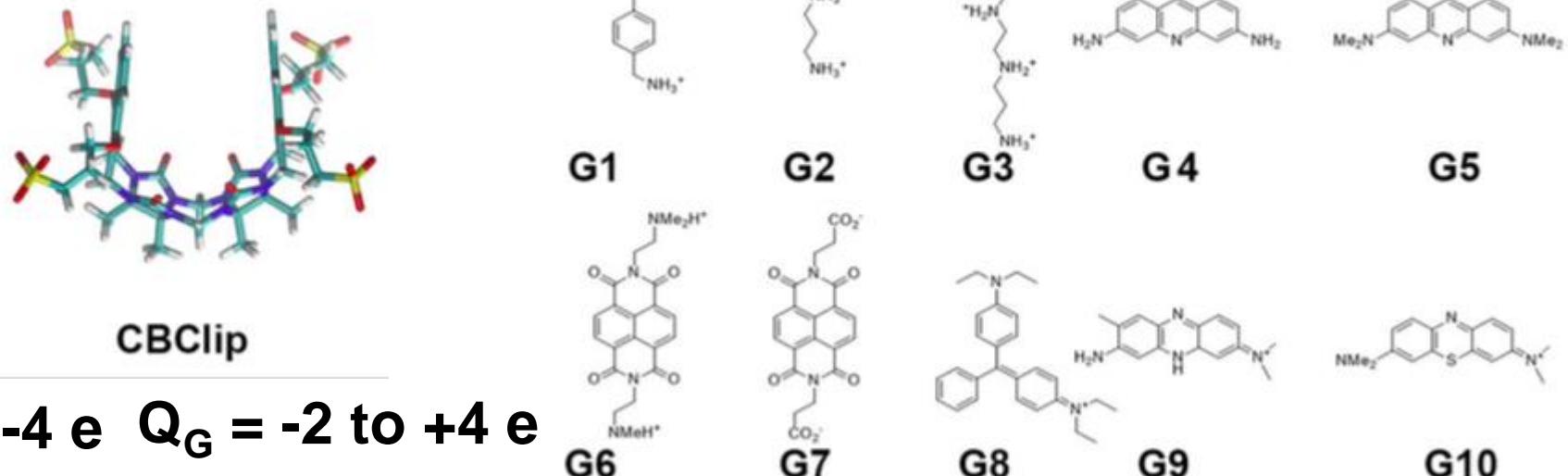
# SAMPL5 blind predictions: host/guest systems



