TEACHING FREE ENERGY CALCULATIONS TO LEARN

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Sildes will be posted to http://www.choderalab.org/news

DISCLOSURES:
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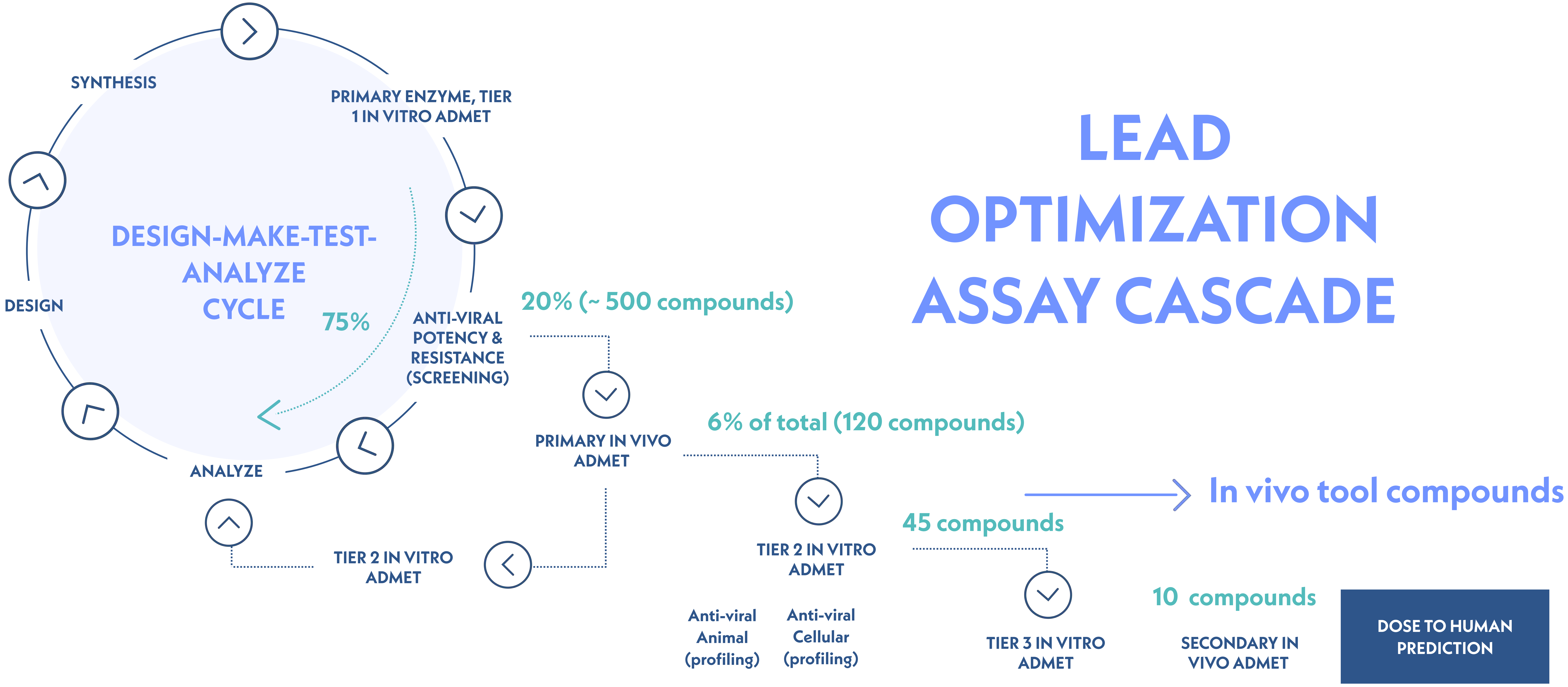
* Denotes equity interests

29 Apr 2022 - ICML MLDD - Cyberspace

MODELS TO STEER DESIGN-MAKE-TEST-ANALYZE CYCLES CAN DIRECTLY IMPACT DISCOVERY PROGRAMS

LEAD OPTIMIZATION ASSAY CASCADE



DESIGN-MAKE-TEST-ANALYZE CYCLE

SYNTHESIS

PRIMARY ENZYME, TIER 1 IN VITRO ADMET

DESIGN

75%

ANTI-VIRAL POTENCY & RESISTANCE (SCREENING)

ANALYZE

TIER 2 IN VITRO ADMET

20% (~ 500 compounds)

PRIMARY IN VIVO ADMET

6% of total (120 compounds)

TIER 2 IN VITRO ADMET

Anti-viral Animal (profiling)

Anti-viral Cellular (profiling)

In vivo tool compounds

45 compounds

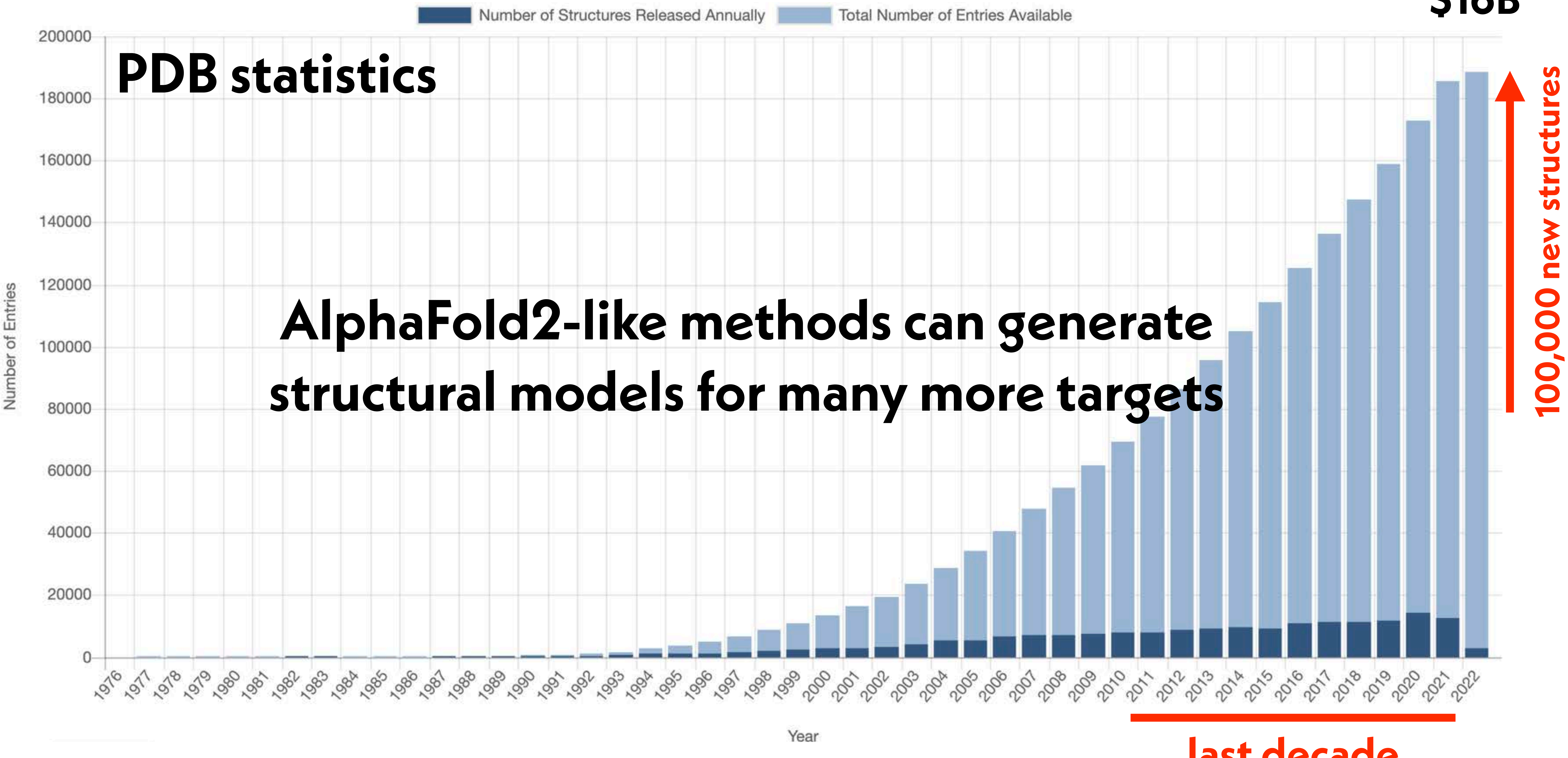
TIER 3 IN VITRO ADMET

10 compounds

SECONDARY IN VIVO ADMET

DOSE TO HUMAN PREDICTION

STRUCTURAL DATA IS NOW AN ABUNDANT RESOURCE FOR DRUG DISCOVERY



$16B

PDB statistics

AlphaFold2-like methods can generate structural models for many more targets

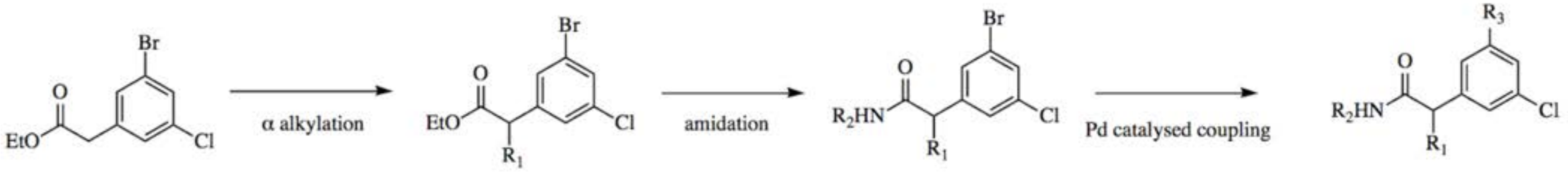
100,000 new structures

last decade

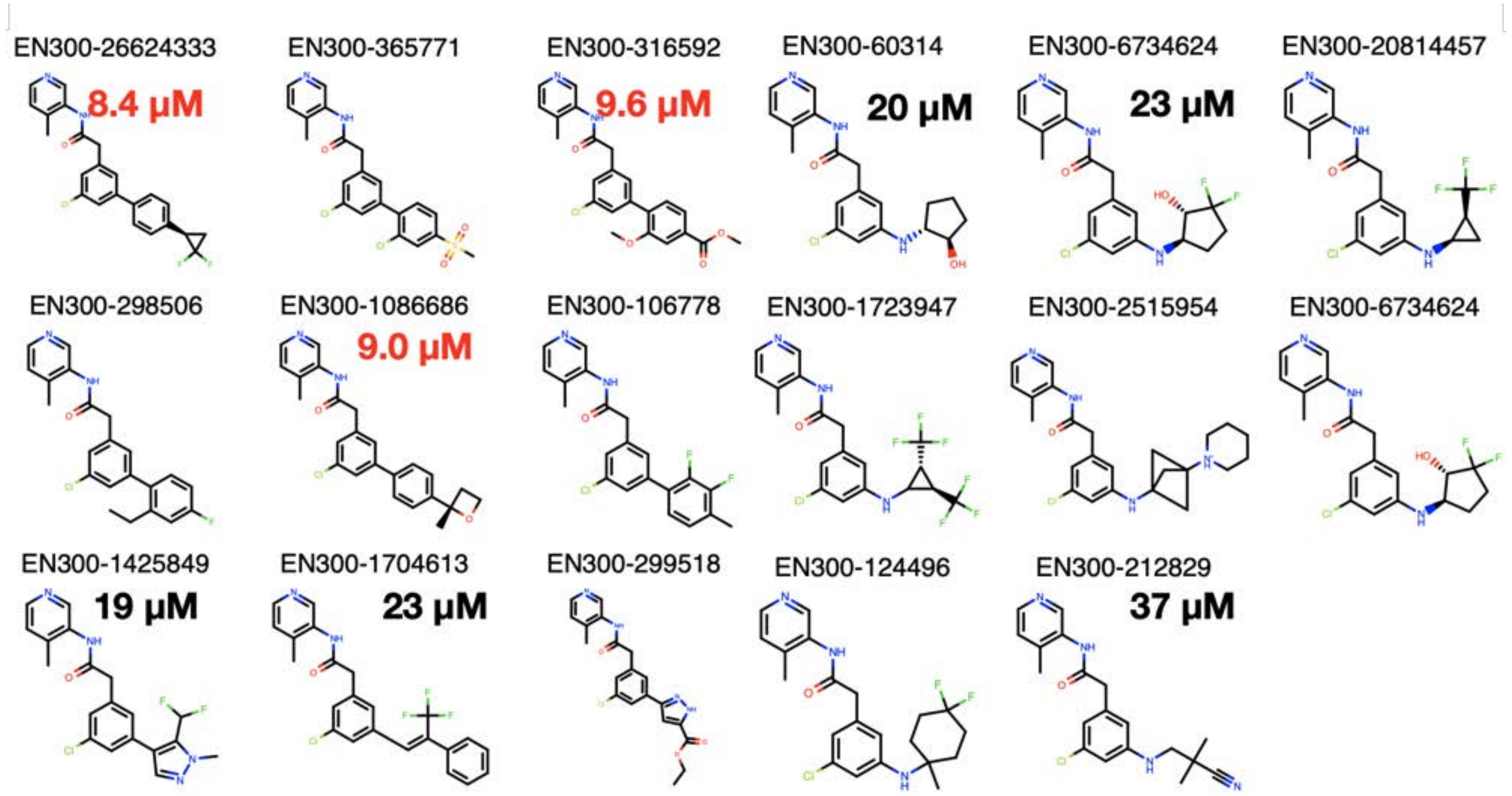
http://www.rcsb.org/stats

WE COMMONLY NEED TO MAKE DECISIONS BETWEEN MANY RELATED SYNTHETICALLY FEASIBLE ANALOGUES

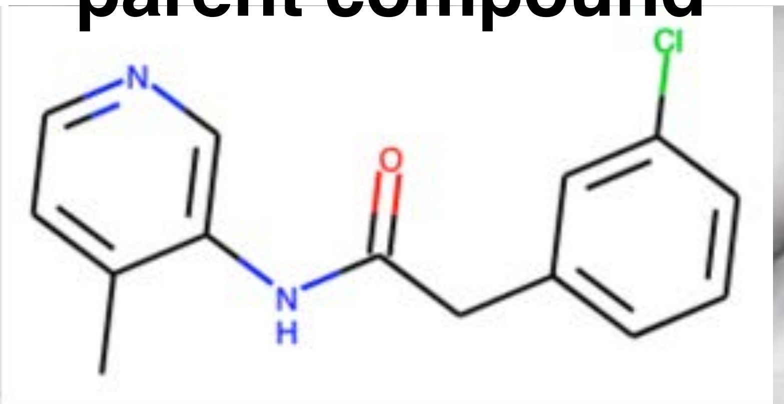
Can we engage S4 from this 5,000-compound virtual synthetic library varying R3



Top free energy calculation compounds and experimental affinity measurements:

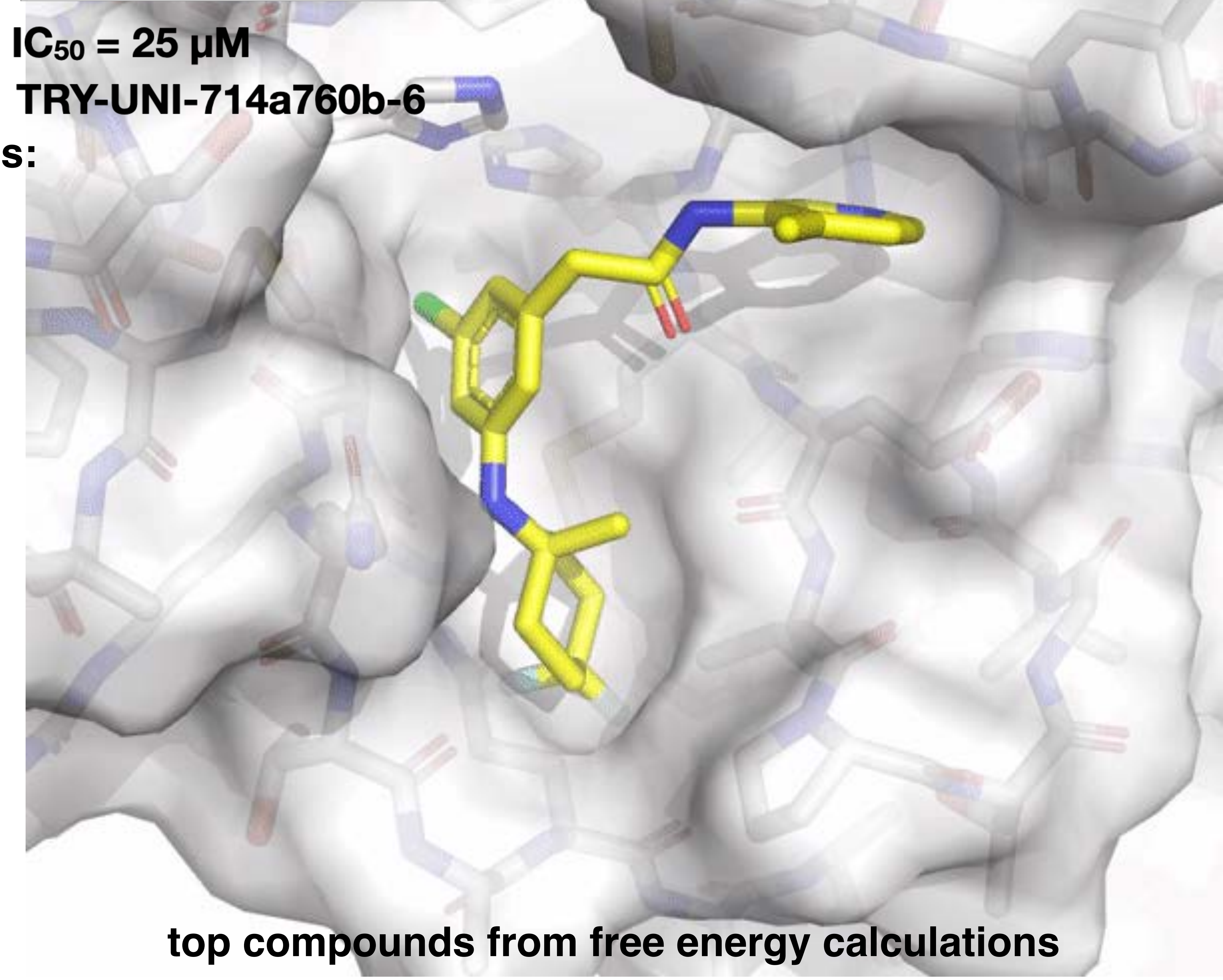


parent compound



IC_{50} = 25 µM

TRY-UNI-714a760b-6



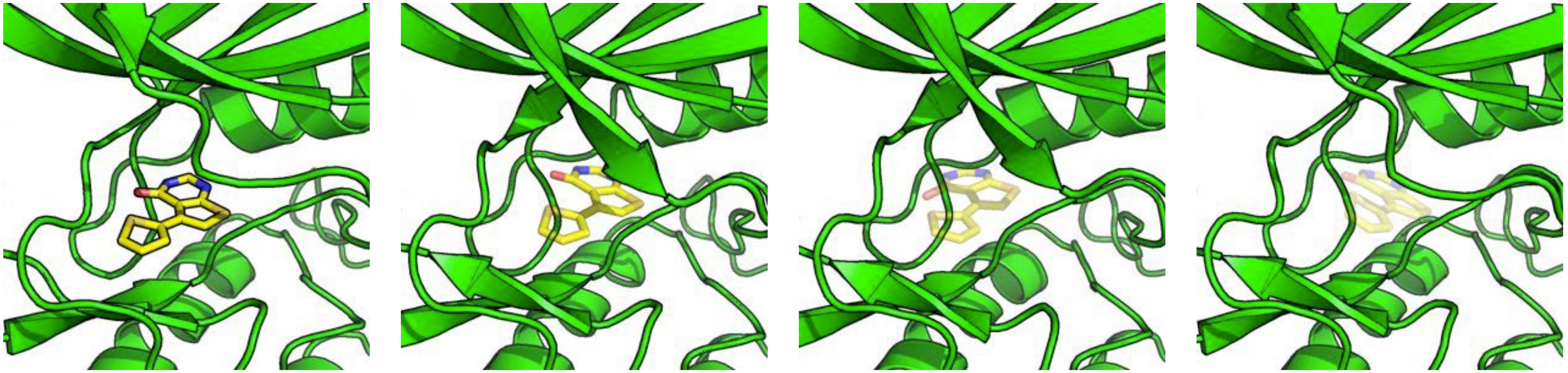
top compounds from free energy calculations

COVID Moonshot: [Moonshot] [Fragalysis] [Dashboard]

ALCHEMICAL FREE ENERGY CALCULATIONS HAVE PROVEN TO BE A USEFUL WAY TO EXPLOIT STRUCTURAL DATA TO PREDICT AFFINITIES

$$\begin{tikzcd}
\mathbf{P + L} \arrow[r, "\Delta G_{\text{bind}}"] \arrow[d] \arrow[dr, phantom, "\text{thermodynamic cycle}"] & \mathbf{PL} \\
\mathbf{P + ø} \arrow[r] & \mathbf{Pø} \arrow[u, "\Delta G_{1\to N}"']
\end{tikzcd}$$

simulations of alchemical intermediates with attenuated interactions



restraint imposition | discharging | steric decoupling | noninteracting

Includes all contributions from enthalpy and entropy of binding to a flexible receptor

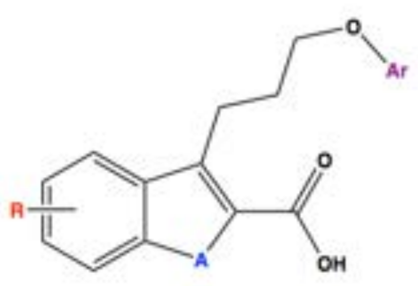
$$\Delta G_{1\to N} = -\beta^{-1} \ln \frac{Z_N}{Z_1} = -\beta^{-1} \ln \frac{Z_2}{Z_1} \cdot \frac{Z_3}{Z_2} \cdots \frac{Z_N}{Z_{N-1}}$$

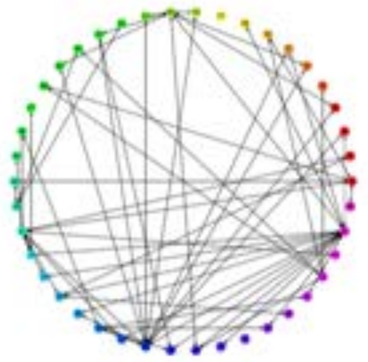
$$Z_n = \int dx\, e^{-\beta U_n(x)}$$ partition function

Pioneering work from many: McCammon, van Gunsteren, Kollman, Jorgensen, Chipot, Roux, Boresch, Fujitani, Pande, Shirts, Swope, Christ, Mobley, Schrödinger, and many more

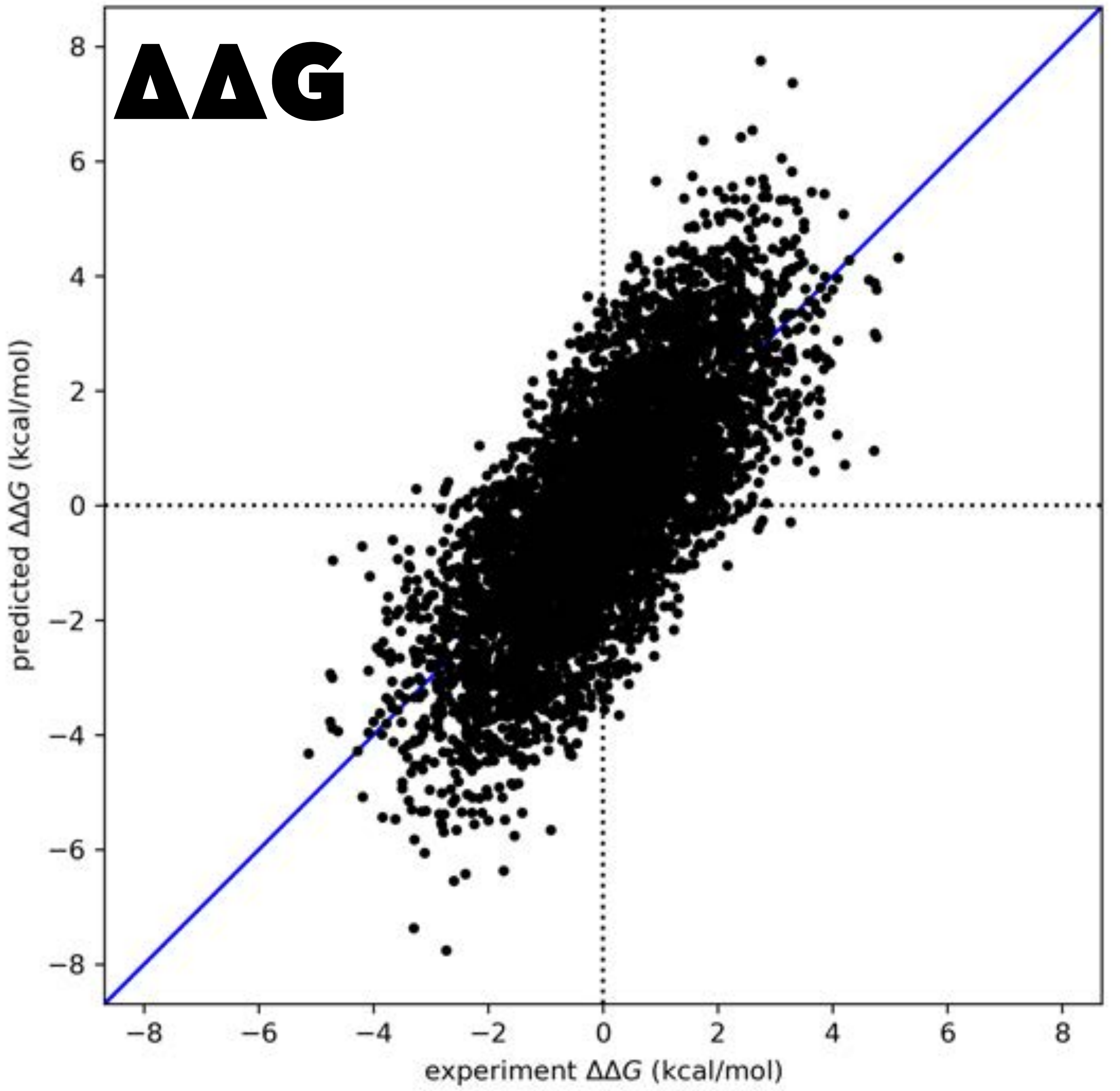
CURRENT ACCURACIES ARE SUFFICIENT TO ACCELERATE DISCOVERY, BUT HOW CAN WE GO FURTHER?

RELATIVE





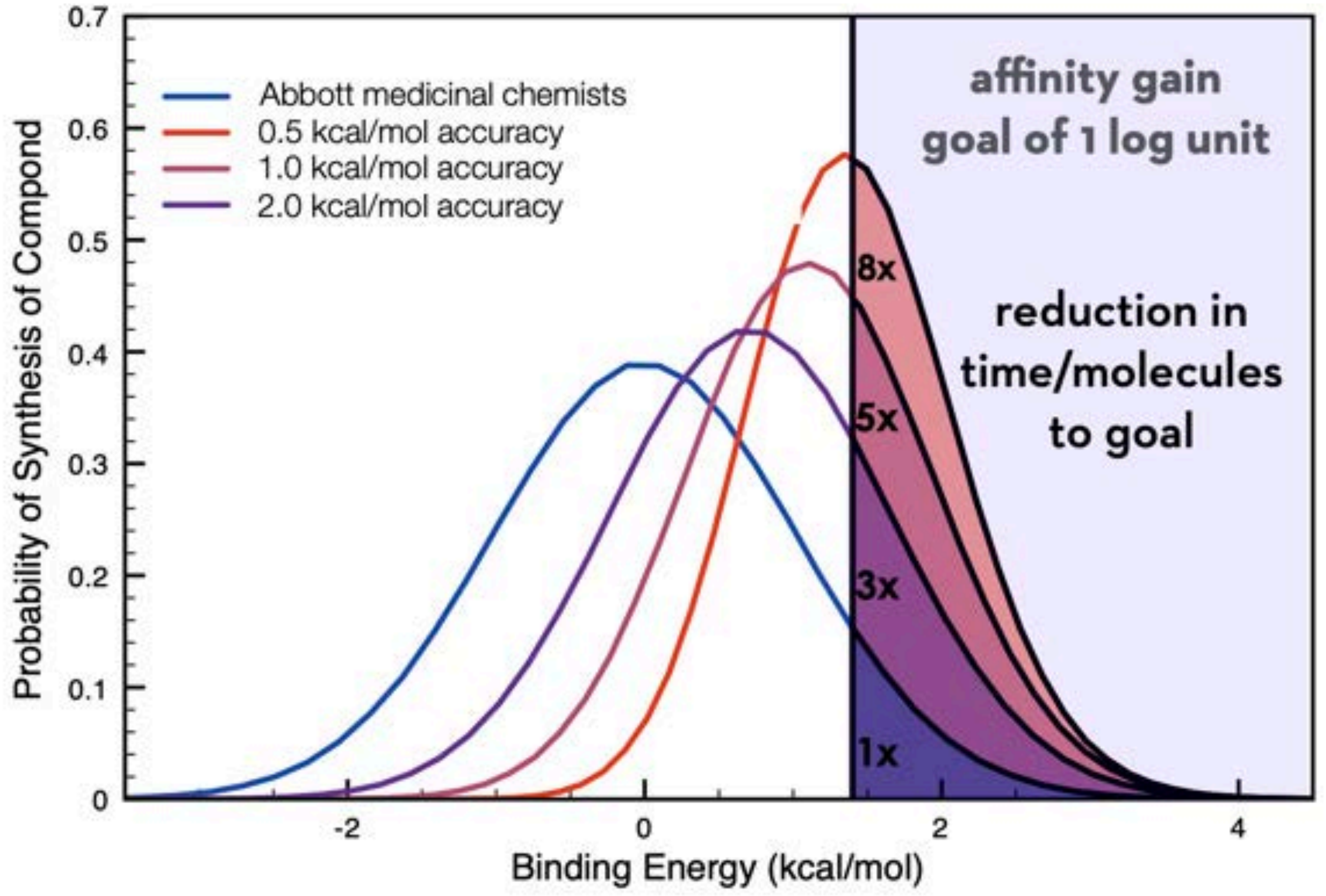
```
                all within-target pairs ΔΔG (N = 5620)
RMSE: OPLS      1.37 [95%:   1.34,   1.39] kcal/mol
MUE : OPLS      1.09 [95%:   1.07,   1.11] kcal/mol
R2  : OPLS      0.10 [95%:   0.06,   0.15] kcal/mol
rho : OPLS      0.73 [95%:   0.72,   0.74] kcal/mol
```



Wang et al. (Schrödinger) JACS 137:2695, 2015
https://doi.org/10.1021/ja512751q
Reanalysis: http://github.com/jchodera/jacs-dataset-analysis

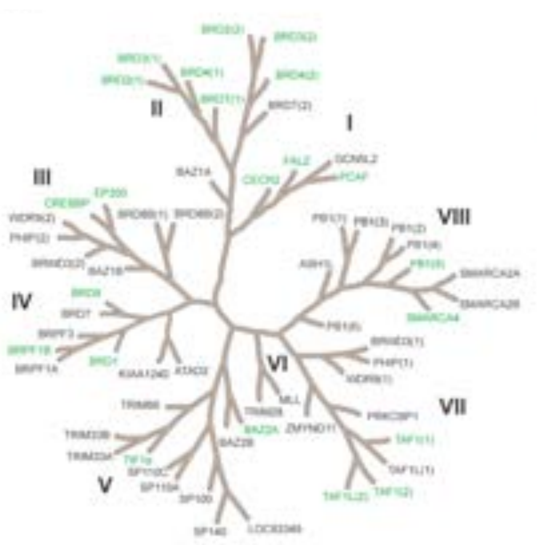
ΔΔG RMSE ~ 1.4 kcal/mol for well-behaved* proteins/chemistries:

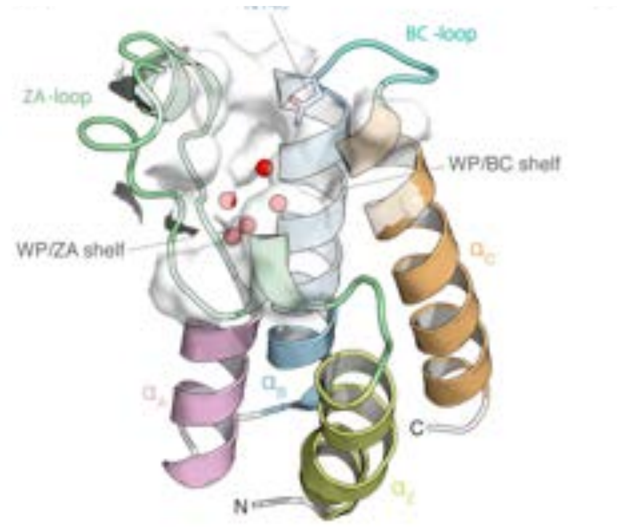
3-5x reduction in molecules synthesized

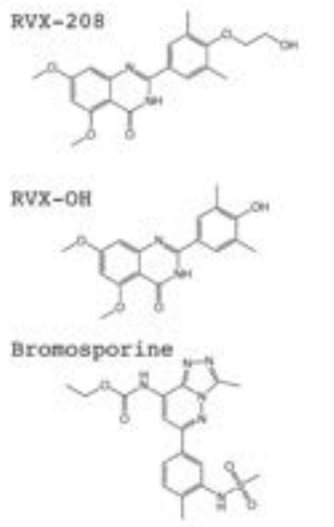


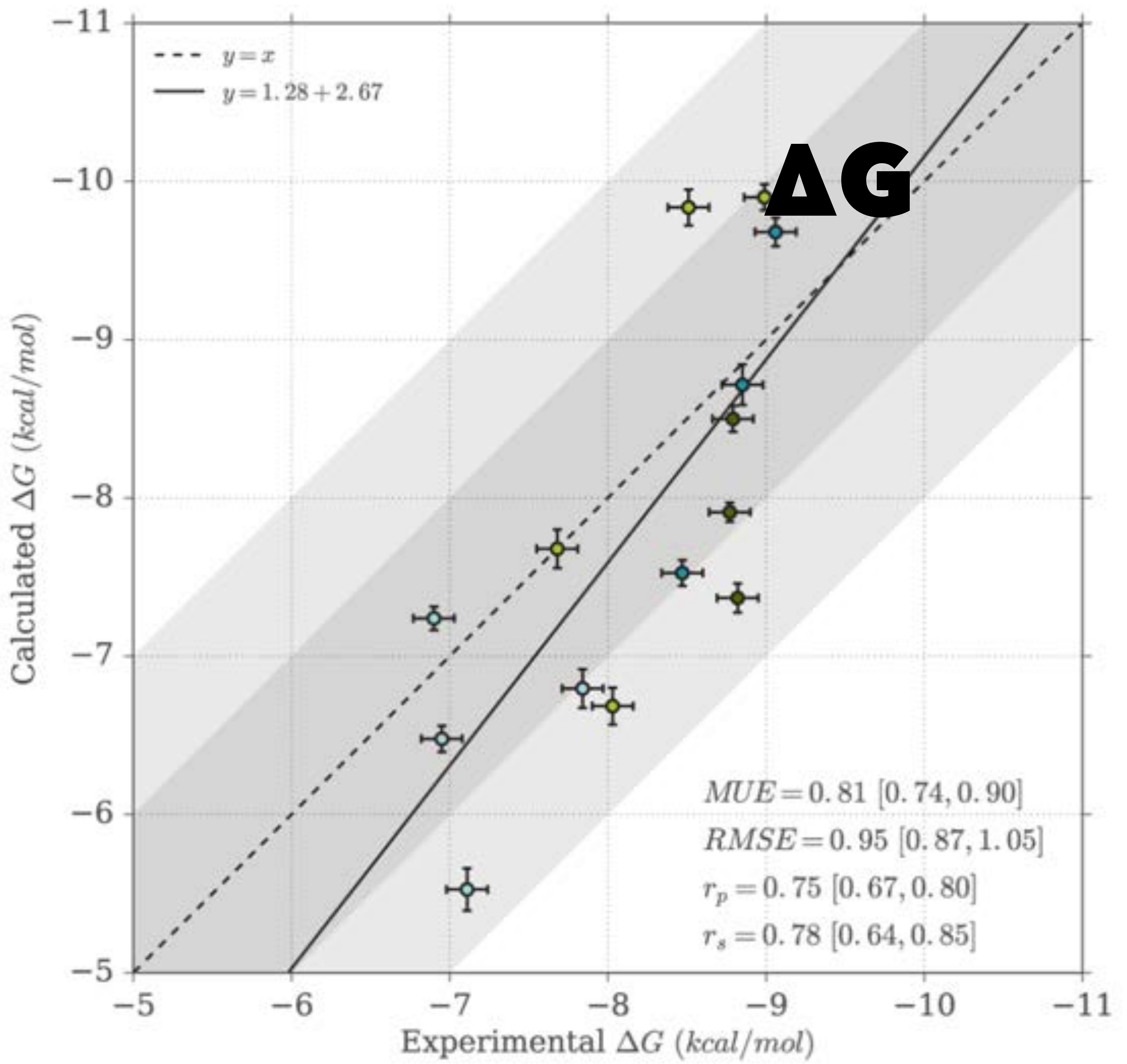
***best-case scenarios!**

ABSOLUTE







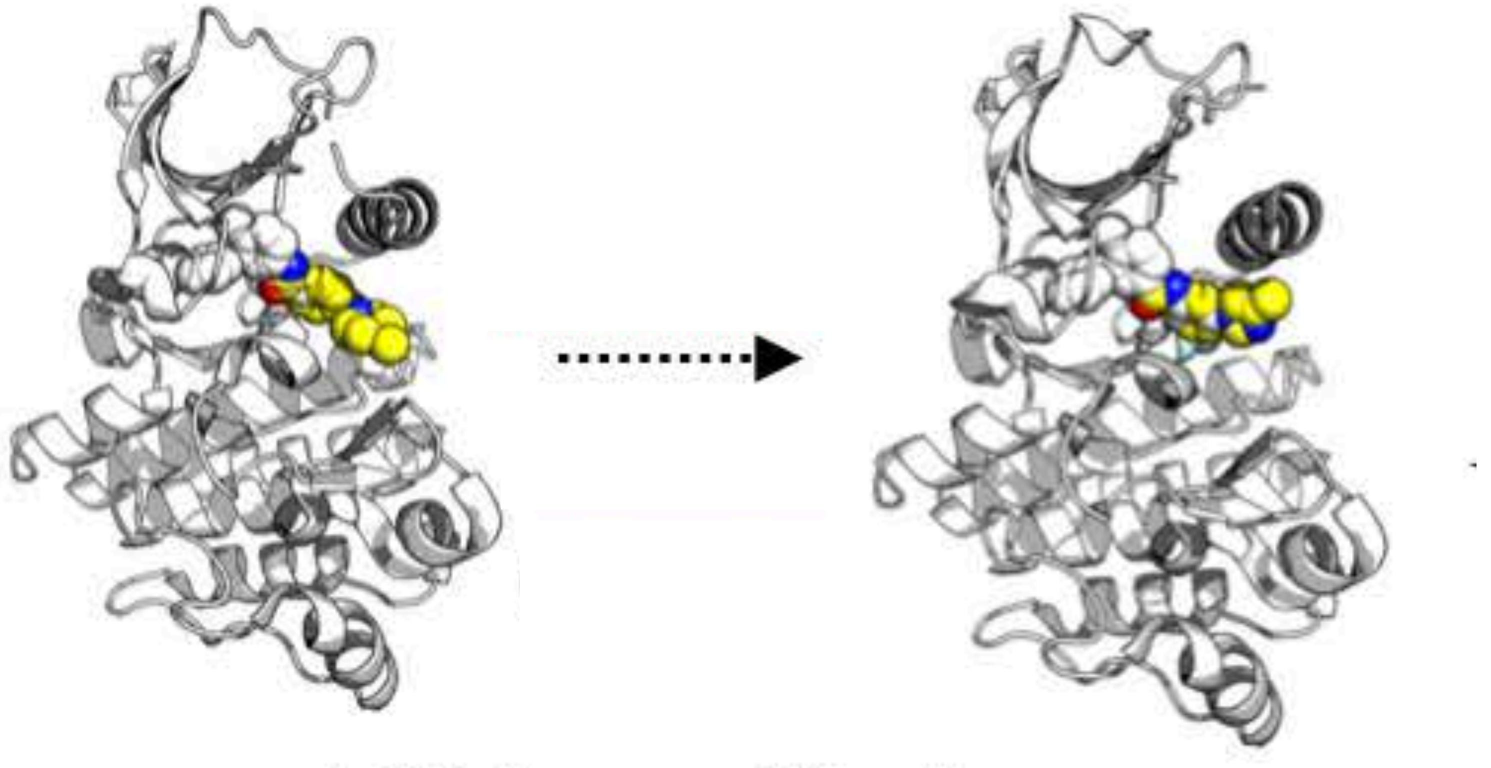


Aldeghi et al. JACS 139:946, 2017.
https://doi.org/10.1021/jacs.6b11467

ALCHEMICAL FREE ENERGY CALCULATIONS HAVE A BROAD DOMAIN OF APPLICABILITY

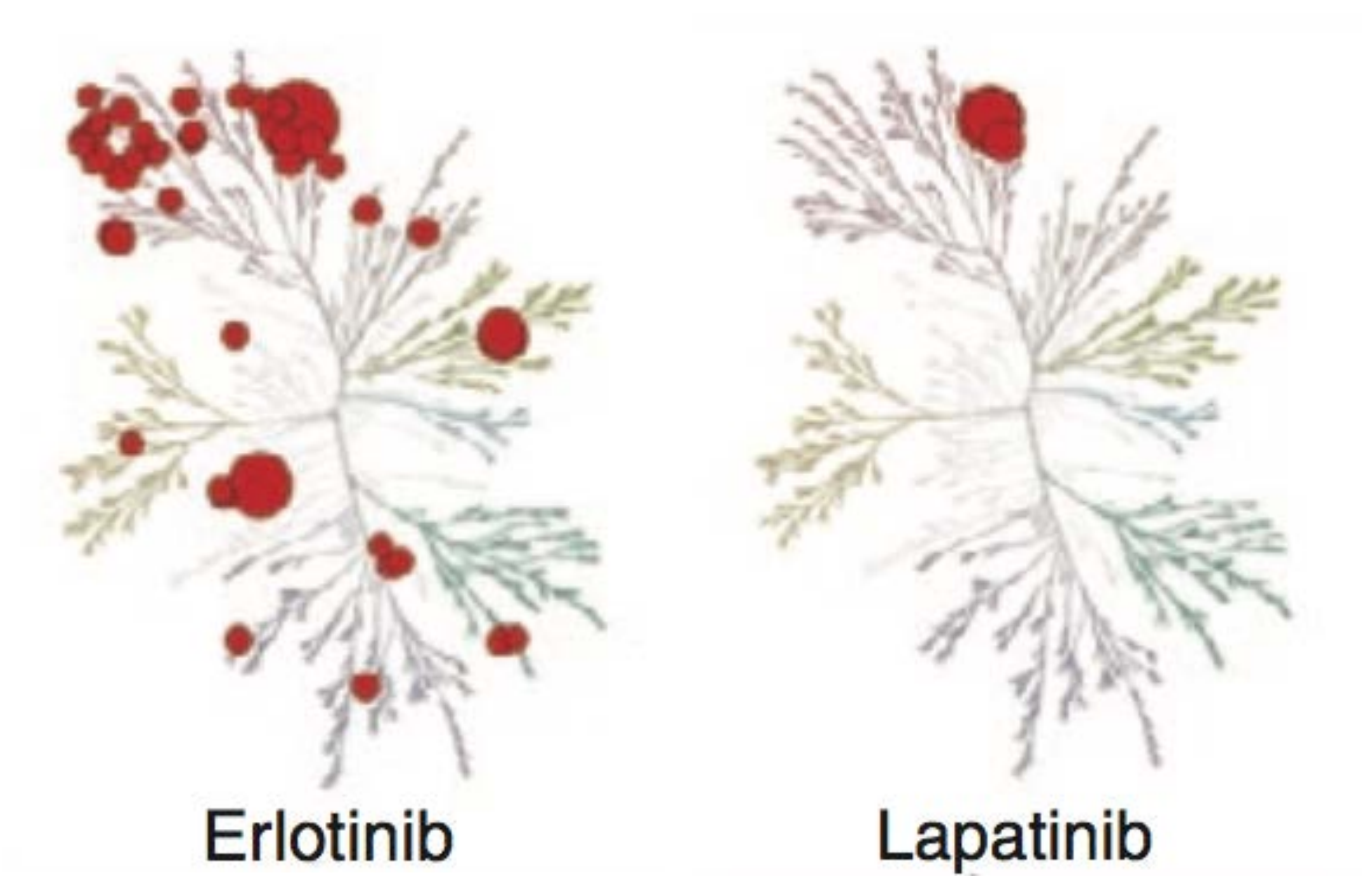
driving affinity / potency

Schindler, Baumann, Blum et al. JCIM 11:5457, 2020
https://doi.org/10.1021/acs.jcim.0c00900



