Overview of the SAMPL6 host-guest challenge

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D3R 2018 Workshop

La Jolla, 2/22/2018

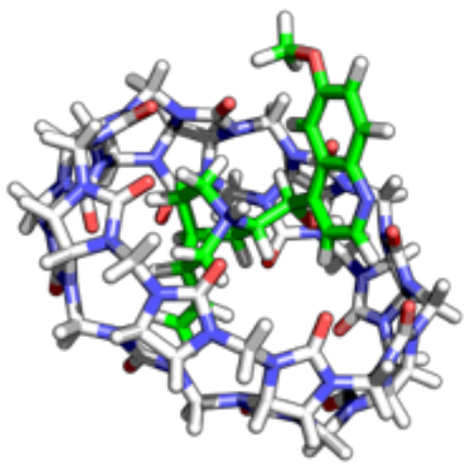
Fail fast, fail cheap

Testing algorithms to predict vehicle collisions

Del Vecchio lab, MIT, Boston

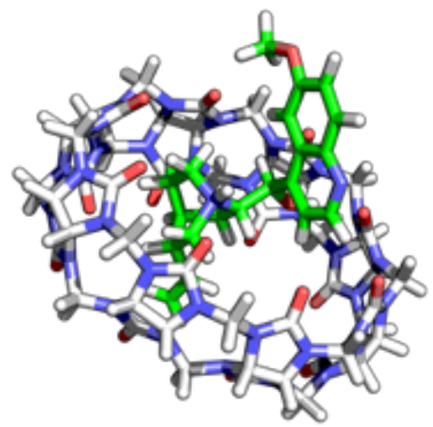
vs

Testing algorithms to predict binding free energies

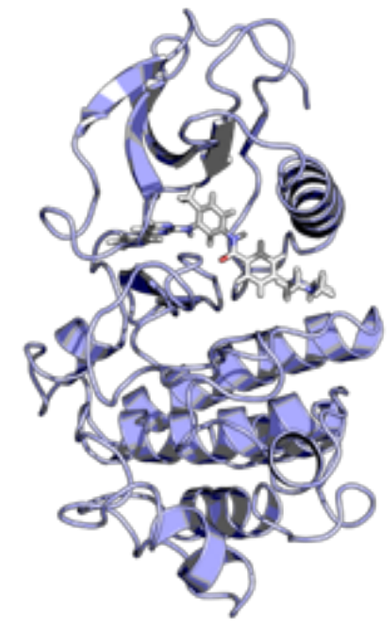


vs

Chemical hosts as testbeds for evaluating methods and force fields



vs

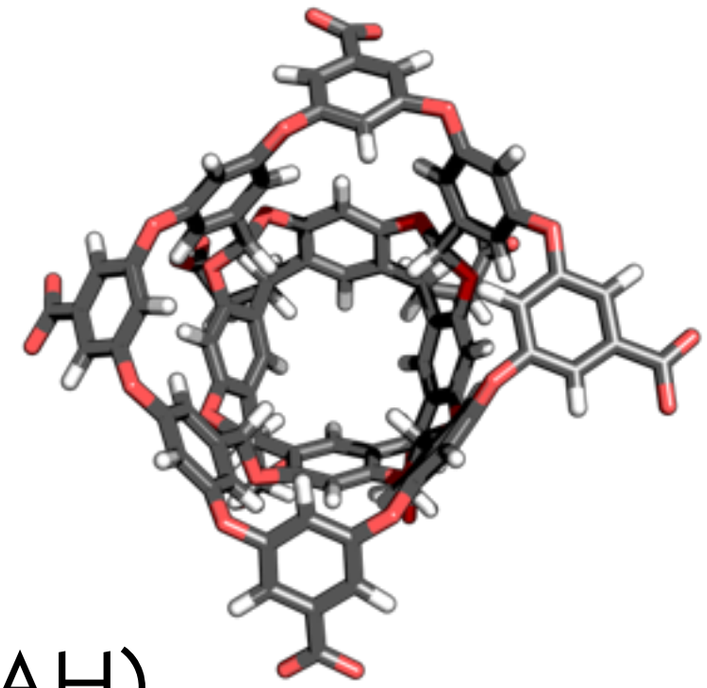


- Less conformational and chemical degrees of freedom
- Same physics of binding
- Can bind small molecules with high affinity
- Challenge: 3 hosts, 22 guests, 30 host-guest systems

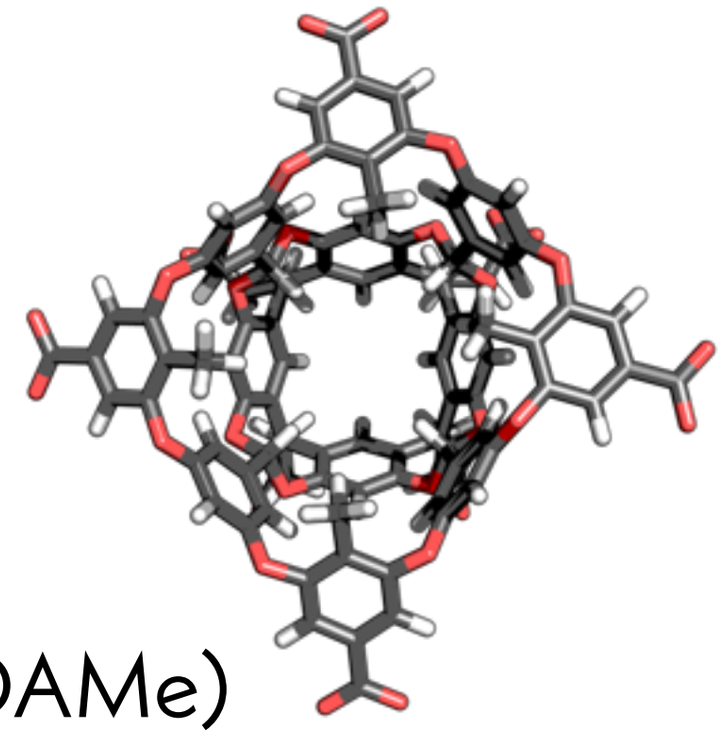
Outline

- Host-guest systems
- Experimental measurements
- Overview of methods and results

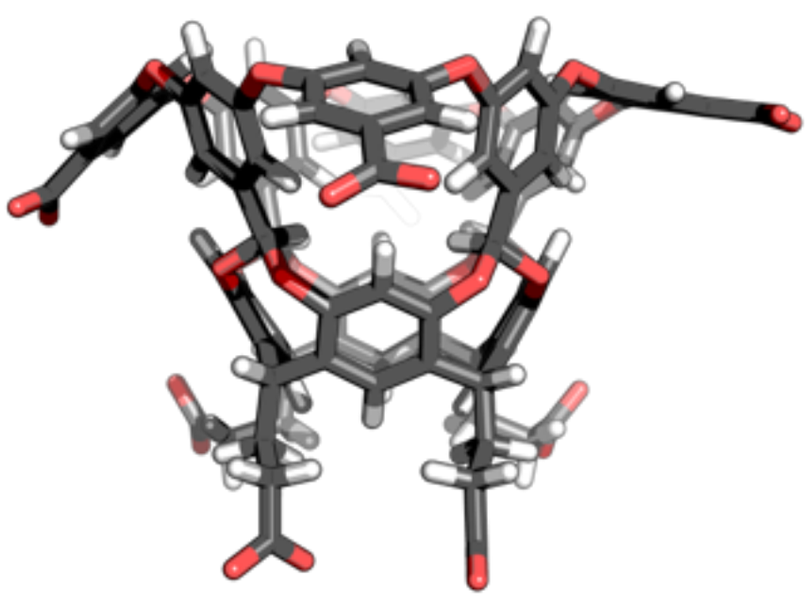
Re-introducing Gibb Deep Cavity Cavitands (Octa Acids): OA and TEMOA