$$Q_H = -8 \text{ e} \quad Q_G = -1 \text{ to } +1 \text{ e}$$



Stefano  
Bosisio

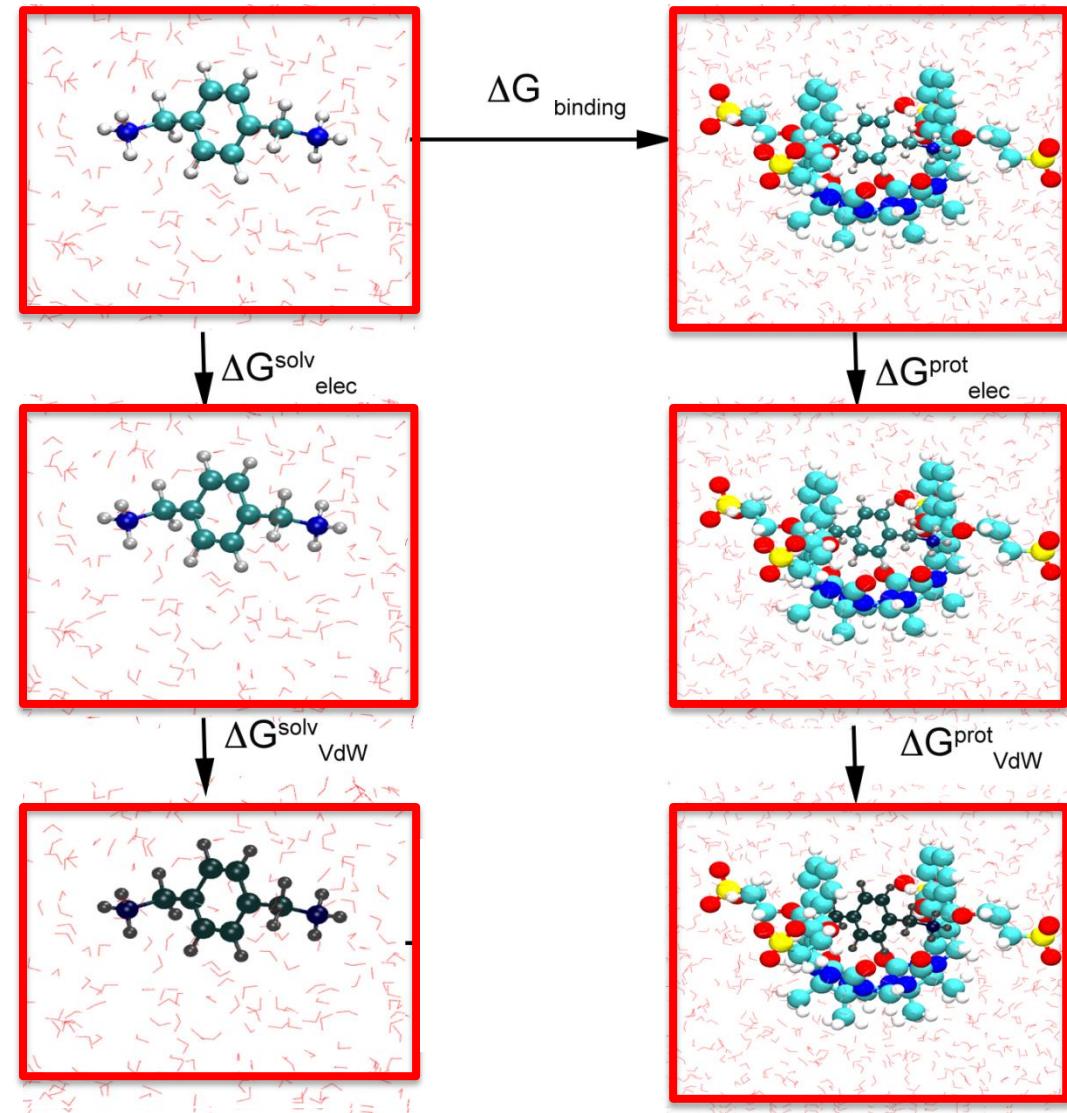


$$Q_H = -4 \text{ e} \quad Q_G = -2 \text{ to } +4 \text{ e}$$

# SAMPL5 host/guest: protocol A

- A) Absolute binding free energy via double decoupling
- Host/guest restraints
- Raw SOMD free energies

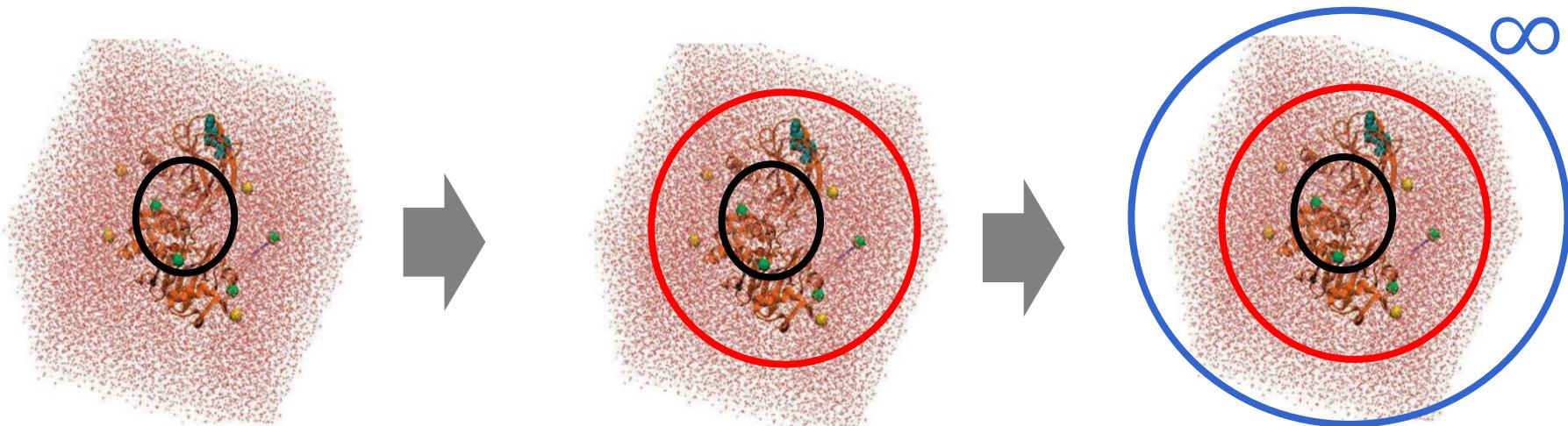
$$\Delta G_{bind} = (\Delta G_{elec}^{wat} + \Delta G_{VdW}^{wat}) - (\Delta G_{elec}^{host} + \Delta G_{VdW}^{host})$$



# SAMPL5 host/guest: protocol B

- B) Protocol A + Zwanzig style long-range correction for missing dispersion interactions