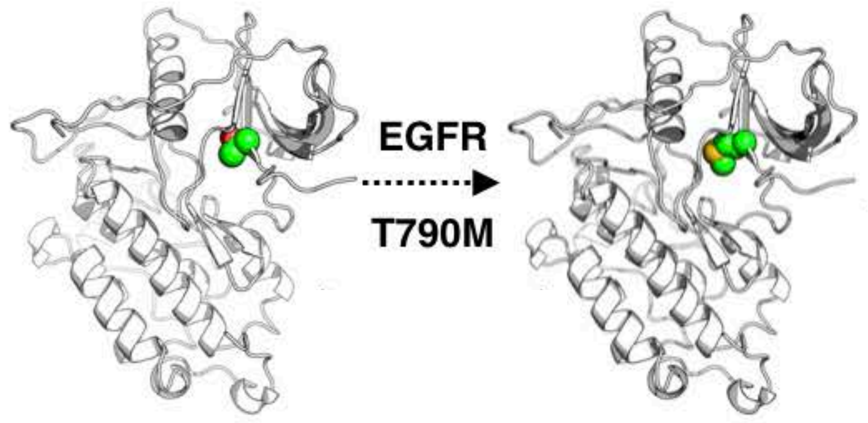
driving selectivity

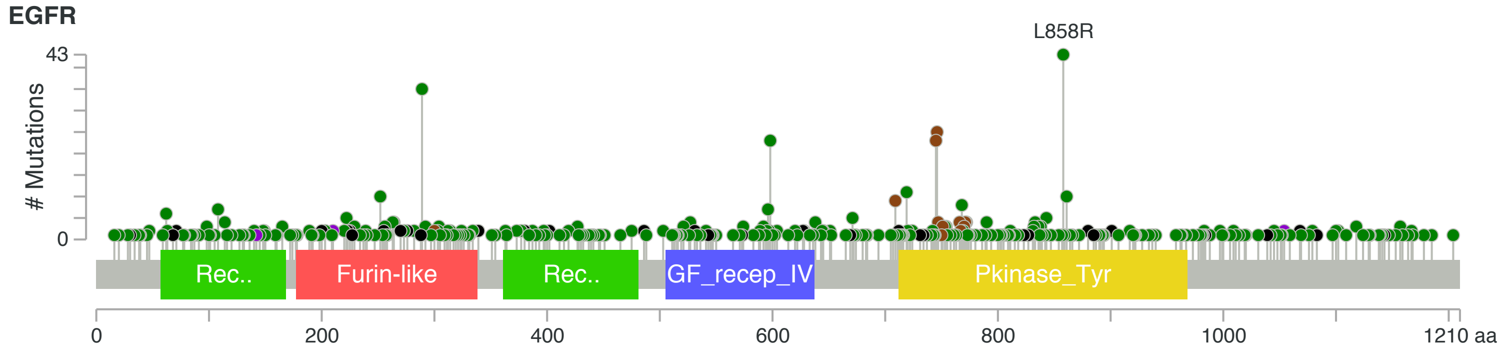
Moraca, Negri, de Olivera, Abel JCIM 2019
https://doi.org/10.1021/acs.jcim.9b00106
Aldeghi et al. JACS 139:946, 2017.
https://doi.org/10.1021/jacs.6b11467



predicting clinical drug resistance/sensitivity

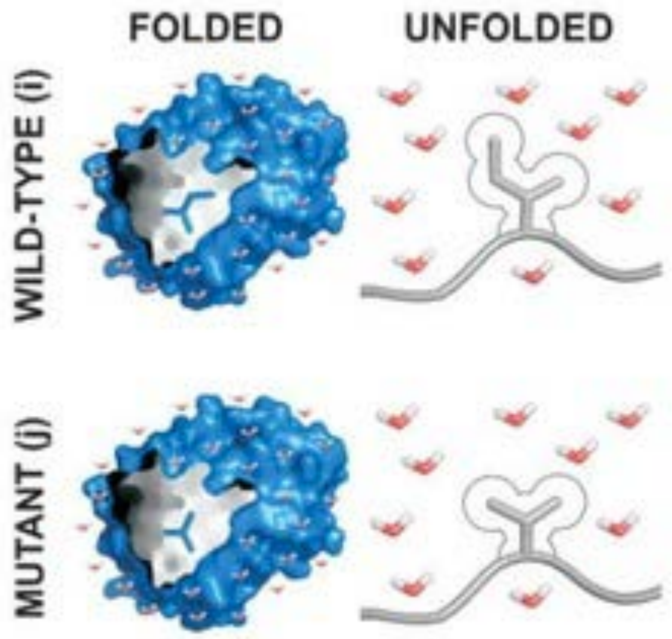
Hauser, Negron, Albanese, Ray, Steinbrecher, Abel, Chodera, Wang. Communications Biology 1:70, 2018
https://doi.org/10.1038/s42003-018-0075-x
Aldeghi, Gapsys, de Groot. ACS Central Science 4:1708, 2018
https://doi.org/10.1021/acscentsci.8b00717

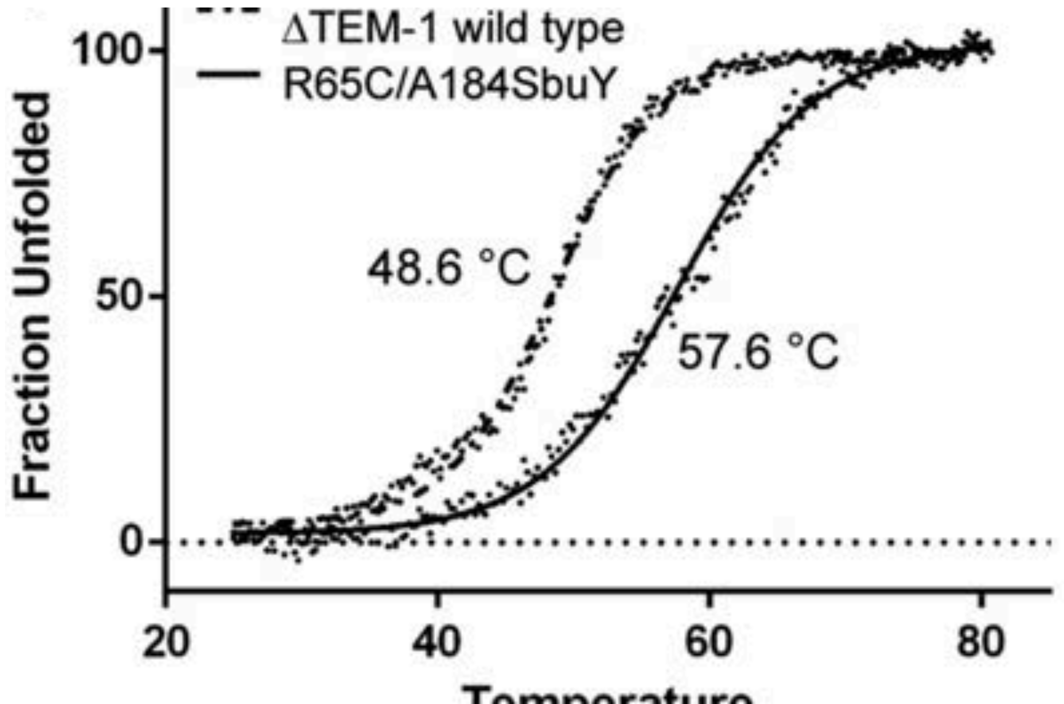




optimizing thermostability

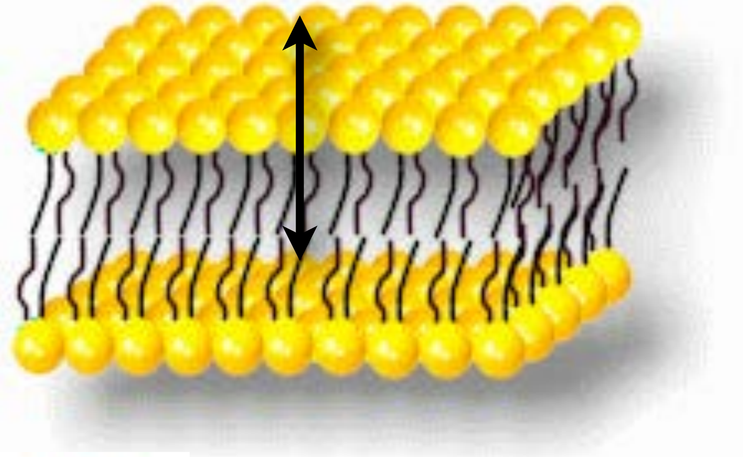
Gapsys, Michielssens, Seeliger, and de Groot. Angew Chem 55:7364, 2016
https://doi.org/10.1002/anie.201510054



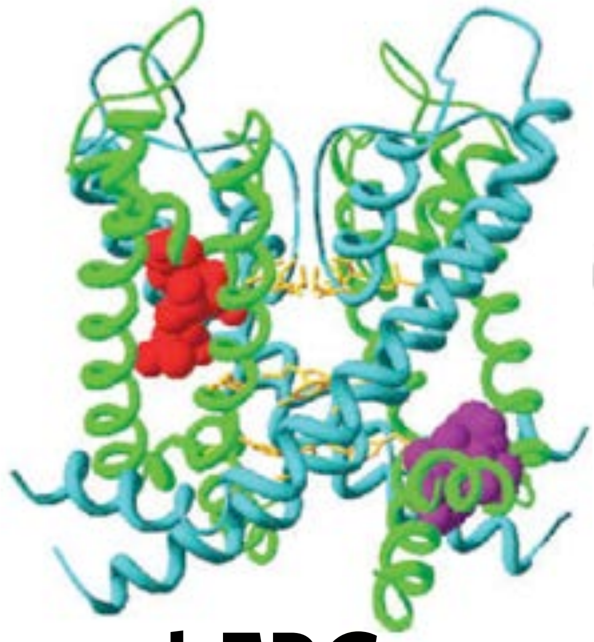


…AND HOLD THE POTENTIAL FOR EVEN BROADER APPLICABILITY AS MORE STRUCTURAL DATA EMERGES

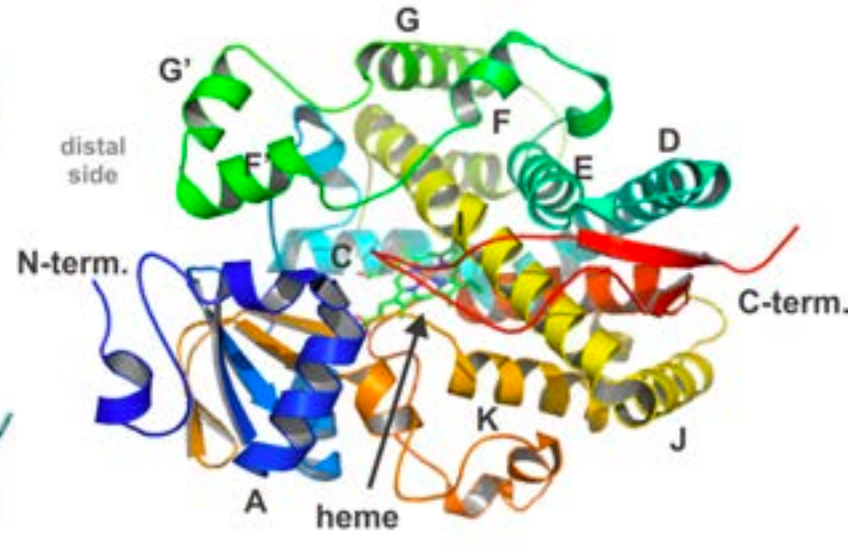
partition coefficients (logP, logD) and permeabilities



structure-enabled ADME/Tox targets

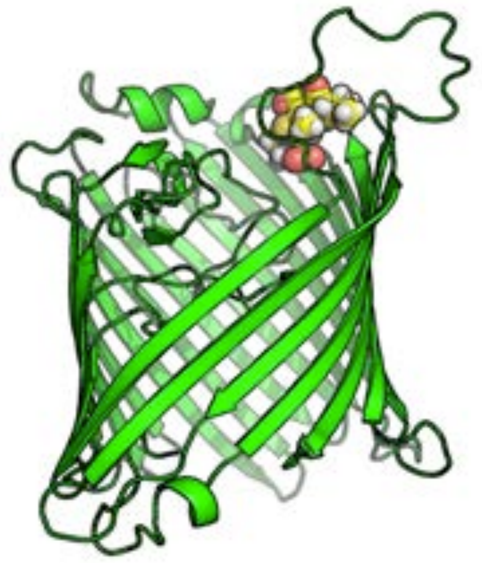


hERG

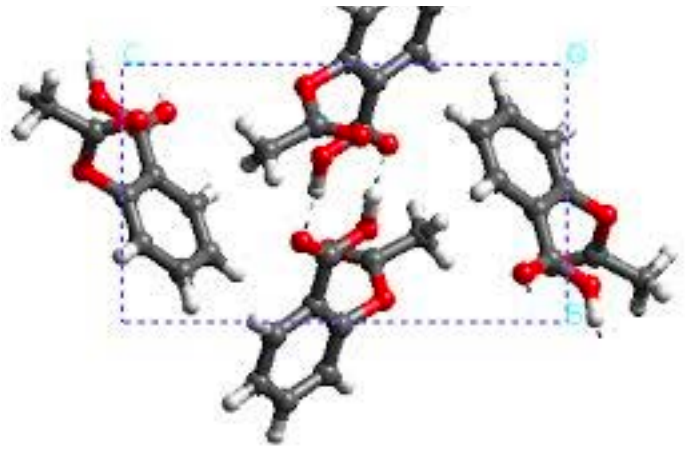


CYP3A4

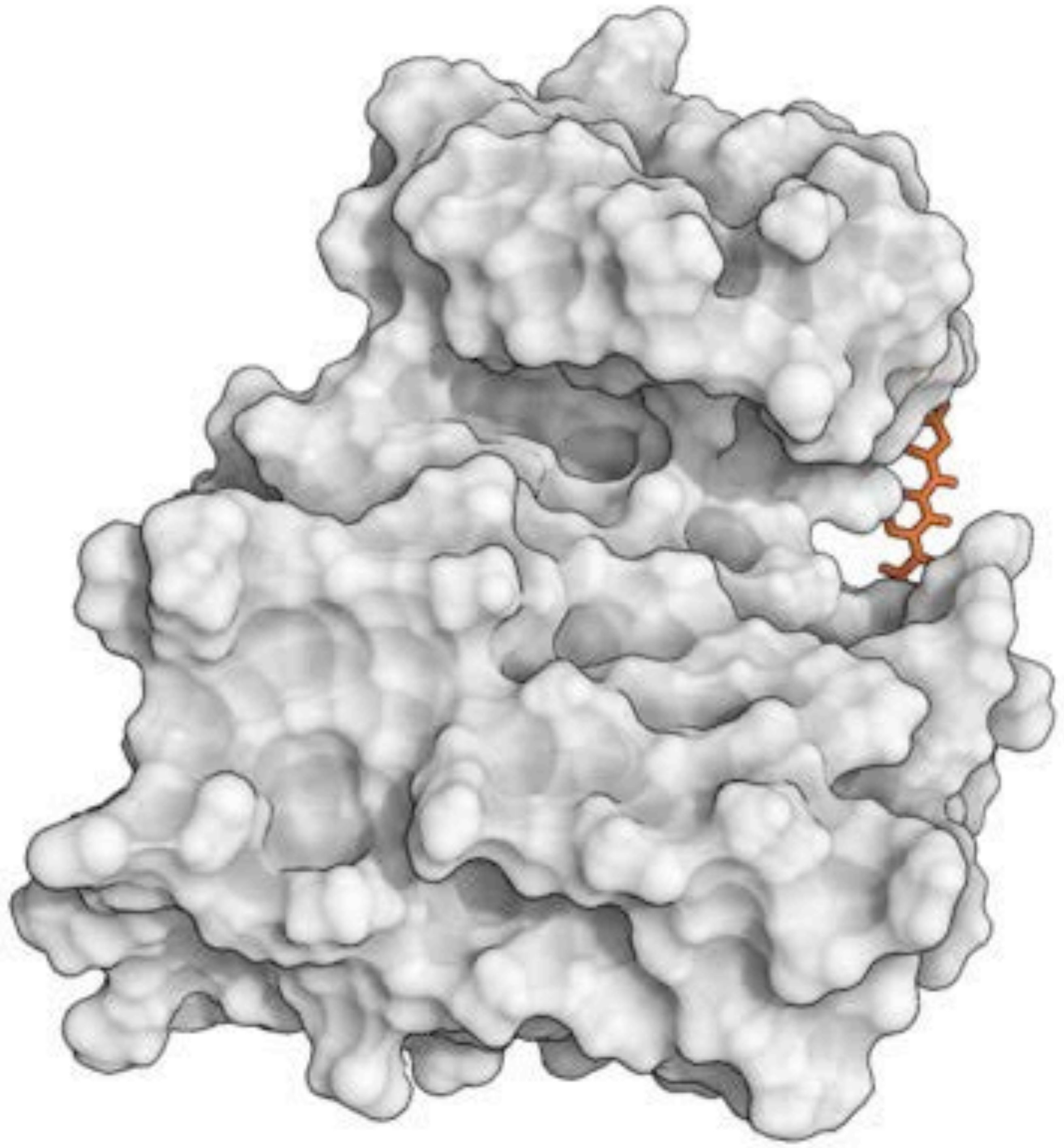
porin permeation



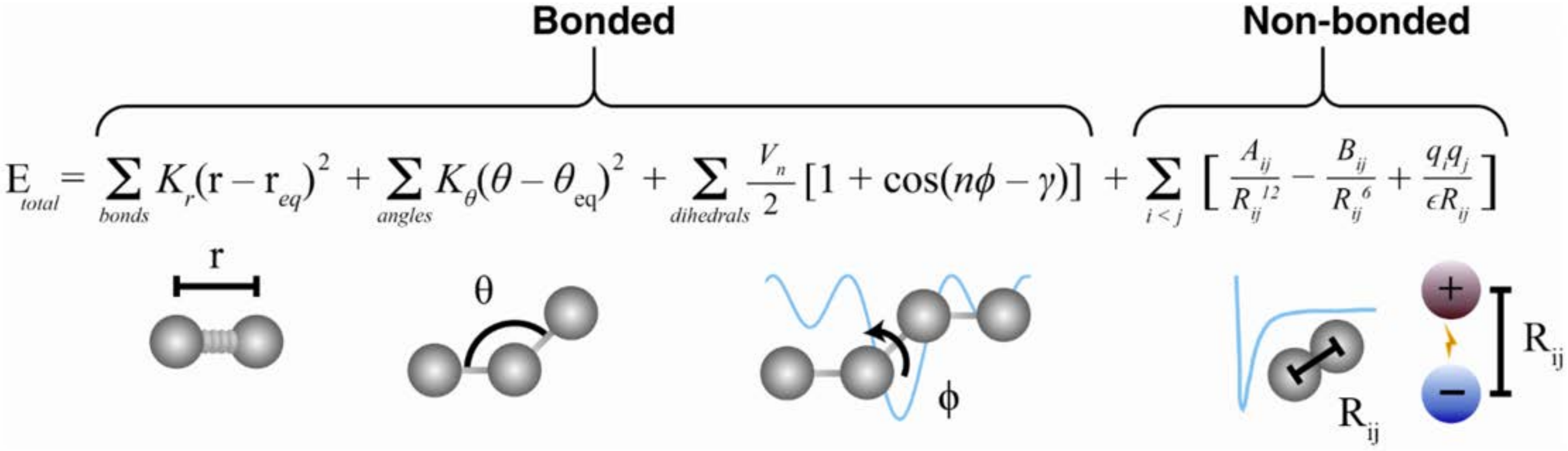
crystal polymorphs, etc.



FREE ENERGY CALCULATIONS (AND MUCH OF COMP CHEM) FUNDAMENTALLY RELIES ON MOLECULAR MECHANICS FORCE FIELDS



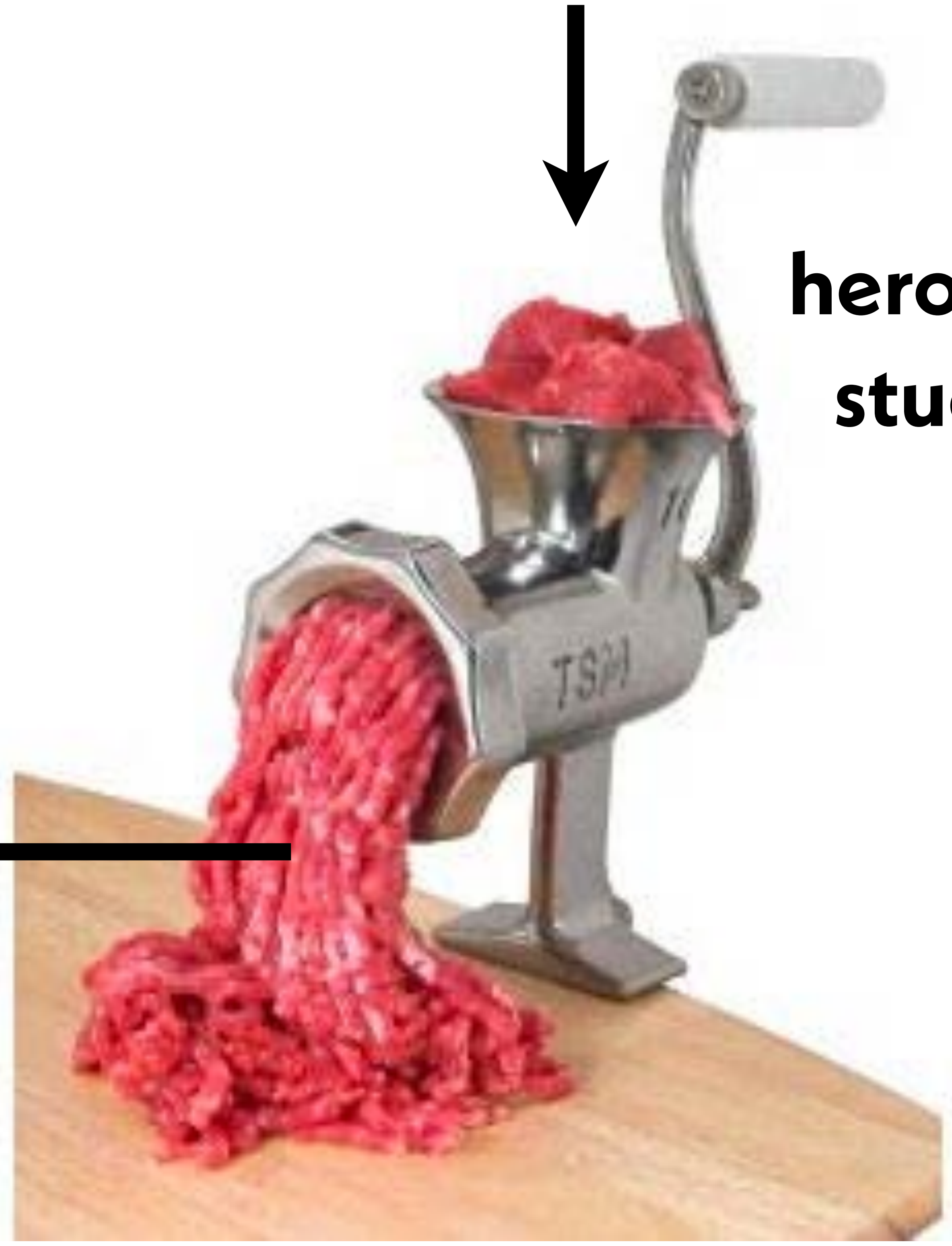
typical class I molecular mechanics force field



$$E_{total} = \underbrace{\sum_{bonds} K_r(\mathrm{r}-\mathrm{r}_{eq})^2 + \sum_{angles} K_\theta(\theta-\theta_{eq})^2 + \sum_{dihedrals} \frac{V_n}{2}[1+\cos(n\phi-\gamma)]}_{\text{Bonded}} + \underbrace{\sum_{i<j}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\epsilon R_{ij}}\right]}_{\text{Non-bonded}}$$

Shan, Kim, Eastwood, Dror, Seeliger, Shaw. JACS 133:9181, 2011
Durrant, McCammon. Molecular dynamics simulations and drug discovery. BMC Biology, 2011

FORCE FIELDS HAVE TRADITIONALLY BEEN HEROIC PRODUCTS OF HUMAN EFFORT

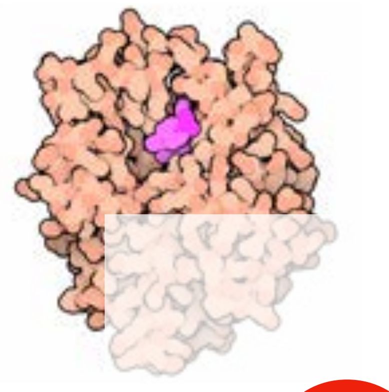


experimental data
quantum chemistry
keen chemical intuition

heroic effort by graduate
students and postdocs

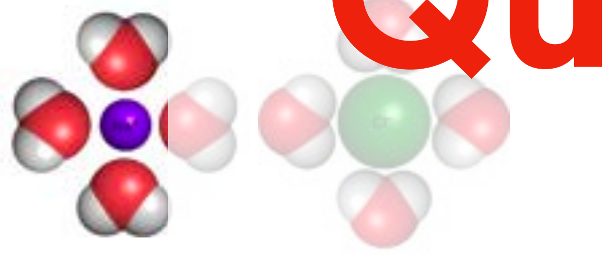
a parameter set we
desperately hope someone
actually uses

FORCE FIELDS HAVE TRADITIONALLY BEEN HEROIC PRODUCTS OF HUMAN EFFORT



proteins

post-translational modifications

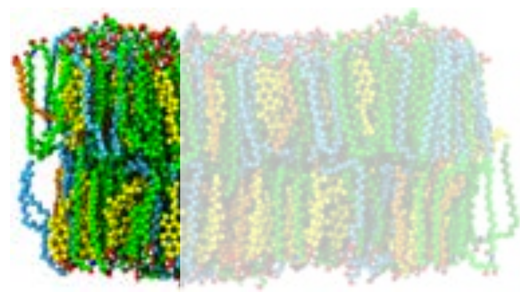


water

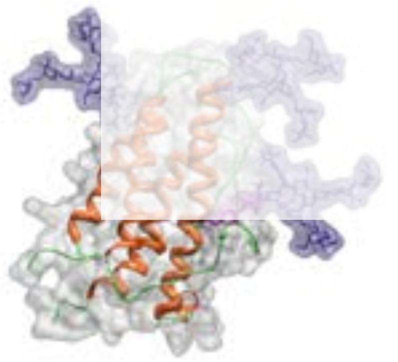
ions

small molecules

nucleic acids



lipids



carbohydrates

Quickly adds up to >100 human-years

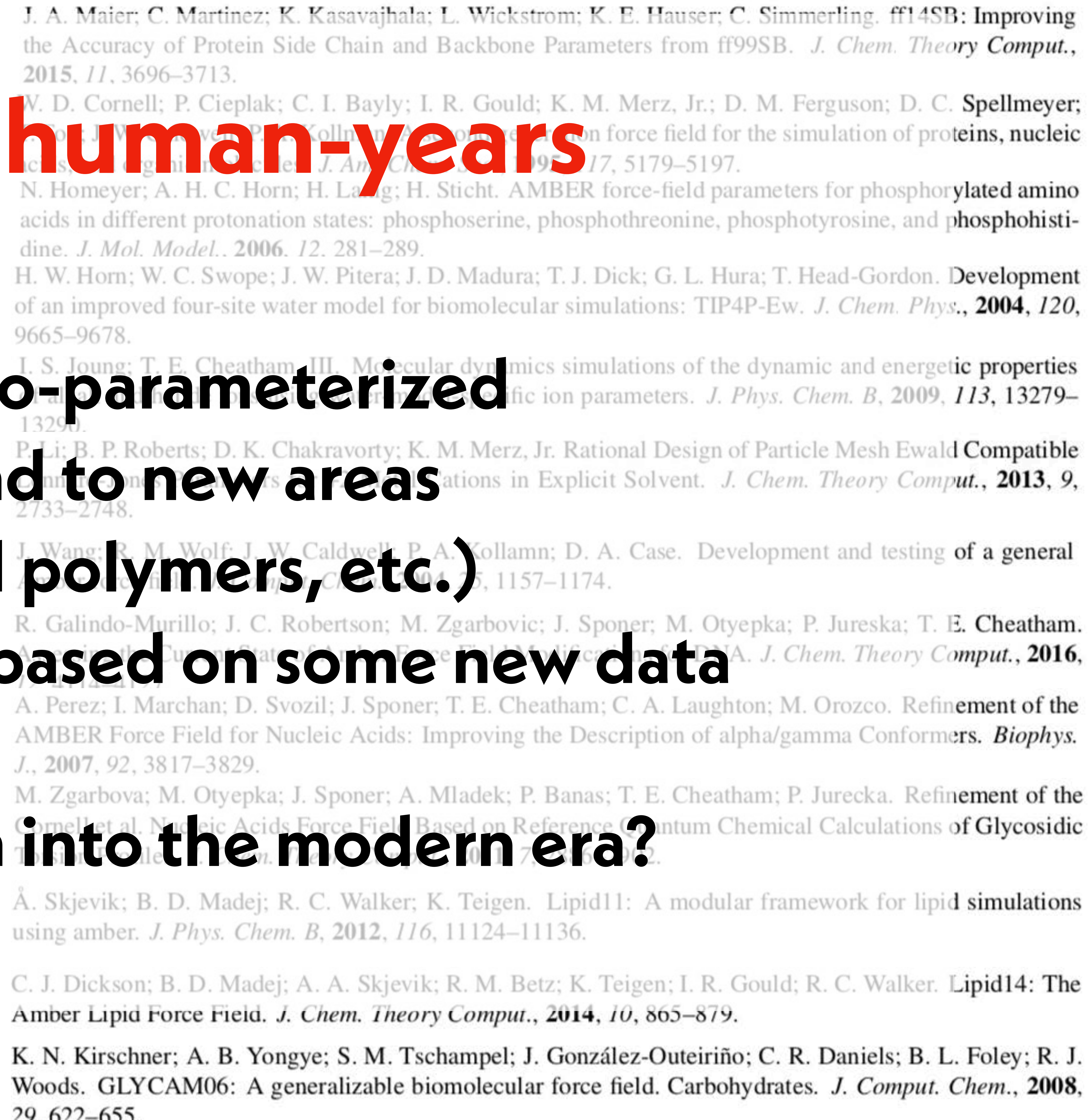
Intended to be compatible, but not co-parameterized

Significant effort is required to extend to new areas (e.g. covalent inhibitors, bio-inspired polymers, etc.)

Nobody is going to want to refit this based on some new data

How can we bring this problem into the modern era?

Amber20 recommendations



J. A. Maier; C. Martinez; K. Kasavajhala; L. Wickstrom; K. E. Hauser; C. Simmerling. ff14SB: Improving the Accuracy of Protein Side Chain and Backbone Parameters from ff99SB. *J. Chem. Theory Comput.*, **2015**, *11*, 3696–3713.

W. D. Cornell; P. Cieplak; C. I. Bayly; I. R. Gould; K. M. Merz, Jr.; D. M. Ferguson; D. C. Spellmeyer; T. Fox; J. W. Caldwell; P. A. Kollman. A second generation force field for the simulation of proteins, nucleic acids, and organic molecules. *J. Am. Chem. Soc.*, **1995**, *117*, 5179–5197.

N. Homeyer; A. H. C. Horn; H. Lang; H. Sticht. AMBER force-field parameters for phosphorylated amino acids in different protonation states: phosphoserine, phosphothreonine, phosphotyrosine, and phosphohistidine. *J. Mol. Model.*, **2006**, *12*, 281–289.

H. W. Horn; W. C. Swope; J. W. Pitera; J. D. Madura; T. J. Dick; G. L. Hura; T. Head-Gordon. Development of an improved four-site water model for biomolecular simulations: TIP4P-Ew. *J. Chem. Phys.*, **2004**, *120*, 9665–9678.

I. S. Joung; T. E. Cheatham, III. Molecular dynamics simulations of the dynamic and energetic properties of alkali and halide ions using water-model-specific ion parameters. *J. Phys. Chem. B*, **2009**, *113*, 13279–13290.

P. Li; B. P. Roberts; D. K. Chakravorty; K. M. Merz, Jr. Rational Design of Particle Mesh Ewald Compatible Lennard-Jones Parameters for +2 Metal Cations in Explicit Solvent. *J. Chem. Theory Comput.*, **2013**, *9*, 2733–2748.

J. Wang; R. M. Wolf; J. W. Caldwell; P. A. Kollamn; D. A. Case. Development and testing of a general Amber force field. *J. Comput. Chem.*, **2004**, *25*, 1157–1174.

R. Galindo-Murillo; J. C. Robertson; M. Zgarbovic; J. Sponer; M. Otyepka; P. Jureska; T. E. Cheatham. Assessing the Current State of Amber Force Field Modifications for DNA. *J. Chem. Theory Comput.*, **2016**, *12*, 4114–4127.

A. Perez; I. Marchan; D. Svozil; J. Sponer; T. E. Cheatham; C. A. Laughton; M. Orozco. Refinement of the AMBER Force Field for Nucleic Acids: Improving the Description of alpha/gamma Conformers. *Biophys. J.*, **2007**, *92*, 3817–3829.

M. Zgarbova; M. Otyepka; J. Sponer; A. Mladek; P. Banas; T. E. Cheatham; P. Jurecka. Refinement of the Cornell et al. Nucleic Acids Force Field Based on Reference Quantum Chemical Calculations of Glycosidic Torsion Profiles. *J. Chem. Theory Comput.*, **2011**, *7*, 2886–2902.

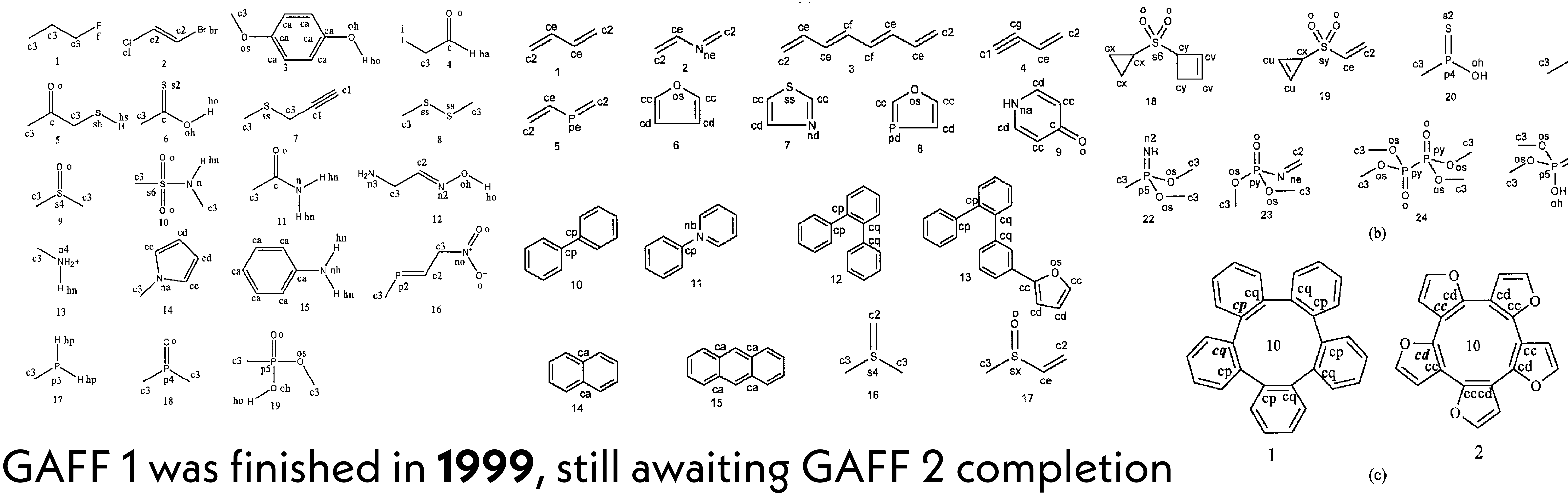
Å. Skjevik; B. D. Madej; R. C. Walker; K. Teigen. Lipid11: A modular framework for lipid simulations using amber. *J. Phys. Chem. B*, **2012**, *116*, 11124–11136.

C. J. Dickson; B. D. Madej; A. A. Skjevik; R. M. Betz; K. Teigen; I. R. Gould; R. C. Walker. Lipid14: The Amber Lipid Force Field. *J. Chem. Theory Comput.*, **2014**, *10*, 865–879.

K. N. Kirschner; A. B. Yongye; S. M. Tschampel; J. González-Outeiriño; C. R. Daniels; B. L. Foley; R. J. Woods. GLYCAM06: A generalizable biomolecular force field. Carbohydrates. *J. Comput. Chem.*, **2008**, *29*, 622–655.

AS DRUG DISCOVERY EXPLORES NEW PARTS OF CHEMICAL SPACE, HOW CAN FORCEFIELDS KEEP UP?

The Generalized Amber Forcefield (GAFF) only understands this space of chemistries:



GAFF 1 was finished in **1999**, still awaiting GAFF 2 completion

Extension to new chemical space is **nontrivial**

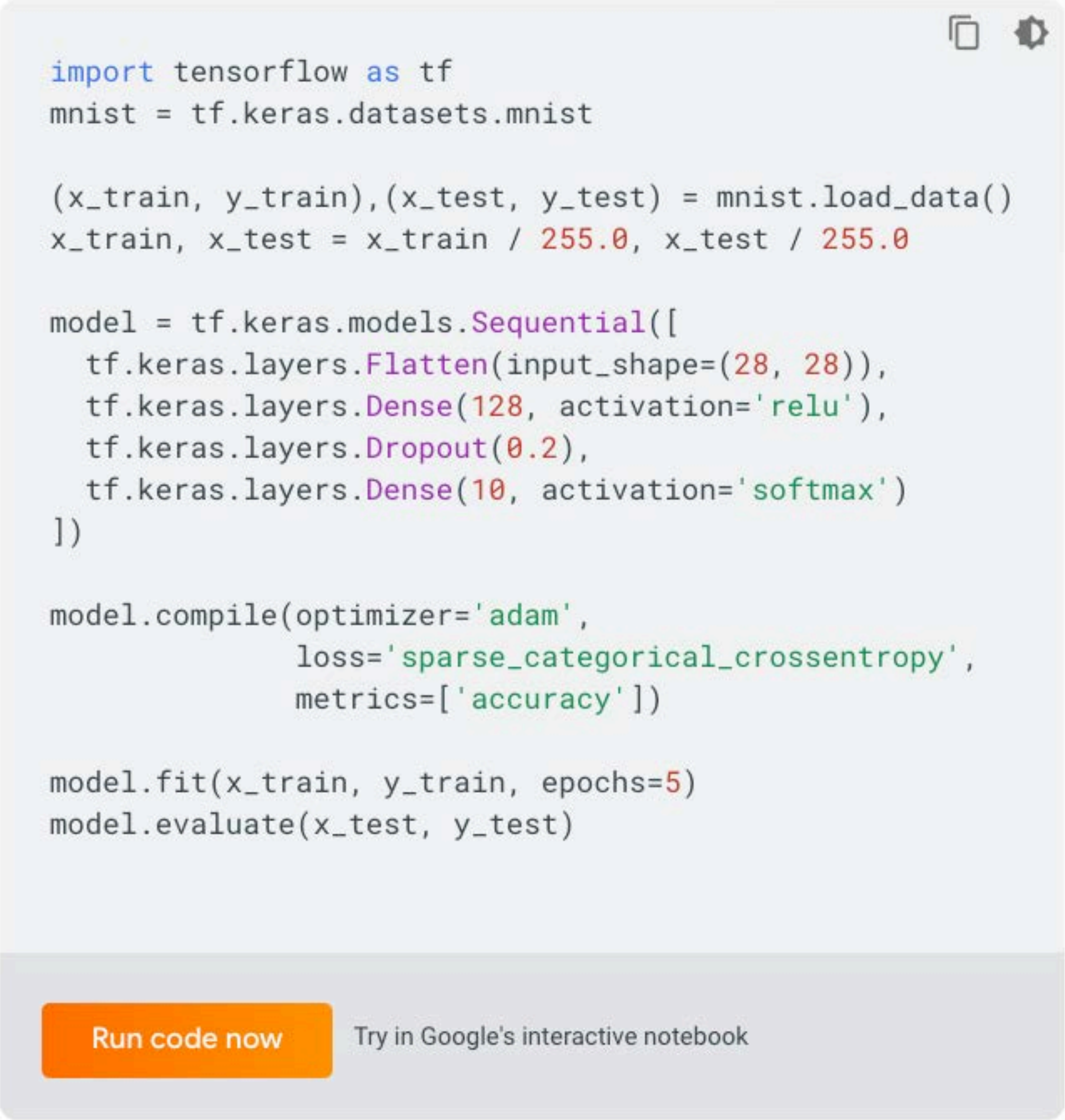
Parameter fitting code was **never released**

Atom types have introduced numerous **errors**

Wang J, Wolf RM, Caldwell JW, Kollman PA, and Case DA. J Comput Chem 25:1157, 2004.