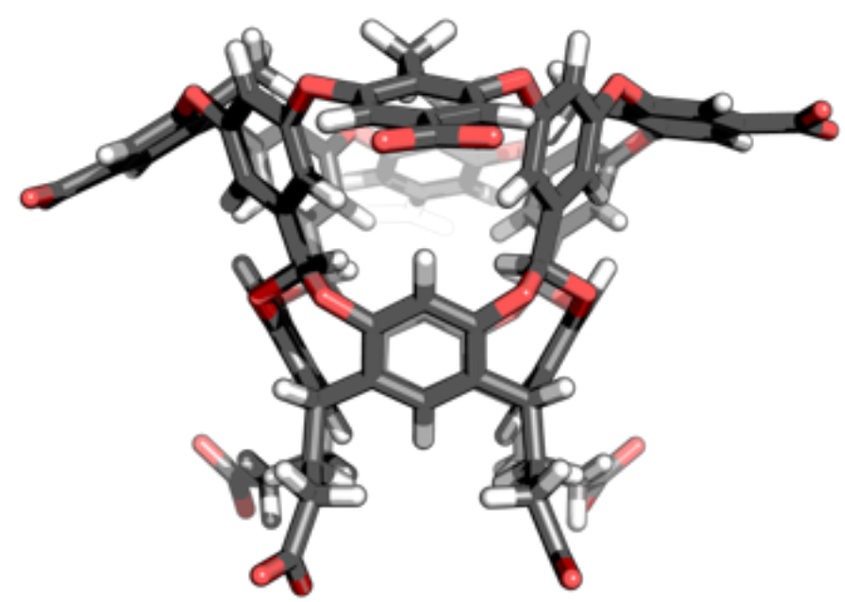


OA (OAH)



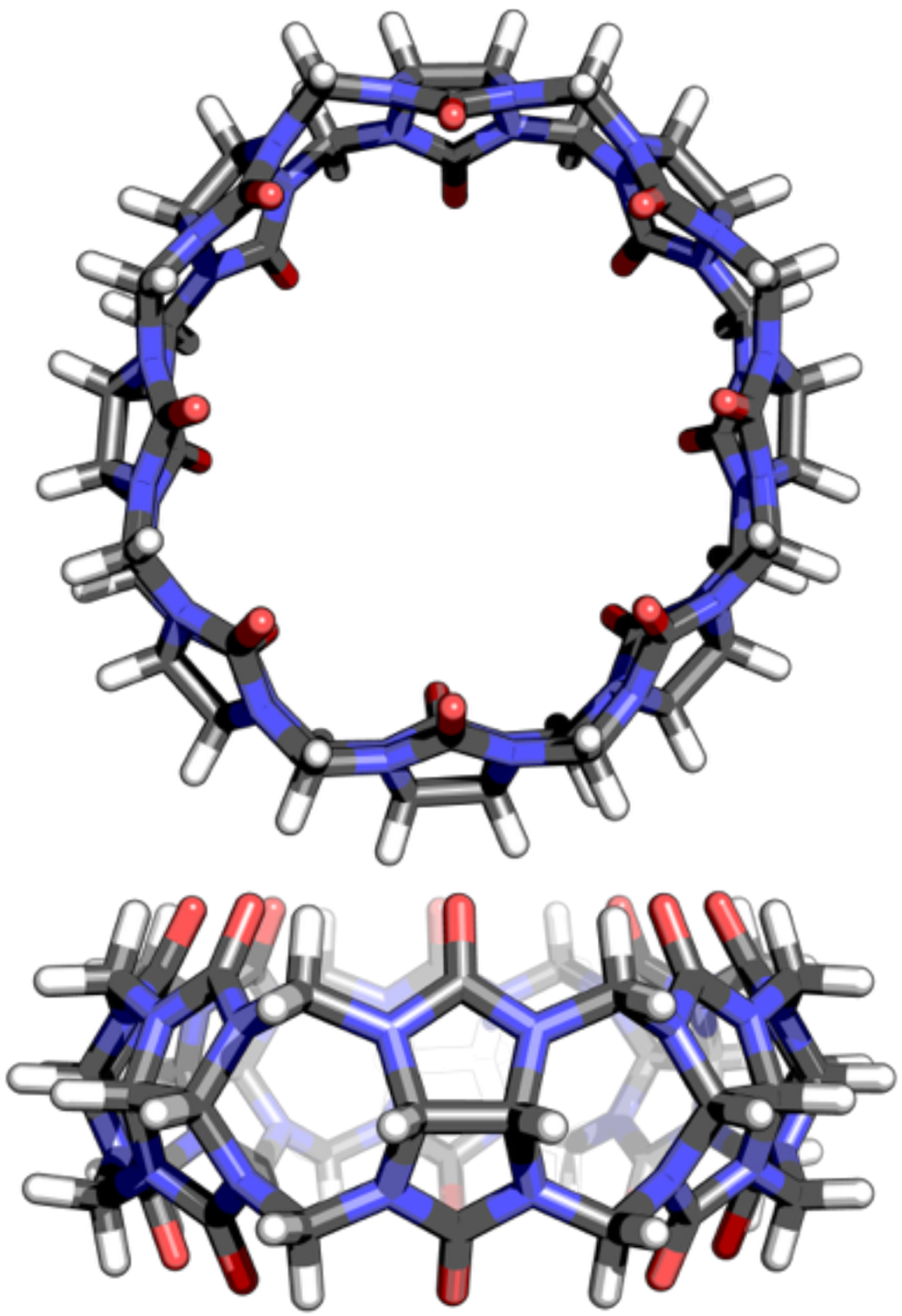
TEMOA (OAMe)





Gibb CL, Gibb BC. Journal of computer-aided molecular design. 2014 Apr 1;28(4):319-25
Gan H, Benjamin CJ, Gibb BC. Journal of the American Chemical Society. 2011 Mar 14;133(13):4770-3

Re-introducing Cucurbit[8]uril (CB8)



- No acidic/basic groups
- Top-bottom symmetric binding
- Large portal make possible binding stoichiometries ≠ 1:1