Shirts et al. J. Phys. Chem. B, Vol. 111, No. 45, 2007



$U_{LJ,sim}$

$U_{LJ,LRC-num}$

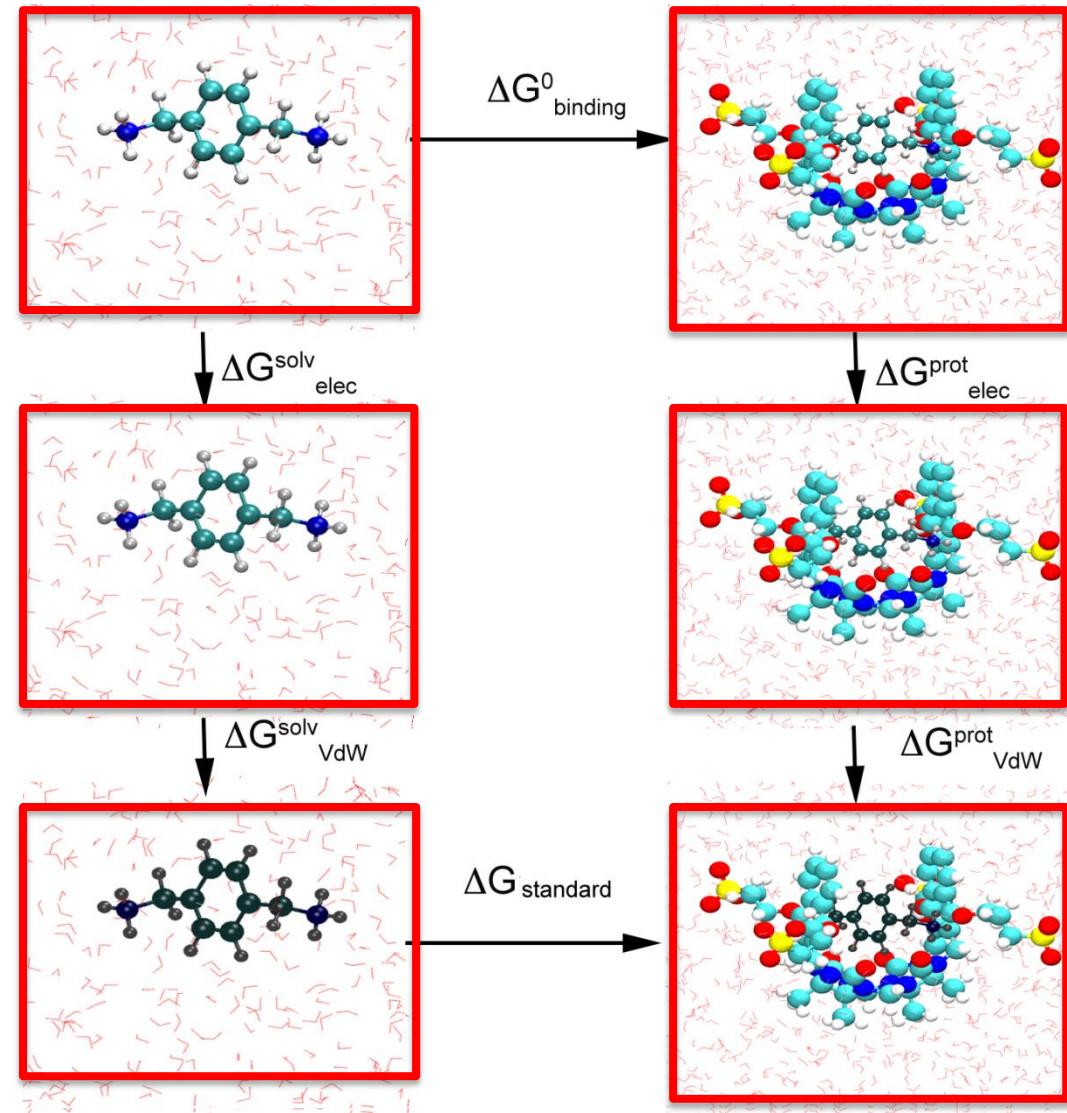
$U_{LJ,LRC-ana}$

$$\Delta G_{LJ,LRC} = -\beta^{-1} \ln \left\langle e^{-\beta(U_{LJ,long}(r) - U_{LJ,sim}(r))} \right\rangle_{sim} + \Delta G_{LJ,ANA}$$

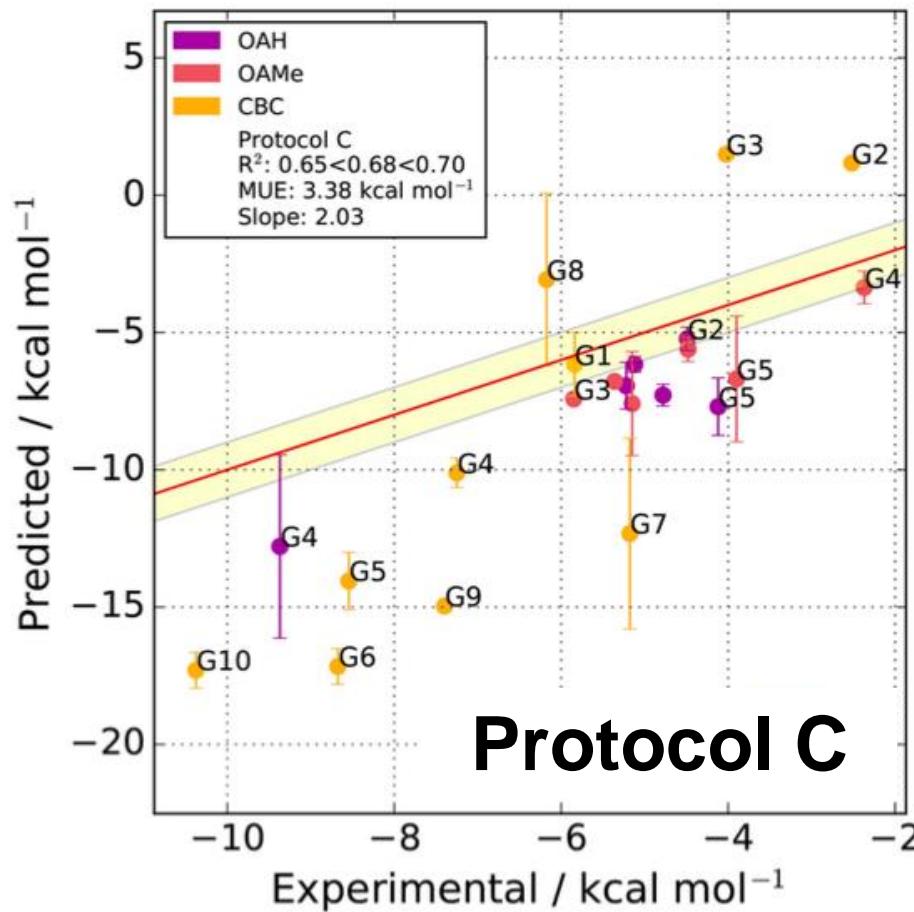
# SAMPL5 host/guest: protocol C

- A) B + standard state correction

$$\begin{aligned}\Delta G_{bind}^0 = & (\Delta G_{elec}^{wat} + \Delta G_{VdW}^{wat}) \\ & - (\Delta G_{elec}^{host} + \Delta G_{VdW}^{host}) \\ & + \Delta G_{standard}\end{aligned}$$