CAN WE MAKE BUILDING BIMOLECULAR FORCE FIELDS AS EASY AS TRAINING A MACHINE LEARNING MODEL?

training a neural network



```python
import tensorflow as tf
mnist = tf.keras.datasets.mnist

(x_train, y_train),(x_test, y_test) = mnist.load_data()
x_train, x_test = x_train / 255.0, x_test / 255.0

model = tf.keras.models.Sequential([
  tf.keras.layers.Flatten(input_shape=(28, 28)),
  tf.keras.layers.Dense(128, activation='relu'),
  tf.keras.layers.Dropout(0.2),
  tf.keras.layers.Dense(10, activation='softmax')
])

model.compile(optimizer='adam',
              loss='sparse_categorical_crossentropy',
              metrics=['accuracy'])

model.fit(x_train, y_train, epochs=5)
model.evaluate(x_test, y_test)
```

https://www.tensorflow.org/overview

import your tools

grab a standard, curated dataset

define a novel model architecture

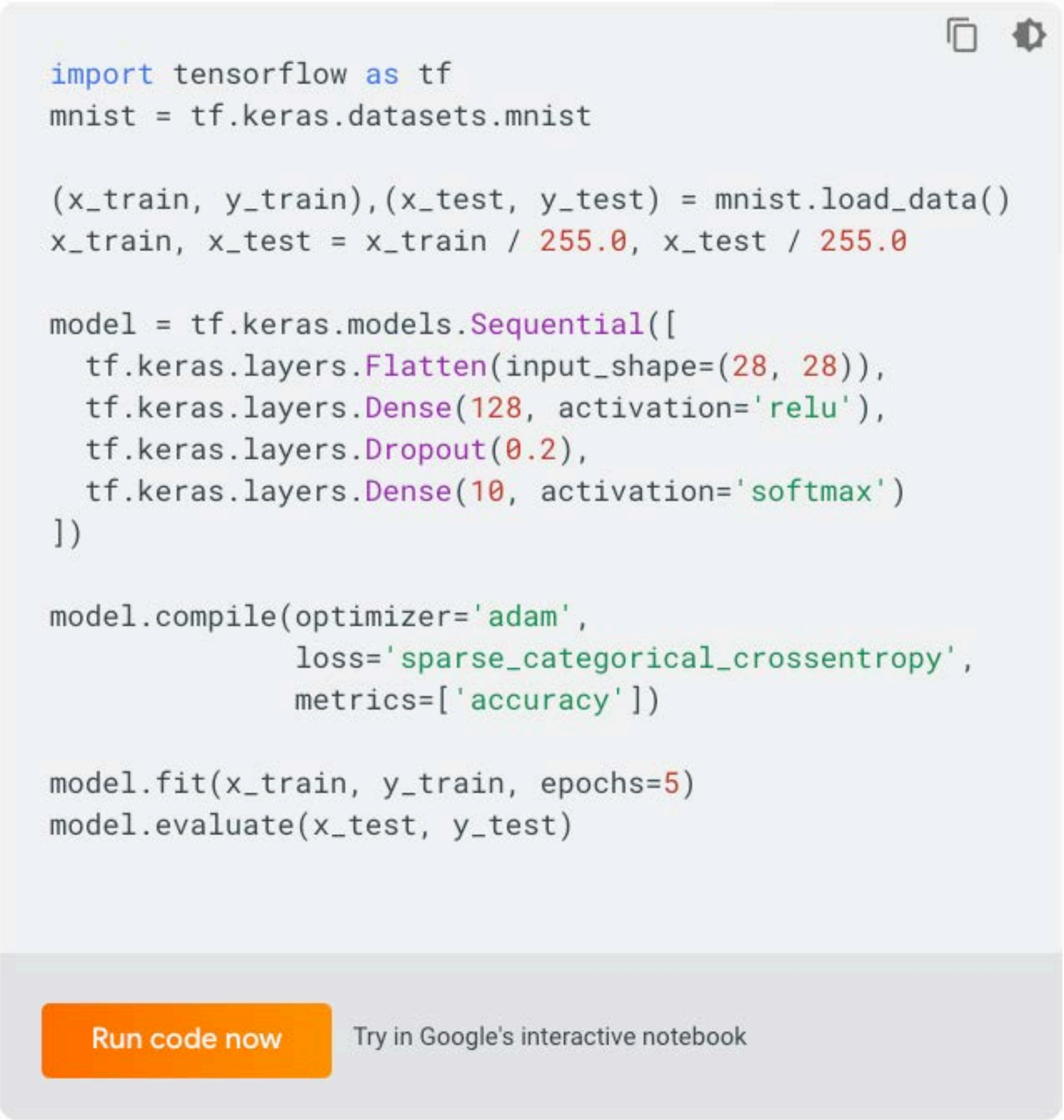
declare your objectives in training it

fit it

use it

CAN WE MAKE BUILDING BIMOLECULAR FORCE FIELDS AS EASY AS TRAINING A MACHINE LEARNING MODEL?

training a neural network



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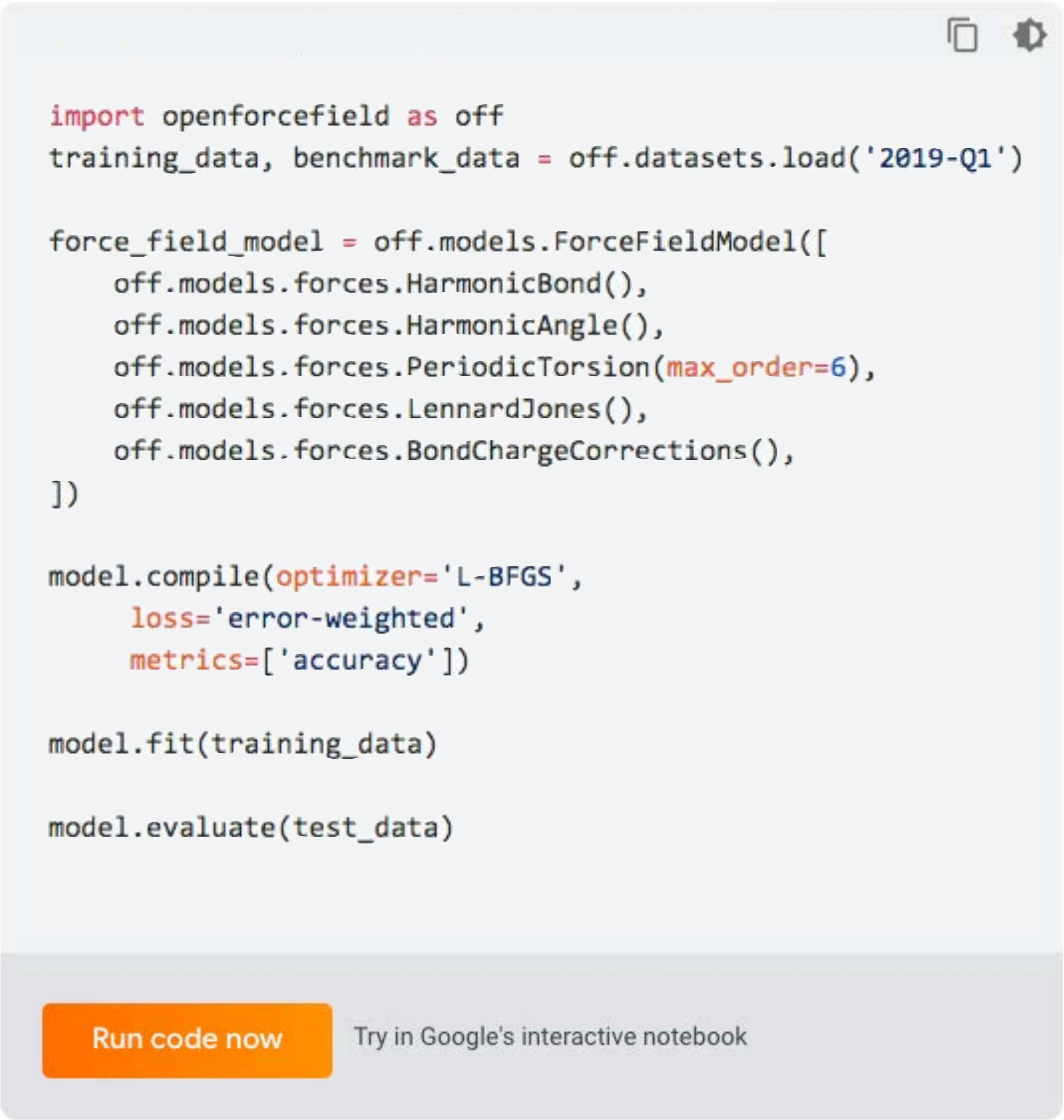
model.evaluate(x_test, y_test)
```

https://www.tensorflow.org/overview

fitting a force field



```
import openforcefield as off
training_data, benchmark_data = off.datasets.load('2019-Q1')

force_field_model = off.models.ForceFieldModel([
    off.models.forces.HarmonicBond(),
    off.models.forces.HarmonicAngle(),
    off.models.forces.PeriodicTorsion(max_order=6),
    off.models.forces.LennardJones(),
    off.models.forces.BondChargeCorrections(),
])

model.compile(optimizer='L-BFGS',
     loss='error-weighted',
     metrics=['accuracy'])

model.fit(training_data)

model.evaluate(test_data)
```

open forcefield

An open and collaborative approach to better force fields

OPEN SOURCE

Software permissively licensed under the MIT License and developed openly on GitHub.

OPEN SCIENCE

Scientific reports as blog posts, webinars and preprints

OPEN DATA

Curated quantum chemical and experimental datasets used to parameterize and benchmark Open Force Fields.

http://openforcefield.org

THE OPEN FORCE FIELD INITIATIVE AIMS TO BUILD A MODERN INFRASTRUCTURE FOR FORCE FIELD SCIENCE

Open source Python Toolkit: use the parameters in most simulation packages

Open curated QM / physical property datasets: build your own force fields
MolSSI QCArchive quantum chemical data: http://qcarchive.molssi.org

Open source infrastructure: for improving force fields with in-house data

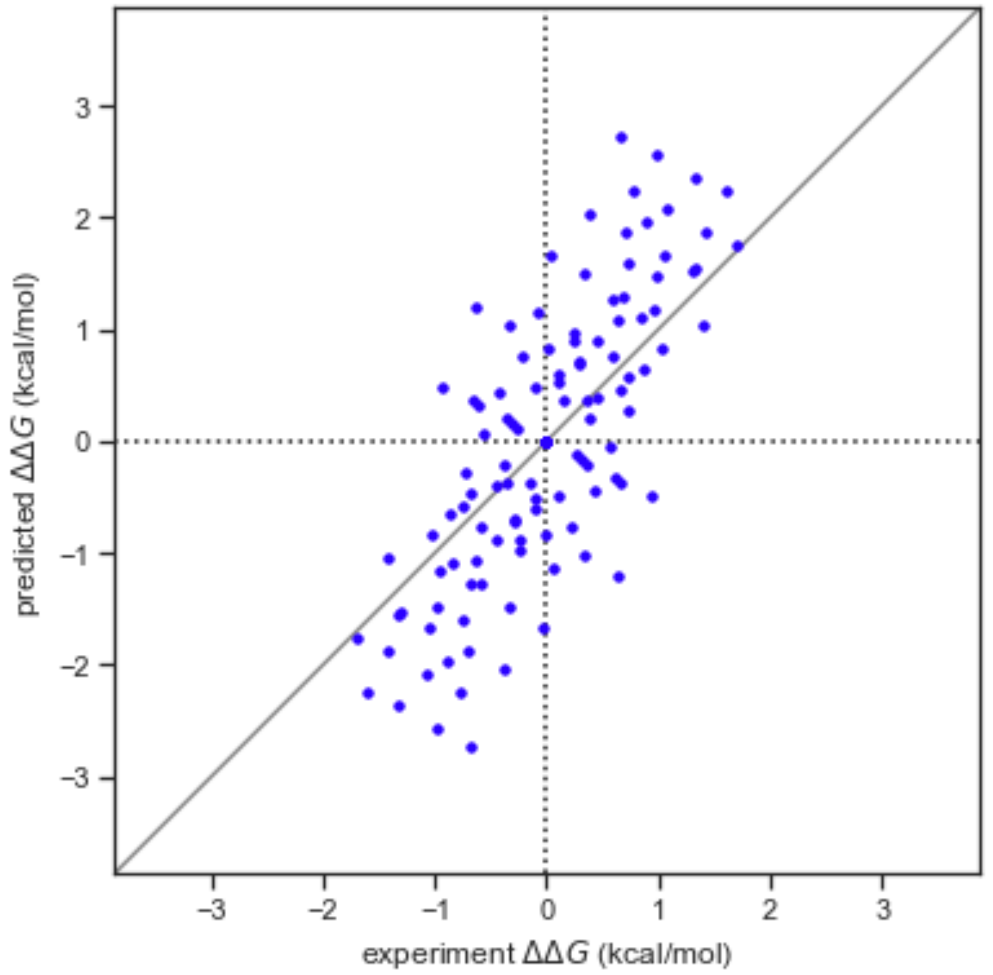
Open science: everything we do is free, permissively licensed, and online

http://openforcefield.org

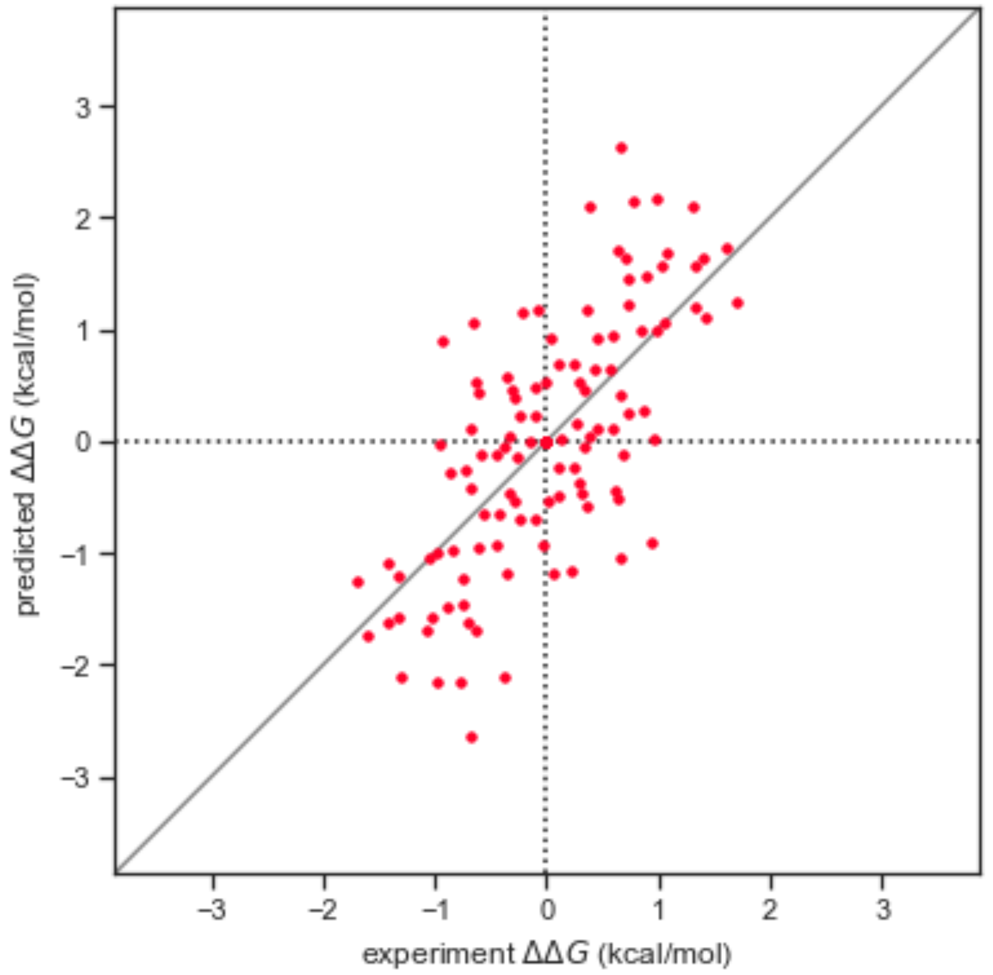
WE’VE MADE RAPID AND SIGNIFICANT PROGRESS IN ACCURACY, BUT WE’RE STILL STICK WITH SLOW GENERATIONS

Open Force Field Initiative

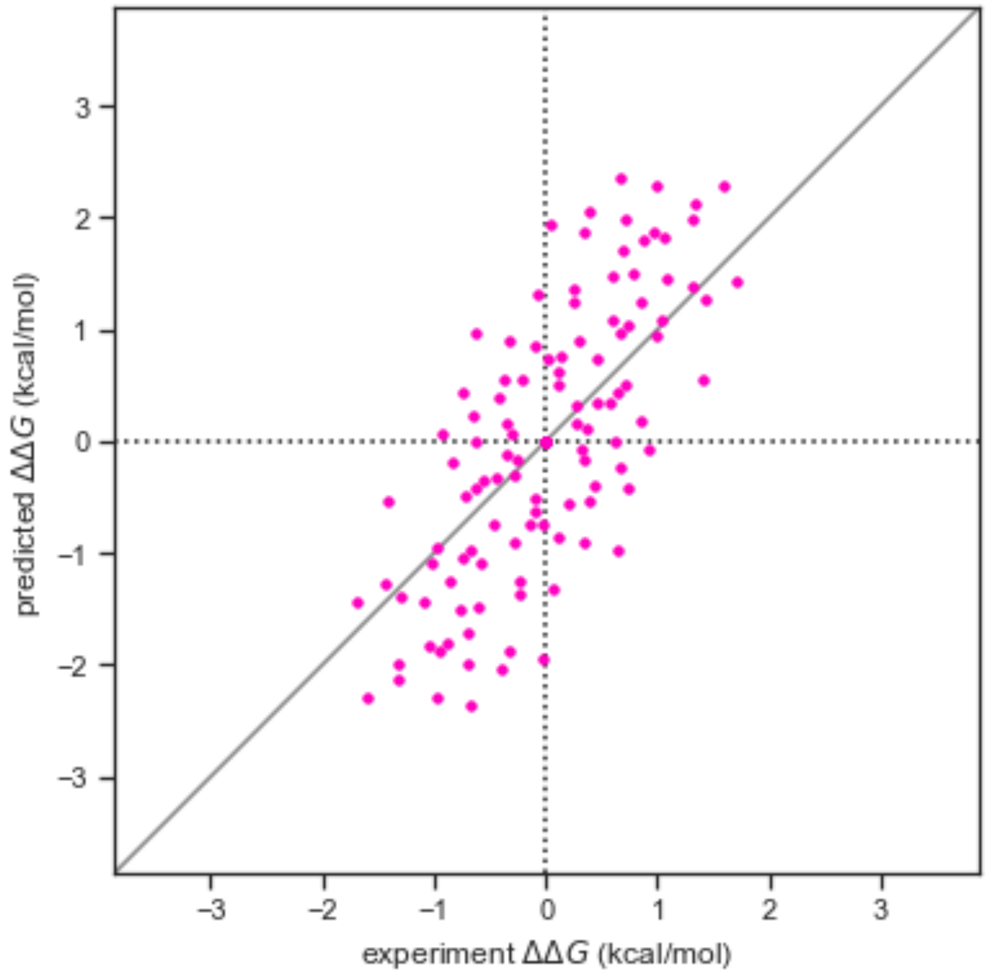
GAFF 1 (1999)



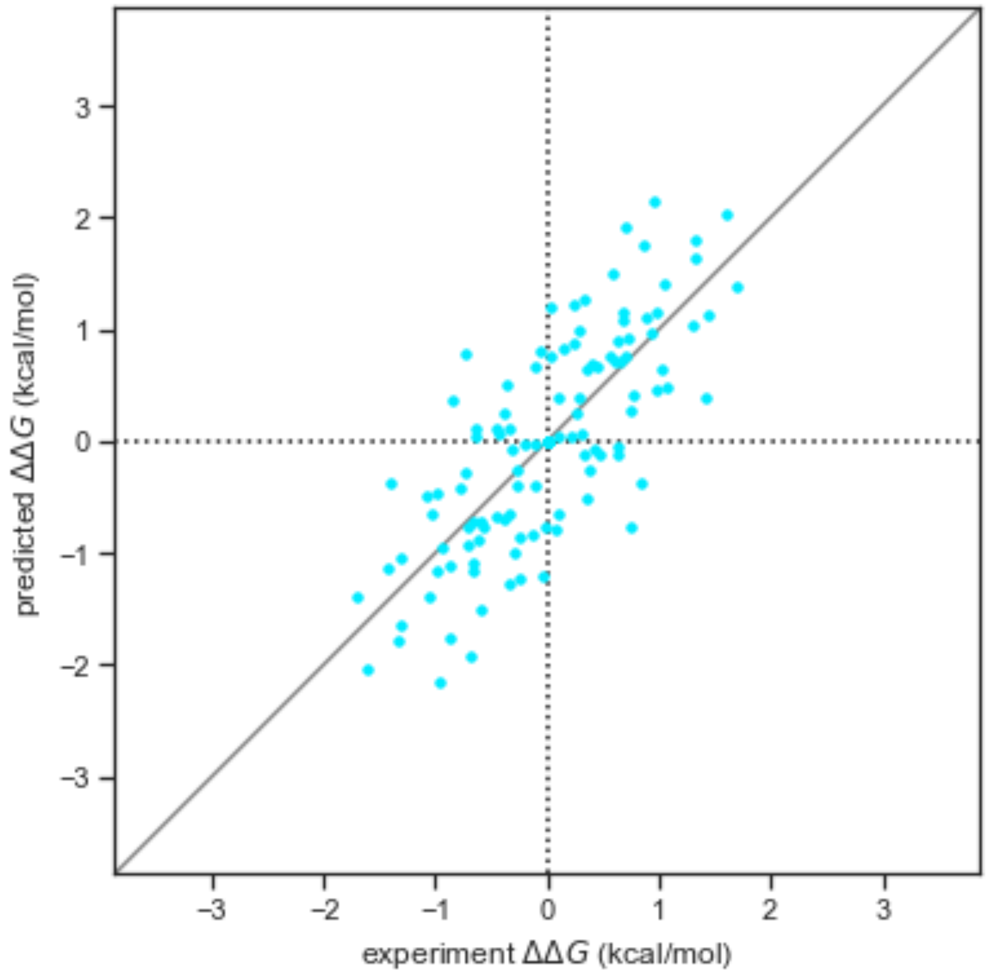
OPLS2.1 (2015)



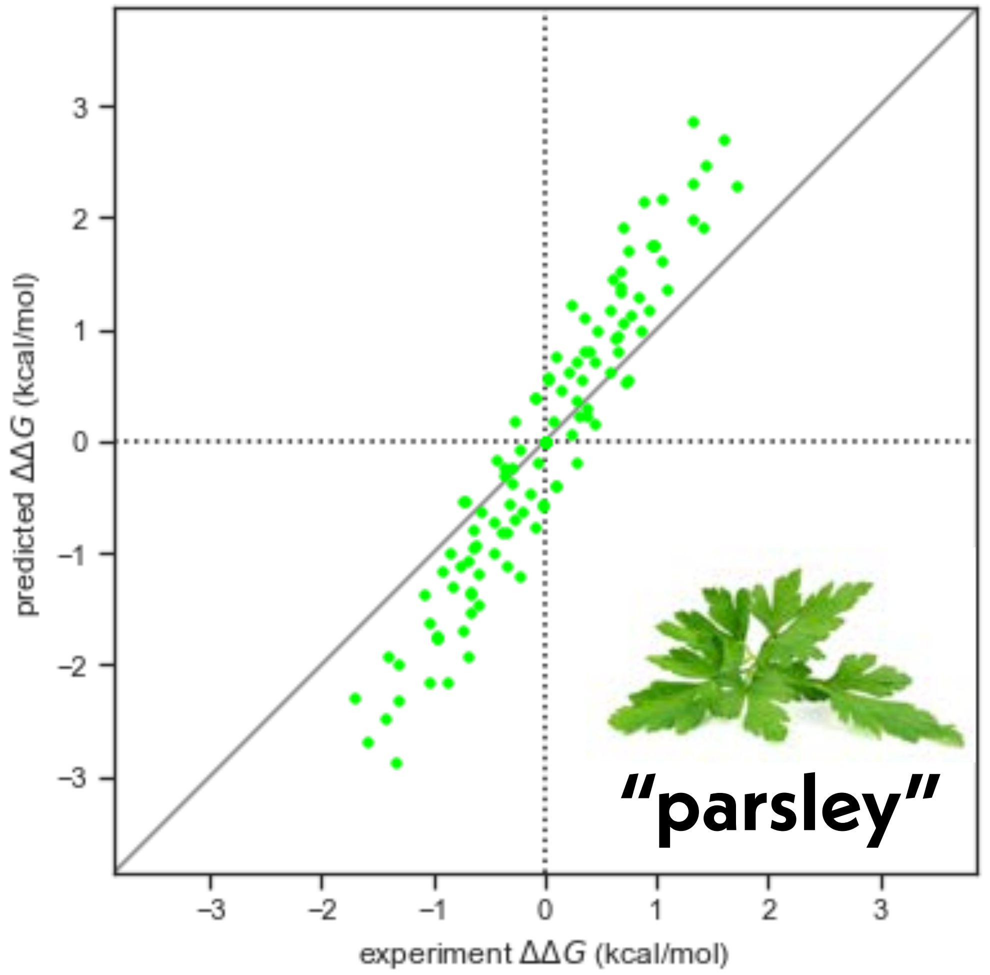
GAFF 2 (2016)



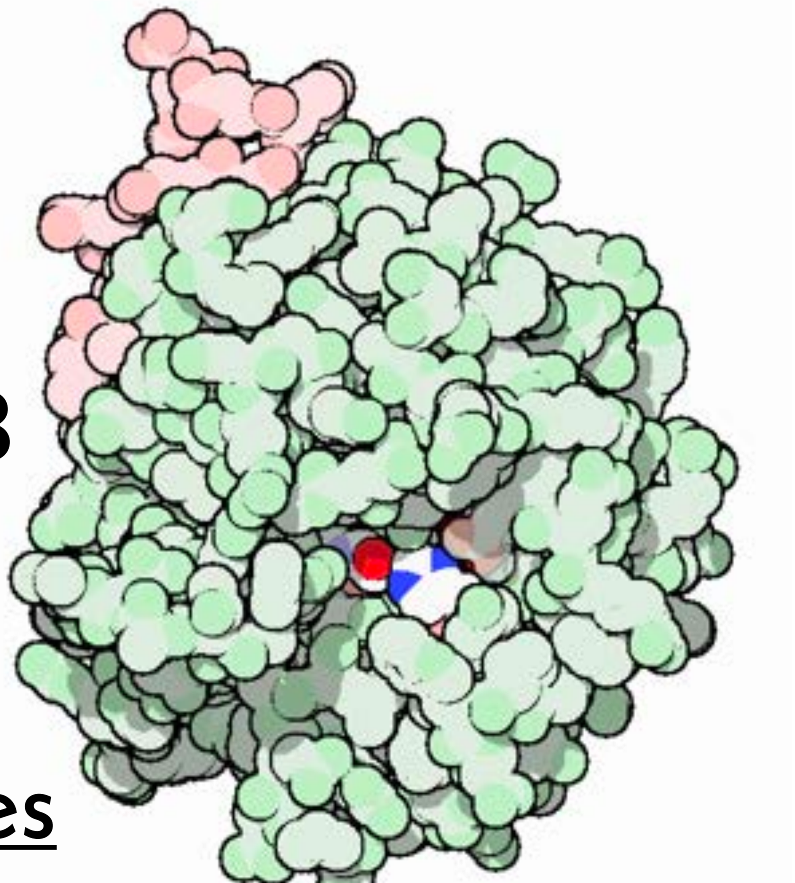
smirnoff99Frosst (2018)



openff 1.0 (2019)



thrombin
PDB101: 1PPB

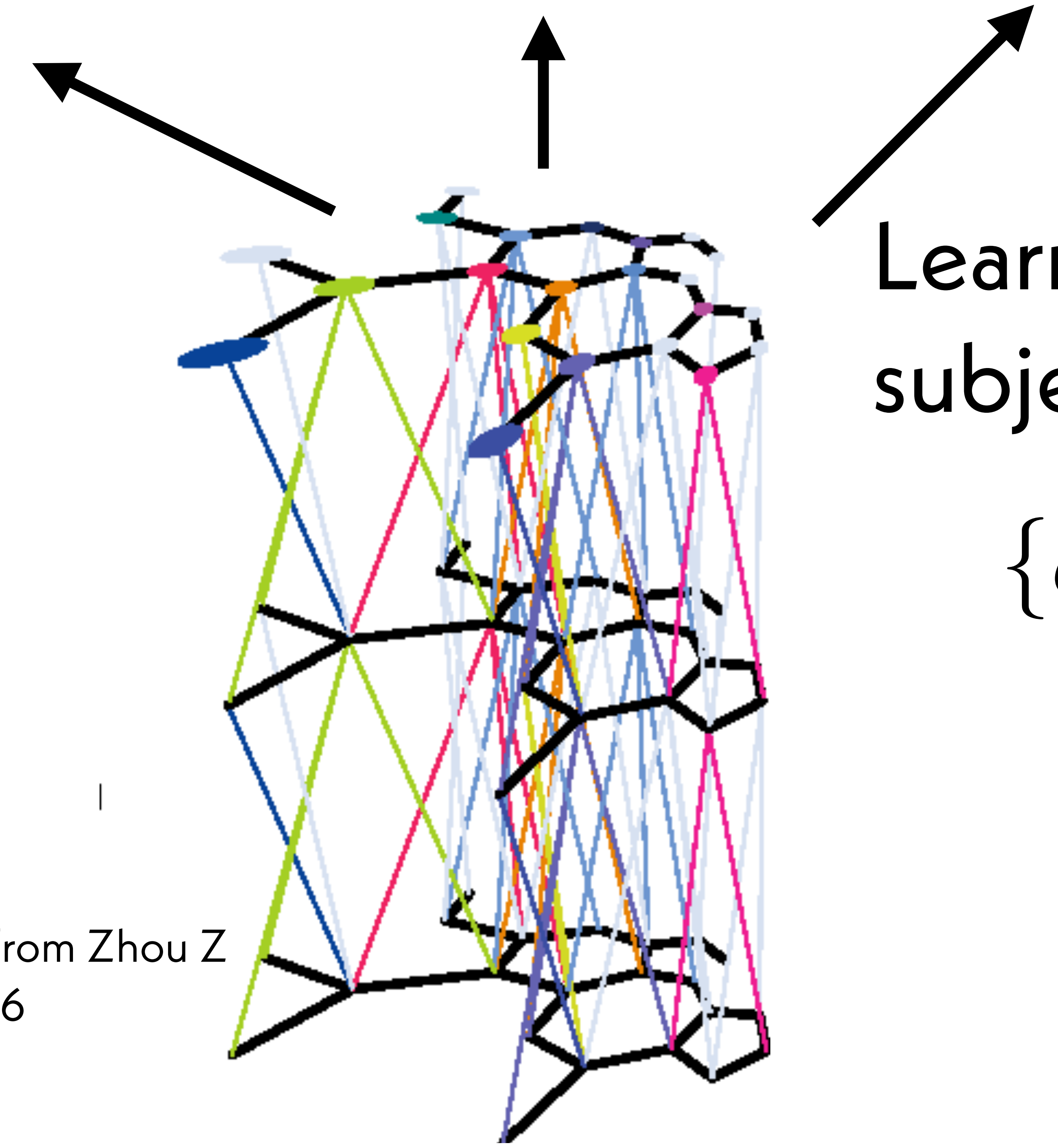


HANNAH BRUCE MACDONALD
MSKCC

http://github.com/choderalab/perses

DOMINIC RUFA

NEW GENERATIONS OF MACHINE LEARNING MODELS ARE PARTICULARLY WELL-SUITED TO CHEMISTRY



molecule

bond

atom

predict properties

Figure adapted from Zhou Z arXiv:1706.09916

$$\mathbf{e}_k^{(t+1)} = \phi^e(\mathbf{e}_k^{(t)}, \sum_{i \in \mathcal{N}_k^e} \mathbf{v}_i, \mathbf{u}^{(t)}), \qquad \text{(edge update)}$$

$$\bar{\mathbf{e}}_i^{(t+1)} = \rho^{e \to v}(E_i^{(t+1)}), \qquad \text{(edge to node aggregate)}$$

$$\mathbf{v}_i^{(t+1)} = \phi^v(\bar{\mathbf{e}}_i^{(t+1)}, \mathbf{v}_i^{(t)}, \mathbf{u}^{(t)}), \qquad \text{(node update)}$$

$$\bar{\mathbf{e}}^{(t+1)} = \rho^{e \to u}(E^{(t+1)}), \qquad \text{(edge to global aggregate)}$$

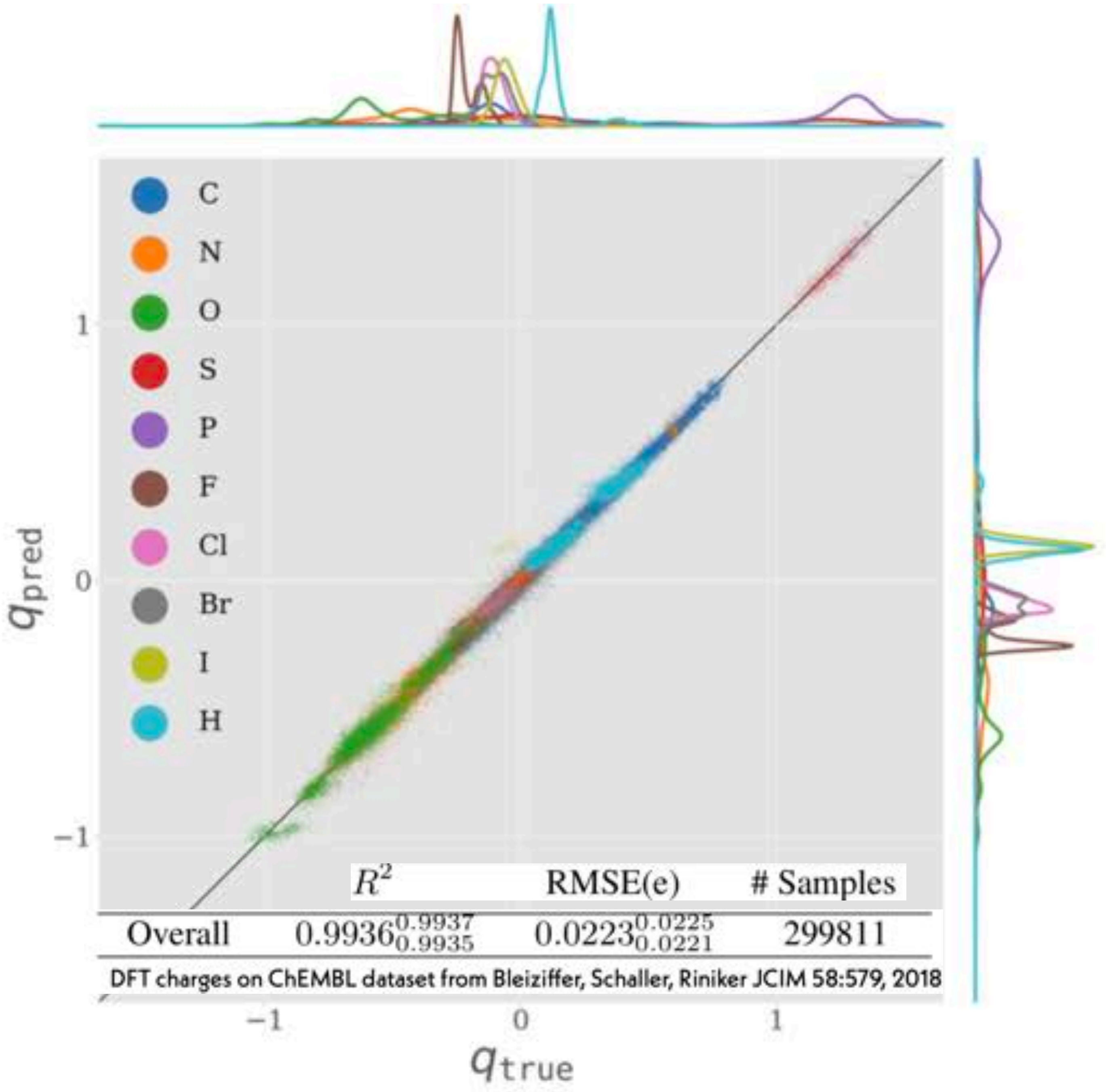
$$\bar{\mathbf{v}}^{(t+1)} = \rho^{v \to u}(V^{(t)}), \qquad \text{(node to global aggregate)}$$

$$\mathbf{u}^{(t+1)} = \phi^u(\bar{\mathbf{e}}^{(t+1)}, \bar{\mathbf{v}}^{(t+1)}, \mathbf{u}^{(t)}), \qquad \text{(global update)}$$

Learns **electronegativity** (e_i) and **hardness** (s_i) subject to fixed charge sum constraint:

$$\{\hat{q}_i\} = \underset{q_i}{\operatorname{argmin}} \sum_i \hat{e}_i q_i + \frac{1}{2} \hat{s}_i q_i^2$$

$$\sum_i \hat{q}_i = \sum_i q_i = Q$$



	R^2	RMSE(e)	# Samples
Overall	$0.9936^{0.9937}_{0.9935}$	$0.0223^{0.0225}_{0.0221}$	299811

DFT charges on ChEMBL dataset from Bleiziffer, Schaller, Riniker JCIM 58:579, 2018

control experiment:
direct prediction of charges: RMSE **0.2800 e**

γimlet

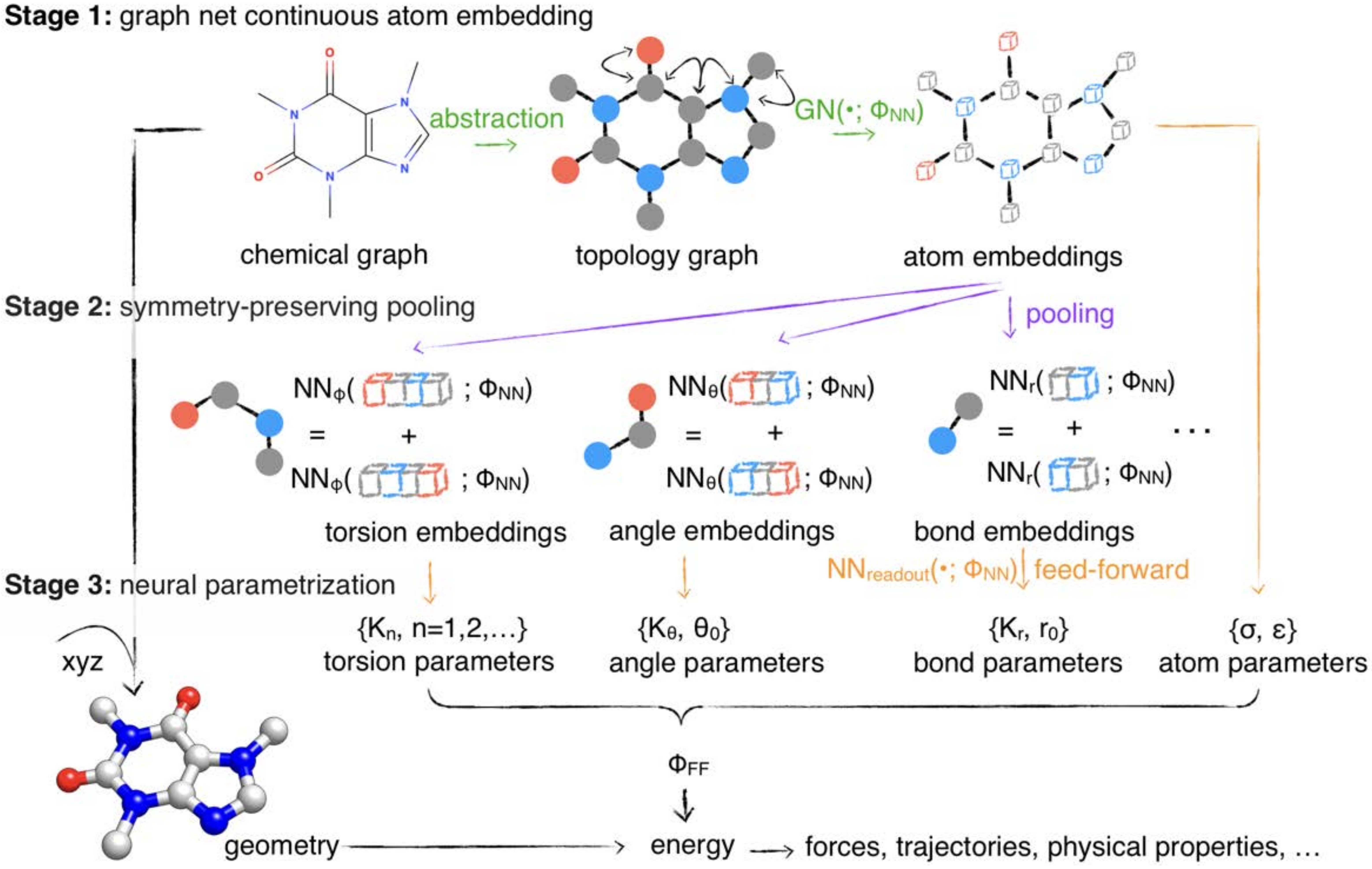
Graph Inference on MoLEcular Topology

preprint: https://arxiv.org/abs/1909.07903
code: http://github.com/choderalab/gimlet

YUANQING WANG

espaloma: **e**xtensible **s**urrogate **p**otential of **a**b *initio* **l**earned and **o**ptimized by **m**essage-passing **a**lgorithm

use of only **chemical graph** means that model can generate parameters for small molecules, proteins, nucleic acids, covalent ligands, carbohydrates, etc.



Stage 1: graph net continuous atom embedding
abstraction
GN(•; Φ_{NN})
chemical graph
topology graph
atom embeddings
Stage 2: symmetry-preserving pooling
pooling
NN_ϕ(; Φ_{NN}) = + NN_ϕ(; Φ_{NN})
NN_θ(; Φ_{NN}) = + NN_θ(; Φ_{NN})
NN_r(; Φ_{NN}) = + NN_r(; Φ_{NN})
...
torsion embeddings
angle embeddings
bond embeddings
$NN_{readout}$(•; Φ_{NN})
feed-forward
Stage 3: neural parametrization
xyz
$\{K_n, n=1,2,\ldots\}$
torsion parameters
$\{K_\theta, \theta_0\}$
angle parameters
$\{K_r, r_0\}$
bond parameters
$\{\sigma, \varepsilon\}$
atom parameters
Φ_{FF}
geometry
energy
forces, trajectories, physical properties, ...

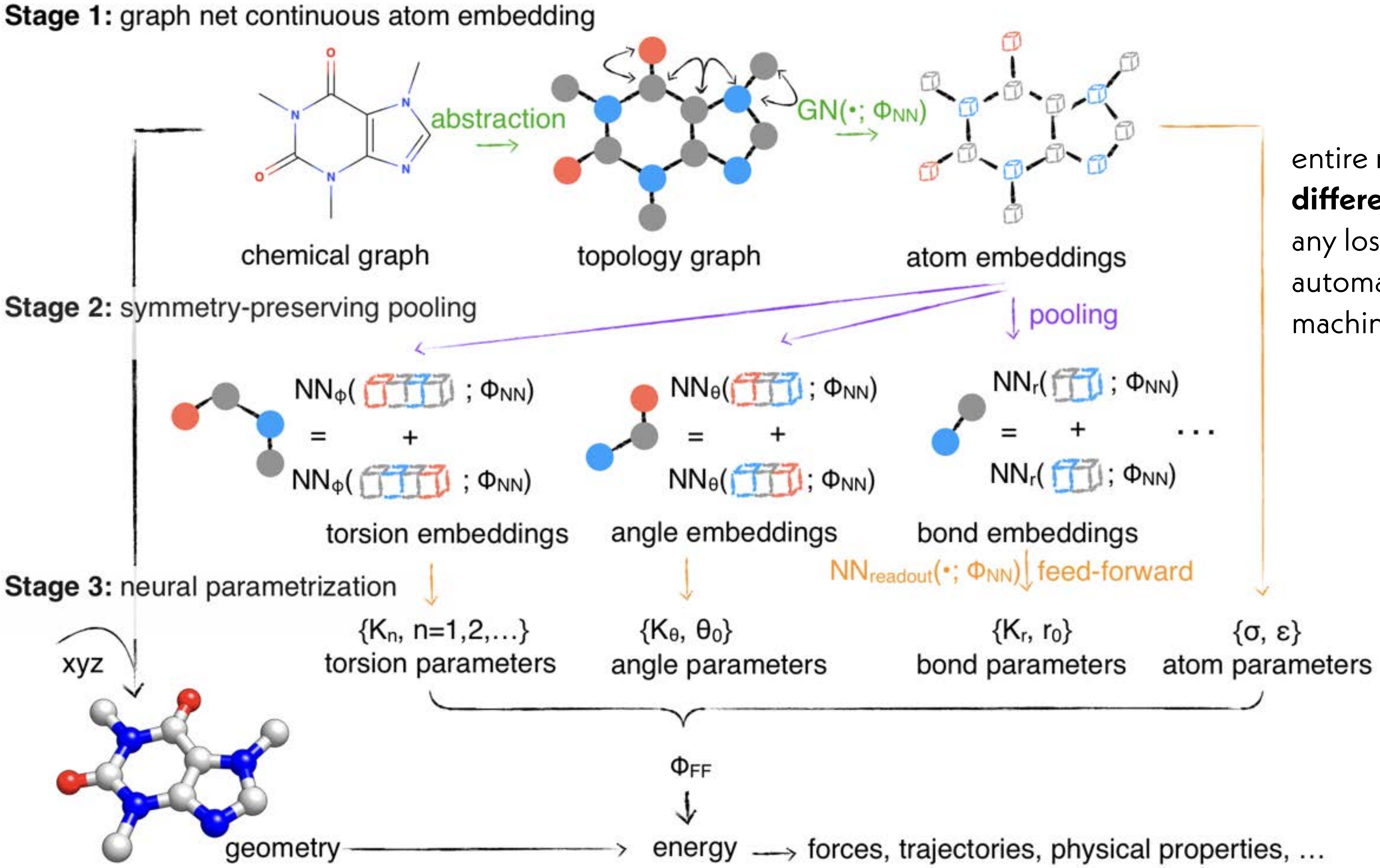
JOSH FASS

YUANQING WANG

preprint: https://arxiv.org/abs/2010.01196

code: https://github.com/choderalab/espaloma

espaloma: **e**xtensible **s**urrogate **p**otential of **a**b *initio* **l**earned and **o**ptimized by **m**essage-passing **a**lgorithm



Stage 1: graph net continuous atom embedding
abstraction
GN(•; Φ_{NN})
chemical graph
topology graph
atom embeddings
Stage 2: symmetry-preserving pooling
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$NN_\phi($; $\Phi_{NN})$ = + $NN_\phi($; $\Phi_{NN})$
$NN_\theta($; $\Phi_{NN})$ = + $NN_\theta($; $\Phi_{NN})$
$NN_r($; $\Phi_{NN})$ = + $NN_r($; $\Phi_{NN})$
. . .
torsion embeddings
angle embeddings
bond embeddings
$NN_{readout}(\cdot; \Phi_{NN})$ feed-forward
Stage 3: neural parametrization
xyz
$\{K_n, n=1,2,\ldots\}$
torsion parameters
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angle parameters
$\{K_r, r_0\}$
bond parameters
$\{\sigma, \varepsilon\}$
atom parameters
Φ_{FF}
geometry
energy
forces, trajectories, physical properties, …

entire model is **end-to-end differentiable** so can be fit to any loss function by standard automatic differentiation machine learning frameworks

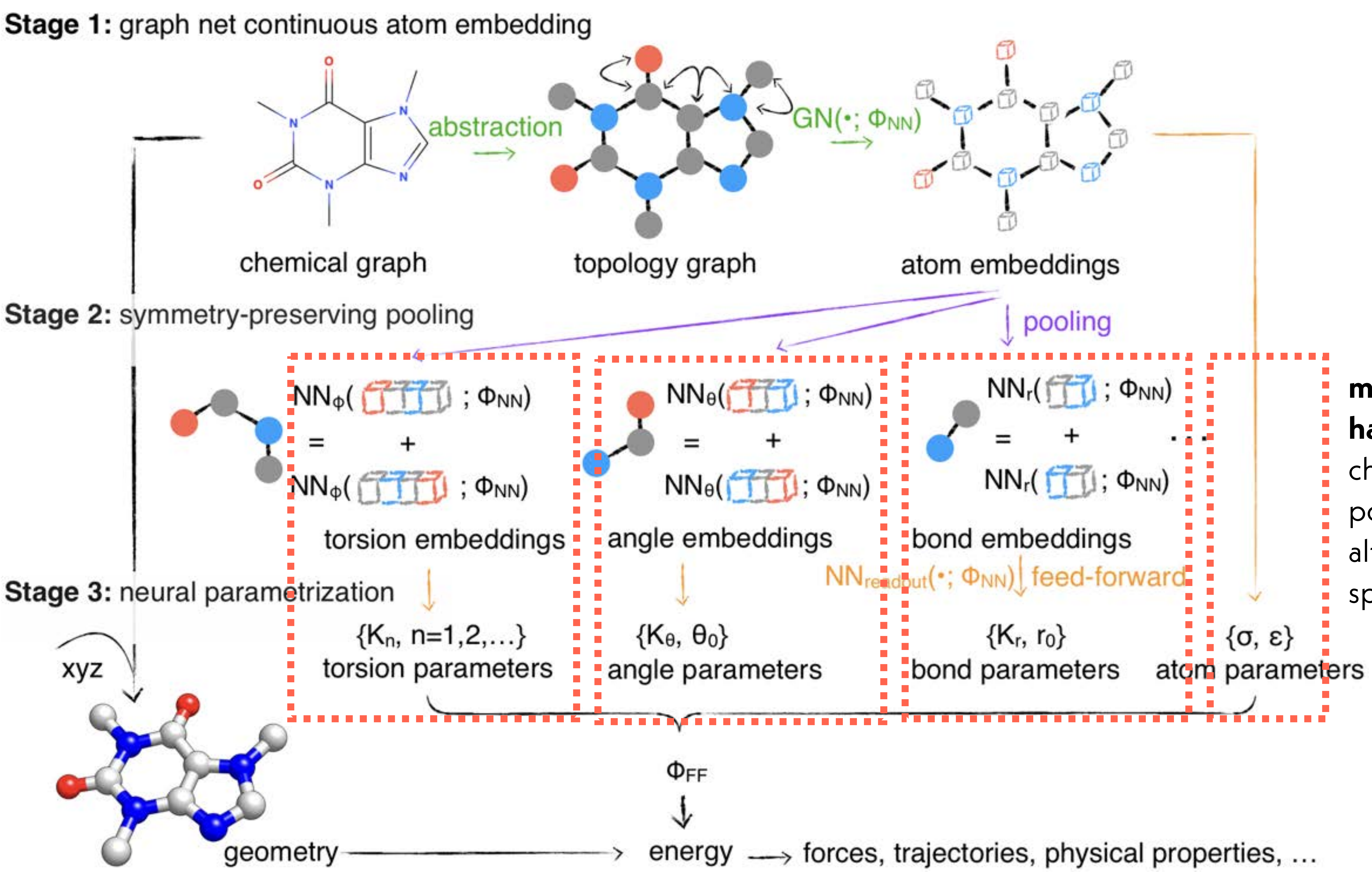
JOSH FASS

YUANQING WANG

preprint: https://arxiv.org/abs/2010.01196

code: https://github.com/choderalab/espaloma

espaloma: **e**xtensible **s**urrogate **p**otential of ***a**b initio* **l**earned and **o**ptimized by **m**essage-passing **a**lgorithm



modular and extensible handling of potential terms:
charge model parameters,
point polarizabilities,
alternative vdW forms,
special 1-4 parameters, etc.

JOSH FASS

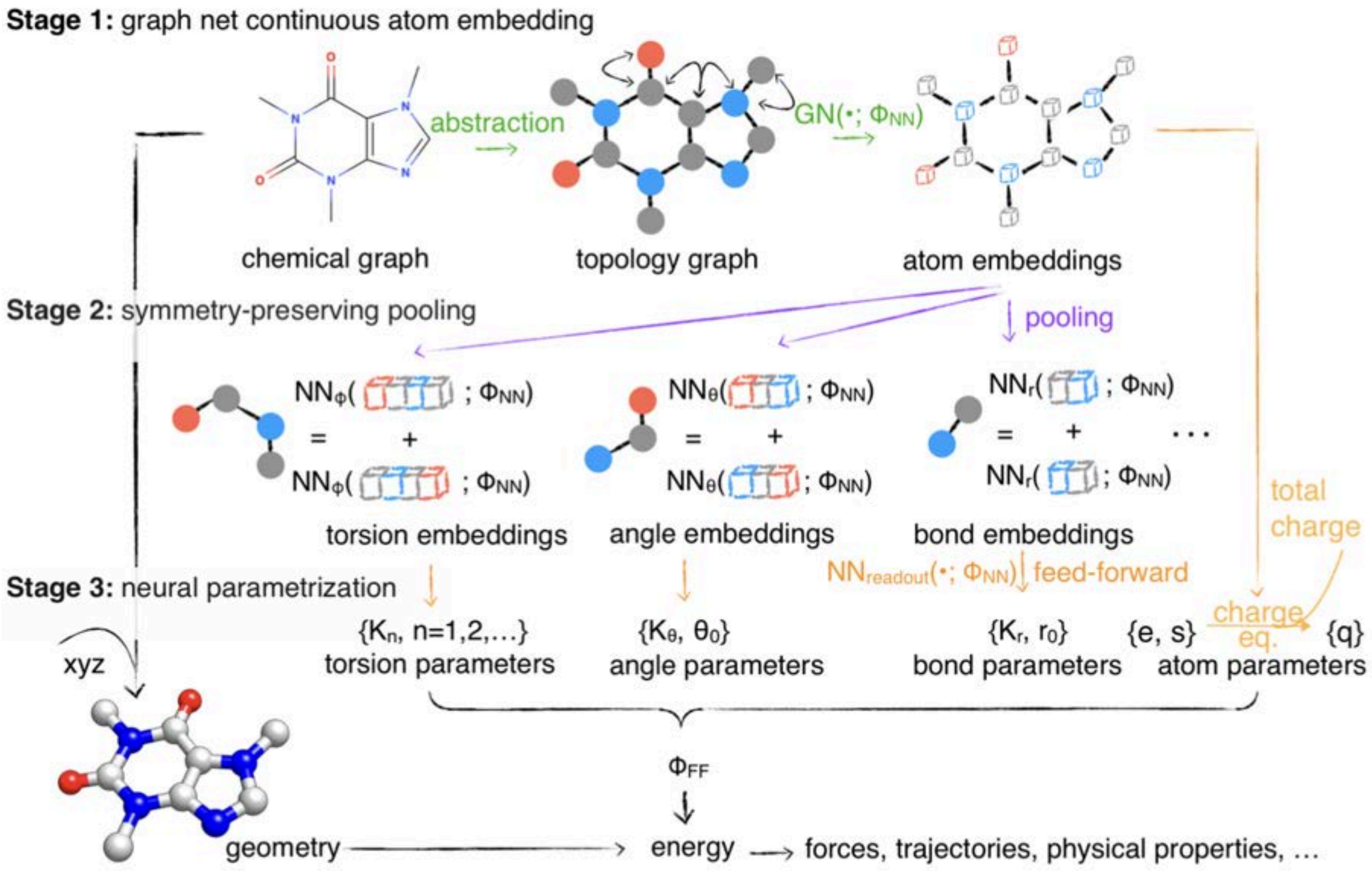
YUANQING WANG

preprint: https://arxiv.org/abs/2010.01196

code: https://github.com/choderalab/espaloma

ESPALOMA MAKES BUILDING A NEW FORCE FIELD EASY

espaloma architecture

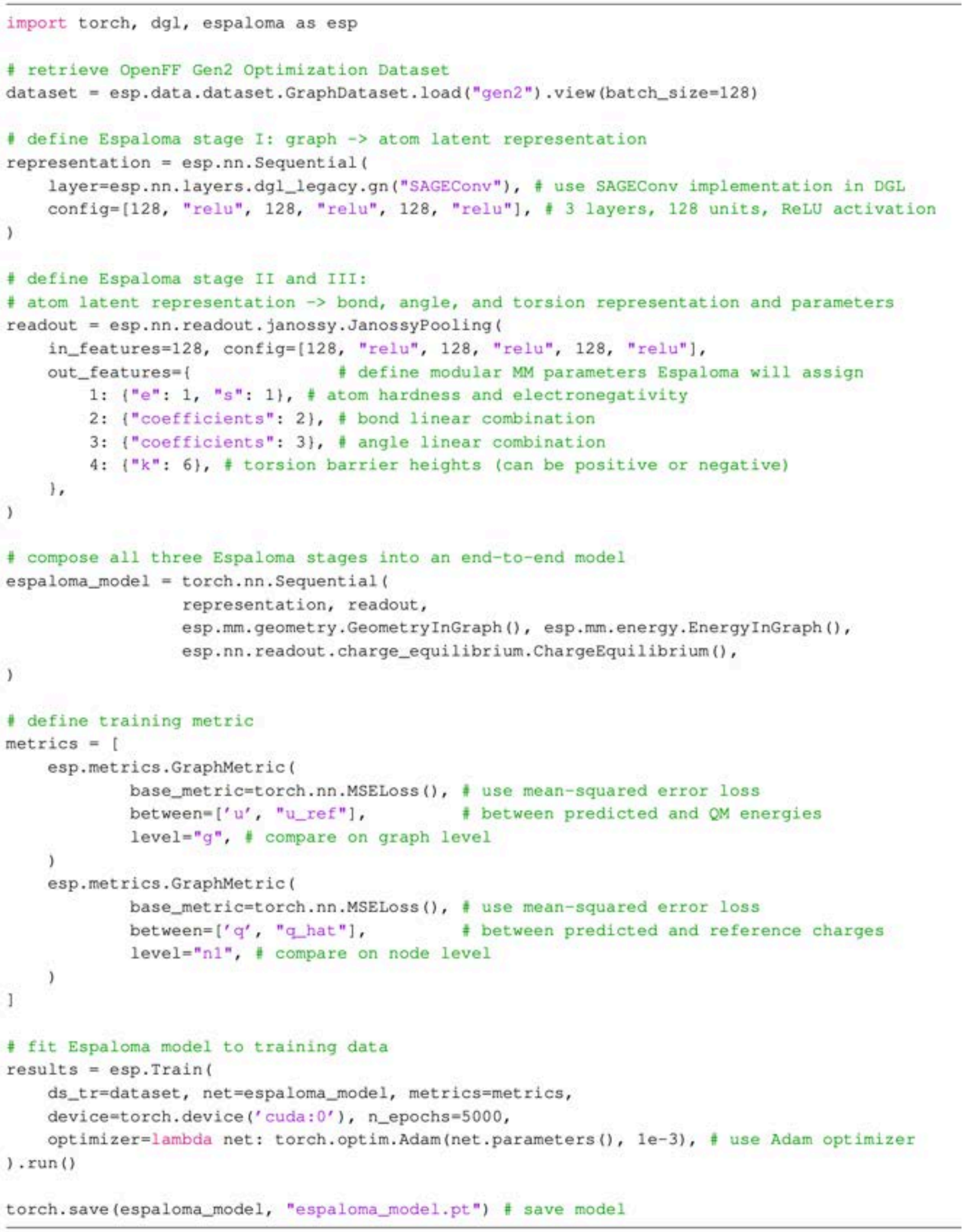


(implemented in pytorch)

http://github.com/choderalab/espaloma

YUANQING WANG

building a new force field