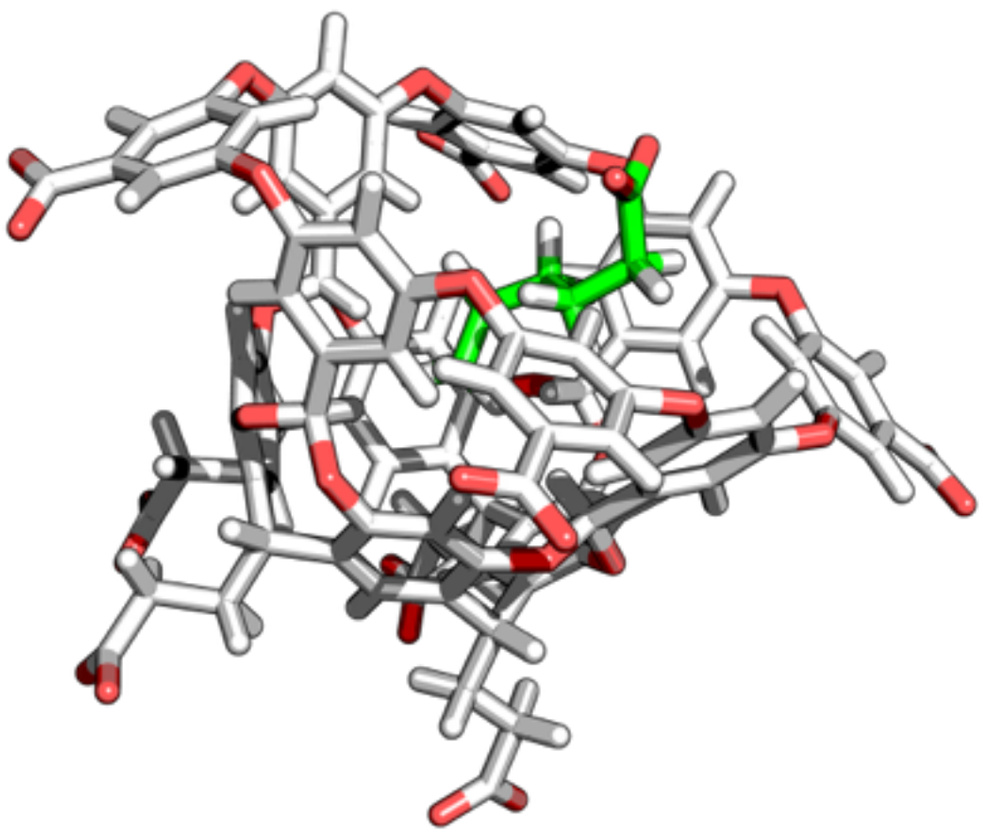
Liu S, Ruspic C, Mukhopadhyay P, Chakrabarti S, Zavalij PY, Isaacs L. Journal of the American Chemical Society. 2005 Nov 16;127(45):15959-67.

Both families of chemical host offer common challenges

- Water binding/unbinding
- Experiments and calculations are sensitive to ionic strength

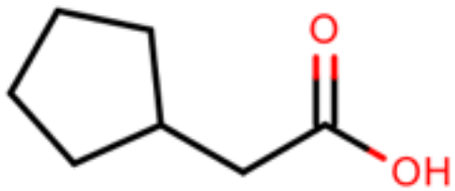
Ewell J, Gibb BC, Rick SW. The Journal of Physical Chemistry B. 2008 Jul 29;112(33):10272-9.
Rogers KE, Ortiz-Sánchez JM, Baron R, Fajer M, de Oliveira CA, McCammon JA. 2012 Nov 2;9(1):46-53.