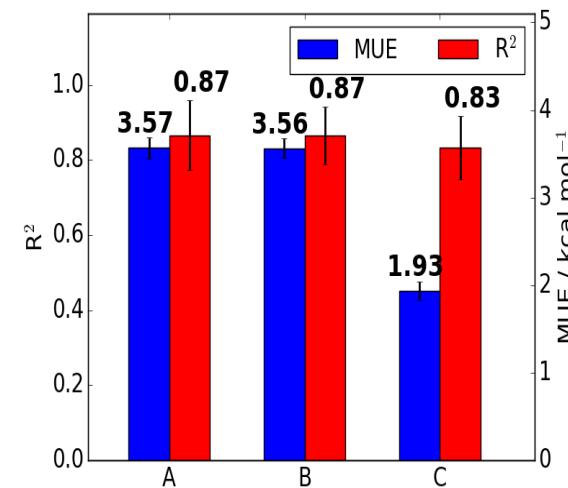


# SAMPL5 host/guest: blind prediction results

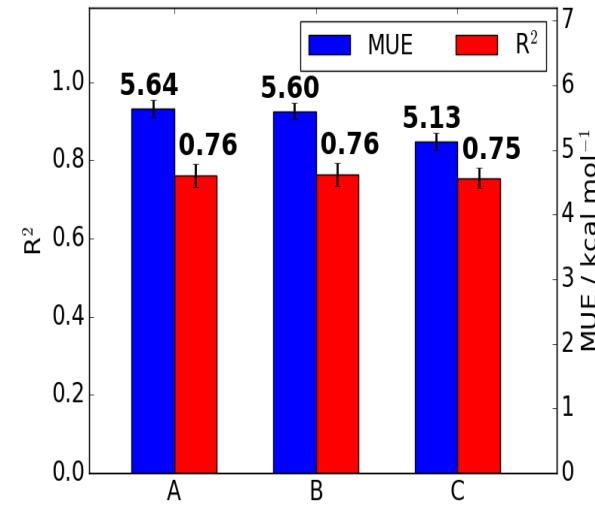


- LJ long-range correction term has negligible effect
- Standard state correction helps for MUE
- Among **top-ranked entries for  $R^2$ , but not MUE**