```
import torch, dgl, espaloma as esp

# retrieve OpenFF Gen2 Optimization Dataset
dataset = esp.data.dataset.GraphDataset.load("gen2").view(batch_size=128)

# define Espaloma stage I: graph -> atom latent representation
representation = esp.nn.Sequential(
    layer=esp.nn.layers.dgl_legacy.gn("SAGEConv"), # use SAGEConv implementation in DGL
    config=[128, "relu", 128, "relu", 128, "relu"], # 3 layers, 128 units, ReLU activation
)

# define Espaloma stage II and III:
# atom latent representation -> bond, angle, and torsion representation and parameters
readout = esp.nn.readout.janossy.JanossyPooling(
    in_features=128, config=[128, "relu", 128, "relu", 128, "relu"],
    out_features={              # define modular MM parameters Espaloma will assign
        1: {"e": 1, "s": 1}, # atom hardness and electronegativity
        2: {"coefficients": 2}, # bond linear combination
        3: {"coefficients": 3}, # angle linear combination
        4: {"k": 6}, # torsion barrier heights (can be positive or negative)
    },
)

# compose all three Espaloma stages into an end-to-end model
espaloma_model = torch.nn.Sequential(
                 representation, readout,
                 esp.mm.geometry.GeometryInGraph(), esp.mm.energy.EnergyInGraph(),
                 esp.nn.readout.charge_equilibrium.ChargeEquilibrium(),
)

# define training metric
metrics = [
    esp.metrics.GraphMetric(
            base_metric=torch.nn.MSELoss(), # use mean-squared error loss
            between=['u', "u_ref"],         # between predicted and QM energies
            level="g", # compare on graph level
    )
    esp.metrics.GraphMetric(
            base_metric=torch.nn.MSELoss(), # use mean-squared error loss
            between=['q', "q_hat"],         # between predicted and reference charges
            level="n1", # compare on node level
    )
]

# fit Espaloma model to training data
results = esp.Train(
    ds_tr=dataset, net=espaloma_model, metrics=metrics,
    device=torch.device('cuda:0'), n_epochs=5000,
    optimizer=lambda net: torch.optim.Adam(net.parameters(), 1e-3), # use Adam optimizer
).run()