OA/TEMOA guests are simulated in a highly charged environment

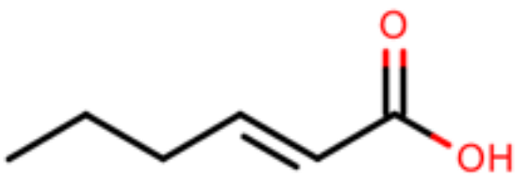


Experiment pH = 11.7 ± 0.1

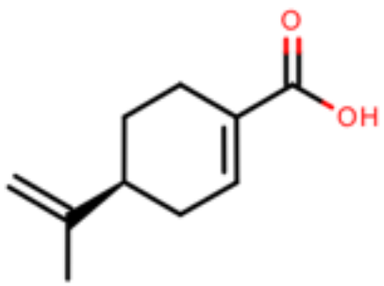
cyclopentyl acetic acid



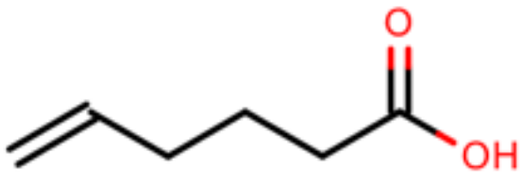
trans-2-hexenoic acid



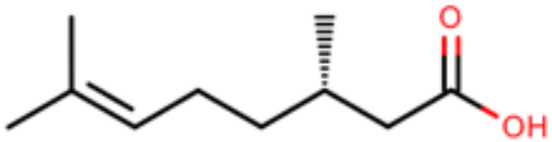
(s)-(-)-perillic acid



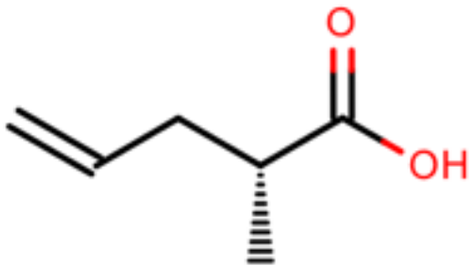
5-hexenoic acid



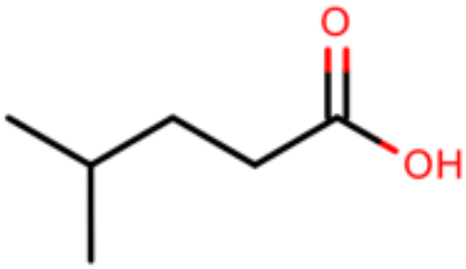
(s)-(-)-citronellic acid



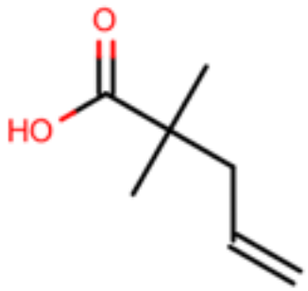
2-methyl-4-pentenoic acid



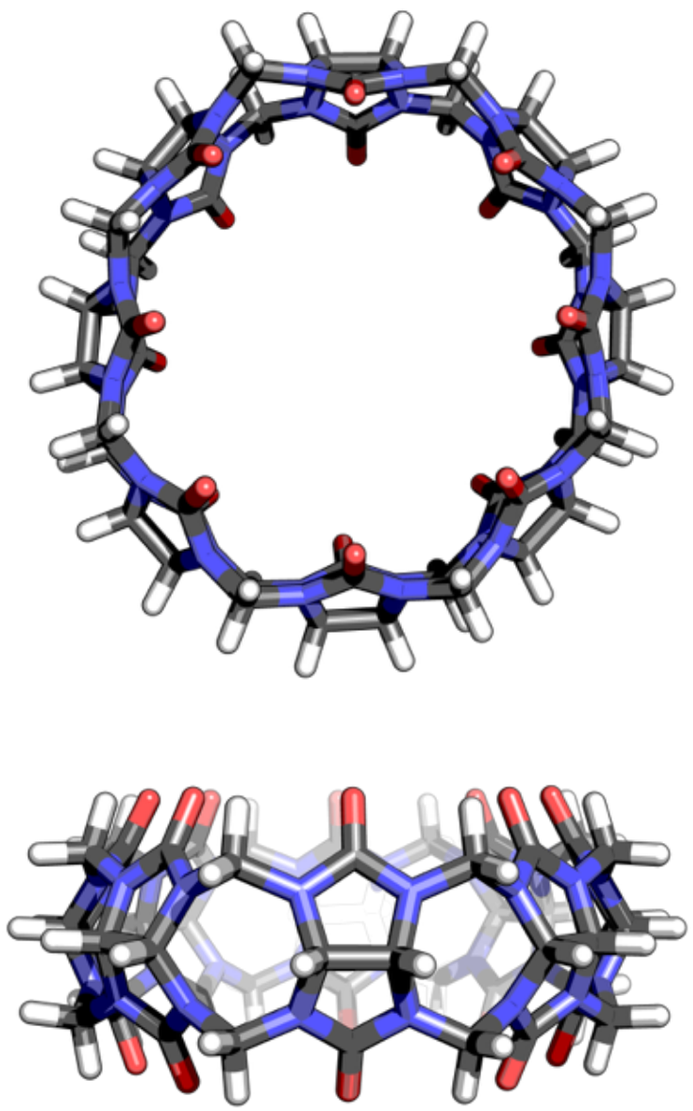
4-methylpentanoic acid



2,2-dimethyl-4-pentenoic acid



CB8 guests



Lexapro
CAS 219861-08-2
TCI

Aricept
CAS 120011-70-3
TCI

Detrol
CAS 124937-52-6
AvaChem Scientific

Palonosetron
CAS 135729-62-3
AvaChem Scientific

Oxaliplatin
CAS 61825-94-3
Selleck Chemicals

Quinine
CAS 130-95-0
OakWood Chemical

Gallamine triethiodate
CAS 65-29-2
BIOMOL International

(1*R*,2*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine

Experiment pH = 7.4

Outline

- Host-guest systems
- Experimental measurements
- Overview of methods and results

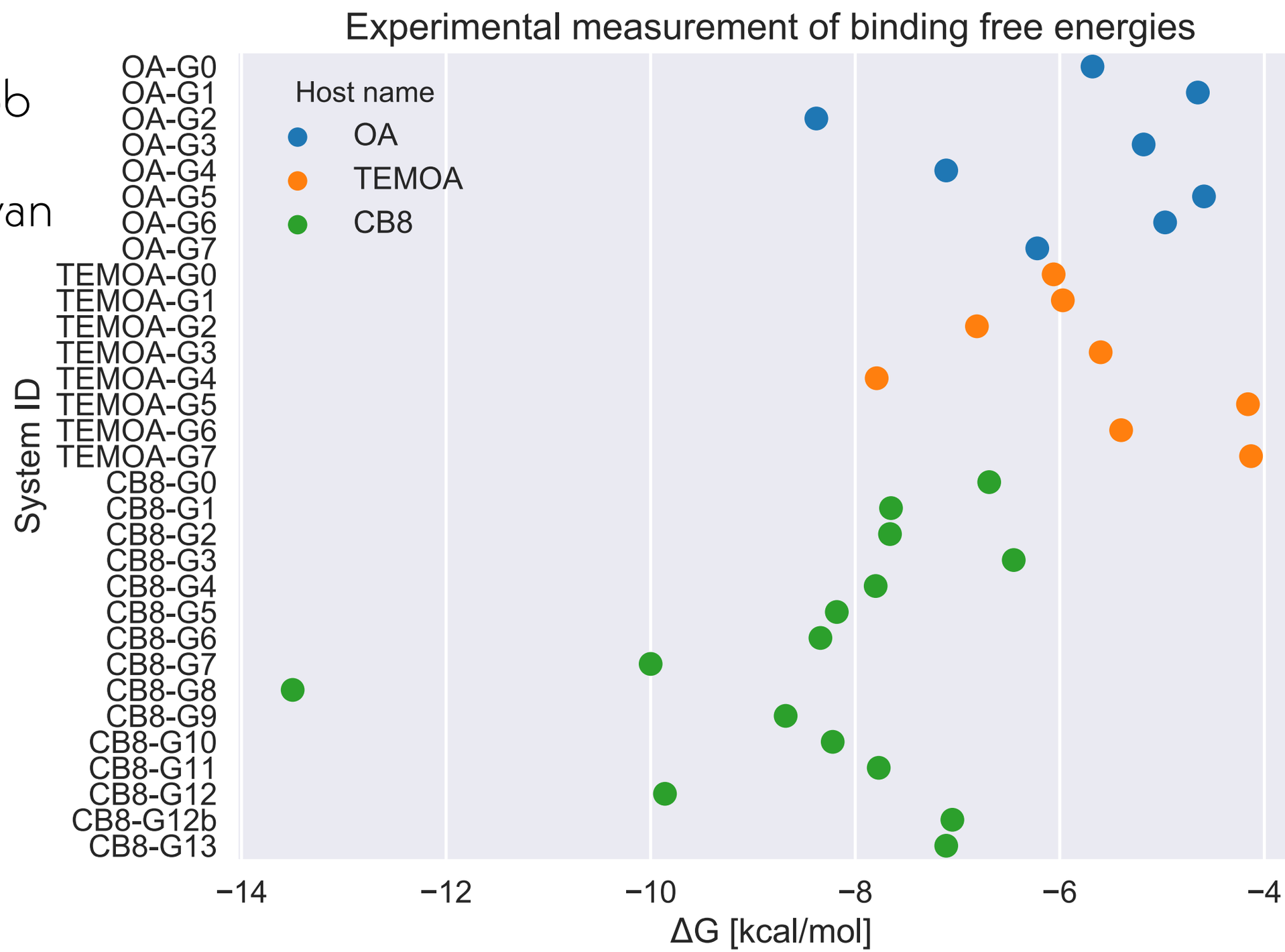
Overall, ITC binding free energies span a dynamic range of 6-10 kcal/mol