## OAH & OAME

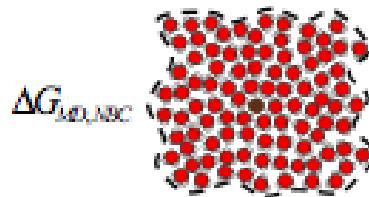


## CBC

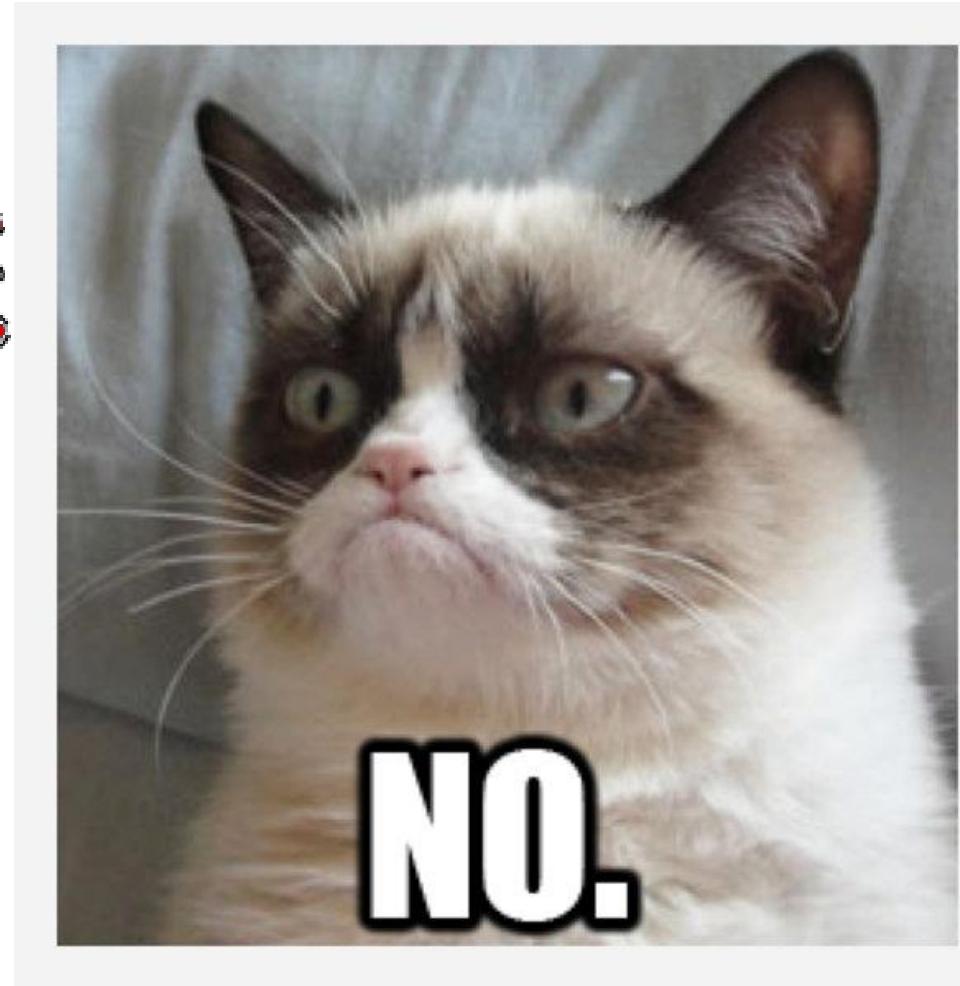


# SAMPL5 host/guest: protocol D

- D) C + finite-size electrostatics correction\*

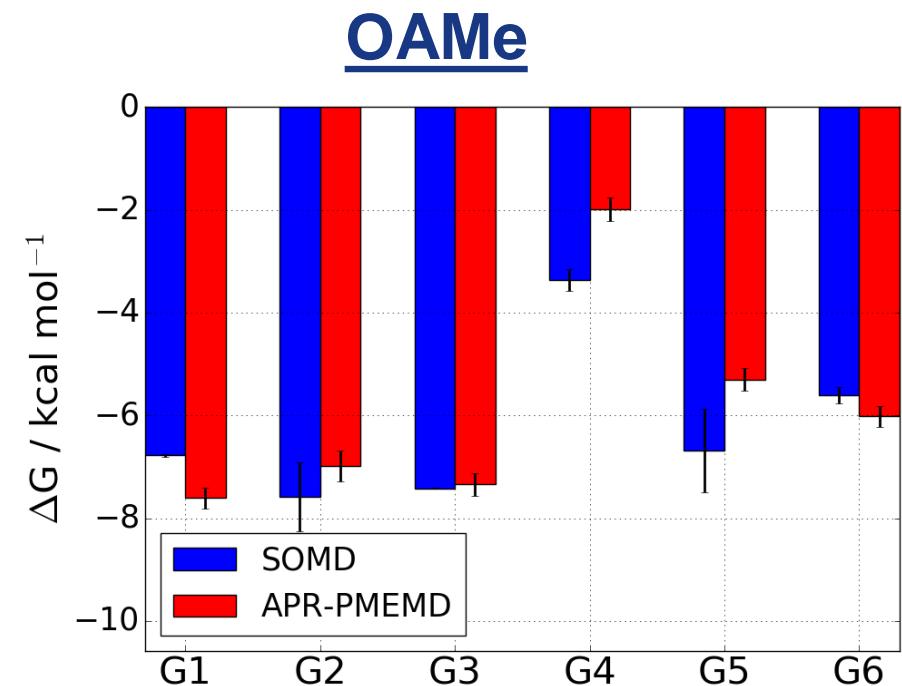
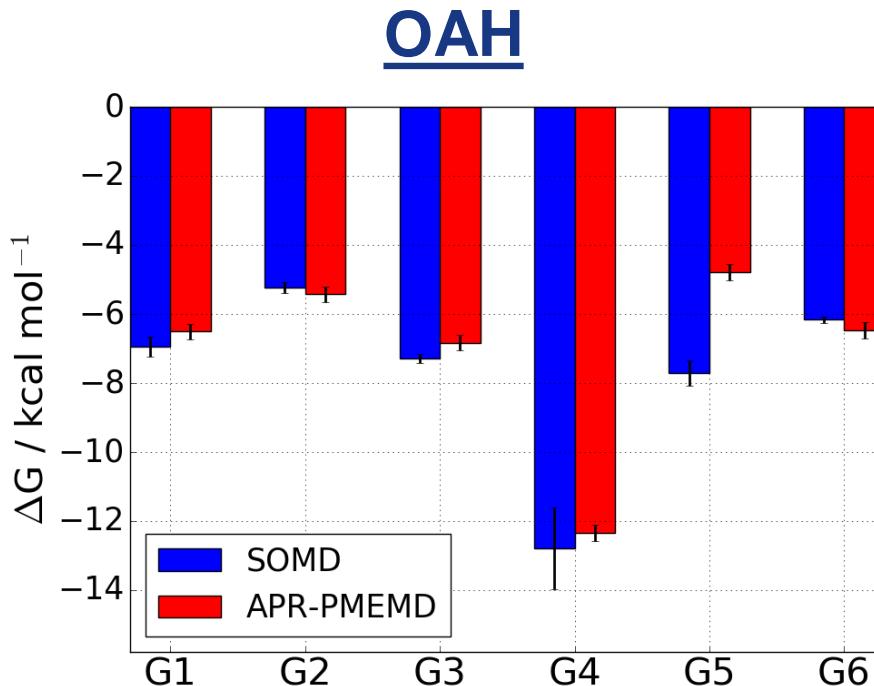


\* atom-based Barker-Watts reaction-field conditions



# SAMPL5 host/guest comparison with Yin et al.

- APR protocol from Mike Gilson's lab
  - PMF style pulling + standard state correction, PMEMD



- $R^2 = 0.80 \pm 0.07$
- $MUD = 0.82 \pm 0.10 \text{ kcal/mol}$



# D3R blind predictions: HSP90 ligands

- Blind predictions on dataset of 180 Hsp90 ligands
  - Data donated by Abbvie, managed by D3R.