torch.save(espaloma_model, "espaloma_model.pt") # save model
```

Listing 1. Defining and training a modular Espaloma model.

ESPALOMA CAN LEARN TO REPRODUCE LEGACY MM FORCE FIELDS WITH LOW RMSE ERROR IN CONFORMATIONAL ENERGIES

conformer energies

force field parameters

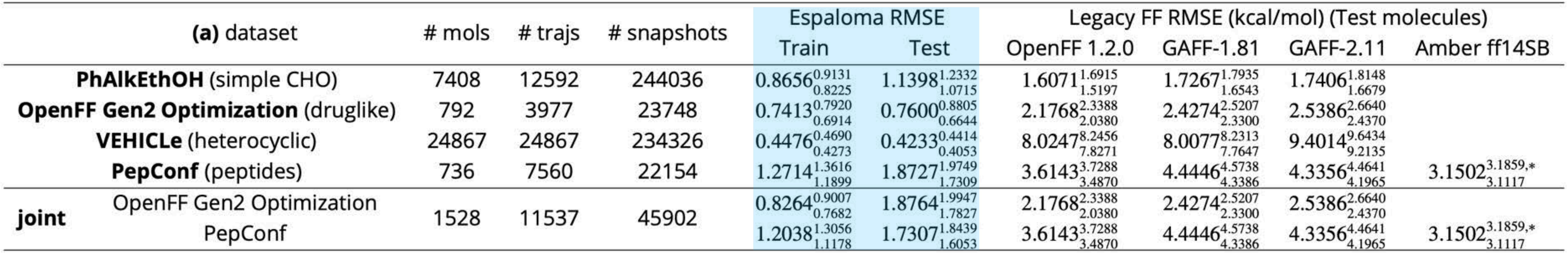
Total Energy RMSE=
0.0169$^{0.0187}_{0.0151}$
0.0169$^{0.0188}_{0.0150}$
Bond Energy RMSE=
0.0173$^{0.0264}_{0.0083}$
0.0173$^{0.0305}_{0.0088}$
Angle Energy RMSE=
0.0554$^{0.0625}_{0.0464}$
0.0554$^{0.0644}_{0.0460}$
Bond Force Const. MAPE=
0.0009$^{0.0009}_{0.0009}$
0.0009$^{0.0009}_{0.0009}$
Eq. Bond MAPE=
0.0000$^{0.0000}_{0.0000}$
0.0000$^{0.0000}_{0.0000}$
Angle Force Const. MAPE=
0.0010$^{0.0010}_{0.0009}$
0.0010$^{0.0010}_{0.0009}$
Eq. Angle. MAPE=
0.0005$^{0.0005}_{0.0005}$
0.0005$^{0.0005}_{0.0005}$
Test Predicted
Train Predicted
20
10
0
−10
−20
60
40
20
0
900
800
700
600
1.4
1.2
1.0
140
120
100
80
2.1
2.0
1.9
−20
0
20
0
25
50
25
50
600
800
1.00
1.25
1.50
75
100
125
1.9
2.0
2.1
Ref. U_{total} kcal/mol
U_{bond} kcal/mol
U_{angle} kcal/mol
k_r kcal/(mol*Å^2)
r_0 Å
k_θ kcal/(mol * rad^2)
θ_0 rad

preprint: https://arxiv.org/abs/2010.01196
code: http://github.com/choderalab/espaloma

reference force field: GAFF 1.81 [https://doi.org/10.1002/jcc.20035]
dataset: PhAlkEthOH [https://dx.doi.org/10.1021/acs.jctc.8b00640]

YUANQING WANG

ESPALOMA OUTPERFORMS CURRENT FORCE FIELDS IN QM ACCURACY AND CAN BE EASILY TRAINED FOR HETEROGENEOUS SYSTEMS



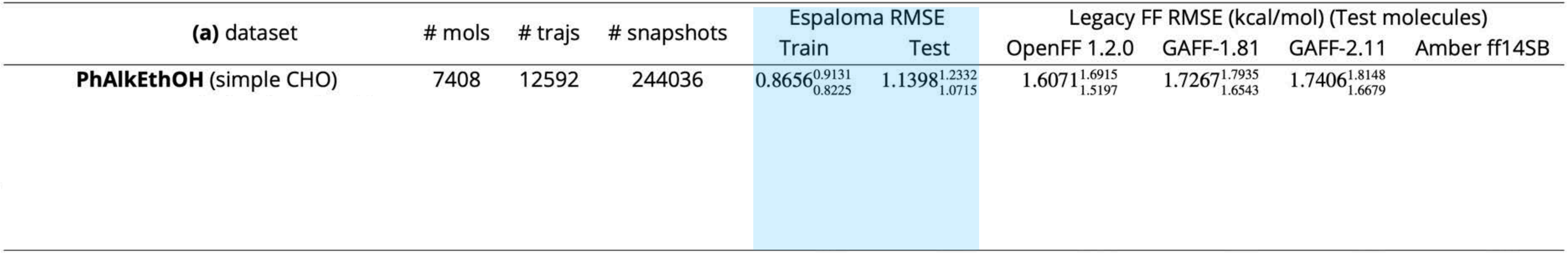
(a) dataset	# mols	# trajs	# snapshots	Espaloma RMSE		Legacy FF RMSE (kcal/mol) (Test molecules)			
				Train	Test	OpenFF 1.2.0	GAFF-1.81	GAFF-2.11	Amber ff14SB
PhAlkEthOH (simple CHO)	7408	12592	244036	$0.8656^{0.9131}_{0.8225}$	$1.1398^{1.2332}_{1.0715}$	$1.6071^{1.6915}_{1.5197}$	$1.7267^{1.7935}_{1.6543}$	$1.7406^{1.8148}_{1.6679}$	
OpenFF Gen2 Optimization (druglike)	792	3977	23748	$0.7413^{0.7920}_{0.6914}$	$0.7600^{0.8805}_{0.6644}$	$2.1768^{2.3388}_{2.0380}$	$2.4274^{2.5207}_{2.3300}$	$2.5386^{2.6640}_{2.4370}$	
VEHICLe (heterocyclic)	24867	24867	234326	$0.4476^{0.4690}_{0.4273}$	$0.4233^{0.4414}_{0.4053}$	$8.0247^{8.2456}_{7.8271}$	$8.0077^{8.2313}_{7.7647}$	$9.4014^{9.6434}_{9.2135}$	
PepConf (peptides)	736	7560	22154	$1.2714^{1.3616}_{1.1899}$	$1.8727^{1.9749}_{1.7309}$	$3.6143^{3.7288}_{3.4870}$	$4.4446^{4.5738}_{4.3386}$	$4.3356^{4.4641}_{4.1965}$	$3.1502^{3.1859,*}_{3.1117}$
joint OpenFF Gen2 Optimization	1528	11537	45902	$0.8264^{0.9007}_{0.7682}$	$1.8764^{1.9947}_{1.7827}$	$2.1768^{2.3388}_{2.0380}$	$2.4274^{2.5207}_{2.3300}$	$2.5386^{2.6640}_{2.4370}$	
PepConf				$1.2038^{1.3056}_{1.1178}$	$1.7307^{1.8439}_{1.6053}$	$3.6143^{3.7288}_{3.4870}$	$4.4446^{4.5738}_{4.3386}$	$4.3356^{4.4641}_{4.1965}$	$3.1502^{3.1859,*}_{3.1117}$

preprint: https://arxiv.org/abs/2010.01196

code: http://github.com/choderalab/espaloma

YUANQING WANG

ESPALOMA OUTPERFORMS CURRENT FORCE FIELDS IN QM ACCURACY AND CAN BE EASILY TRAINED FOR HETEROGENEOUS SYSTEMS



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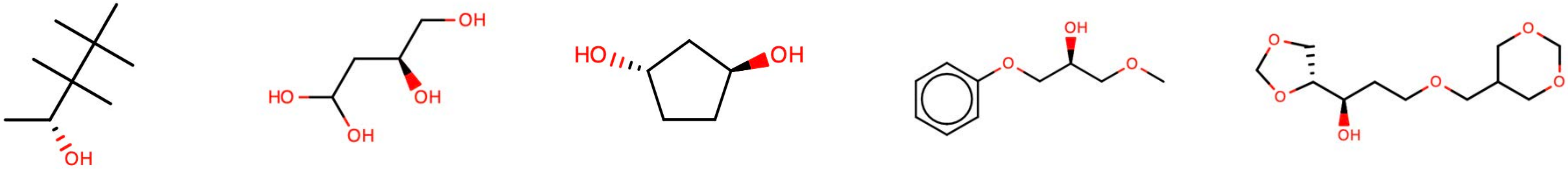
PhAlkEthOh: **Ph**enyls, **Alk**anes, **Eth**ers, and alcohols (**OH**)

(a low-complexity chemical space)

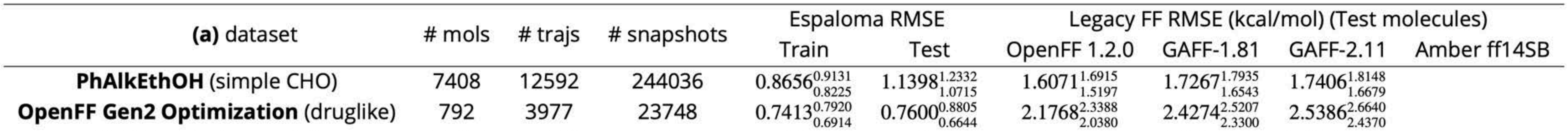


preprint: https://arxiv.org/abs/2010.01196
code: http://github.com/choderalab/espaloma

PhAlkEthOH doi: https://dx.doi.org/10.1021/acs.jctc.8b00640

YUANQING WANG

ESPALOMA OUTPERFORMS CURRENT FORCE FIELDS IN QM ACCURACY AND CAN BE EASILY TRAINED FOR HETEROGENEOUS SYSTEMS



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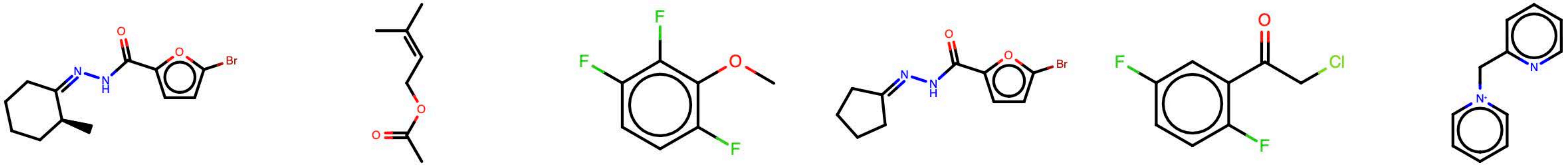
OpenFF Gen2 Optimization set: Diverse druglike fragments challenging for force fields (a moderate-complexity chemical space)



preprint: https://arxiv.org/abs/2010.01196
code: http://github.com/choderalab/espaloma

OpenFF Gen2 QM data doi: https://doi.org/10.1021/acs.jctc.1c00571

YUANQING WANG

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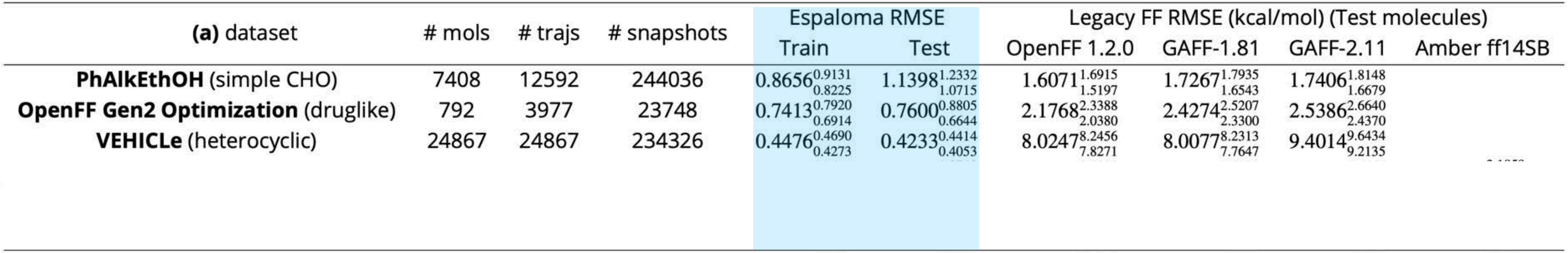

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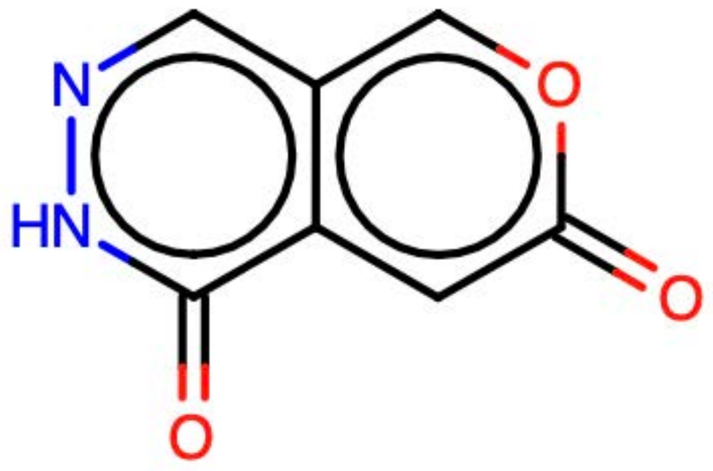
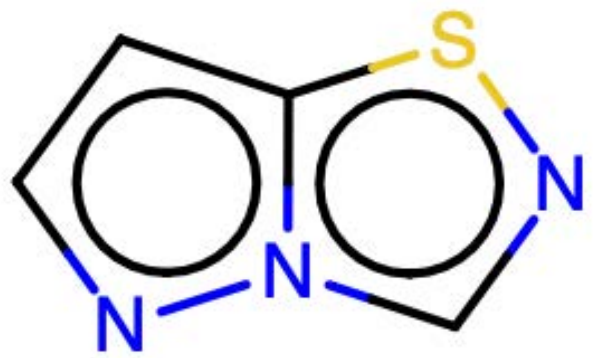
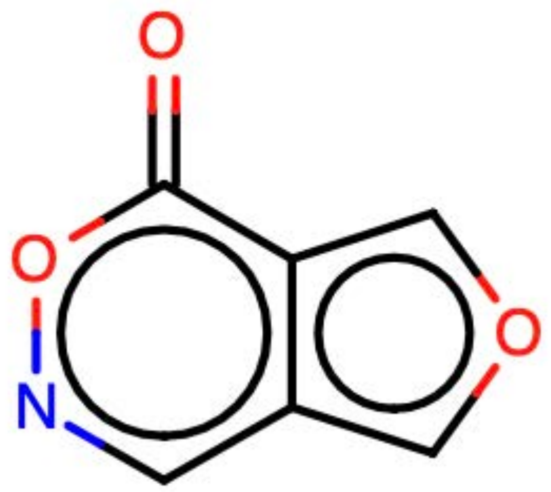
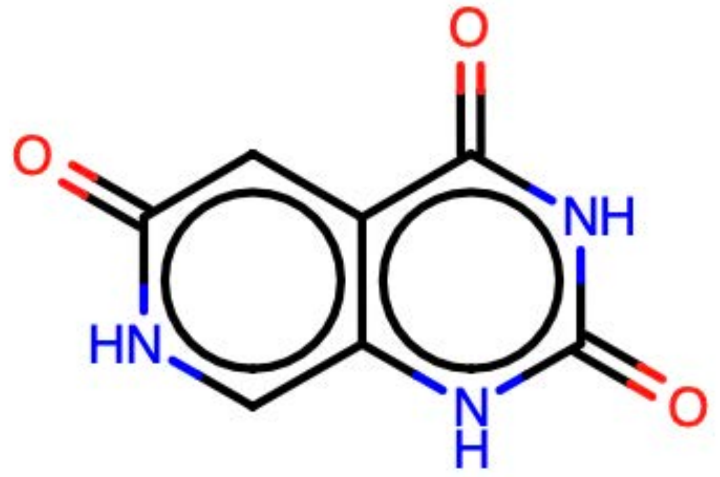
VEHICLe: Virtual exploratory heterocyclic drug scaffold library

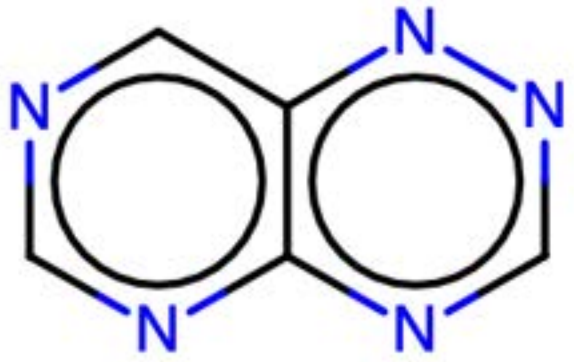
(aromatic bicyclic heterocyclic compounds containing C, N, O, S, H)











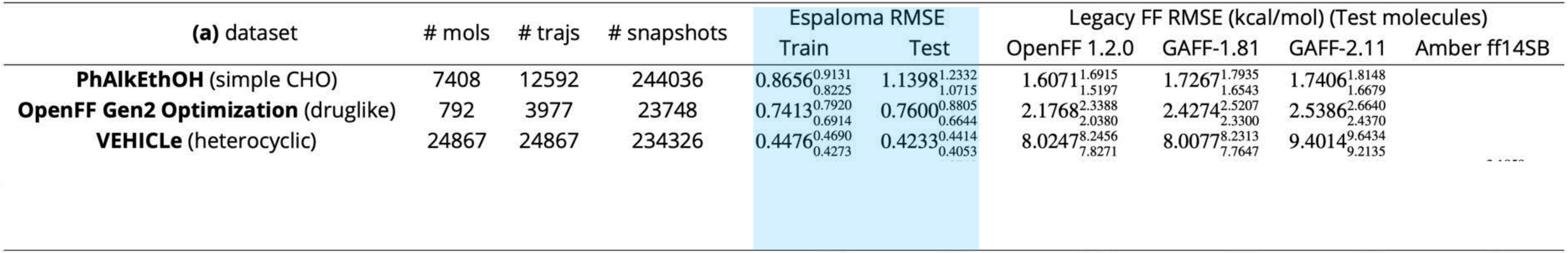
preprint: https://arxiv.org/abs/2010.01196

code: http://github.com/choderalab/espaloma

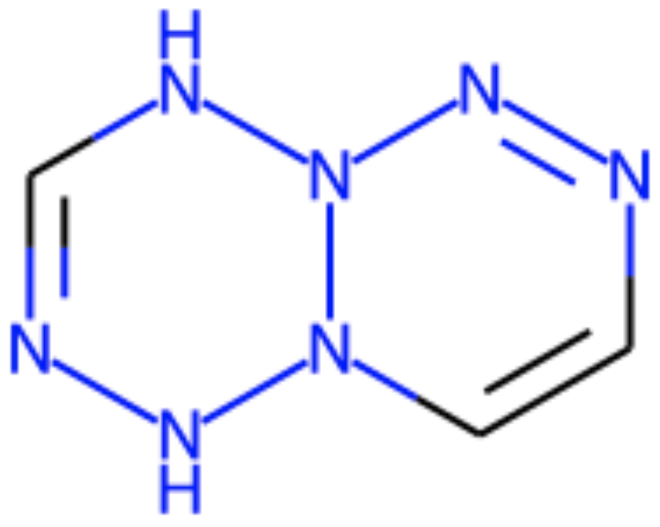
VEHICLe doi: http://doi.org/10.1021/jm801513z

YUANQING WANG

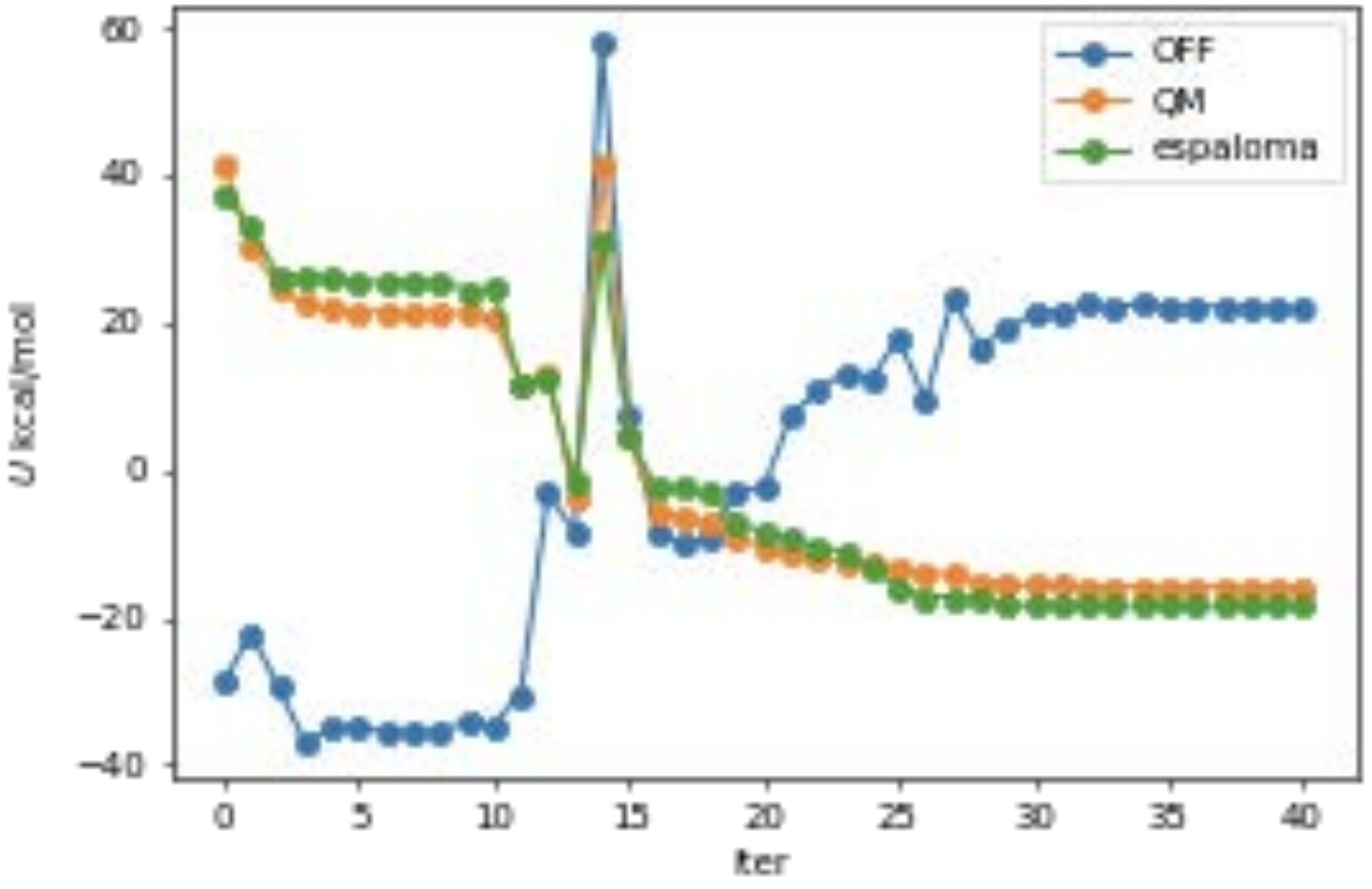
ESPALOMA OUTPERFORMS CURRENT FORCE FIELDS IN QM ACCURACY AND CAN BE EASILY TRAINED FOR HETEROGENEOUS SYSTEMS



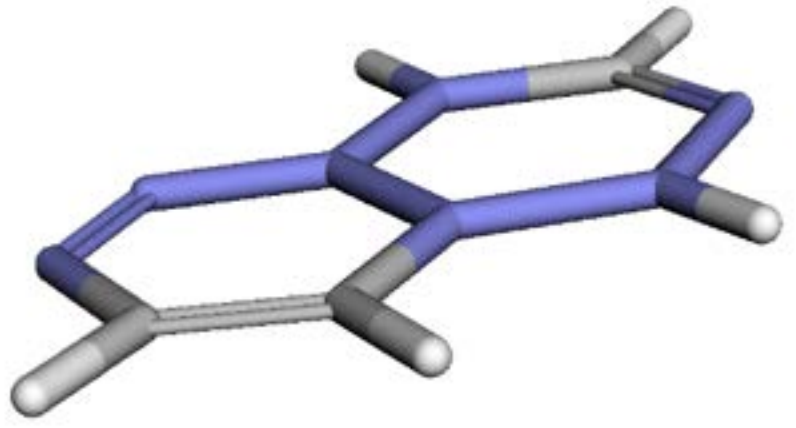
(a) dataset	# mols	# trajs	# snapshots	Espaloma RMSE		Legacy FF RMSE (kcal/mol) (Test molecules)			
				Train	Test	OpenFF 1.2.0	GAFF-1.81	GAFF-2.11	Amber ff14SB
PhAlkEthOH (simple CHO)	7408	12592	244036	$0.8656^{0.9131}_{0.8225}$	$1.1398^{1.2332}_{1.0715}$	$1.6071^{1.6915}_{1.5197}$	$1.7267^{1.7935}_{1.6543}$	$1.7406^{1.8148}_{1.6679}$	
OpenFF Gen2 Optimization (druglike)	792	3977	23748	$0.7413^{0.7920}_{0.6914}$	$0.7600^{0.8805}_{0.6644}$	$2.1768^{2.3388}_{2.0380}$	$2.4274^{2.5207}_{2.3300}$	$2.5386^{2.6640}_{2.4370}$	
VEHICLe (heterocyclic)	24867	24867	234326	$0.4476^{0.4690}_{0.4273}$	$0.4233^{0.4414}_{0.4053}$	$8.0247^{8.2456}_{7.8271}$	$8.0077^{8.2313}_{7.7647}$	$9.4014^{9.6434}_{9.2135}$	



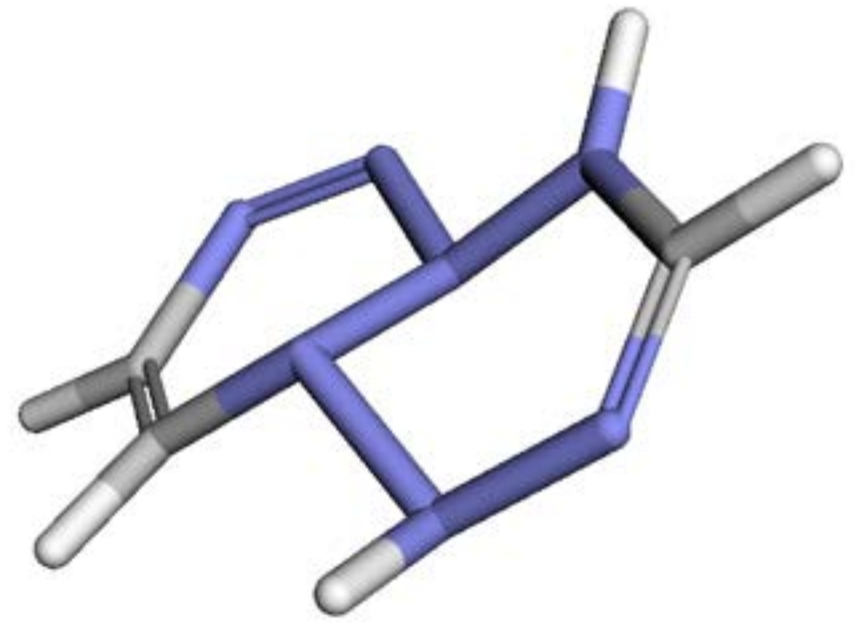
Comparison with QCArchive data



initial



QM minimized

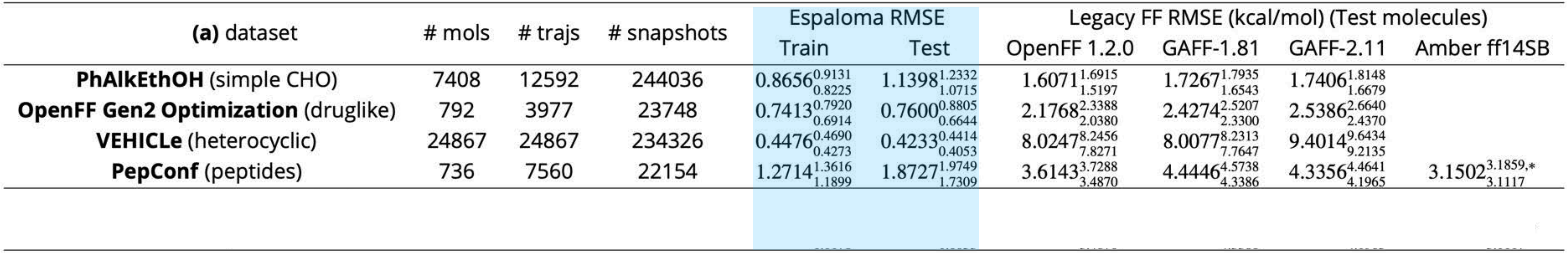


DFT B3LYP-D3(BJ) / DZVP

preprint: https://arxiv.org/abs/2010.01196
code: http://github.com/choderalab/espaloma

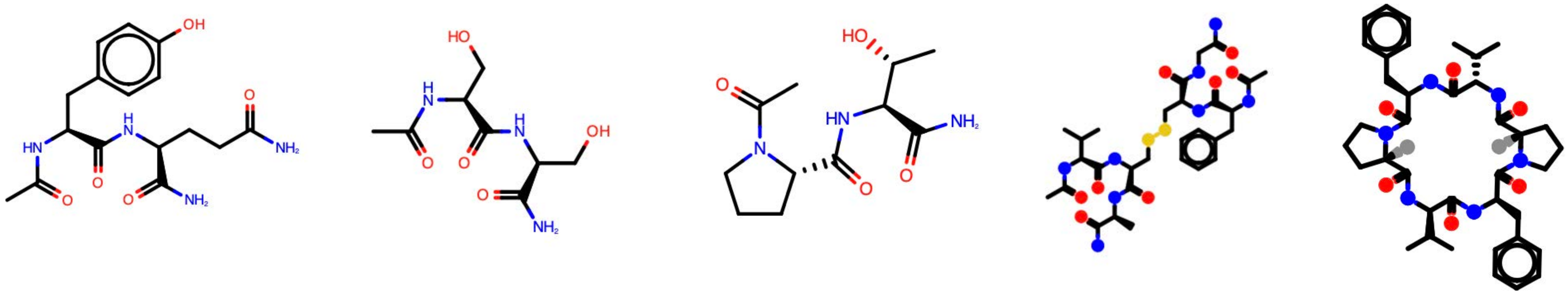
YUANQING WANG

ESPALOMA OUTPERFORMS CURRENT FORCE FIELDS IN QM ACCURACY AND CAN BE EASILY TRAINED FOR HETEROGENEOUS SYSTEMS



(a) dataset	# mols	# trajs	# snapshots	Espaloma RMSE		Legacy FF RMSE (kcal/mol) (Test molecules)			
				Train	Test	OpenFF 1.2.0	GAFF-1.81	GAFF-2.11	Amber ff14SB
PhAlkEthOH (simple CHO)	7408	12592	244036	$0.8656^{0.9131}_{0.8225}$	$1.1398^{1.2332}_{1.0715}$	$1.6071^{1.6915}_{1.5197}$	$1.7267^{1.7935}_{1.6543}$	$1.7406^{1.8148}_{1.6679}$	
OpenFF Gen2 Optimization (druglike)	792	3977	23748	$0.7413^{0.7920}_{0.6914}$	$0.7600^{0.8805}_{0.6644}$	$2.1768^{2.3388}_{2.0380}$	$2.4274^{2.5207}_{2.3300}$	$2.5386^{2.6640}_{2.4370}$	
VEHICLe (heterocyclic)	24867	24867	234326	$0.4476^{0.4690}_{0.4273}$	$0.4233^{0.4414}_{0.4053}$	$8.0247^{8.2456}_{7.8271}$	$8.0077^{8.2313}_{7.7647}$	$9.4014^{9.6434}_{9.2135}$	
PepConf (peptides)	736	7560	22154	$1.2714^{1.3616}_{1.1899}$	$1.8727^{1.9749}_{1.7309}$	$3.6143^{3.7288}_{3.4870}$	$4.4446^{4.5738}_{4.3386}$	$4.3356^{4.4641}_{4.1965}$	$3.1502^{3.1859,*}_{3.1117}$

PepConf: Short peptides, including disulfides and cyclic peptides

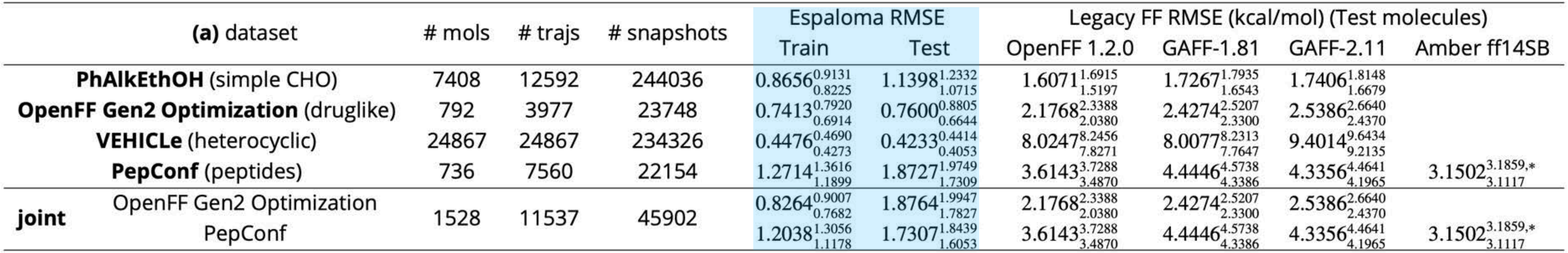


preprint: https://arxiv.org/abs/2010.01196
code: http://github.com/choderalab/espaloma

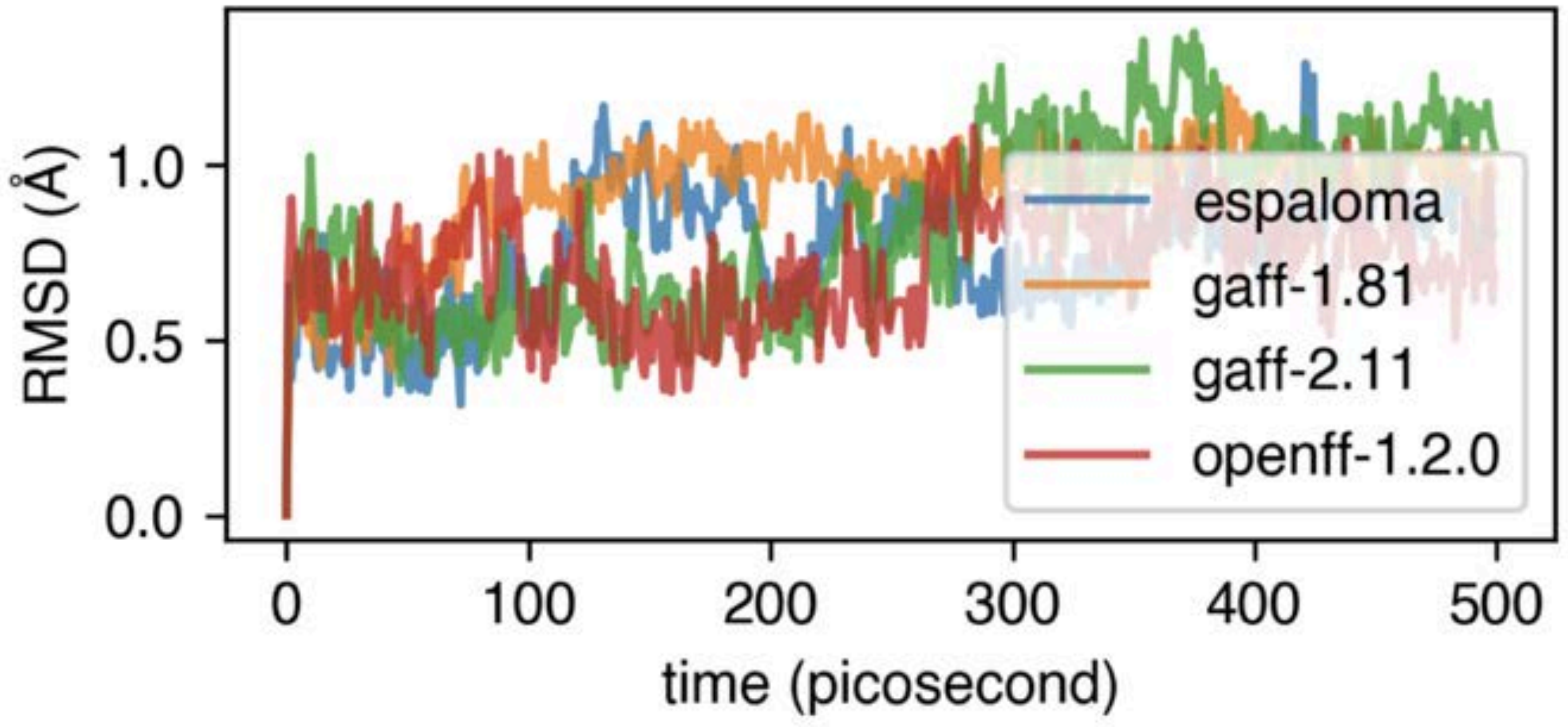
VEHICLe doi: http://doi.org/10.1021/jm801513z

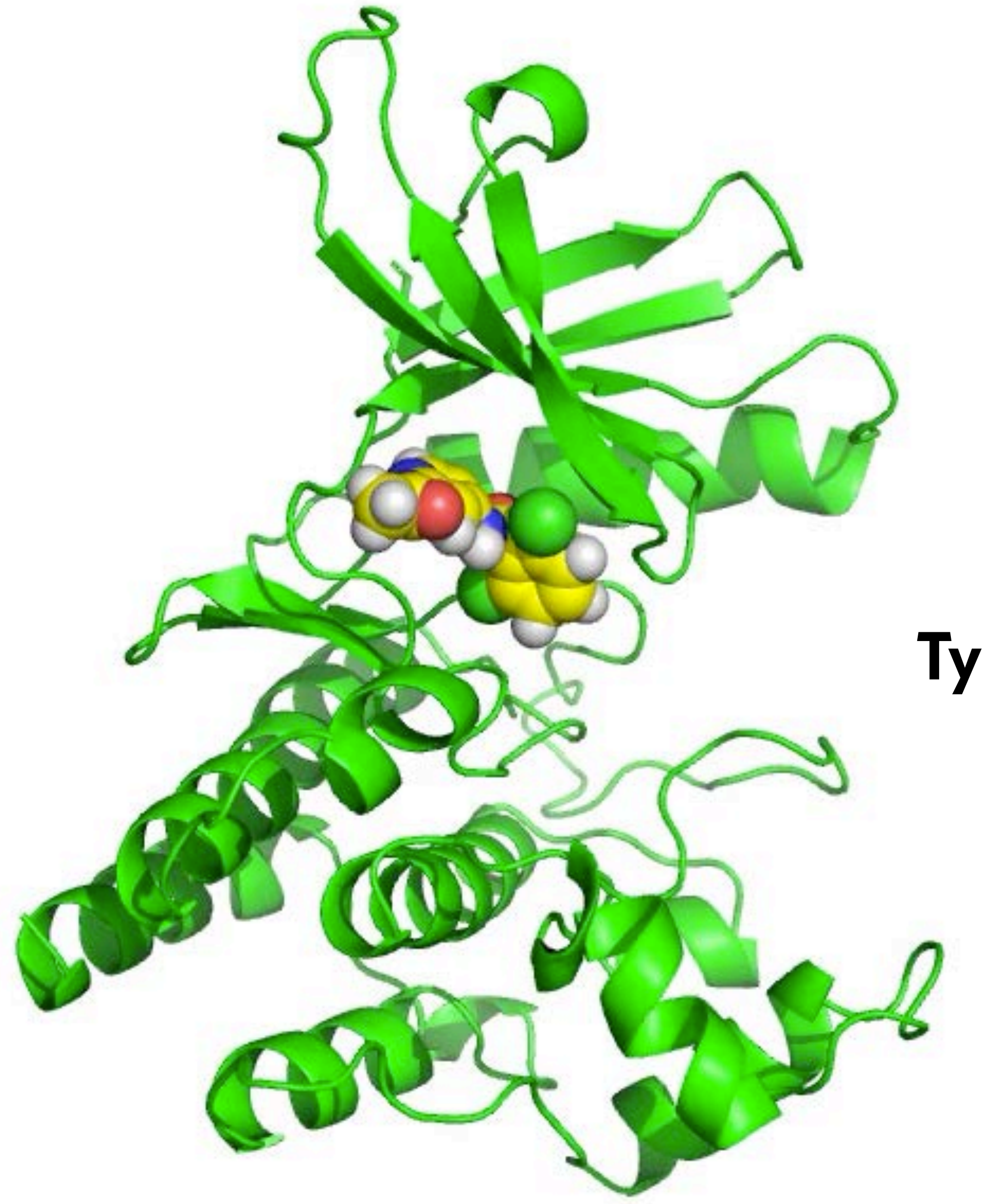
YUANQING WANG

ESPALOMA OUTPERFORMS CURRENT FORCE FIELDS IN QM ACCURACY AND CAN BE EASILY TRAINED FOR HETEROGENEOUS SYSTEMS



(a) dataset		# mols	# trajs	# snapshots	Espaloma RMSE		Legacy FF RMSE (kcal/mol) (Test molecules)			
					Train	Test	OpenFF 1.2.0	GAFF-1.81	GAFF-2.11	Amber ff14SB
PhAlkEthOH (simple CHO)		7408	12592	244036	$0.8656^{0.9131}_{0.8225}$	$1.1398^{1.2332}_{1.0715}$	$1.6071^{1.6915}_{1.5197}$	$1.7267^{1.7935}_{1.6543}$	$1.7406^{1.8148}_{1.6679}$	
OpenFF Gen2 Optimization (druglike)		792	3977	23748	$0.7413^{0.7920}_{0.6914}$	$0.7600^{0.8805}_{0.6644}$	$2.1768^{2.3388}_{2.0380}$	$2.4274^{2.5207}_{2.3300}$	$2.5386^{2.6640}_{2.4370}$	
VEHICLe (heterocyclic)		24867	24867	234326	$0.4476^{0.4690}_{0.4273}$	$0.4233^{0.4414}_{0.4053}$	$8.0247^{8.2456}_{7.8271}$	$8.0077^{8.2313}_{7.7647}$	$9.4014^{9.6434}_{9.2135}$	
PepConf (peptides)		736	7560	22154	$1.2714^{1.3616}_{1.1899}$	$1.8727^{1.9749}_{1.7309}$	$3.6143^{3.7288}_{3.4870}$	$4.4446^{4.5738}_{4.3386}$	$4.3356^{4.4641}_{4.1965}$	$3.1502^{3.1859,*}_{3.1117}$
joint	OpenFF Gen2 Optimization	1528	11537	45902	$0.8264^{0.9007}_{0.7682}$	$1.8764^{1.9947}_{1.7827}$	$2.1768^{2.3388}_{2.0380}$	$2.4274^{2.5207}_{2.3300}$	$2.5386^{2.6640}_{2.4370}$	
	PepConf				$1.2038^{1.3056}_{1.1178}$	$1.7307^{1.8439}_{1.6053}$	$3.6143^{3.7288}_{3.4870}$	$4.4446^{4.5738}_{4.3386}$	$4.3356^{4.4641}_{4.1965}$	$3.1502^{3.1859,*}_{3.1117}$





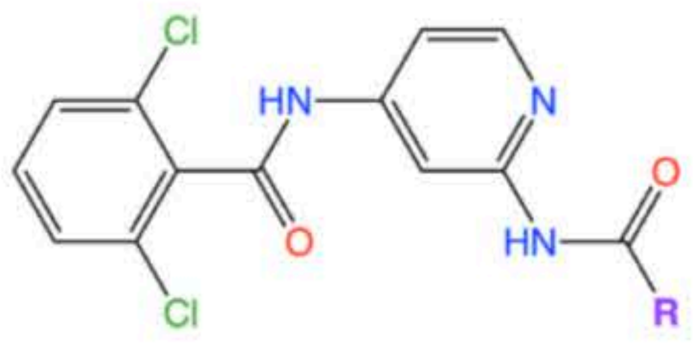
Tyk2 from OpenFF benchmark set
espaloma **joint** model
+ TIP3P water

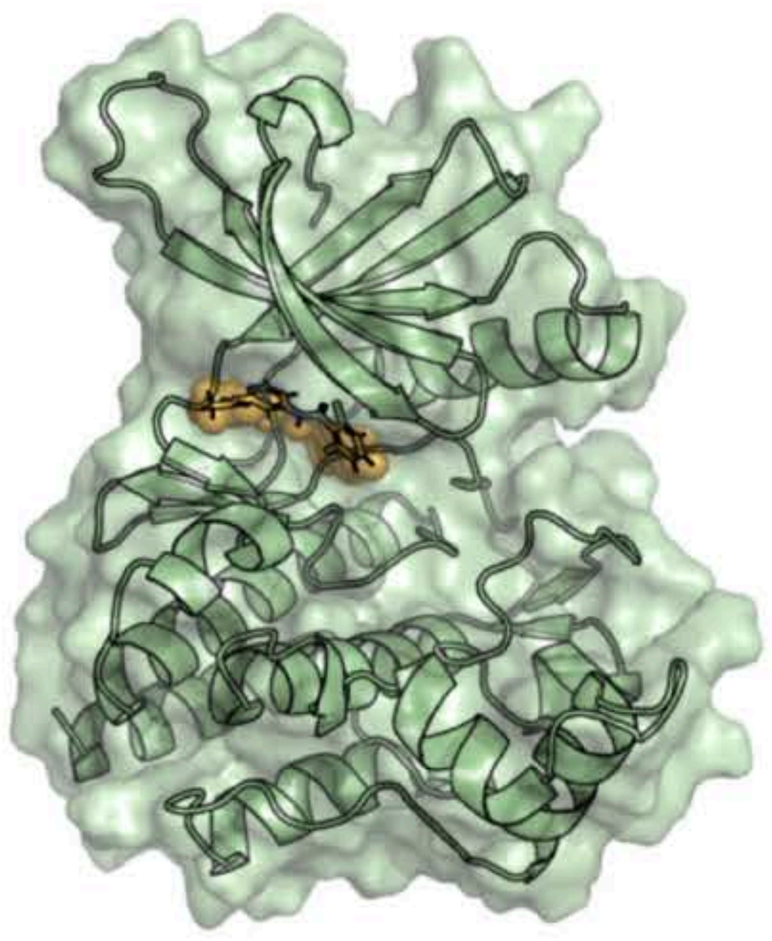
YUANQING WANG

preprint: https://arxiv.org/abs/2010.01196
code: http://github.com/choderalab/espaloma

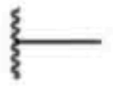
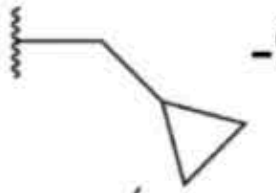
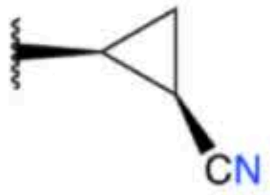
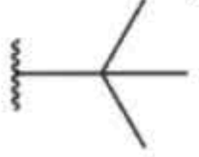
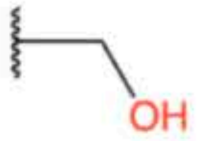
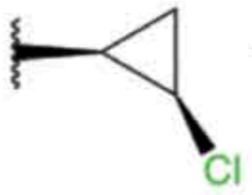
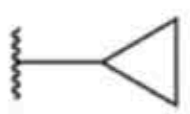
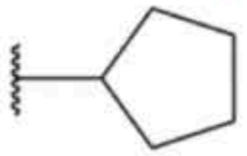
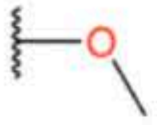
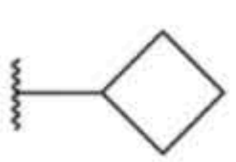
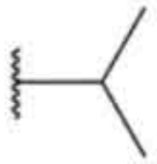
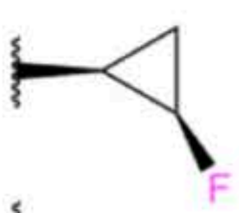
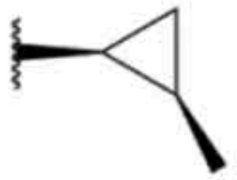
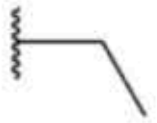
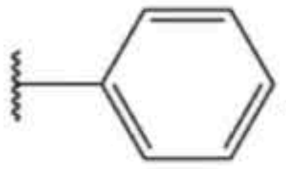
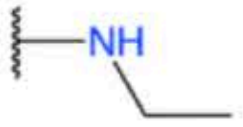
Tyk2 benchmark doi: https://doi.org/10.1021/ja512751q

ESPALOMA SMALL MOLECULE PARAMETERS PERFORM AS WELL OR BETTER THAN MODERN BIOMOLECULAR FORCE FIELDS

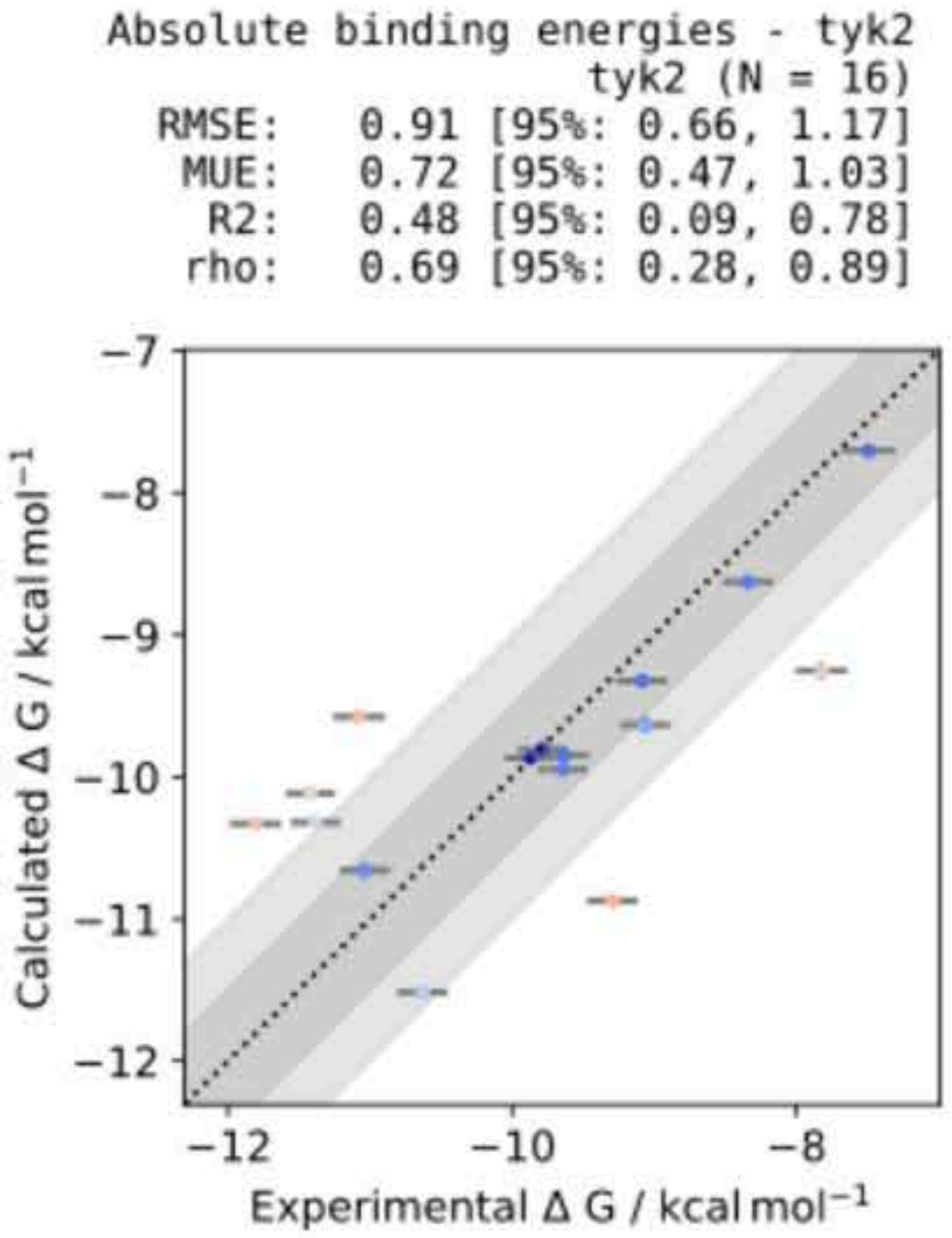




Tyk2
PDBID: 4GIH

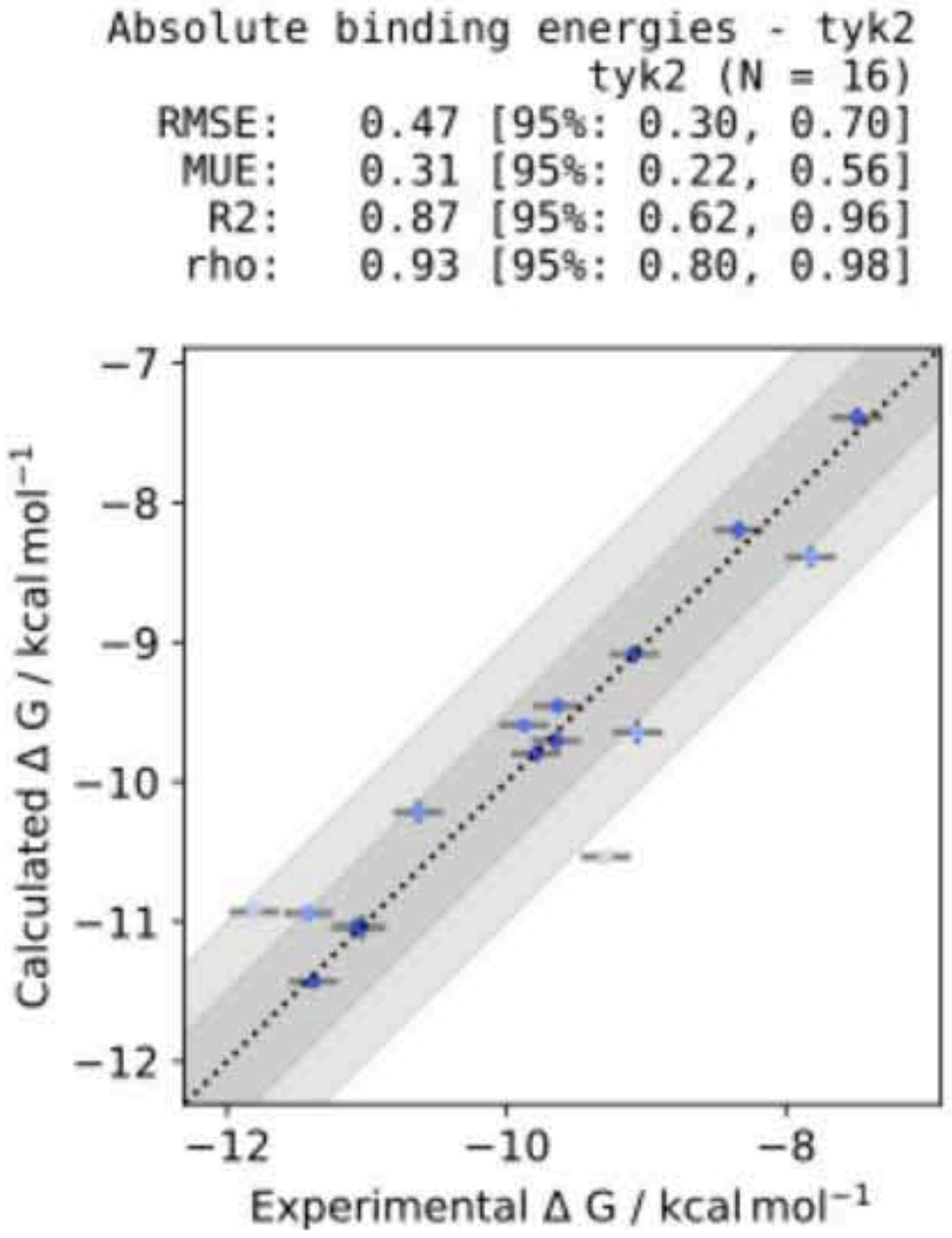
		ΔG_{exp} / kcal mol^{-1}			ΔG_{exp} / kcal mol^{-1}
1		-9.54	9		-9.56
2		-10.94	10		-7.42
3		-8.98	11		-11.28
4		-11.31	12		-9.00
5		-9.21	13		-9.70
6		-8.26	14		-11.70
7		-10.91	15		-9.78
8		-7.75	16		-10.53

OpenFF 1.2.0 small molecule
Amber ff14SB protein
TIP3P water



```
Absolute binding energies - tyk2
                  tyk2 (N = 16)
  RMSE:   0.91 [95%: 0.66, 1.17]
   MUE:   0.72 [95%: 0.47, 1.03]
    R2:   0.48 [95%: 0.09, 0.78]
   rho:   0.69 [95%: 0.28, 0.89]
```

espaloma "joint" 0.2.2 small molecule
Amber ff14SB protein
TIP3P water