GDCC: Bruce Gibb

- Matthew Sullivan
- Wei Yao

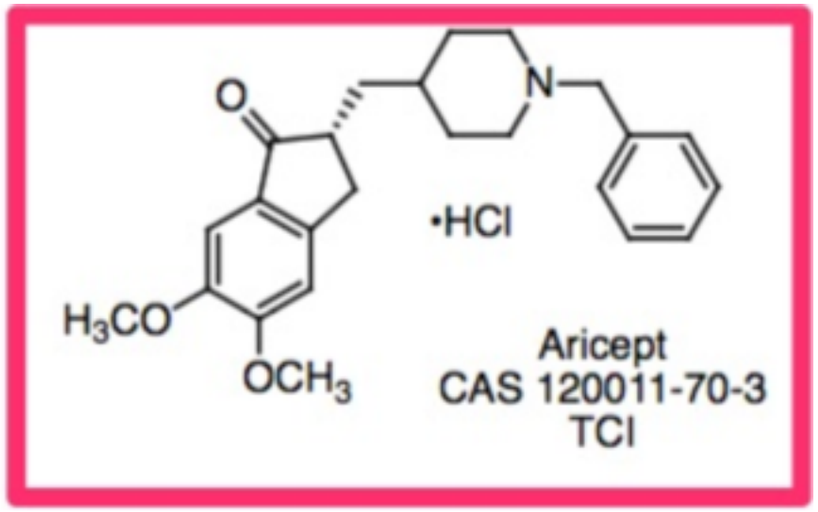
CB8: Lyle Isaacs

- Steven Murkli
- Nolan McNeill

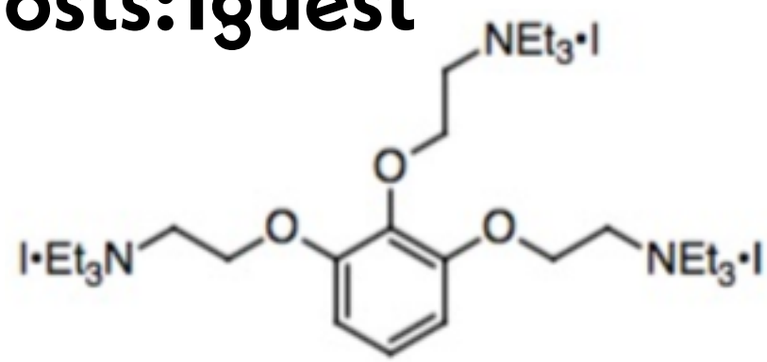


Proton NMR report multiple binding events for some CB8 guests

1host:2guests

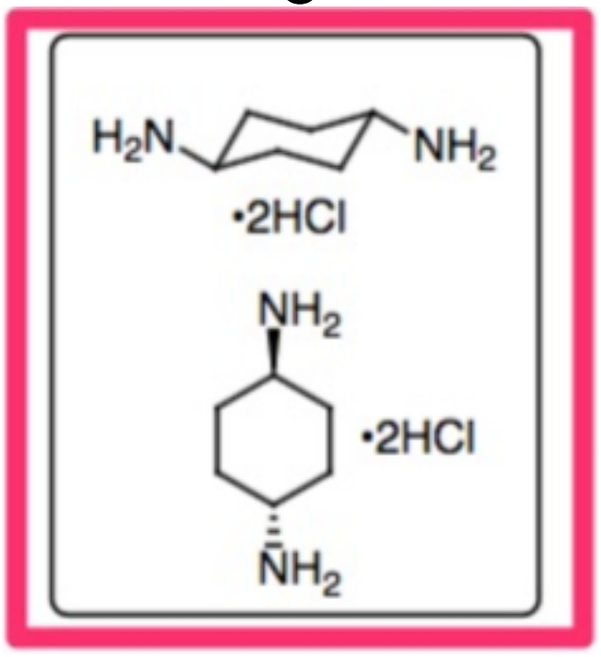


3hosts:1guest

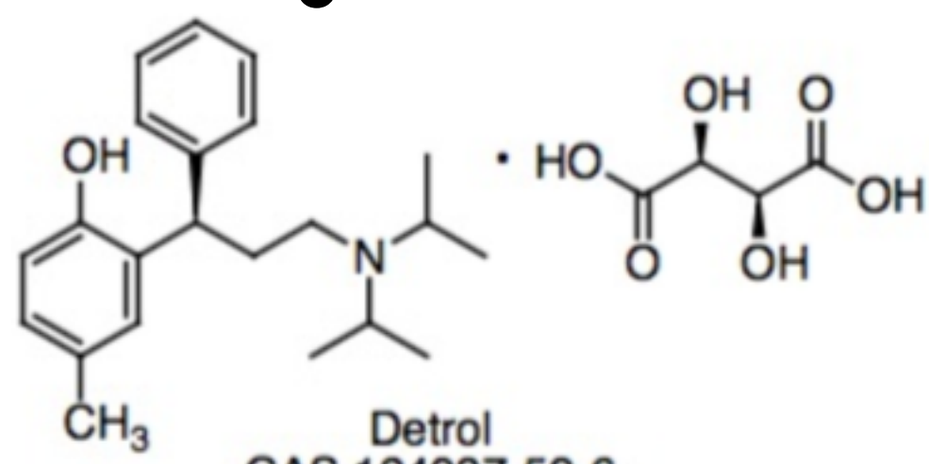


Gallamine triethiodate
CAS 65-29-2
BIOMOL International

1host:1guest



2hosts:1guest



Detrol
CAS 124937-52-6
AvaChem Scientific

Outline

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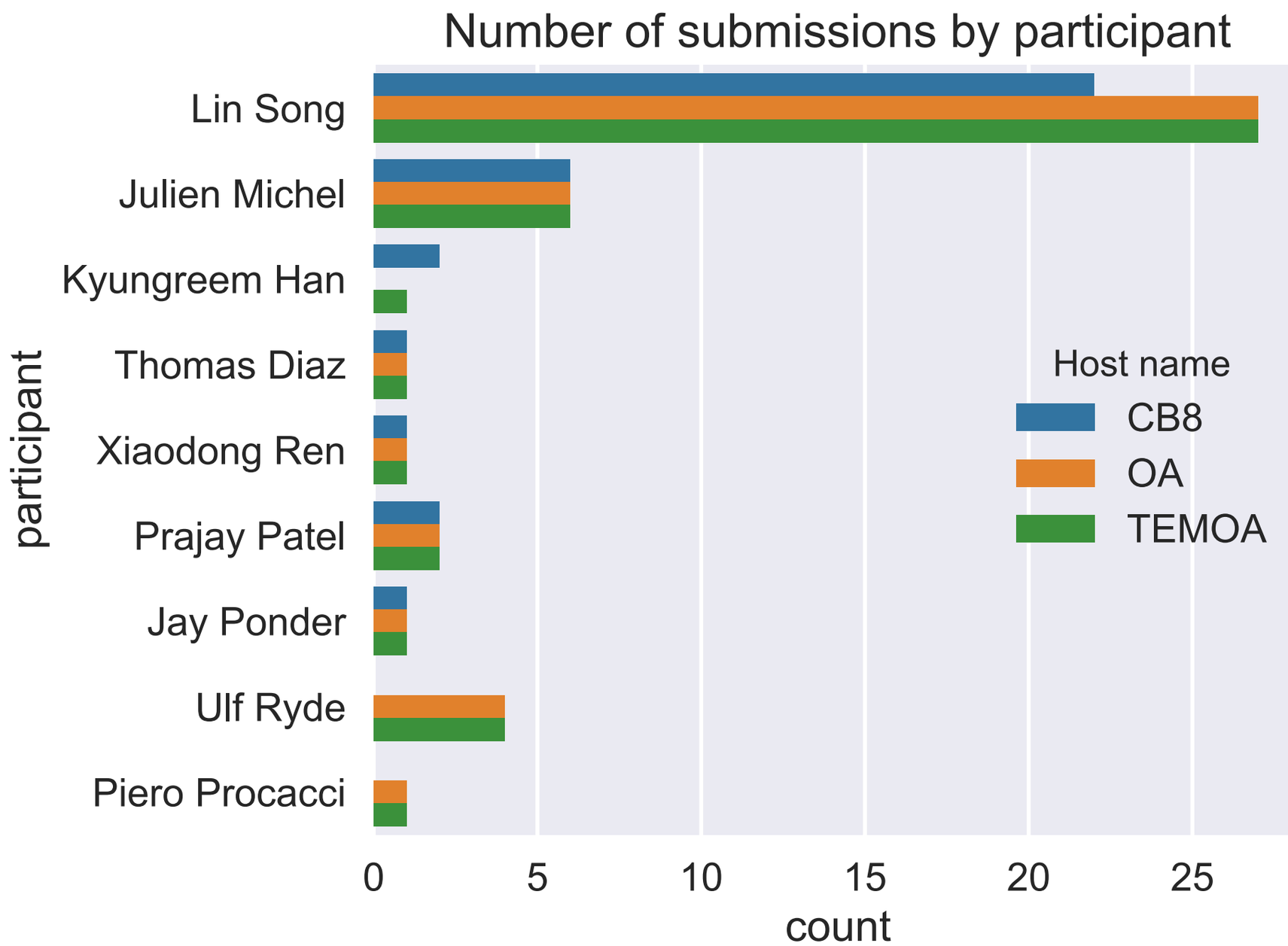
Analysis is available online