Jordi  
Juarez-Jimenez

- Binding modes predictions for 6 ligands

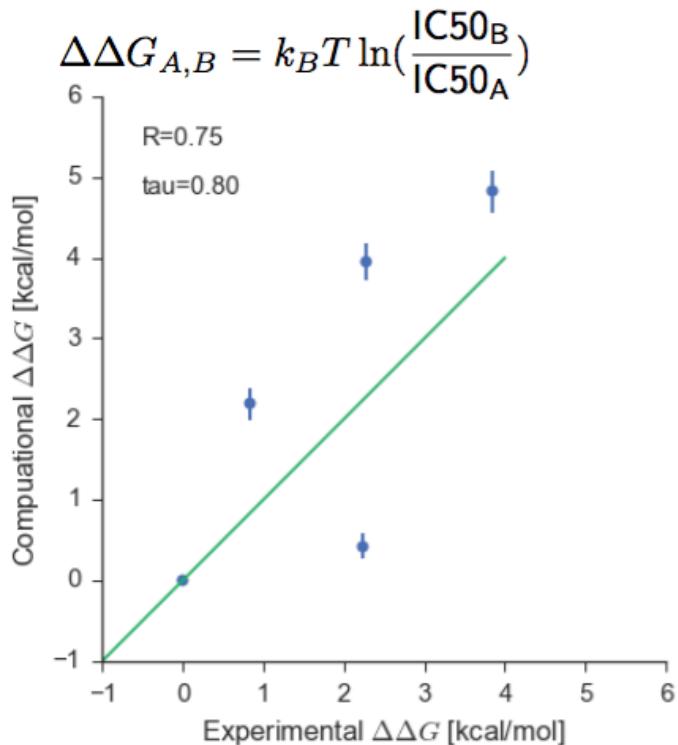
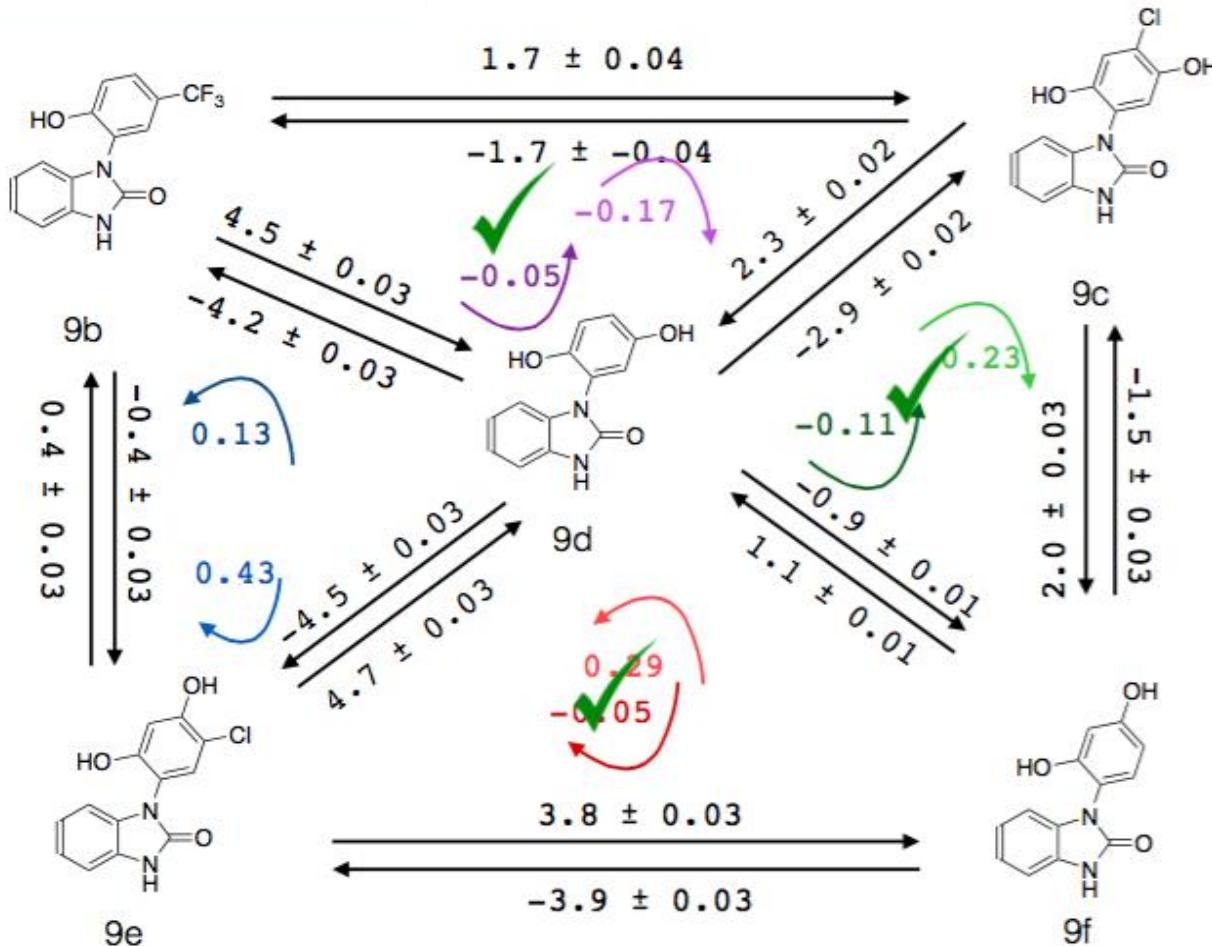
- Scoring dataset of 180 ligands