```
Absolute binding energies - tyk2
                  tyk2 (N = 16)
  RMSE:   0.47 [95%: 0.30, 0.70]
   MUE:   0.31 [95%: 0.22, 0.56]
    R2:   0.87 [95%: 0.62, 0.96]
   rho:   0.93 [95%: 0.80, 0.98]
```

MIKE HENRY

IVÁN PULIDO

IVY ZHANG

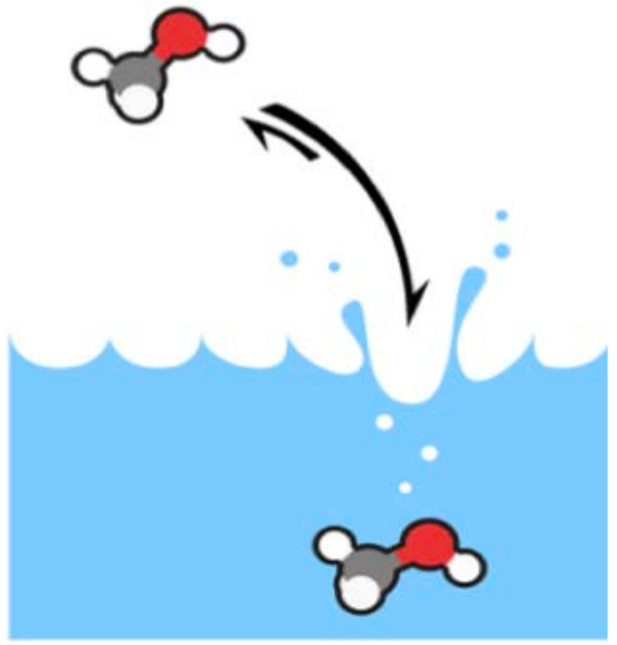
DOMINIC RUFA

HANNAH BRUCE CDONALD

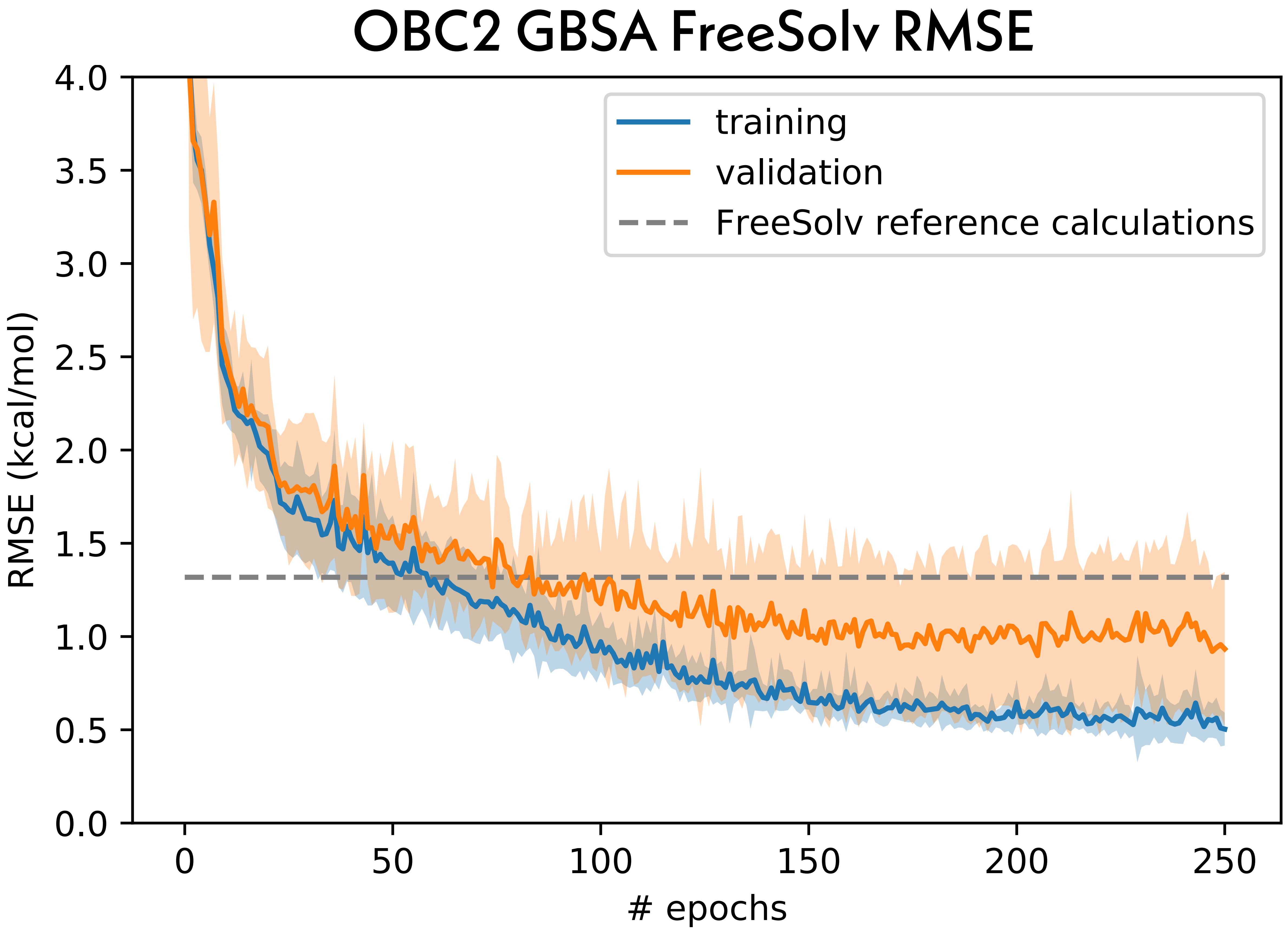
YUANQING WANG

preprint: https://arxiv.org/abs/2010.01196
code: http://github.com/choderalab/espaloma
free energy calculations with http://github.com/choderalab/perses

ESPALOMA CAN ALSO FIT EXPERIMENTAL FREE ENERGIES



experimental hydration
free energies from **FreeSolv**
https://github.com/MobleyLab/FreeSolv

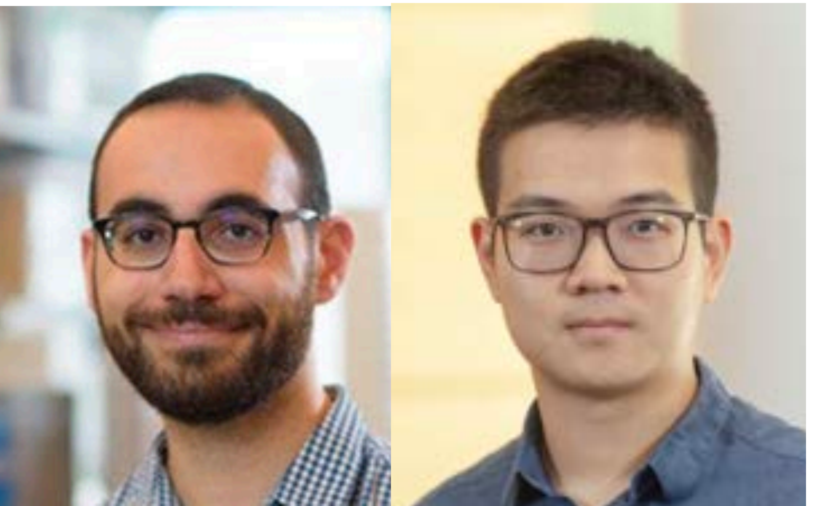


loss function:

$$L(\Phi_{NN}) = \sum_{n=1}^{N} \frac{[\Delta G_n(\Phi_{NN}) - \Delta G_n^{\exp}]^2}{\sigma_n^2}$$

Here, ΔG estimated via one-step free energy perturbation, but can easily differentiate properties through MBAR

JOSH FASS **YUANQING WANG**



preprint: https://arxiv.org/abs/2010.01196
code: https://github.com/choderalab/espaloma

A NEW GENERATION OF QUANTUM MACHINE LEARNING (QML) POTENTIALS PROVIDE SIGNIFICANTLY MORE FLEXIBILITY IN FUNCTIONAL FORM, THOUGH AT MUCH GREATER COST

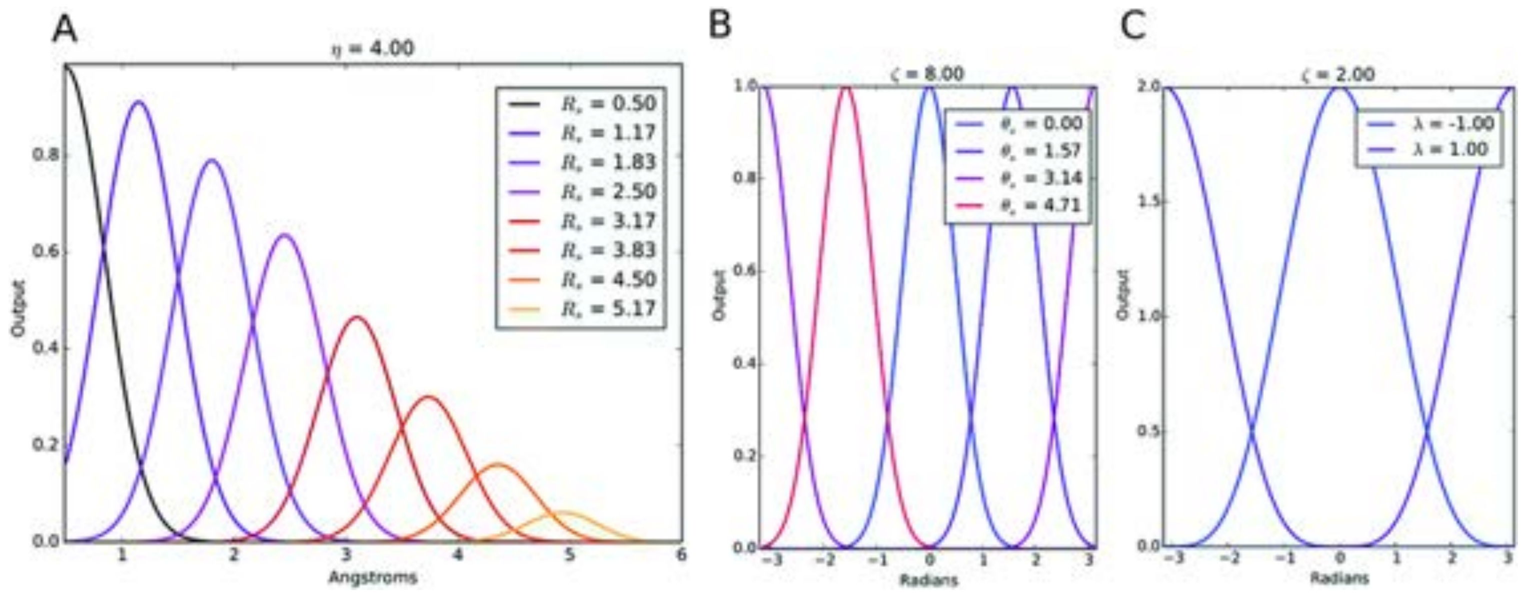
ANI family of quantum machine learning (QML) potentials

radial and **angular** features

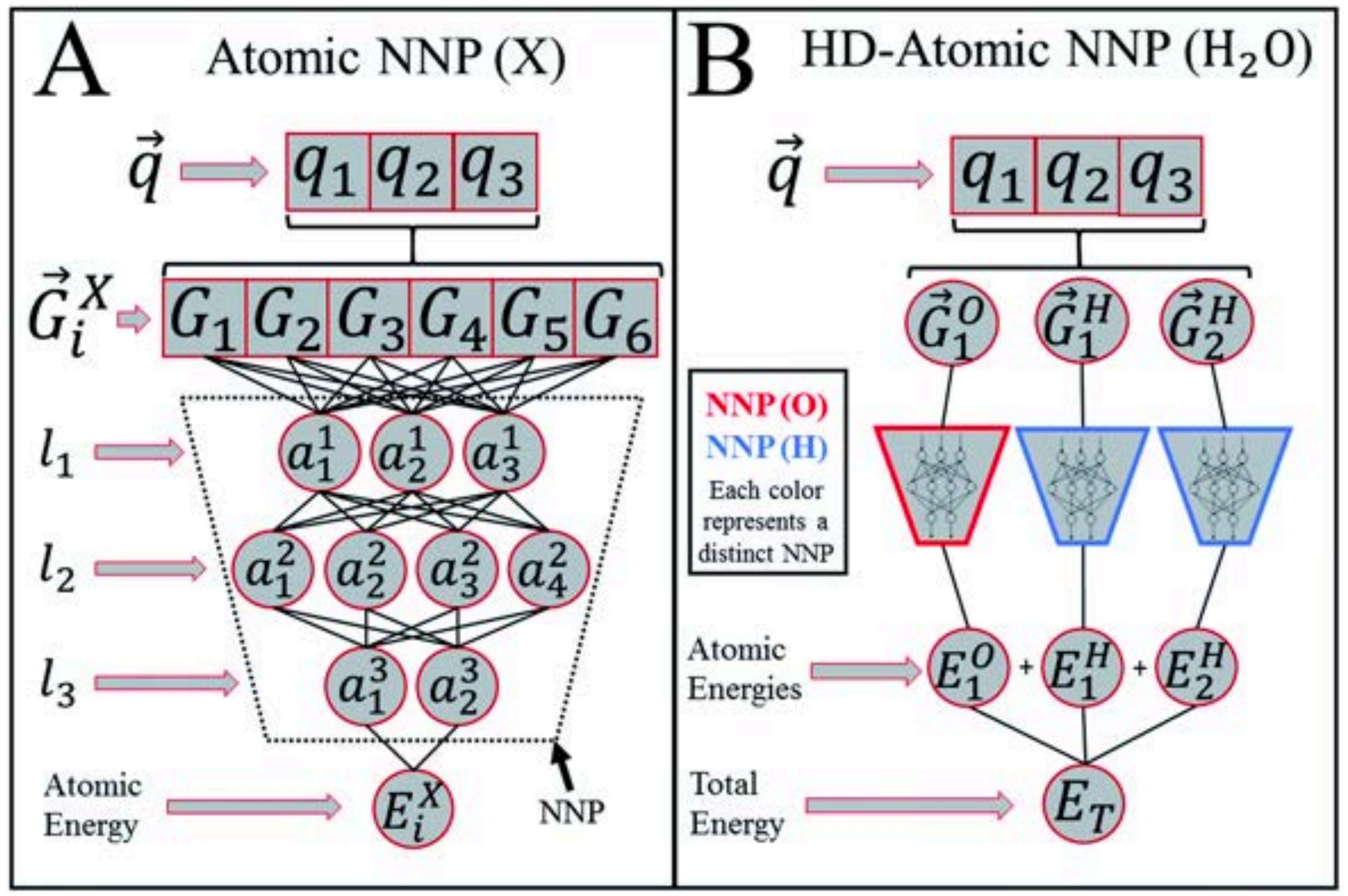
$$f_C(R_{ij}) = \begin{cases} 0.5\times\cos\left(\frac{\pi R_{ij}}{R_C}\right)+0.5 & \text{for } R_{ij} \le R_C \\ 0.0 & \text{for } R_{ij} > R_C \end{cases}$$

$$G_m^R = \sum^{\text{all atoms}} e^{-\eta(R_{ij}-R_s)^2} f_C(R_{ij})$$

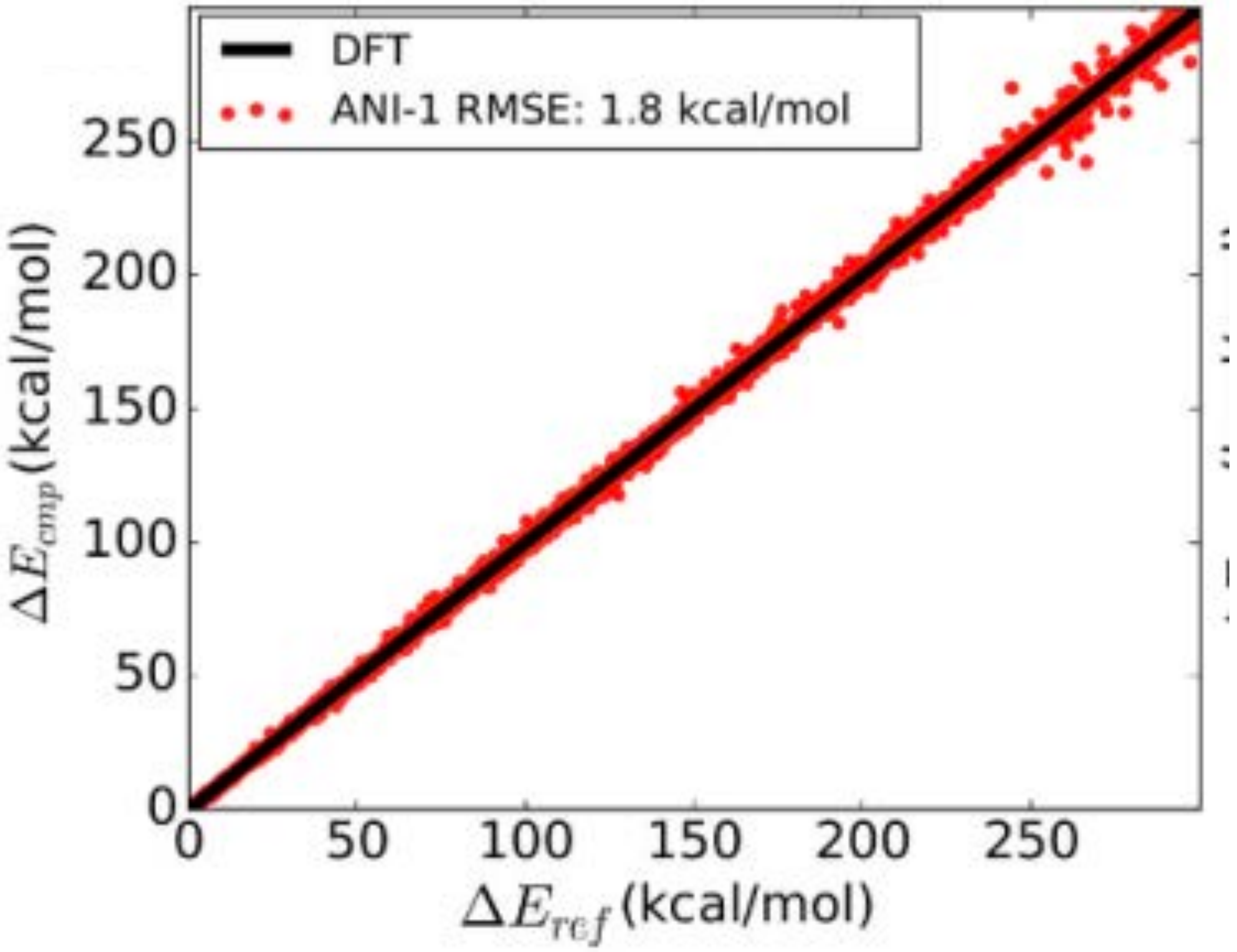
$$G_m^{A_{mod}} = 2^{1-\zeta} \sum_{j,k\neq i}^{\text{all atoms}} \left(1+\cos(\theta_{ijk}-\theta_s)\right)^{\zeta} \exp\left[-\eta\left(\frac{R_{ij}+R_{ik}}{2}-R_s\right)^2\right] f_C(R_{ij}) f_C(R_{ik})$$



deep neural network for each atom



excellent agreement with DFT

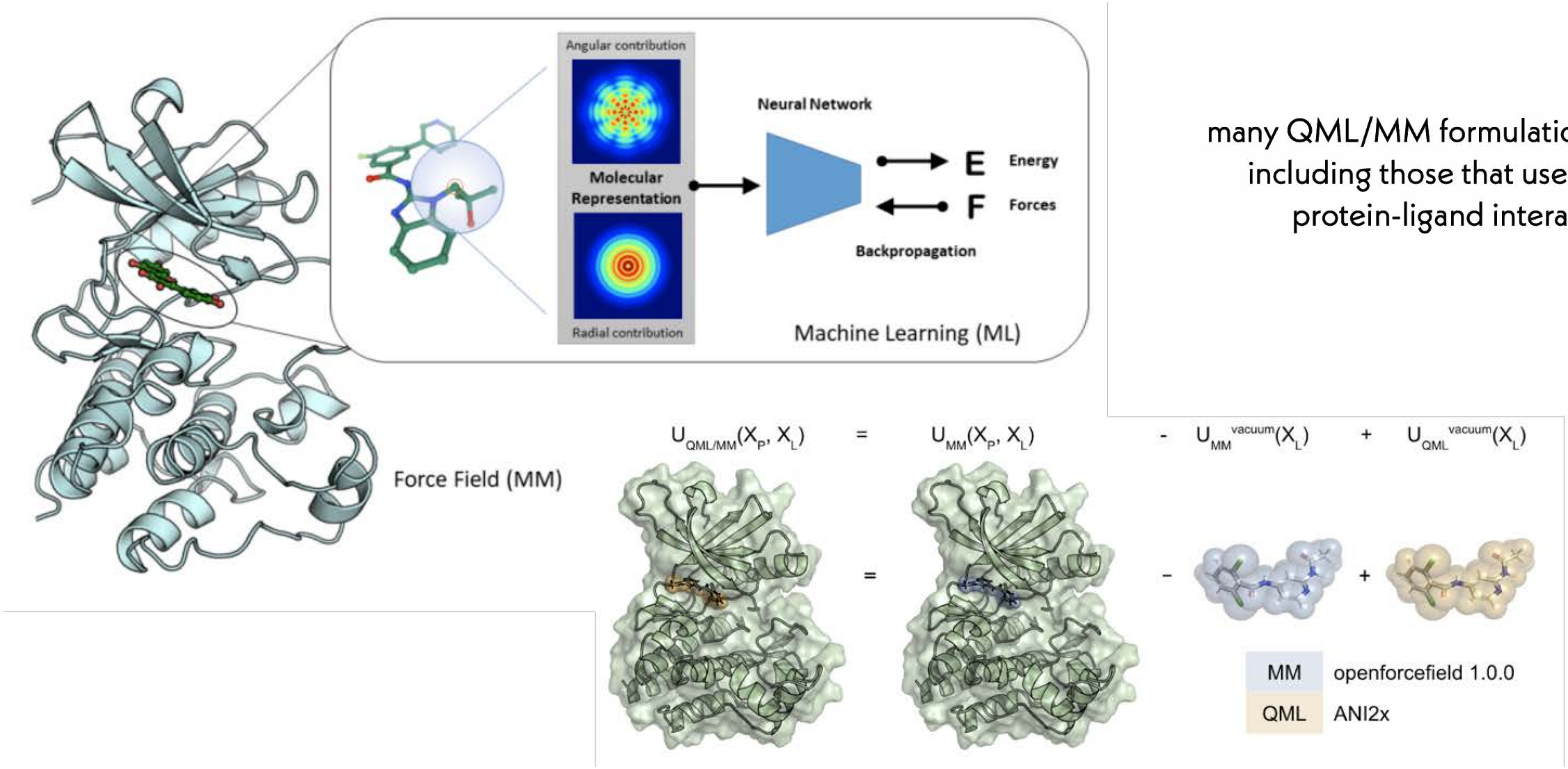


OLEXANDR ISAYEV

ADRIAN ROITBERG

Smith, Isayev, Roitberg. Chemical Science 8:3192, 2017.
http://doi.org/10.1039/c6sc05720a

HYBRID QUANTUM MACHINE LEARNING / MOLECULAR MECHANICS (QML/MM) FREE ENERGY CALCULATIONS CUT ERROR IN HALF



many QML/MM formulations possible, including those that use QML for protein-ligand interactions

$$U_{QML/MM}(X_P, X_L) = U_{MM}(X_P, X_L) - U_{MM}^{vacuum}(X_L) + U_{QML}^{vacuum}(X_L)$$

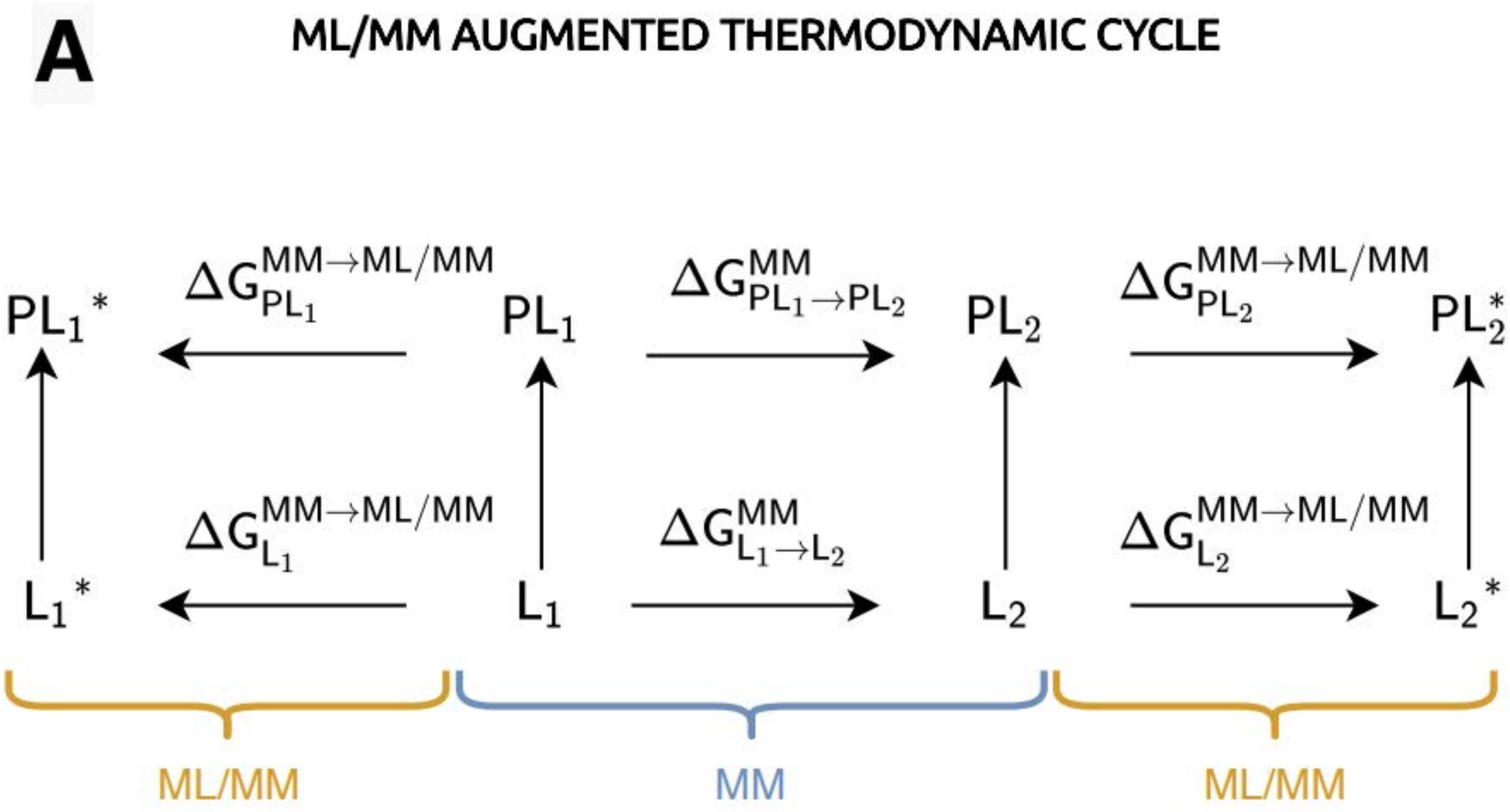
MM	openforcefield 1.0.0
QML	ANI2x

Rufa, Bruce Macdonald, Fass, Wieder, Grinaway, Roitberg, Isayev, and **Chodera**.

preprint: https://doi.org/10.1101/2020.07.29.227959

code: https://github.com/choderalab/qmlify

HYBRID QUANTUM MACHINE LEARNING / MOLECULAR MECHANICS (QML/MM) POST-PROCESSING CAN IMPROVE ACCURACY



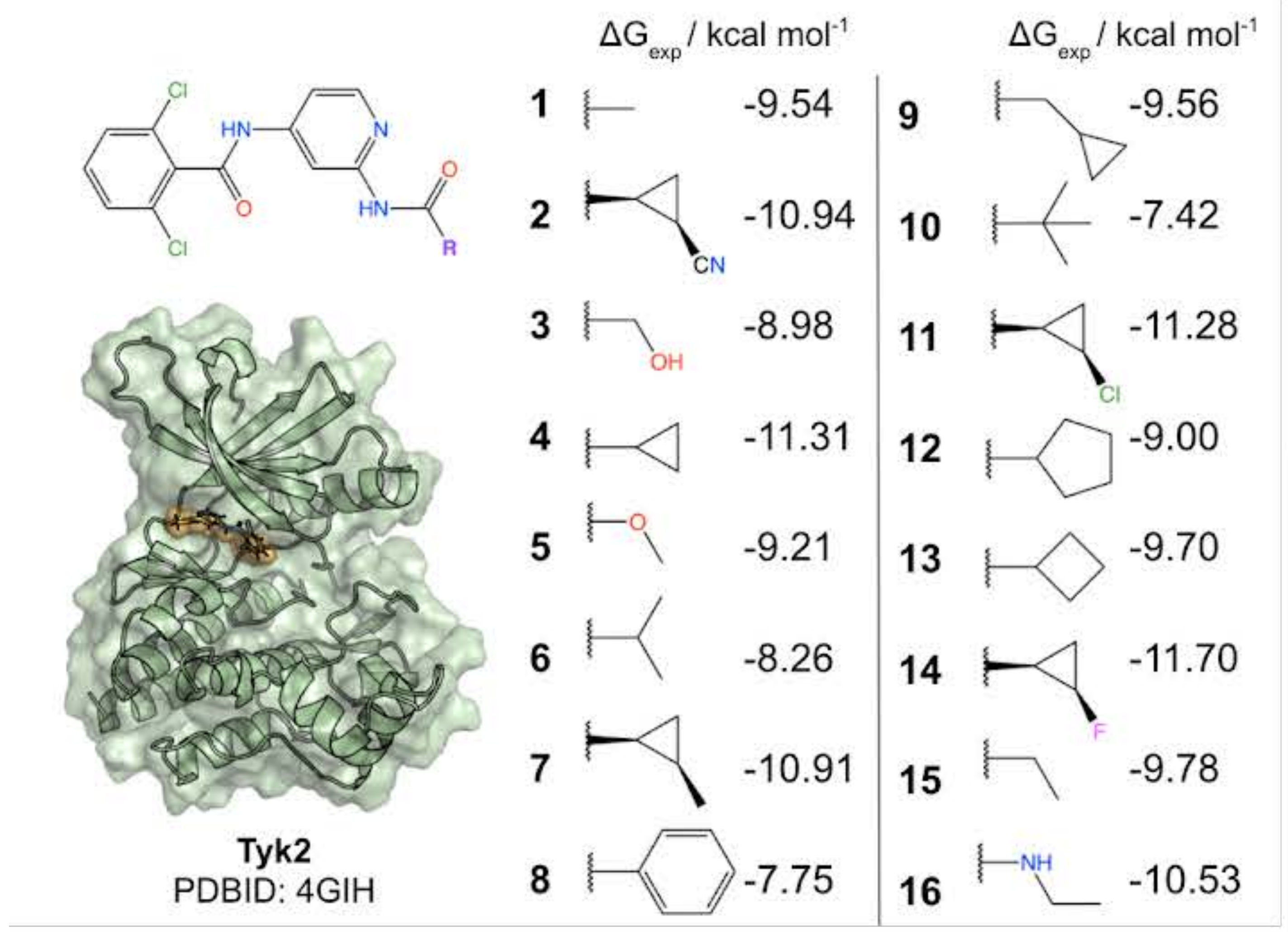
$$\begin{tikzcd}
PL_1{}^{*} & PL_1 \arrow[l, "\Delta G_{PL_1}^{MM\to ML/MM}"'] \arrow[r, "\Delta G_{PL_1\to PL_2}^{MM}"] & PL_2 \arrow[r, "\Delta G_{PL_2}^{MM\to ML/MM}"] & PL_2^{*} \\
L_1{}^{*} \arrow[u] & L_1 \arrow[u] \arrow[l, "\Delta G_{L_1}^{MM\to ML/MM}"'] \arrow[r, "\Delta G_{L_1\to L_2}^{MM}"] & L_2 \arrow[u] \arrow[r, "\Delta G_{L_2}^{MM\to ML/MM}"] & L_2{}^{*} \arrow[u]
\end{tikzcd}$$

HYBRID QUANTUM MACHINE LEARNING / MOLECULAR MECHANICS (QML/MM) FREE ENERGY CALCULATIONS CUT ERROR IN HALF

MM (OPLS2.1 + CM1A-BCC charges)
Missing torsions from LMP2/cc-pVTZ(-f) QM calculations
SPC water

MM (OpenFF 1.0.0 "Parsley")
AMBER14SB protein force field
TIP3P; Joung and Cheatham ions

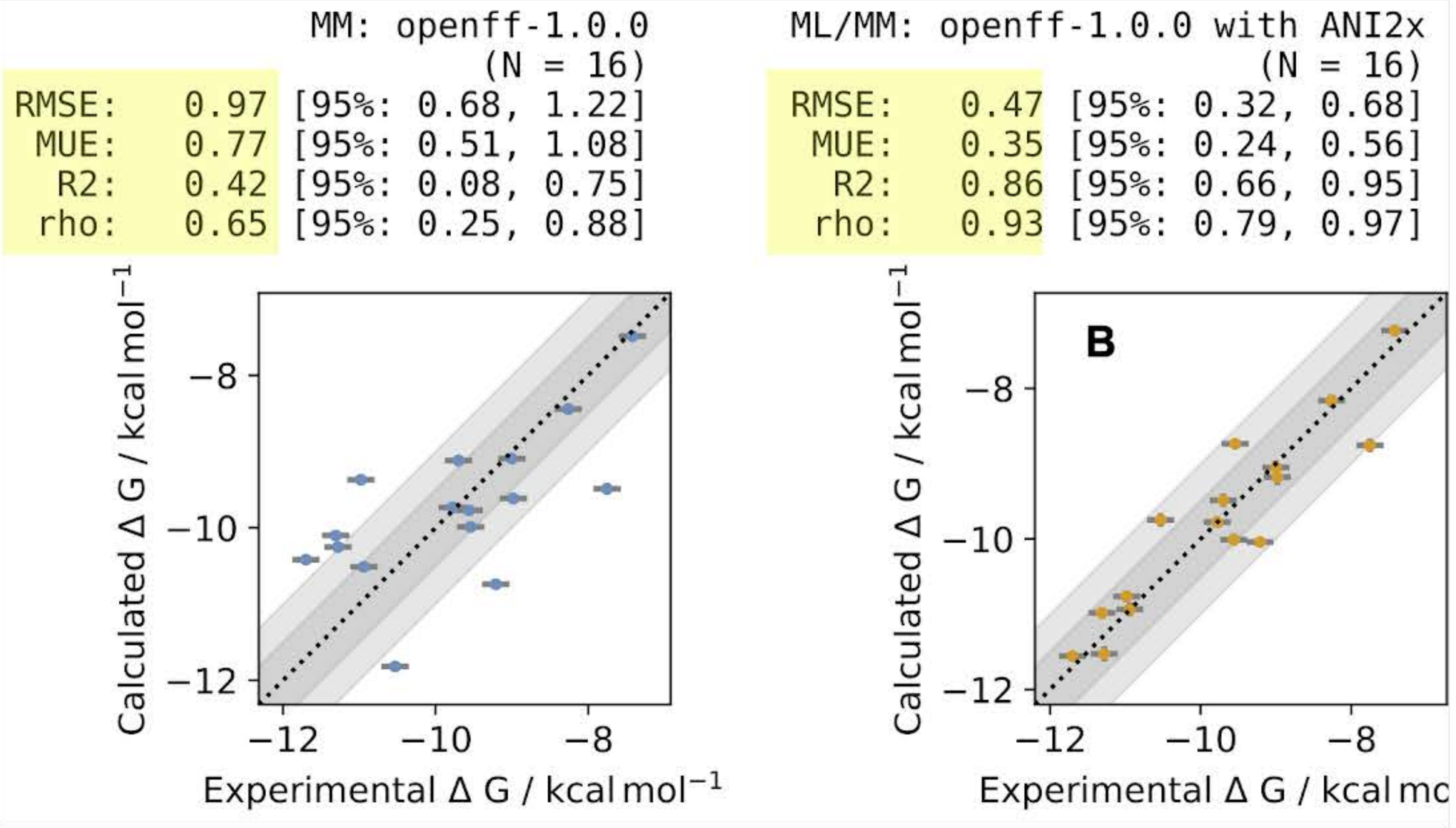
QML/MM (OpenFF 1.0.0 + ANI2x)
AMBER14SB protein force field
TIP3P; Joung and Cheatham ions



	ΔG_{exp} / kcal mol^{-1}		ΔG_{exp} / kcal mol^{-1}
1	-9.54	9	-9.56
2	-10.94	10	-7.42
3	-8.98	11	-11.28
4	-11.31	12	-9.00
5	-9.21	13	-9.70
6	-8.26	14	-11.70
7	-10.91	15	-9.78
8	-7.75	16	-10.53

	Tyk2
no. of compds	16
binding affinity range (kcal/mol)	4.3
crystal structure	4GIH
series ref	52,53
no. of perturbations	24
MUE FEP	0.75 ± 0.11
RMSE FEP	0.93 ± 0.12

Free energies are in units of kilocalories per mole.

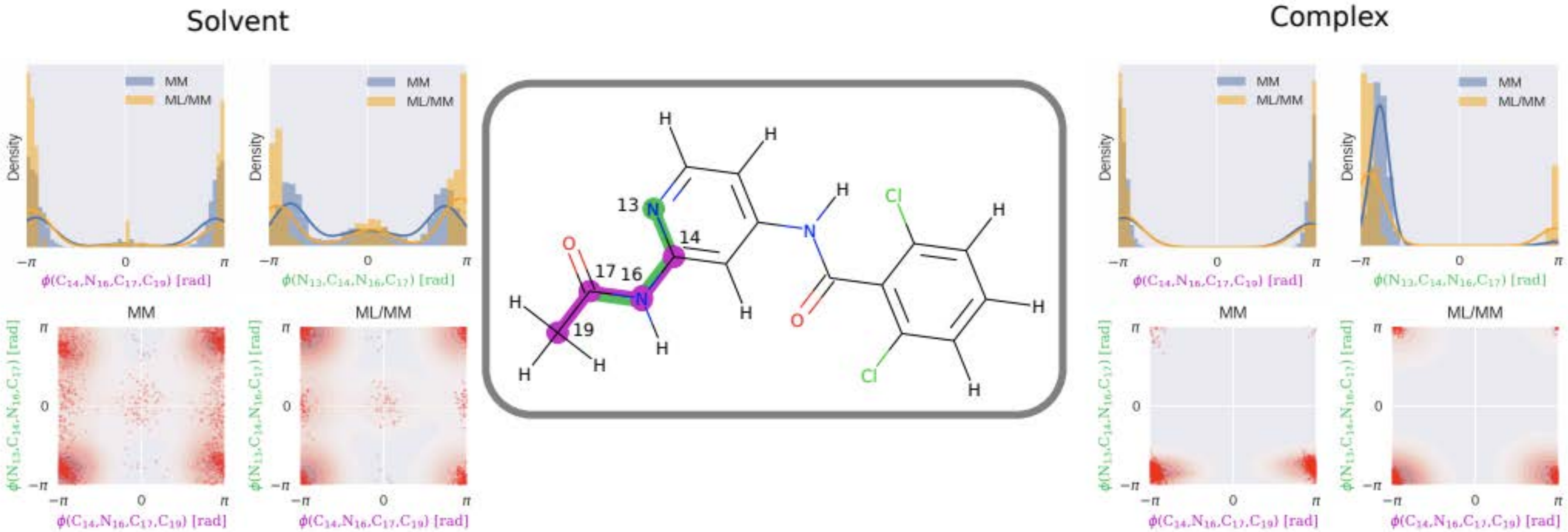