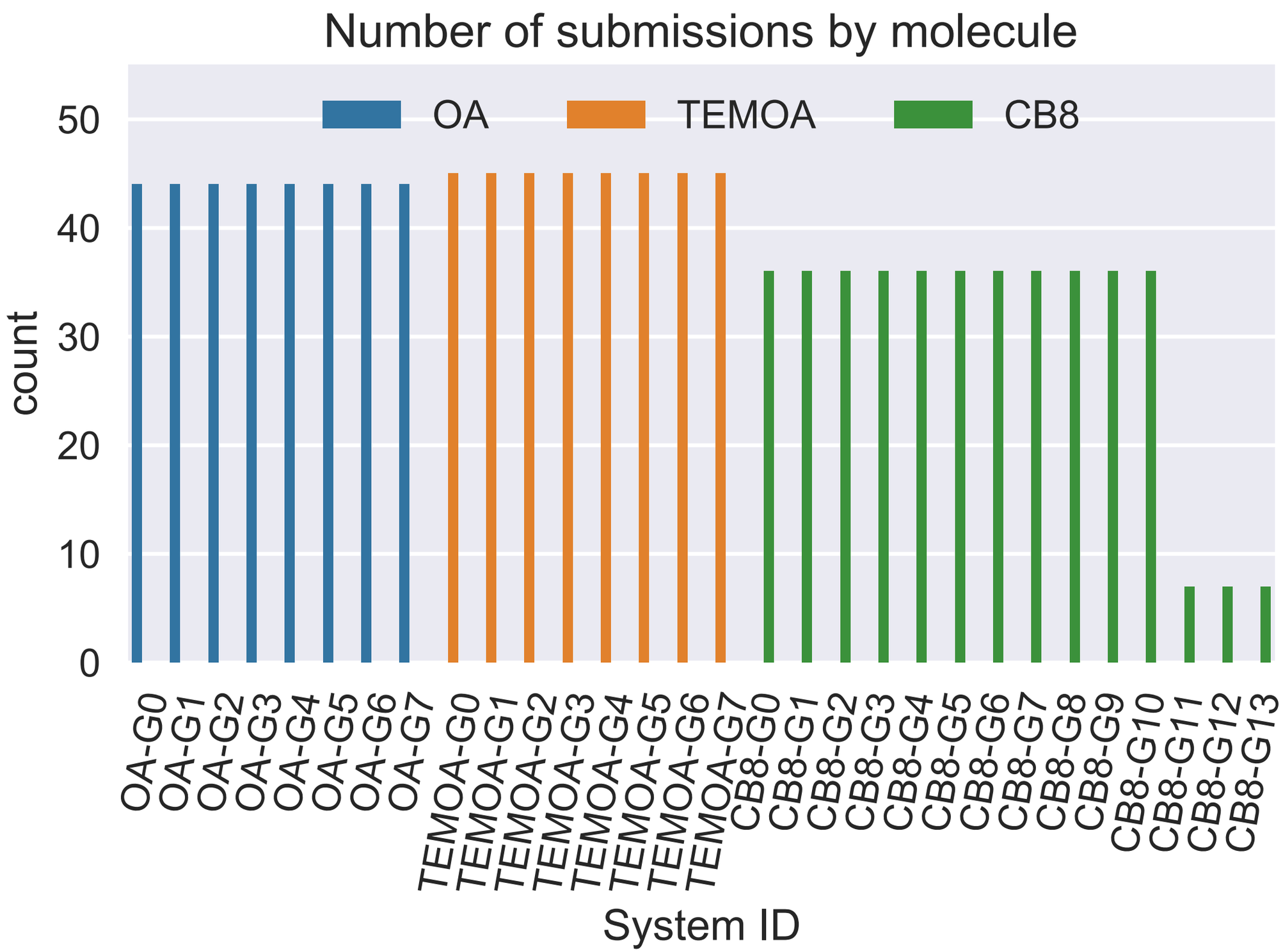
- https://github.com/MobleyLab/SAMPL6/tree/master/host_guest/Analysis
- Correlation plots
- Statistics with 95%-percentile bootstrap confidence interval
  - RMSE, MAE, ME, R2, slope, Kendall Tau
  - Grouped by method or molecules
- Description of the methods from participants