- Free energy scoring for three subsets



Antonia Mey

# HSP90: Preliminary retrospective evaluation

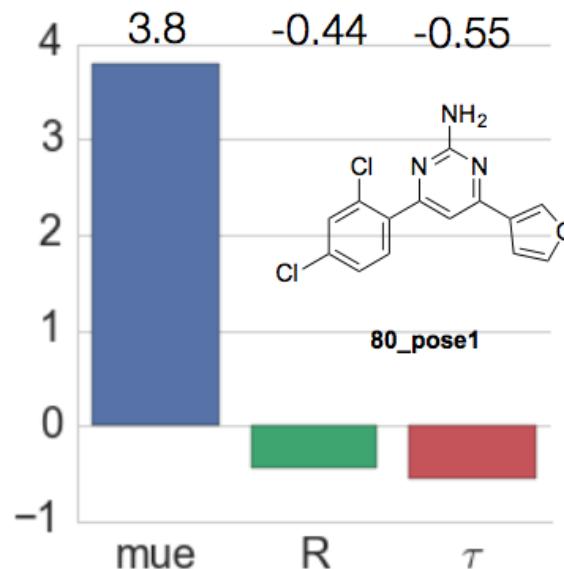


Dataset from **Bruncko et al. 2010**  
(IC50s + X-ray)

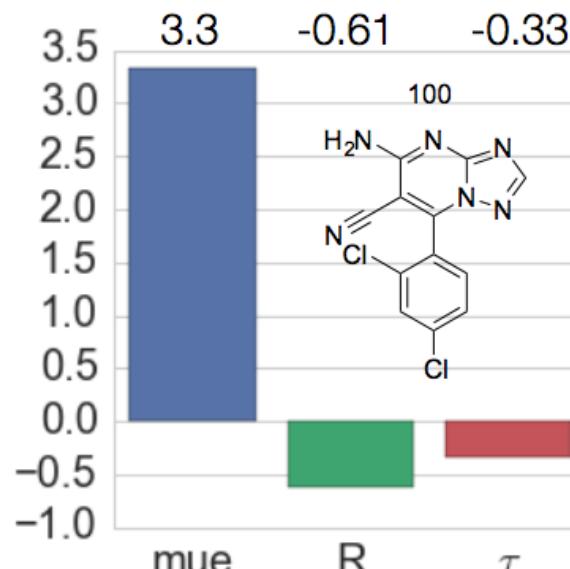
- R =  $0.75 \pm 0.05$
- MUE =  $1.2 \pm 0.2$  kcal/mol

# HSP90: D3R blind predictions results

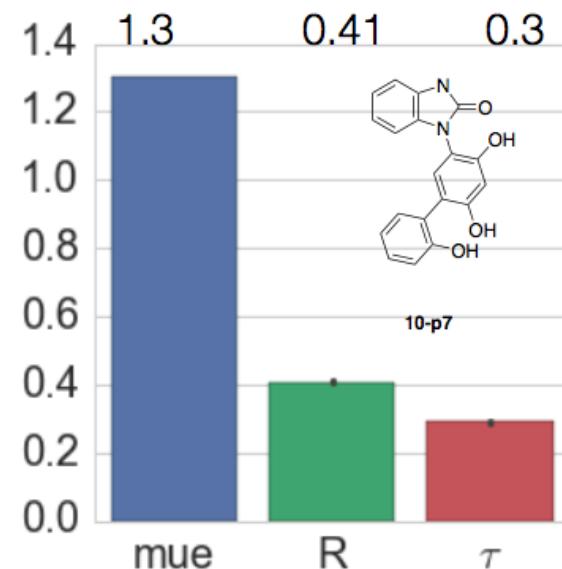
Set 1 (n = 5)



Set 2 (n = 4)



Set 3 (n = 9)