```
           MM: openff-1.0.0                 ML/MM: openff-1.0.0 with ANI2x
                        (N = 16)                                  (N = 16)
RMSE:    0.97 [95%: 0.68, 1.22]         RMSE:    0.47 [95%: 0.32, 0.68]
 MUE:    0.77 [95%: 0.51, 1.08]          MUE:    0.35 [95%: 0.24, 0.56]
  R2:    0.42 [95%: 0.08, 0.75]           R2:    0.86 [95%: 0.66, 0.95]
 rho:    0.65 [95%: 0.25, 0.88]          rho:    0.93 [95%: 0.79, 0.97]
```

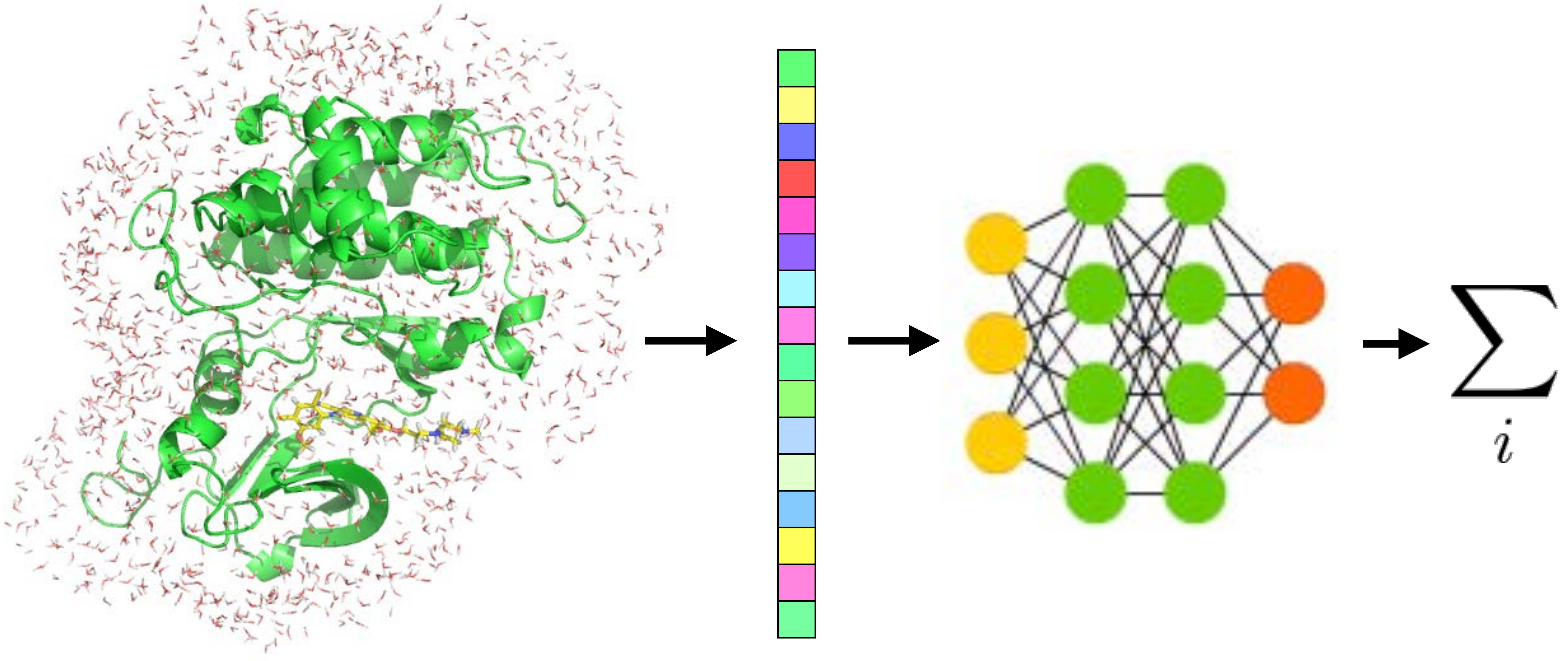
Tyk2 benchmark system from Wang et al. JACS 137:2695, 2015
replica-exchange free energy calculations with solute tempering (FEP/REST)

replica-exchange free energy calculations with perses
preprint: https://doi.org/10.1101/2020.07.29.227959
code: https://github.com/choderalab/perses
https://github.com/choderalab/qmlify

HYBRID QUANTUM MACHINE LEARNING / MOLECULAR MECHANICS (QML/MM) POST-PROCESSING CAN IMPROVE ACCURACY



COMPUTATIONAL BOTTLENECKS IN CURRENT QML MODELS CAN BE SPED UP WITH CUSTOM GPU KERNELS

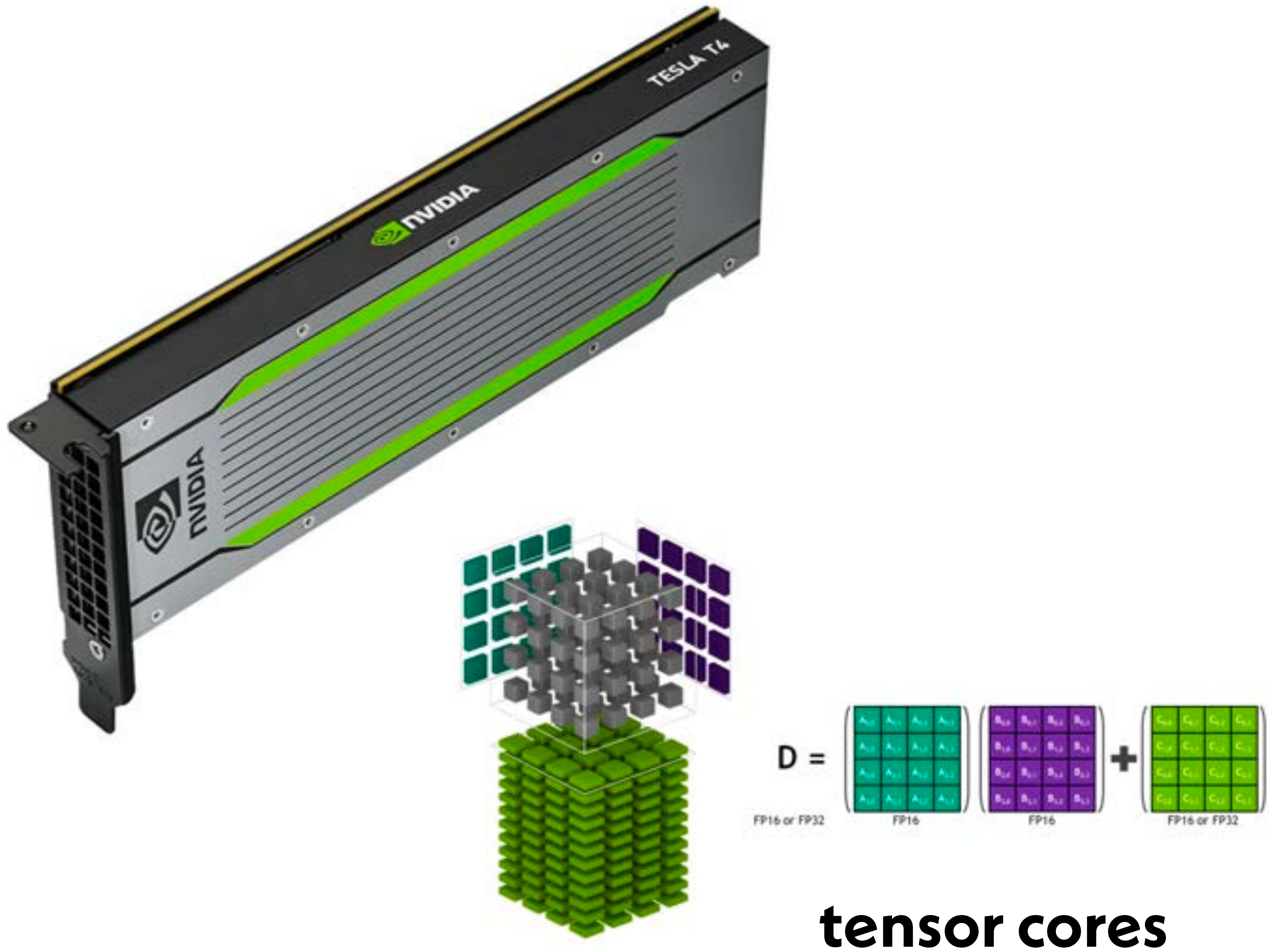


atomic coordinates

feature computation

NN computation

energy/force accumulation



tensor cores

We can speed this up with OpenMM GPU kernels using common pairlists, etc. (e.g. for ANI models)

TensorFlow/PyTorch do this efficiently, and hardware will keep getting better for this step

COMPUTATIONAL BOTTLENECKS IN CURRENT QML MODELS CAN BE SPED UP WITH CUSTOM GPU KERNELS

PDB ID	# res	# heavy atoms	OpenMM ns/day (4 fs timestep)	TorchANI QML/MM ns/day (2 fs timestep)	OpenMM QML/MM* ns/day (2 fs timestep)
3BE9	328	48	436	10.4	96.5 / 50.8
2P95	286	50	430	7.93	96.8 / 49.8
1HPO	198	64	547	9.12	101 / 44.6
1AJV	198	75	666	9.19	101 / 40.7

* ANI ensemble size: 1 / 8

NNPOps library

https://github.com/openmm/nnpops

- CUDA/CPU accelerated kernels
- API for inclusion in MD engines
- Ops wrappers for ML frameworks (PyTorch, TensorFlow, JAX)
- Community-driven, package agnostic

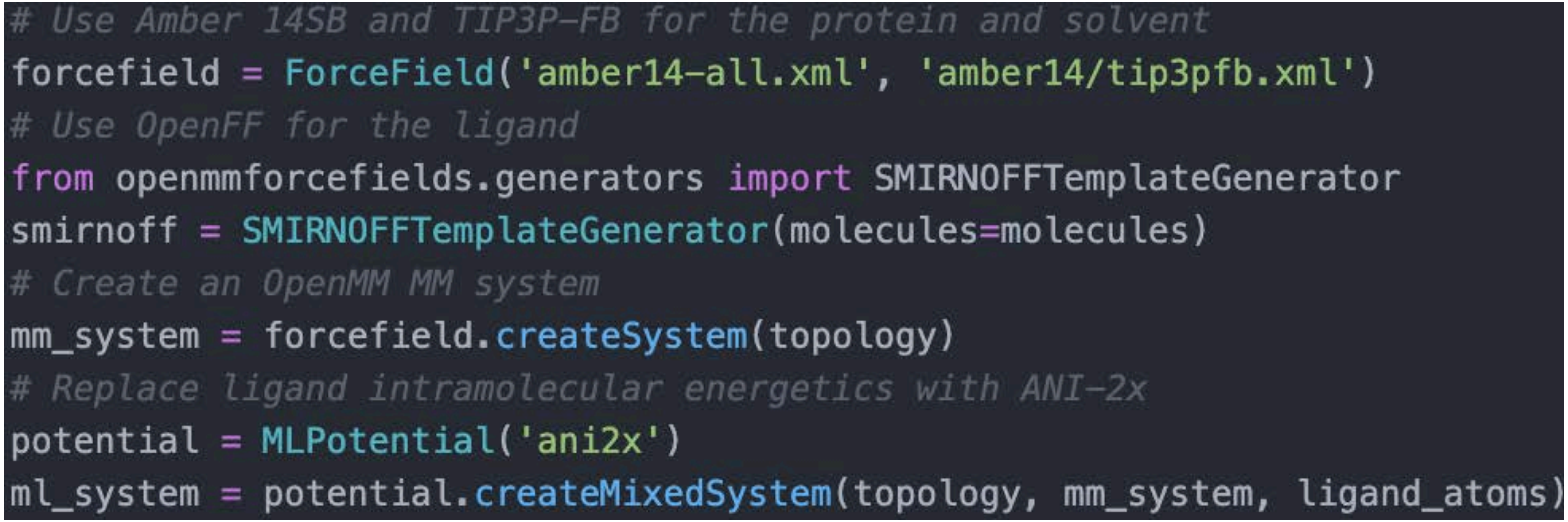
(~2.5x slower than GPU MD right now, but need 2x smaller timestep)

model distillation will become important in building single models that are efficient on hardware

paper: https://arxiv.org/abs/2201.08110

code: https://github.com/openmm/nnpops

WE WANT TO MAKE IT EASY TO RUN QML/MM SIMULATIONS WITH OPENMM



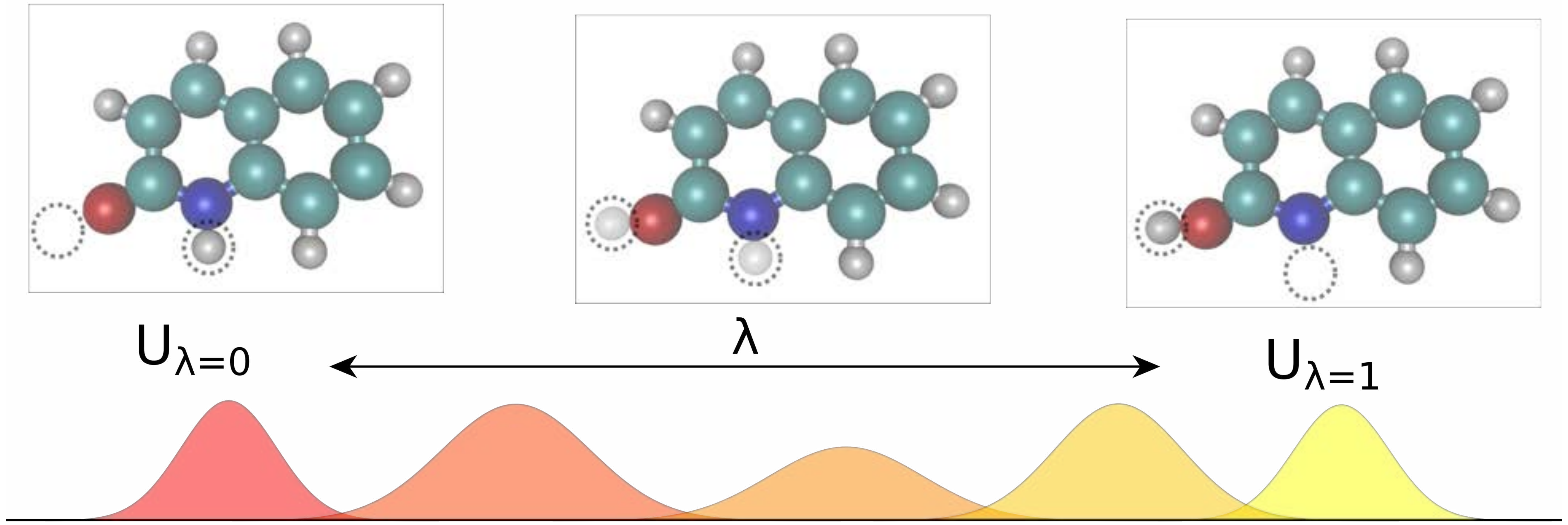
```python
# Use Amber 14SB and TIP3P-FB for the protein and solvent
forcefield = ForceField('amber14-all.xml', 'amber14/tip3pfb.xml')
# Use OpenFF for the ligand
from openmmforcefields.generators import SMIRNOFFTemplateGenerator
smirnoff = SMIRNOFFTemplateGenerator(molecules=molecules)
# Create an OpenMM MM system
mm_system = forcefield.createSystem(topology)
# Replace ligand intramolecular energetics with ANI-2x
potential = MLPotential('ani2x')
ml_system = potential.createMixedSystem(topology, mm_system, ligand_atoms)
```

https://github.com/openmm/openmm-ml

PURE QUANTUM MACHINE LEARNING (QML) POTENTIALS CAN BE USED TO COMPUTE FREE ENERGY DIFFERENCES BETWEEN CHEMICAL SPECIES

Potentials are free of singularities, so **simple linear alchemical potentials** can robustly compute alchemical free energies

$$U(x;\lambda) = (1-\lambda)U_{\lambda=0}(x) + \lambda U_{\lambda=1}(x)$$



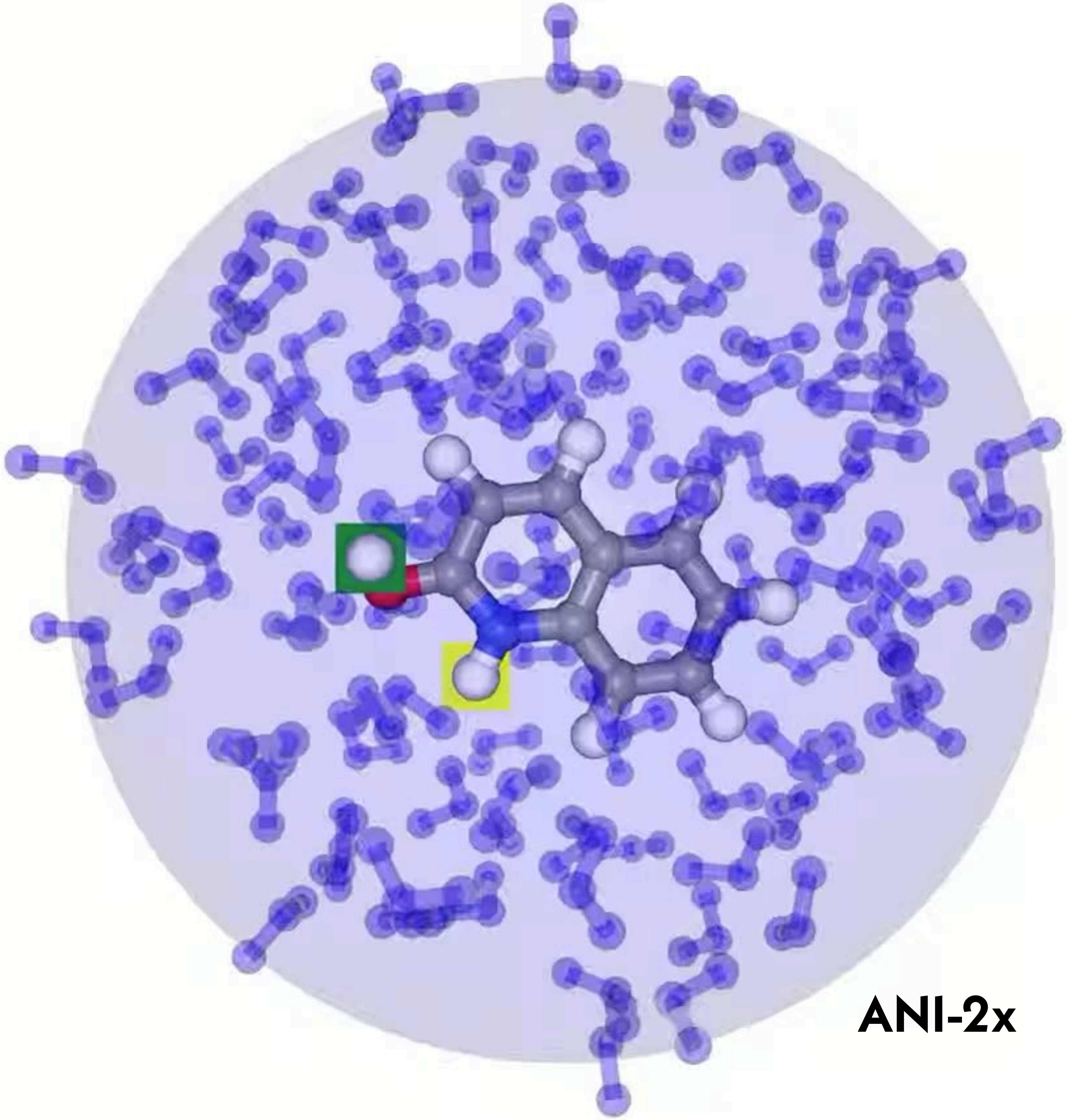
Simple atomic restraints can be used to improve efficiency by preventing atoms from flying away

JOSH FASS

MARCUS WIEDER

preprint: https://doi.org/10.1101/2020.10.24.353318

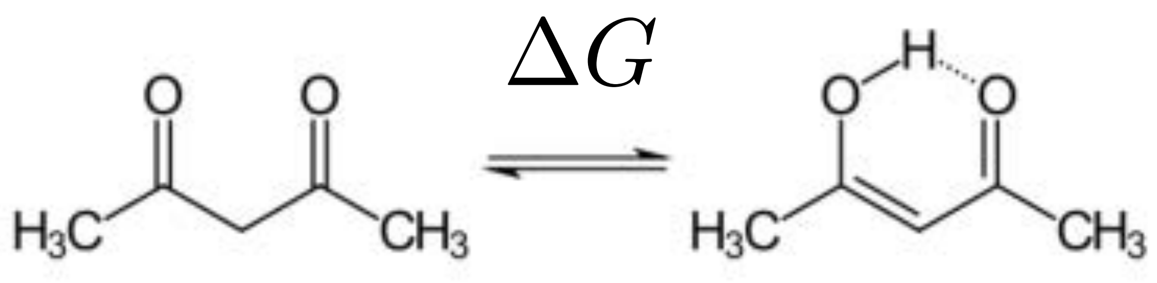
code: https://github.com/choderalab/neutromeratio



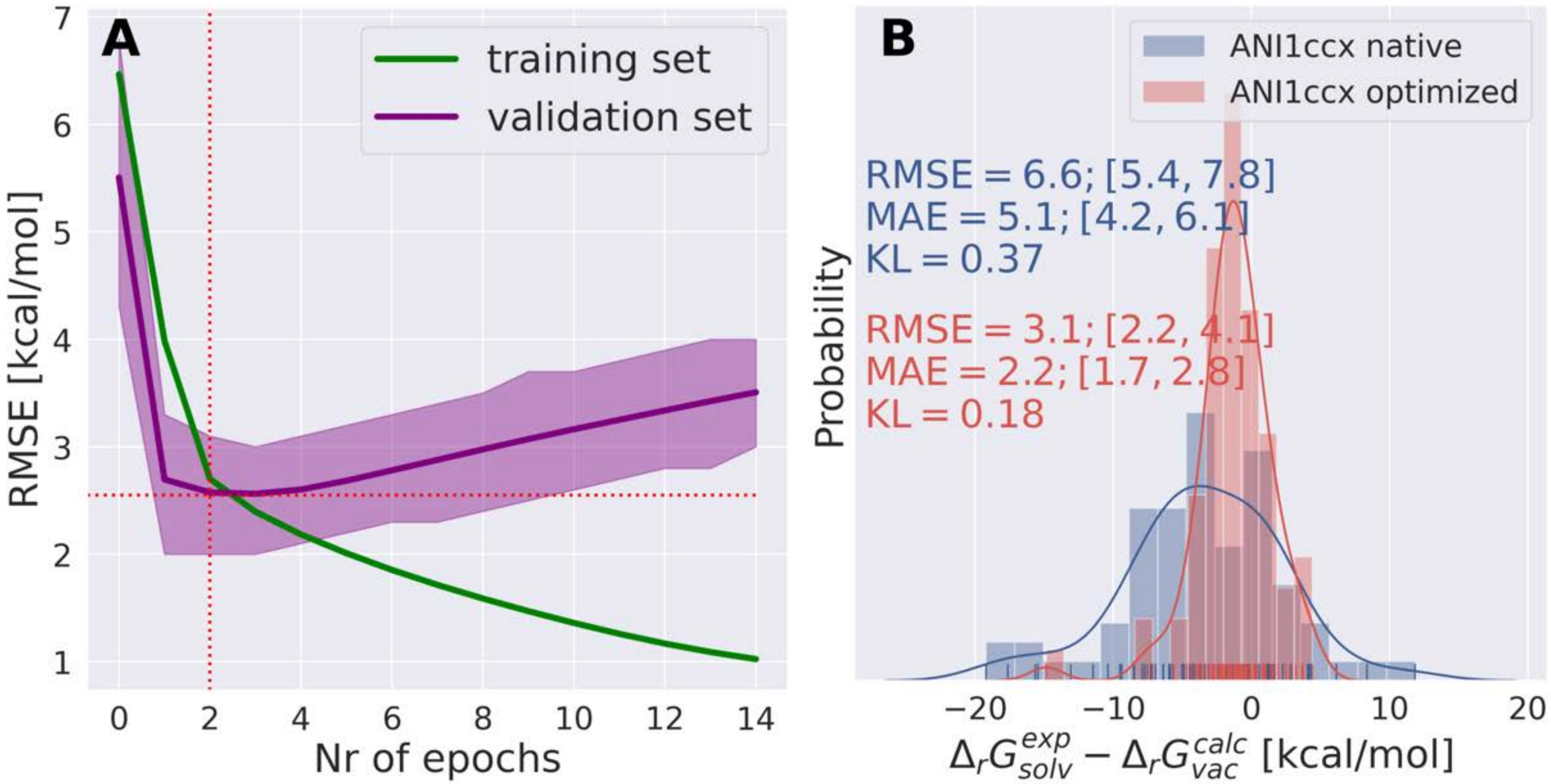
ANI-2x

QML POTENTIALS CAN LEARN FROM EXPERIMENTAL DATA TO IMPROVE PHYSICAL MODELS

physical models are data-efficient: retraining on small number of experimental measurements improves accuracy and generalizes well



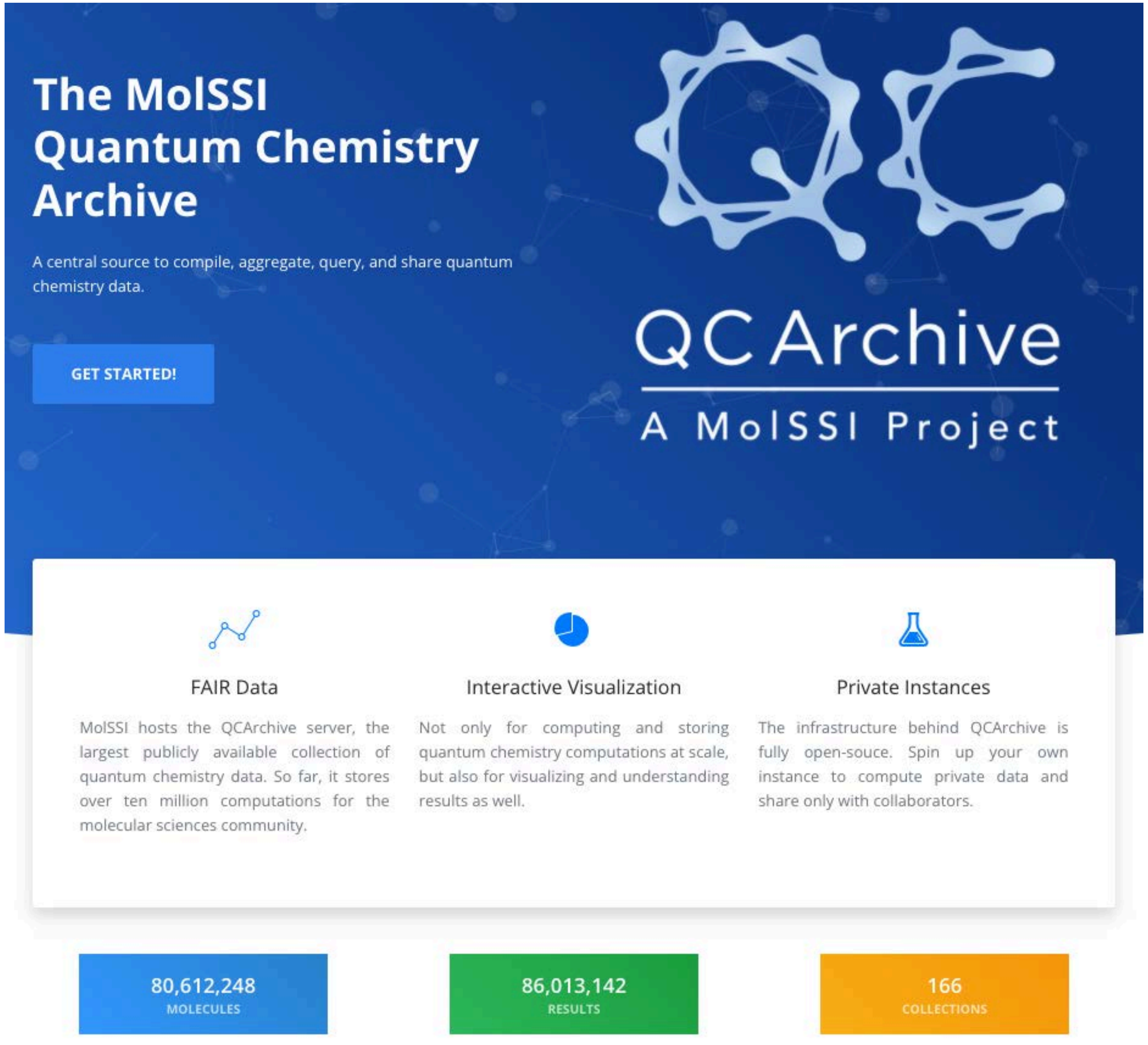
train: 221 tautomer pairs
validate: 57 tautomer pairs
test: 72 tautomer pairs



JOSH FASS

MARCUS WIEDER

preprint: https://doi.org/10.1101/2020.10.24.353318
code: https://github.com/choderalab/neutromeratio



The MolSSI Quantum Chemistry Archive

A central source to compile, aggregate, query, and share quantum chemistry data.

FAIR Data

MolSSI hosts the QCArchive server, the largest publicly available collection of quantum chemistry data. So far, it stores over ten million computations for the molecular sciences community.

Interactive Visualization

Not only for computing and storing quantum chemistry computations at scale, but also for visualizing and understanding results as well.

Private Instances

The infrastructure behind QCArchive is fully open-souce. Spin up your own instance to compute private data and share only with collaborators.

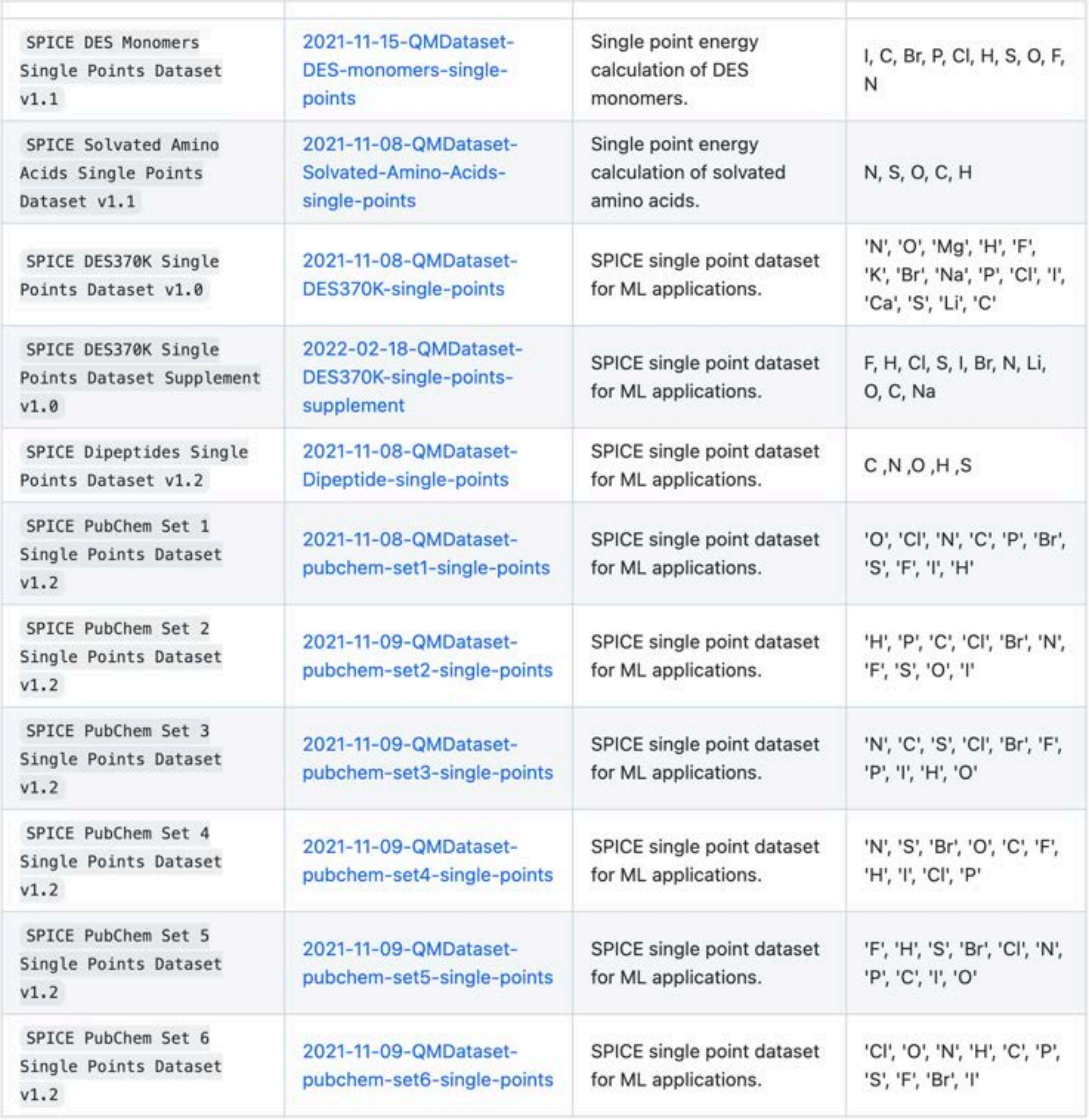
80,612,248 MOLECULES

86,013,142 RESULTS

166 COLLECTIONS

http://qcarchive.molssi.org

OpenMM and the Open Force Field Initiative are working closely with MolSSI to expand the QCArchive to support the construction of next-generation machine learning force fields



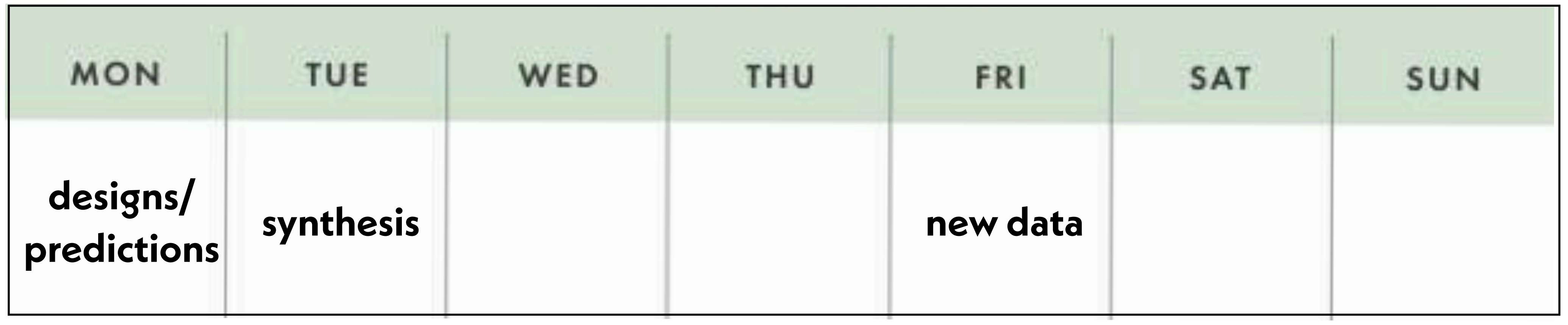
`SPICE DES Monomers Single Points Dataset v1.1`	2021-11-15-QMDataset-DES-monomers-single-points	Single point energy calculation of DES monomers.	I, C, Br, P, Cl, H, S, O, F, N
`SPICE Solvated Amino Acids Single Points Dataset v1.1`	2021-11-08-QMDataset-Solvated-Amino-Acids-single-points	Single point energy calculation of solvated amino acids.	N, S, O, C, H
`SPICE DES370K Single Points Dataset v1.0`	2021-11-08-QMDataset-DES370K-single-points	SPICE single point dataset for ML applications.	'N', 'O', 'Mg', 'H', 'F', 'K', 'Br', 'Na', 'P', 'Cl', 'I', 'Ca', 'S', 'Li', 'C'
`SPICE DES370K Single Points Dataset Supplement v1.0`	2022-02-18-QMDataset-DES370K-single-points-supplement	SPICE single point dataset for ML applications.	F, H, Cl, S, I, Br, N, Li, O, C, Na
`SPICE Dipeptides Single Points Dataset v1.2`	2021-11-08-QMDataset-Dipeptide-single-points	SPICE single point dataset for ML applications.	C ,N ,O ,H ,S
`SPICE PubChem Set 1 Single Points Dataset v1.2`	2021-11-08-QMDataset-pubchem-set1-single-points	SPICE single point dataset for ML applications.	'O', 'Cl', 'N', 'C', 'P', 'Br', 'S', 'F', 'I', 'H'
`SPICE PubChem Set 2 Single Points Dataset v1.2`	2021-11-09-QMDataset-pubchem-set2-single-points	SPICE single point dataset for ML applications.	'H', 'P', 'C', 'Cl', 'Br', 'N', 'F', 'S', 'O', 'I'