Participation

- Submissions
  - 87 GDCC
  - 34 CB8
- Participants
  - 9 GDCC
  - 7 CB8

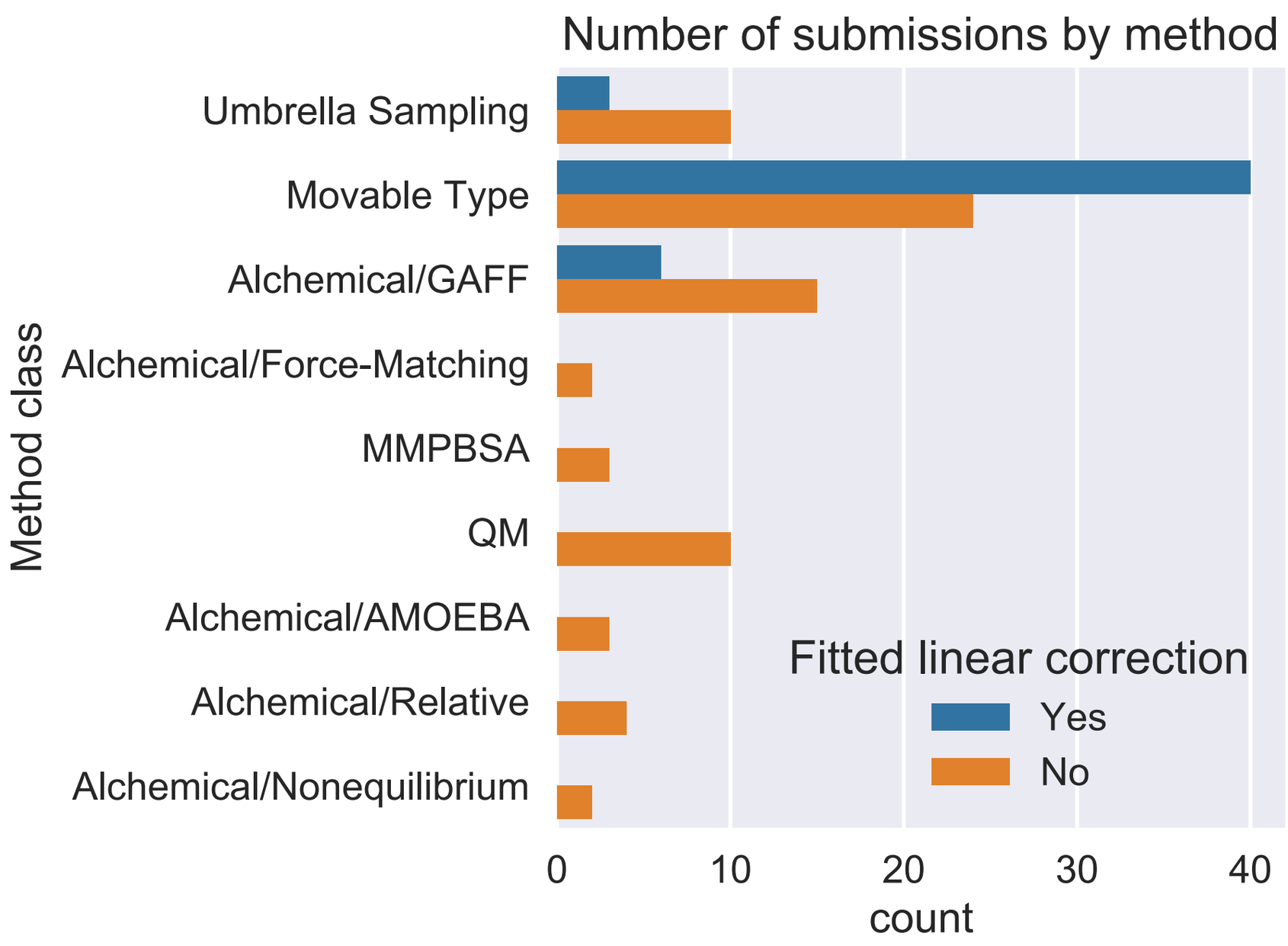


Participation

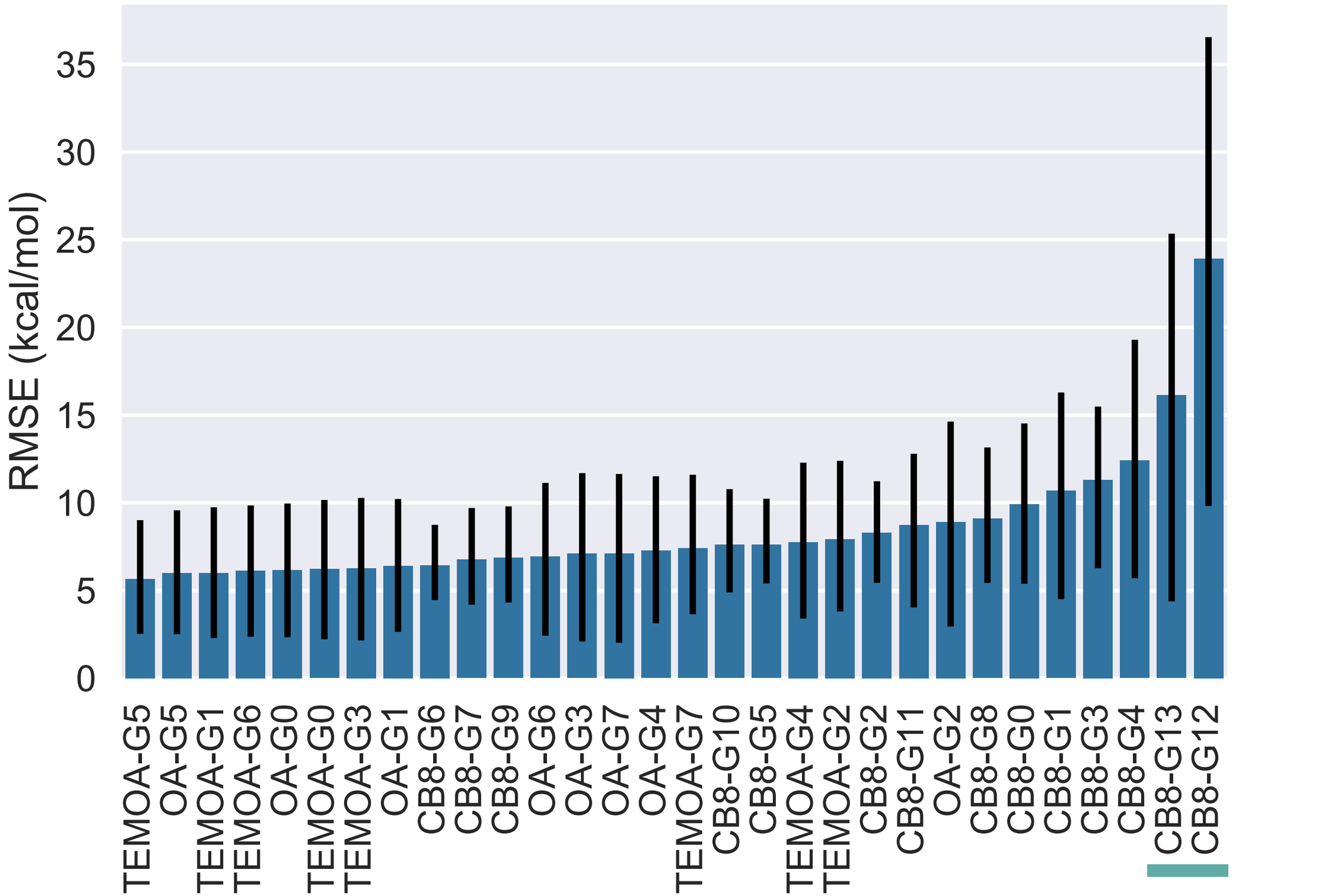


A variety of methods

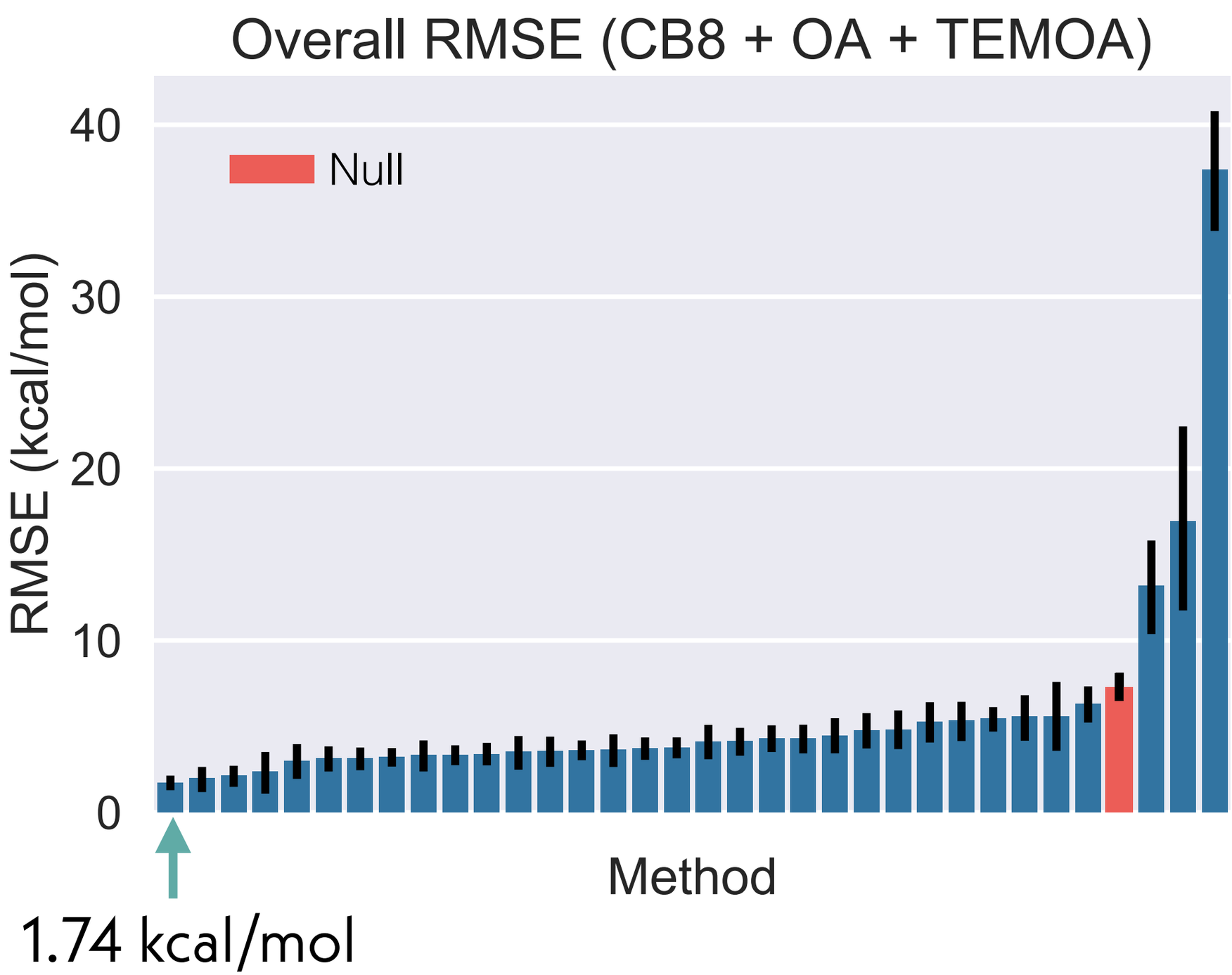
47 different strategies



Statistics by system



Overall statistics by method



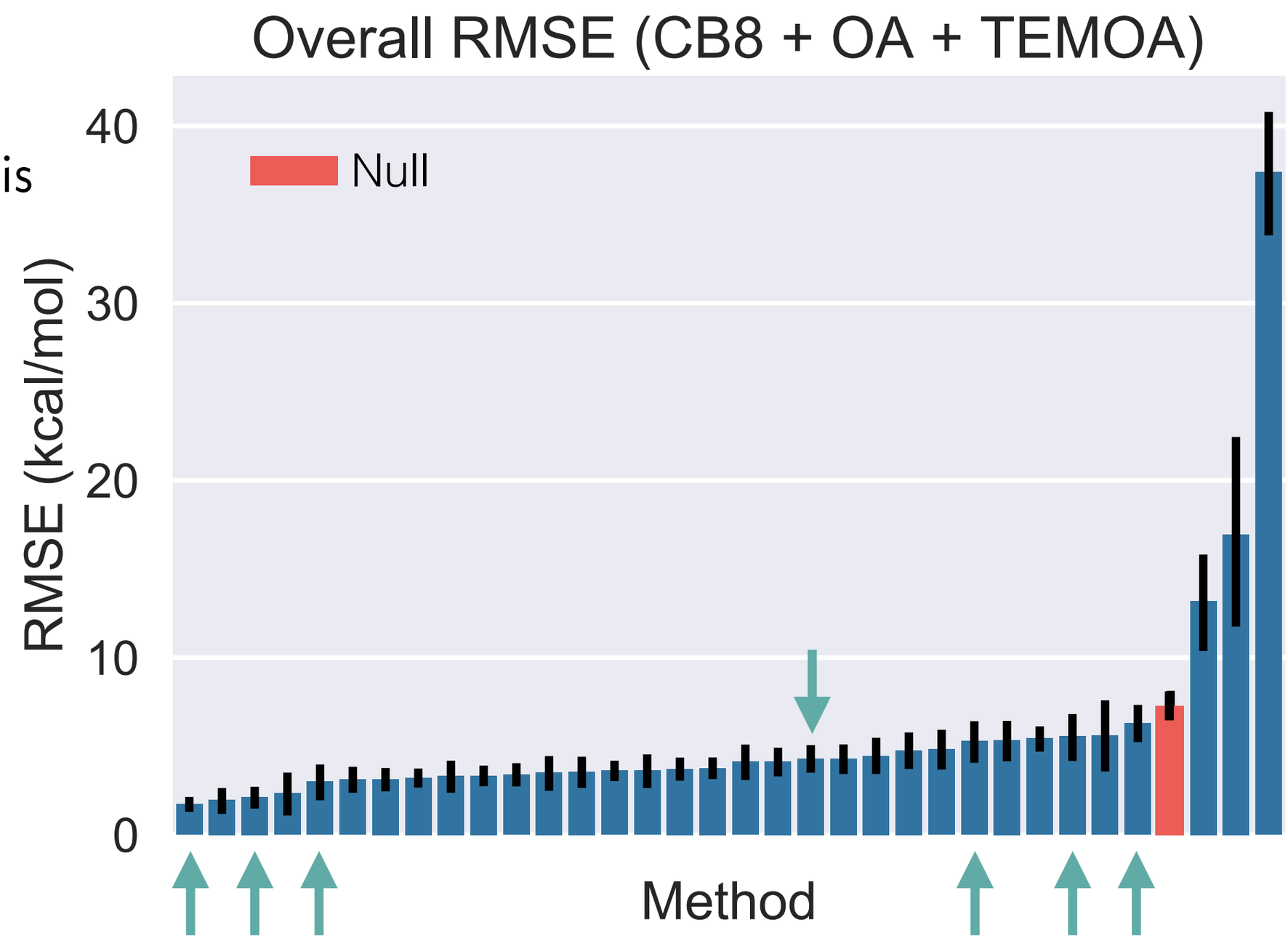
Overall statistics by method

Talks

- Michail Papadourakis
- Marie Laury

Posters

- Phillip Hudson
- Kyngreem Han
- Naohiro Nishikawa



Acknowledgements

Participants

Lin Song
Ulf Ryde
Julien Michel
Michail Papadourakis
Jay Ponder
Marie Laury
Kyungreem Han
Phillip Hudson
Naohiro Nishikawa
Piero Procacci
Prajay Patel
Xiaodong Ren
Thomas Diaz

D3R/SAMPL6 Organizers

David Mobley (UCI)
John Chodera (MSKCC)
Michael Shirts (CU Boulder)
Michael Chiu (UCSD)
Michael Gilson (UCSD)
Rommie Amaro (UCSD)

Experimental measurements

Bruce Gibb (Tulane)
Matthew Sullivan (Tulane)
Wei Yao (Tulane)
Lyle Isaacs (UMD)
Steve Murkli (UMD)
Nolan McNeill (UMD)

Chodera lab

John Chodera
Mehtap Isik
Ariën Sebastiaan (Bas) Rustenburg
Levi Naden

Tri-I CBM PhD Program

David Christini
Christina Leslie
Kathleen Pickering
Margie Hinonangan-Mendoza