Exp range: 2.5 kcal/mol

R rank

**41/44**

MUE rank

**12/44**

Exp range: 3.8 kcal/mol

**11/18**

**10/18**

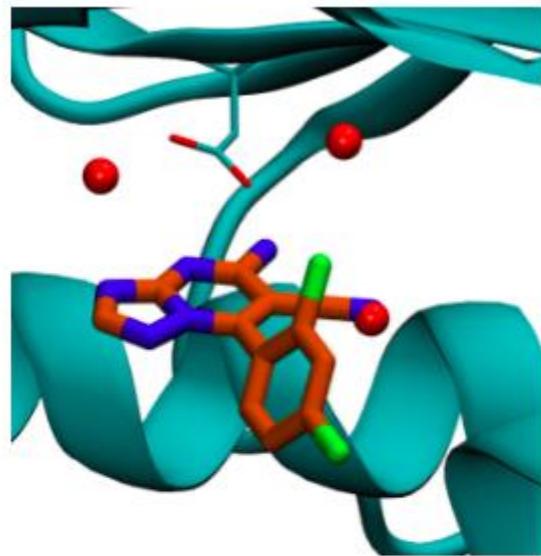
Exp range: 3.4 kcal/mol

**3/20**

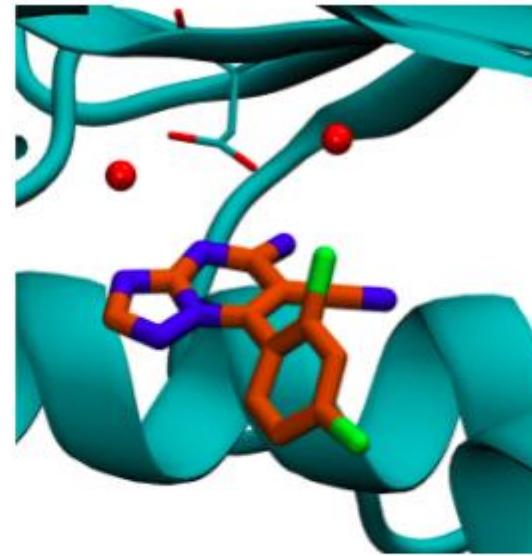
**1/20**

# HSP90: Set2 post-mortem

- Strong influence of water content setup on results



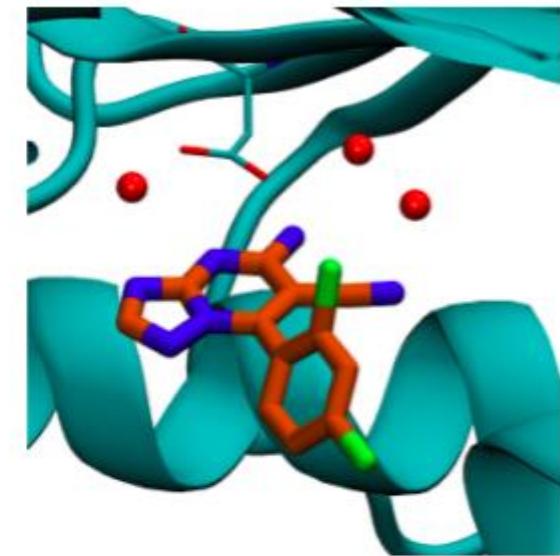
clashing crystal water



original hsp90\_100  
starting structure for  
submission

R  $-0.6 \pm 0.2$

MUE  $3.3 \pm 0.2$  kcal/mol

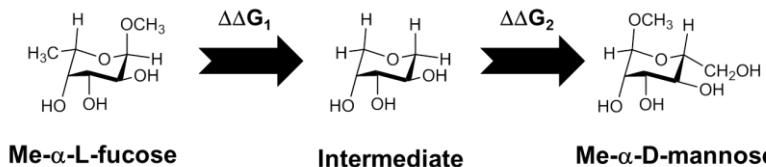
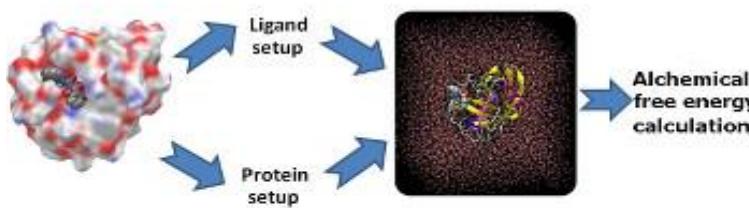


moved and preserved crystal  
water

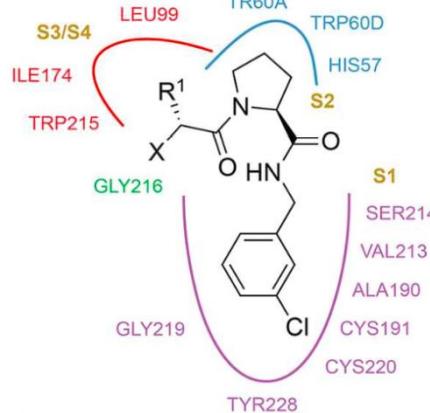
R  $+0.5 \pm 0.2$

MUE  $2.2 \pm 0.2$  kcal/mol

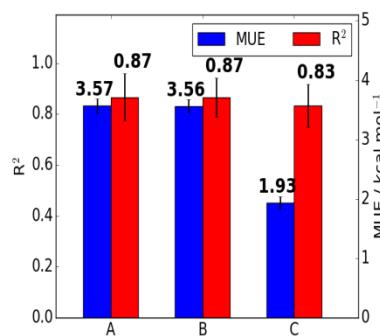
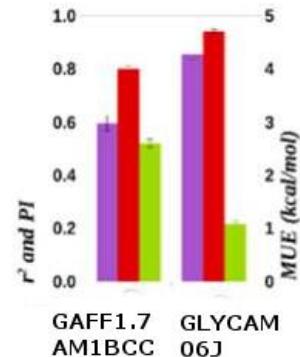
# Summary & perspective (1)



- Trend towards automation
  - Tension between ‘black-box’ and ‘expert-mode’
- Efficiency of different alchemical pathways
  - Strategies for best a priori selection?
- Interpretation of binding energies
  - Too complex for humans?
  - Need better analysis tools?



# Summary & perspective (2)



- Expertise needed to pick force-field
  - Tension between ‘off-the shelf’ and ‘bespoke’
- Correction terms (sometimes) matter
  - Think outside the (periodic) box
- We often don’t get it right the first time
  - For reliable predictions binding modes selection/sampling should be automated