`SPICE PubChem Set 3 Single Points Dataset v1.2`	2021-11-09-QMDataset-pubchem-set3-single-points	SPICE single point dataset for ML applications.	'N', 'C', 'S', 'Cl', 'Br', 'F', 'P', 'I', 'H', 'O'
`SPICE PubChem Set 4 Single Points Dataset v1.2`	2021-11-09-QMDataset-pubchem-set4-single-points	SPICE single point dataset for ML applications.	'N', 'S', 'Br', 'O', 'C', 'F', 'H', 'I', 'Cl', 'P'
`SPICE PubChem Set 5 Single Points Dataset v1.2`	2021-11-09-QMDataset-pubchem-set5-single-points	SPICE single point dataset for ML applications.	'F', 'H', 'S', 'Br', 'Cl', 'N', 'P', 'C', 'I', 'O'
`SPICE PubChem Set 6 Single Points Dataset v1.2`	2021-11-09-QMDataset-pubchem-set6-single-points	SPICE single point dataset for ML applications.	'Cl', 'O', 'N', 'H', 'C', 'P', 'S', 'F', 'Br', 'I'

https://github.com/openmm/spice-dataset

CAN WE CHANGE PRACTICE IN STRUCTURE-ENABLED DRUG DISCOVERY BY LEVERAGING DATA WE GENERATE?

2021

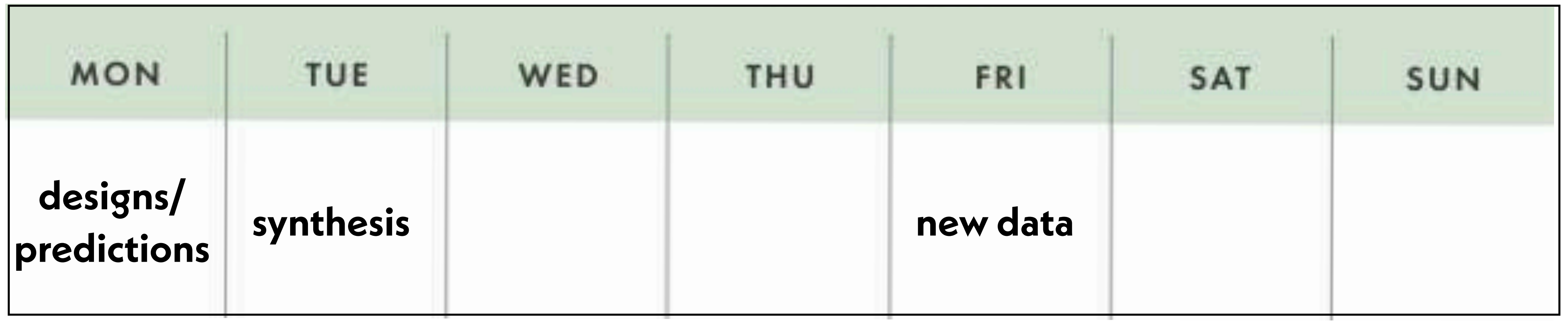
week 1



MON	TUE	WED	THU	FRI	SAT	SUN
designs/ predictions	synthesis			new data		

using published force field model

week 2

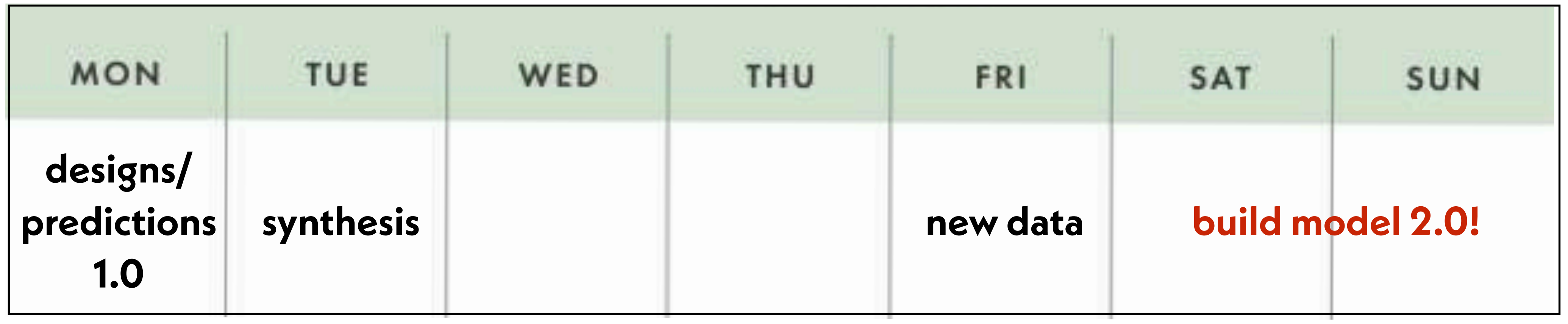


MON	TUE	WED	THU	FRI	SAT	SUN
designs/ predictions	synthesis			new data		

using the **same** published force field model!
we haven't learned anything from the data

2025

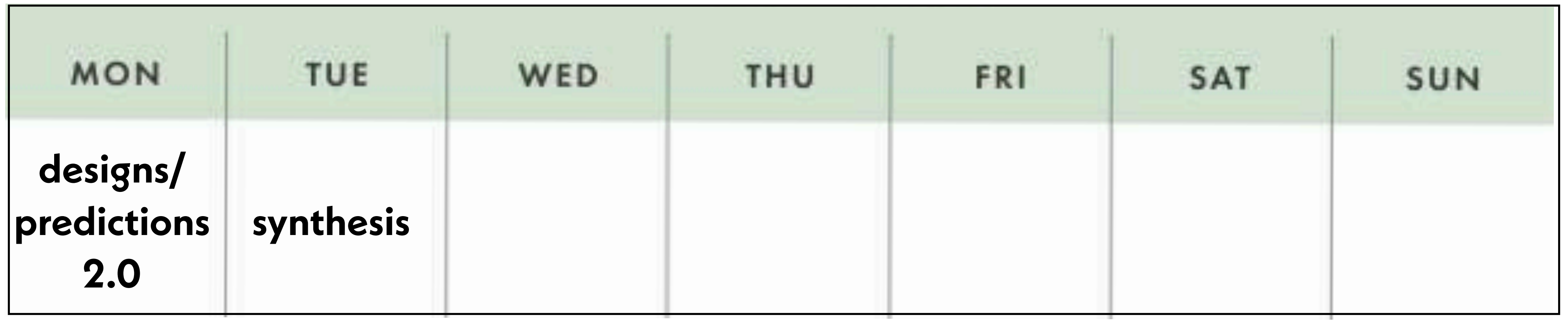
week 1



MON	TUE	WED	THU	FRI	SAT	SUN
designs/ predictions 1.0	synthesis			new data	build model 2.0!	

using force field model
built from public + private data

week 2



MON	TUE	WED	THU	FRI	SAT	SUN
designs/ predictions 2.0	synthesis					

using **new** model tuned to target
from first week's data

PREPRINTS AND CODE

gimlet: graph convolutional networks for partial charge assignment
preprint: https://arxiv.org/abs/1909.07903
code: http://github.com/choderalab/gimlet

espaloma: end-to-end differentiable assignment of force field parameters
preprint: https://arxiv.org/abs/2010.01196
code: https://github.com/choderalab/espaloma

qmlify: hybrid QML/MM alchemical free energy calculations for protein-ligand binding
preprint: https://doi.org/10.1101/2020.07.29.227959
code: https://github.com/choderalab/qmlify

neutromeratio: alchemical free energy calculations with fully QML potentials for tautomer ratio prediction
preprint: https://doi.org/10.1101/2020.10.24.353318
code: https://github.com/choderalab/neutromeratio

CHODERA LAB

National Institutes of Health

STIFTUNG CHARITÉ

SCHRÖDINGER.

SILICON Therapeutics

PARKER INSTITUTE for CANCER IMMUNOTHERAPY

Gerstner FAMILY FOUNDATION

BAYER

STARR CANCER CONSORTIUM

OpenEye SCIENTIFIC

open forcefield consortium

XtalPi

VIR

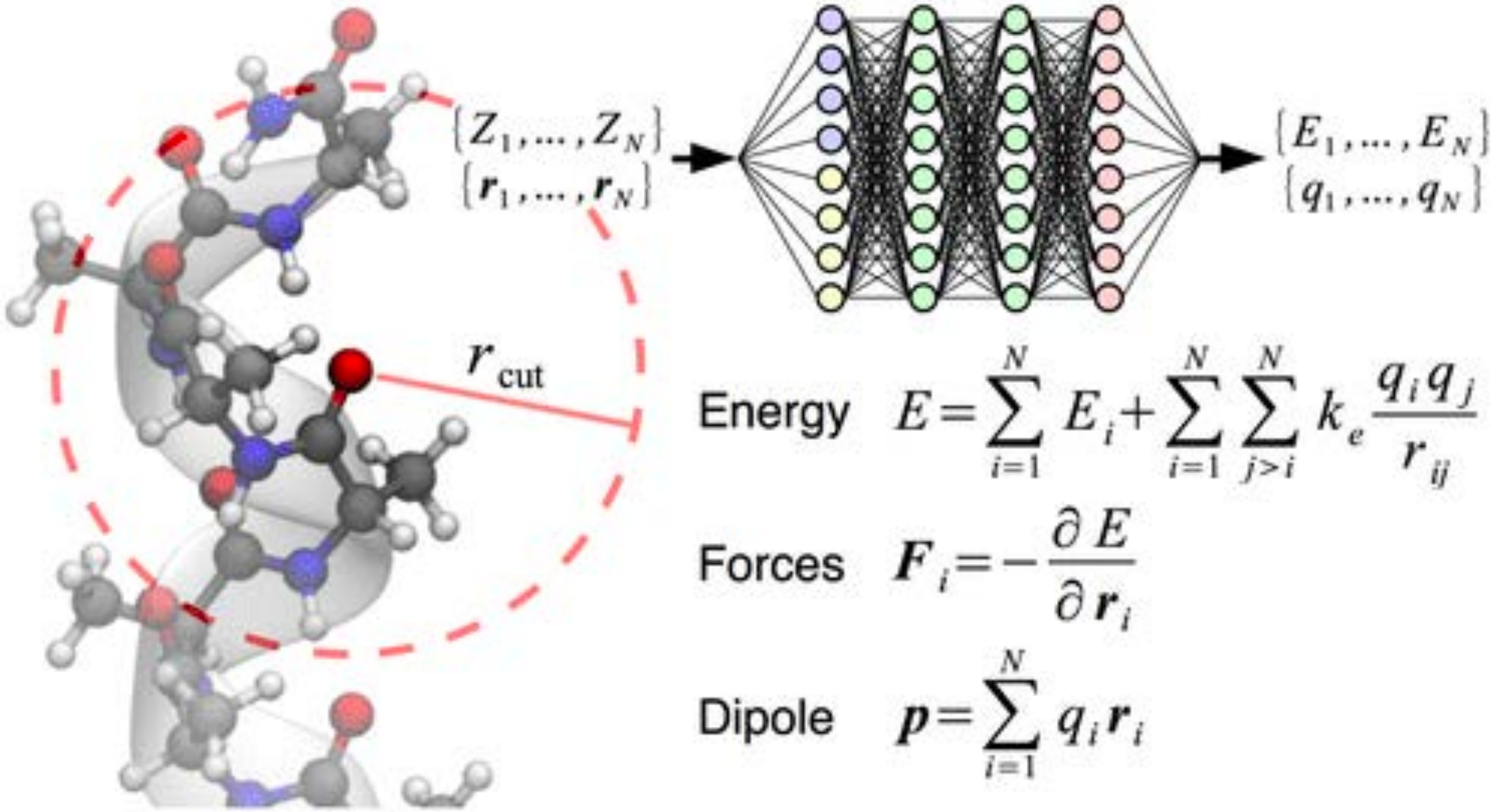
CYCLE FOR SURVIVAL

Scientific Advisor: OpenEye, Foresite Labs

All funding: http://choderalab.org/funding

MM WILL MOVE TOWARD POTENTIALS THAT BLEND SHORT-RANGE ML AND LONG-RANGE PHYSICS

PhysNet

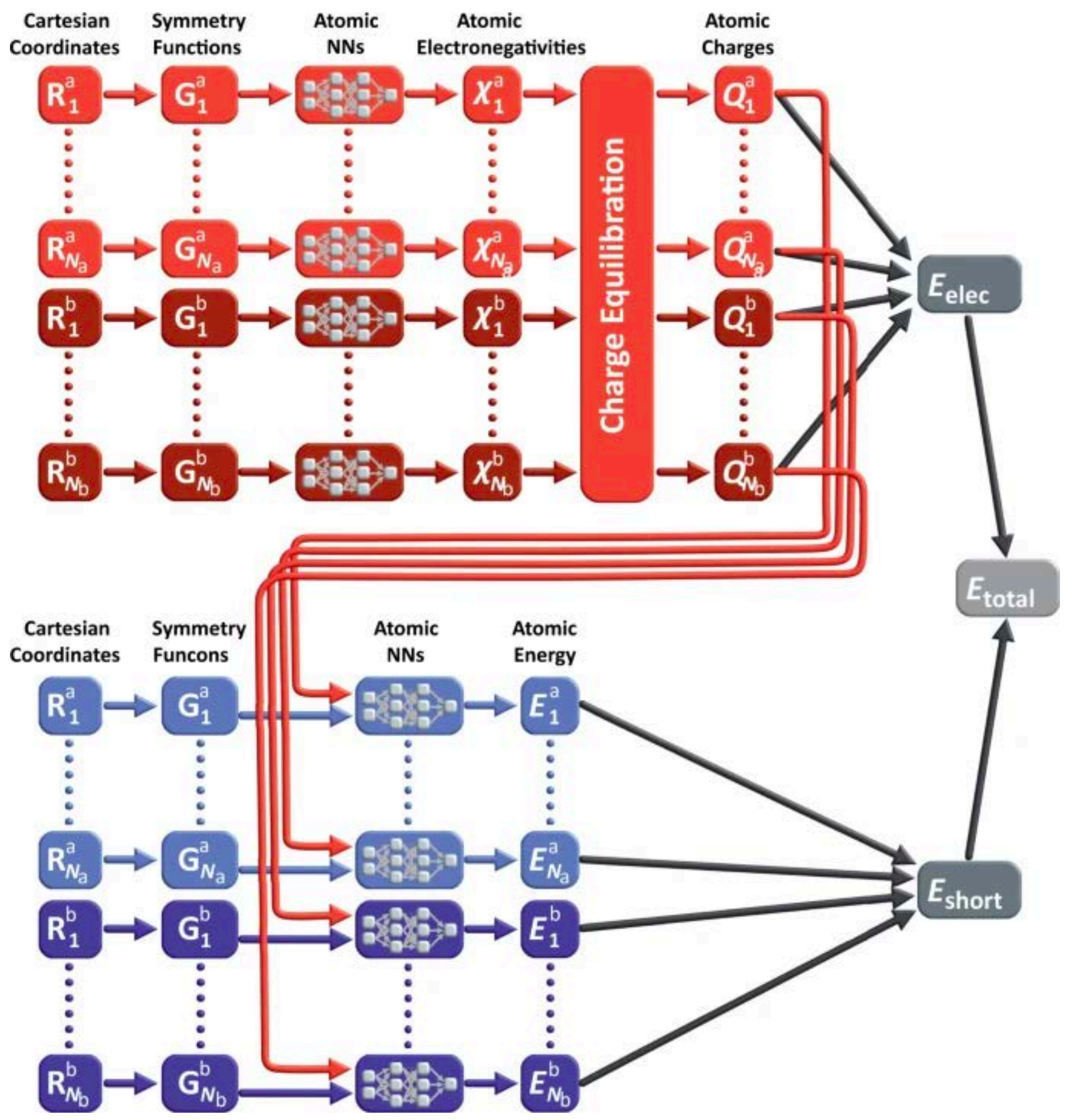


Energy $E=\sum_{i=1}^{N} E_i+\sum_{i=1}^{N}\sum_{j>i}^{N} k_e \frac{q_i q_j}{r_{ij}}$

Forces $\boldsymbol{F}_i=-\frac{\partial E}{\partial \boldsymbol{r}_i}$

Dipole $\boldsymbol{p}=\sum_{i=1}^{N} q_i \boldsymbol{r}_i$

4D-HGNNP

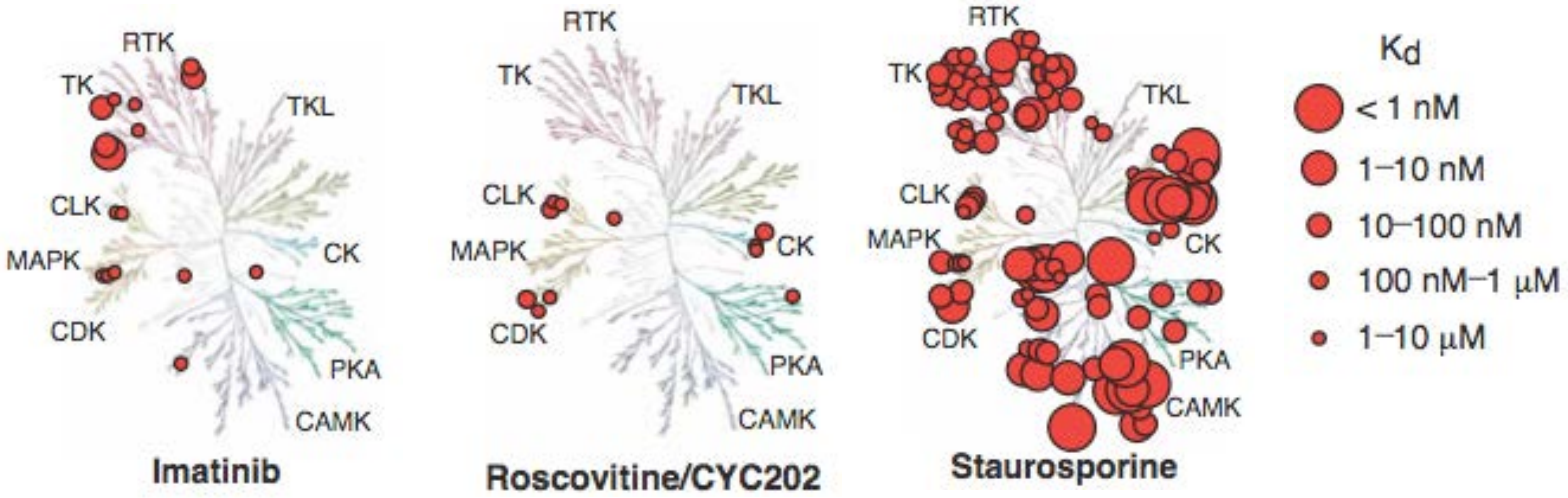

Cartesian Coordinates
Symmetry Functions
Atomic NNs
Atomic Electronegativities
Atomic Charges
Charge Equilibration
R_1^a G_1^a χ_1^a Q_1^a
$R_{N_a}^a$ $G_{N_a}^a$ $\chi_{N_a}^a$ $Q_{N_a}^a$
R_1^b G_1^b χ_1^b Q_1^b
$R_{N_b}^b$ $G_{N_b}^b$ $\chi_{N_b}^b$ $Q_{N_b}^b$
E_{elec}
E_{total}
Cartesian Coordinates
Symmetry Funcons
Atomic NNs
Atomic Energy
R_1^a G_1^a E_1^a
$R_{N_a}^a$ $G_{N_a}^a$ $E_{N_a}^a$
R_1^b G_1^b E_1^b
$R_{N_b}^b$ $G_{N_b}^b$ $E_{N_b}^b$
E_{short}

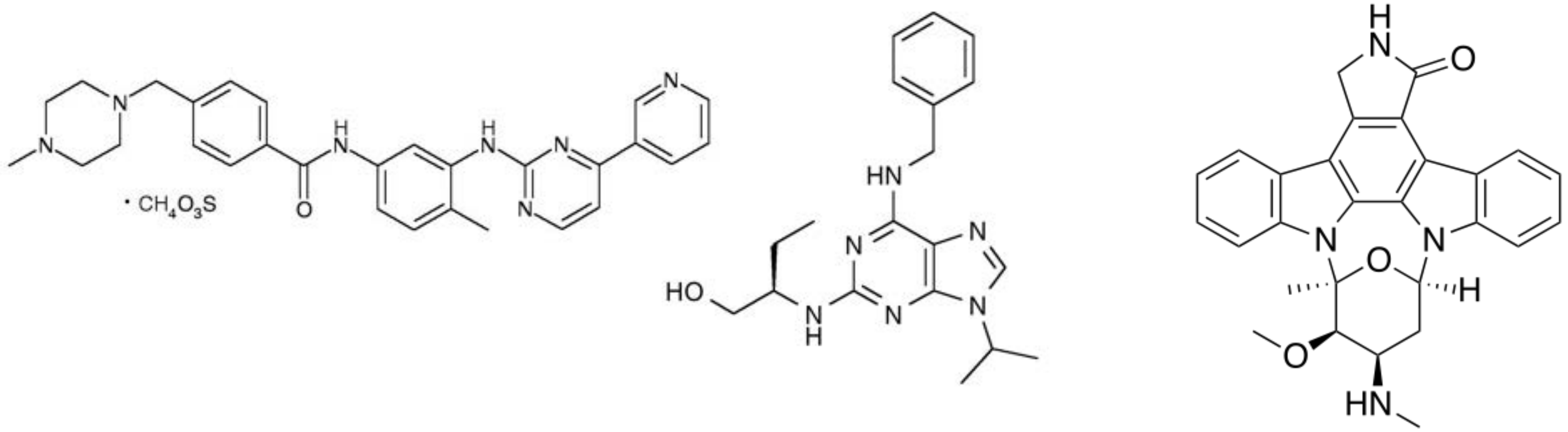
MD codes need to interoperate with ML frameworks and implement optimized ML potentials using common atomic featurizations

Unke and Meuwly
https://doi.org/10.1021/acs.jctc.9b00181

Ko, Finkler, Goedecker, and Behler
https://doi.org/10.1038/s41467-020-20427-2

ALCHEMICAL FREE ENERGY CALCULATIONS CAN PREDICT SELECTIVITIES BETTER THAN AFFINITIES

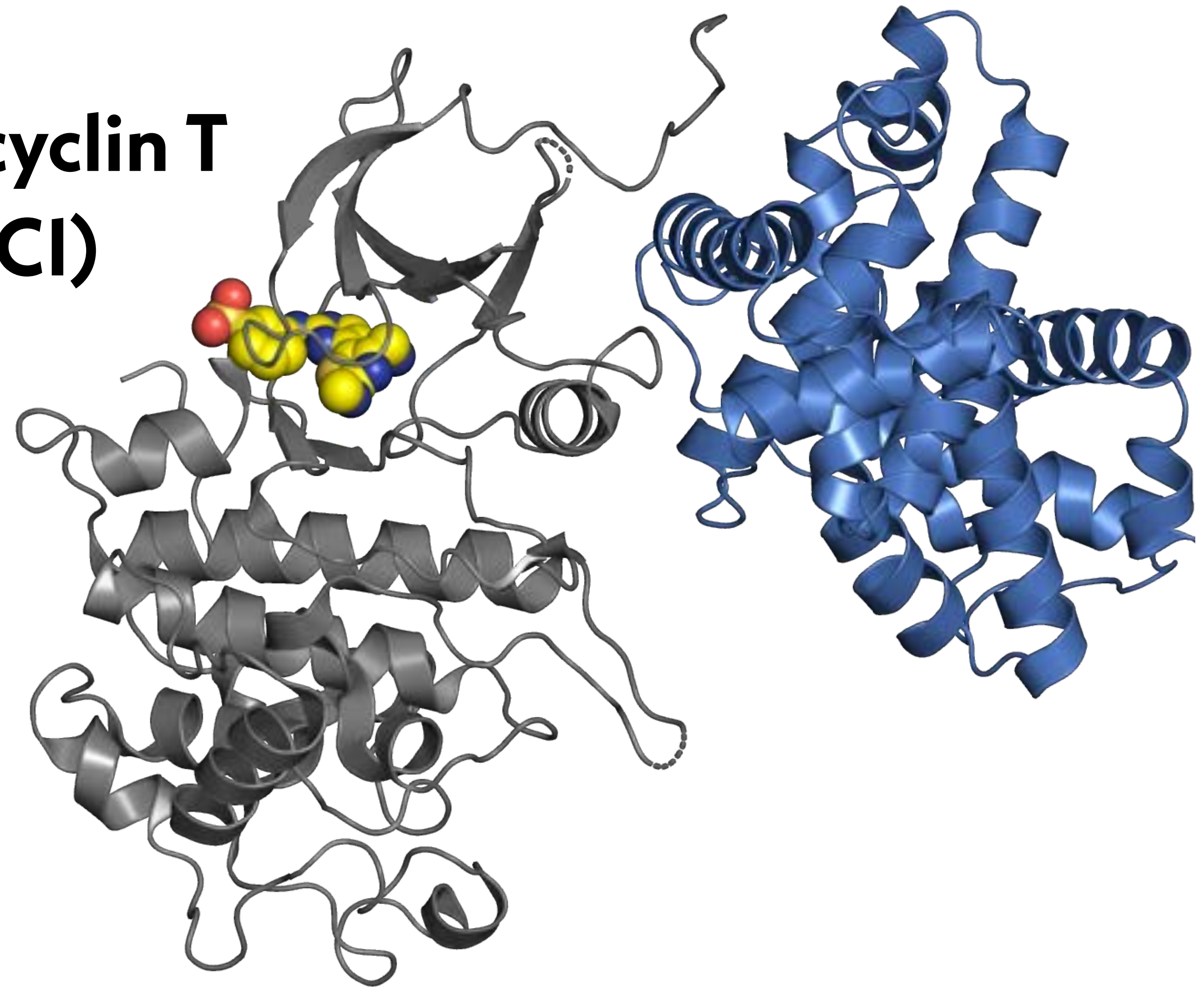




Nature Biotech 26:127, 2008

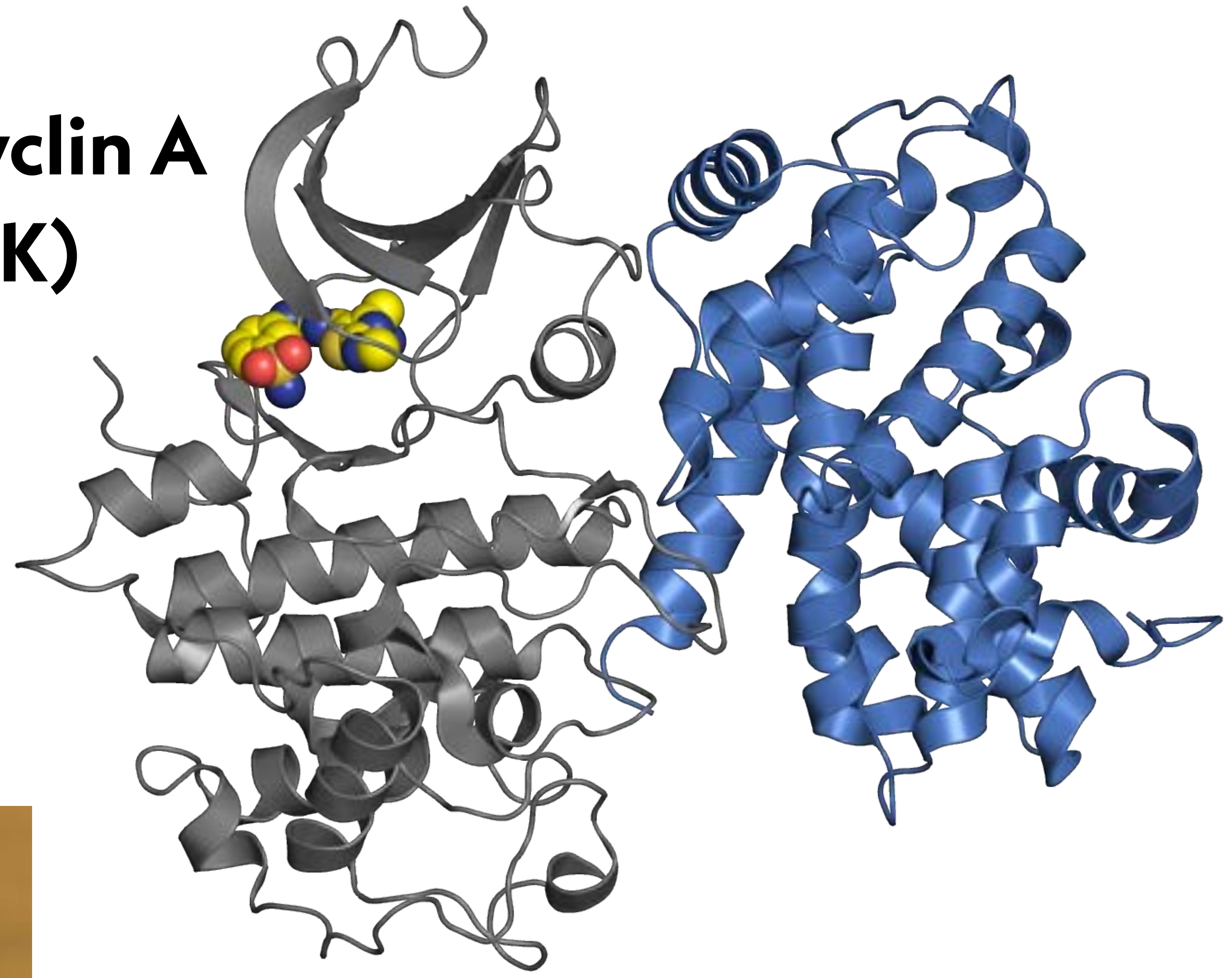
HOW WELL CAN WE PREDICT SELECTIVITY?

CDK9/cyclin T (4BCI)

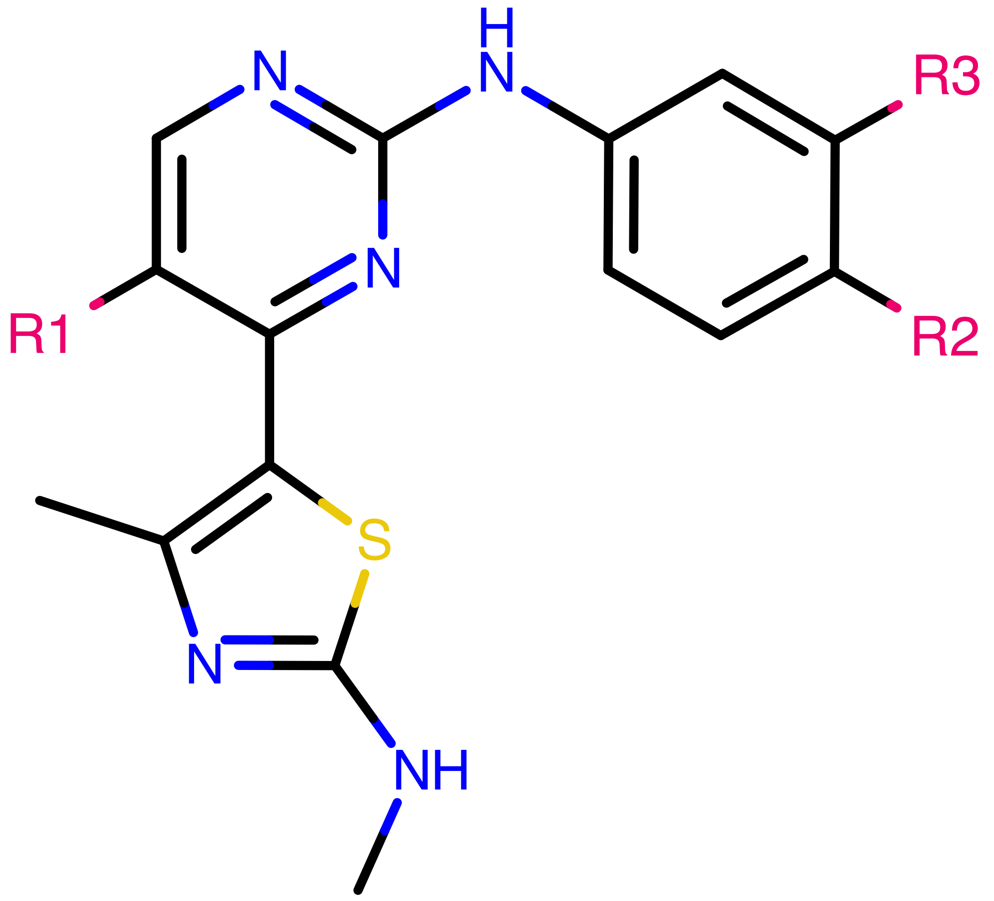


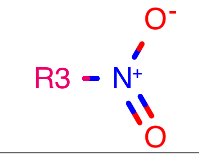
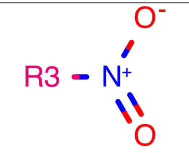
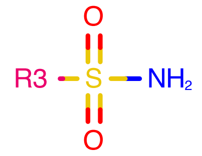
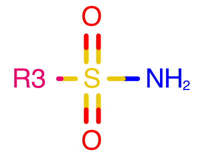
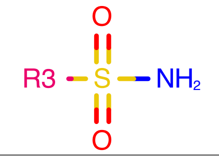
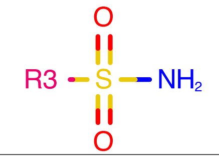
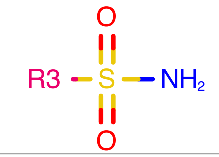
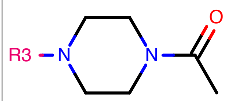
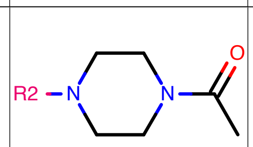
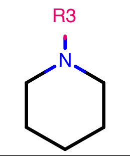
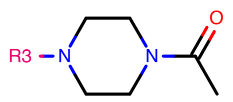
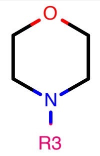
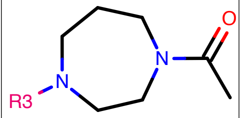
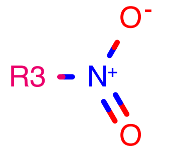
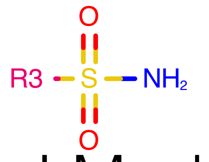
inhibition reinstates apoptosis in cancer cells

CDK2/cyclin A (4BCK)



essential for S-phase progression



Ligand	R1	R2	R3	ΔG CDK2 (kcal/mol)	ΔG CDK9 (kcal/mol)	ΔΔG (kcal/mol)
12a	CN	H		-12.27	-11.21	-1.64
12b	OH	H		-7.23	-8.22	-1.57
12c	CN	H		-11.45	-11.21	-1.57
12e	F	H		-11.62	-11.45	-1.57
12f	Cl	H		-10.91	-10.85	-2.36
12g	Methyl	H		-10.18	-11.32	-1.97
12h	Ethyl	H		-8.28	-9.56	-2.37
12j	CN	H		-10.04	-11.12	-1.56
12l	CN		H	-10.34	-10.44	-1.34
12n	CN	H		-10.06	-10.97	-2.47
12o	F	H		-10.06	-11.12	-0.75
12q	F	H		-10.91	-11.62	-2.31
12t	CN	H		-9.38	-11.12	-1.91
1a	H	H		-11.62	-11.86	-2.77
1b	H	H		-11.45	-11.86	-1.77

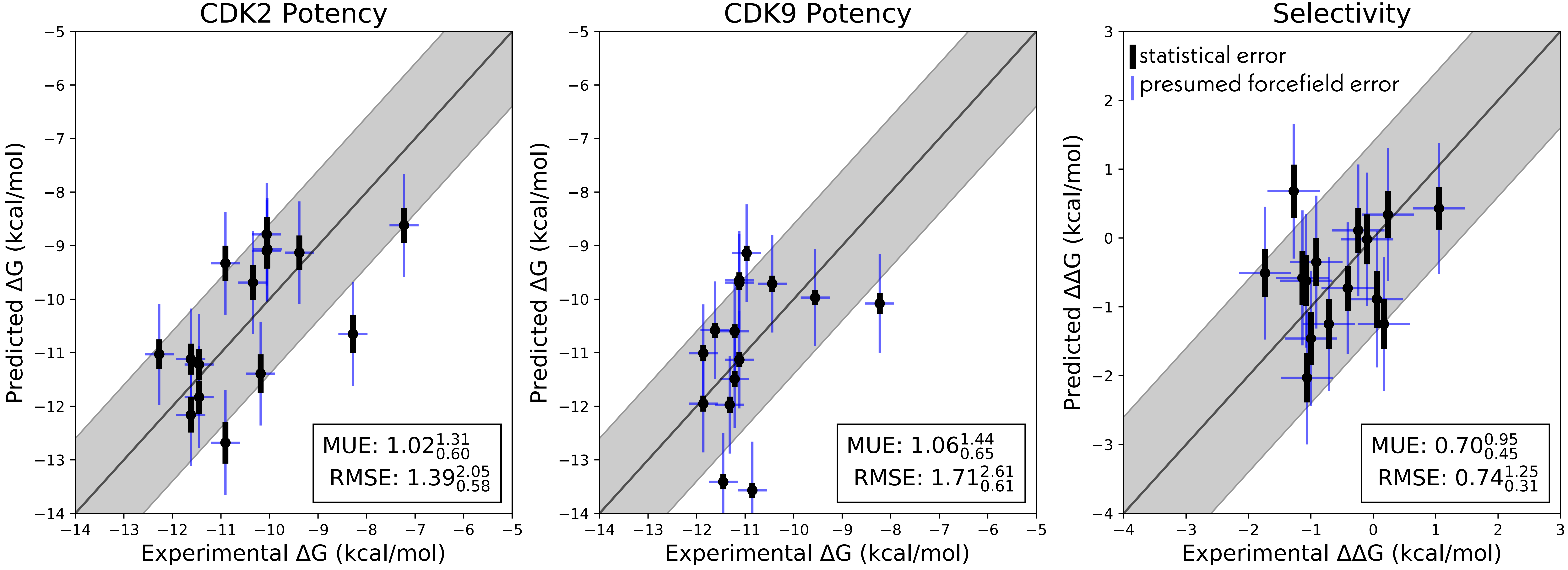
Shao et *al.*, J Med Chem 56(3), 640–659

STEVEN ALBANESE

ALCHEMICAL METHODS CAN ACCURATELY PREDICT BINDING AFFINITIES TO INDIVIDUAL CDKS

ΔG

ΔΔG (CDK9 - CDK2)



STEVEN ALBANESE

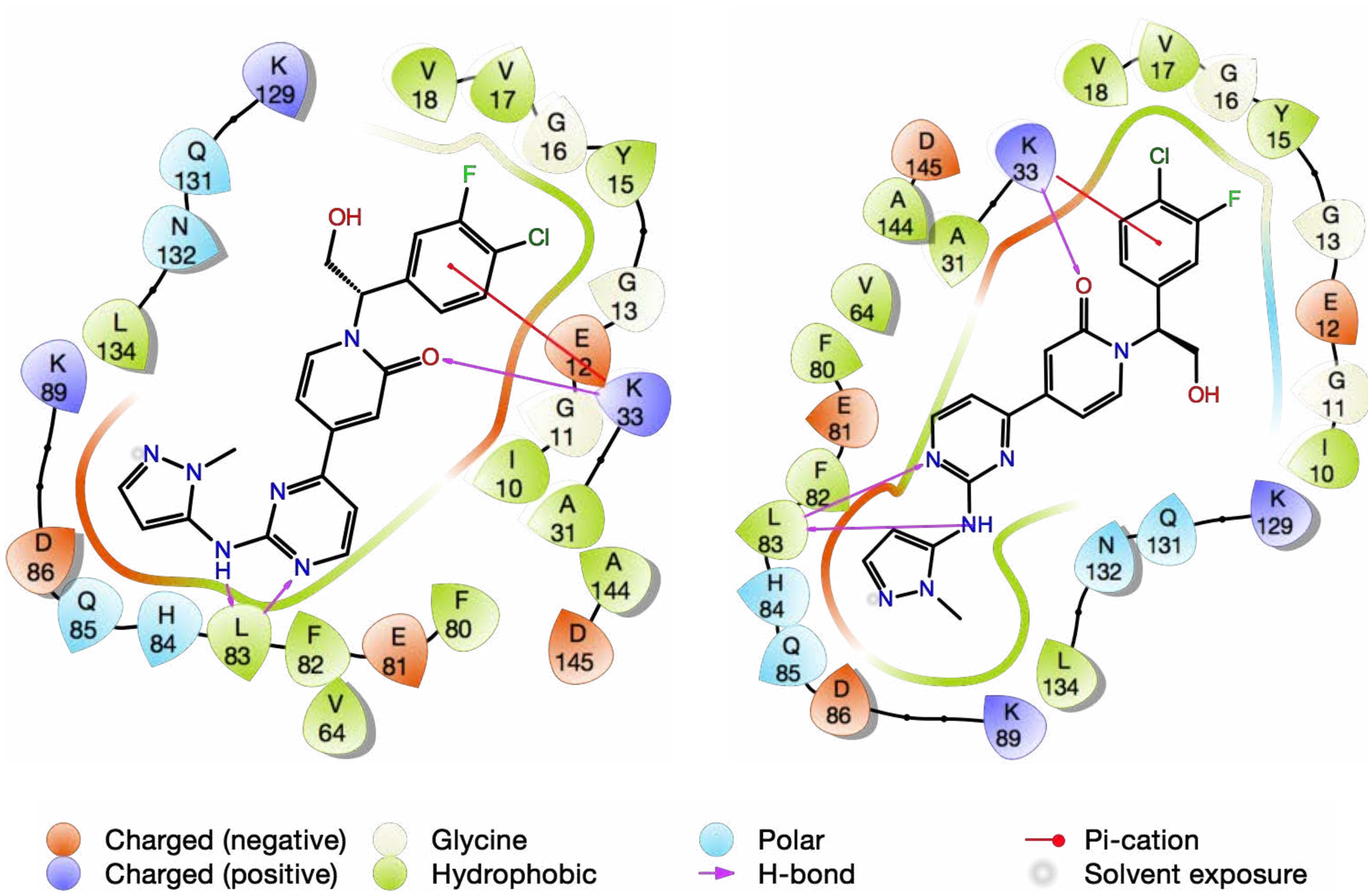
Individual affinities predicted confidently, but what does this mean for selectivity?

FEP+/OPLS3

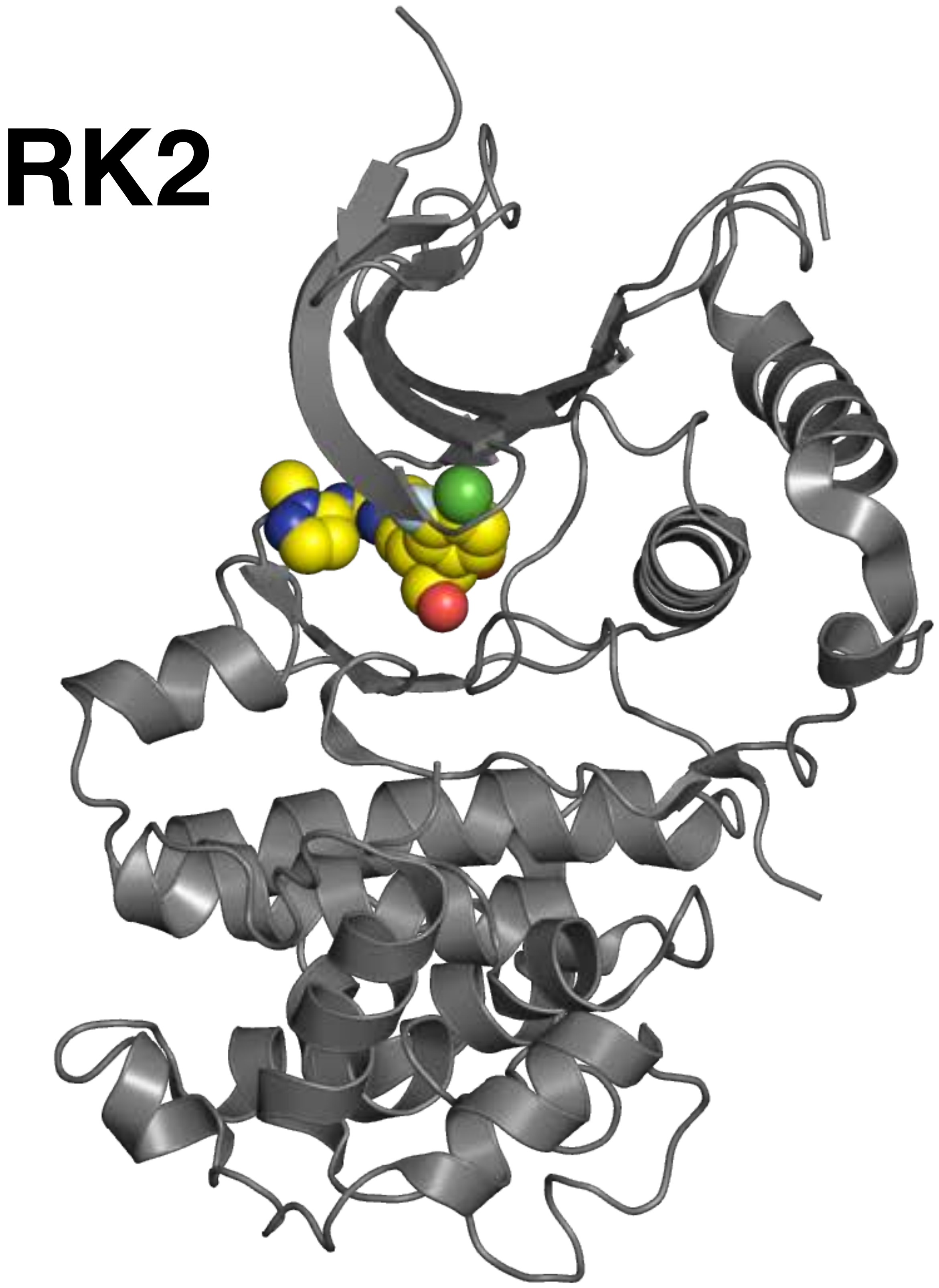
LINGLE WANG
SCHRÖDINGER

HOW MUCH DOES CANCELLATION OF ERROR HELP SELECTIVITY PREDICTION?

CDK2



ERK2



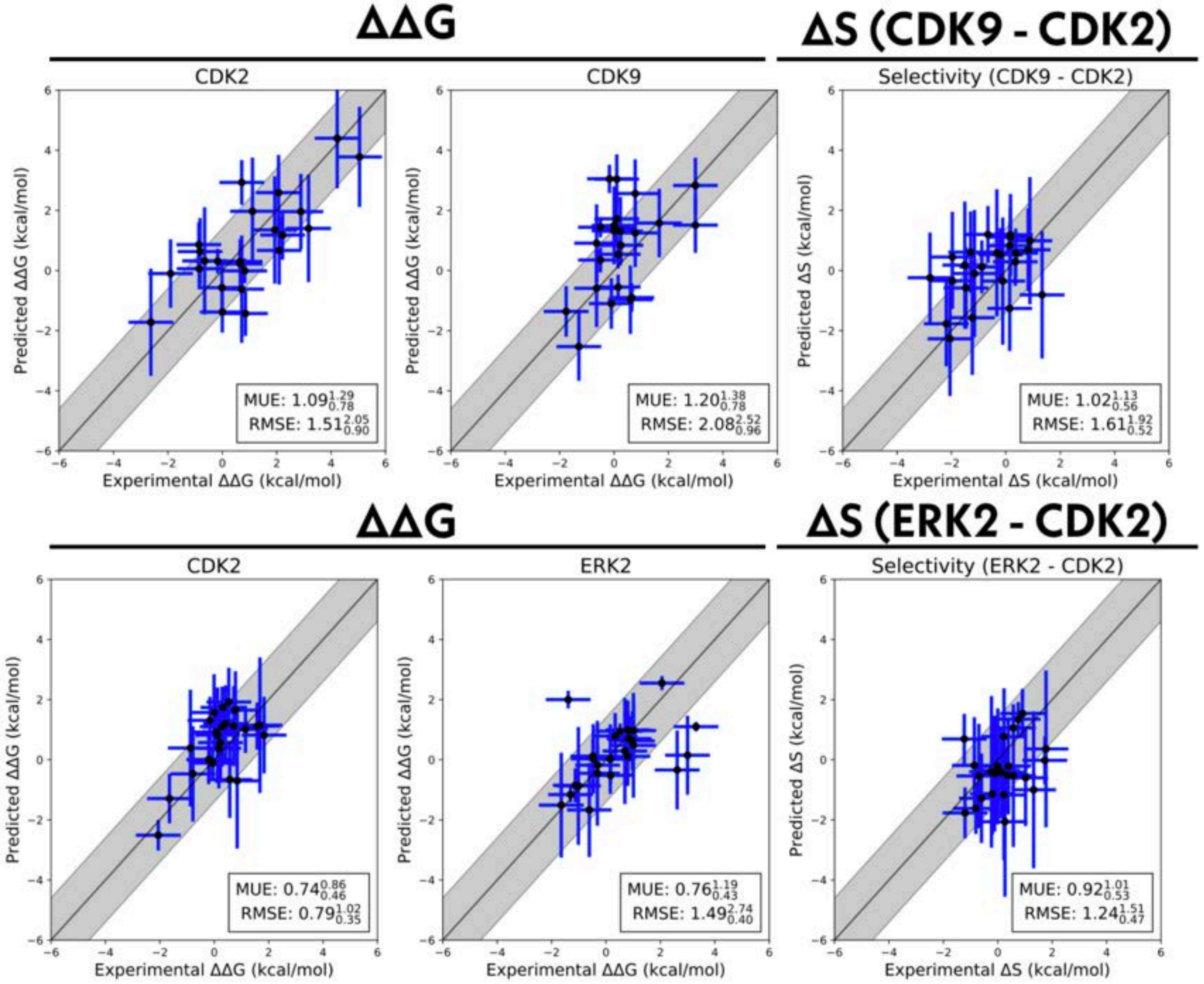
Quantify via the **correlation coefficient**

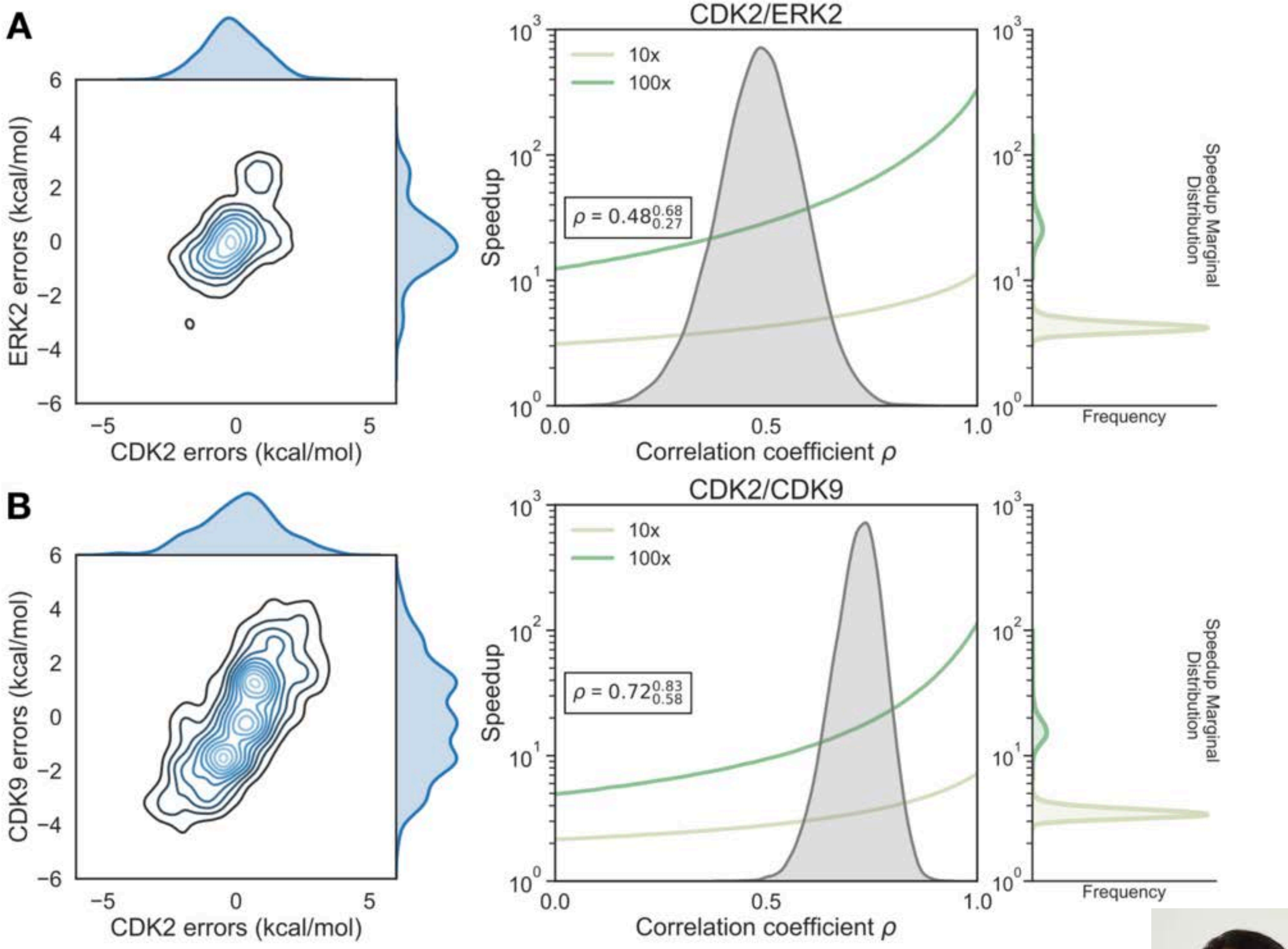
$$\rho \equiv \frac{\mathrm{cov}(\epsilon_1, \epsilon_2)}{\sqrt{\mathrm{var}(\epsilon_1)\mathrm{var}(\epsilon_2)}}$$

of the **error**

$$\epsilon_* \equiv \Delta\Delta G_*^{\mathrm{FEP}} - \Delta\Delta G_*^{\mathrm{exp}}$$

DIFFERENT SELECTIVITY PROBLEMS SHOW DIFFERENT DEGREES OF CANCELLATION



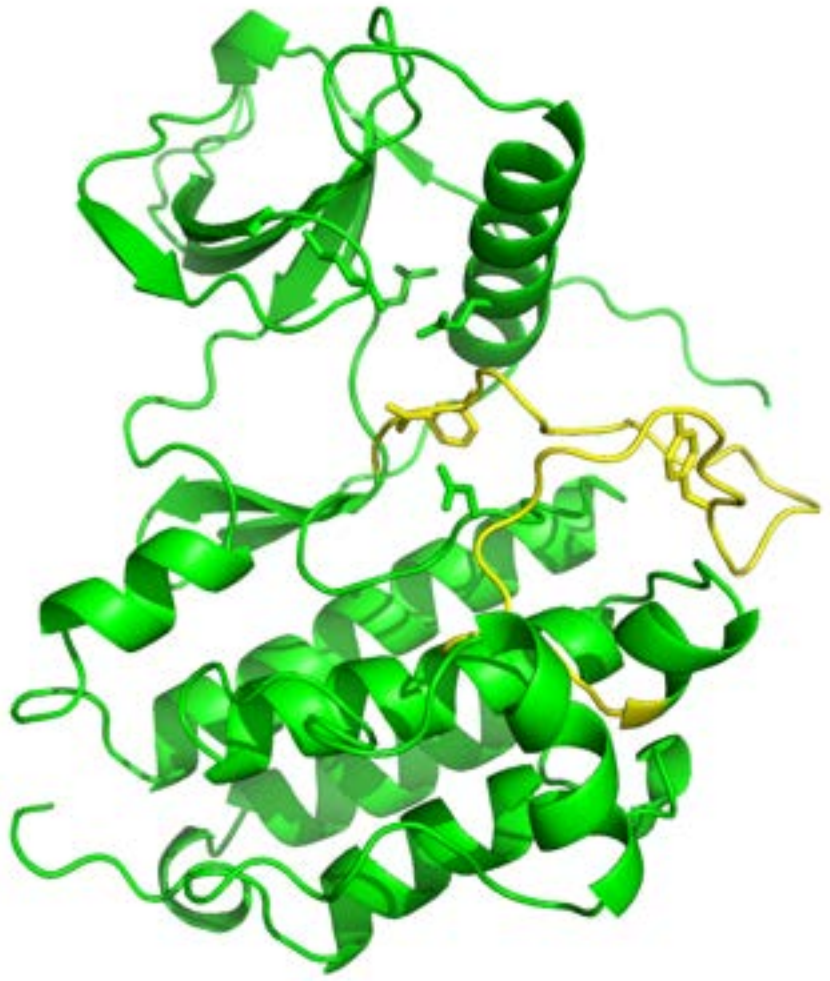


STEVEN ALBANESE

FEP+/OPLS3

LINGLE WANG
SCHRÖDINGER

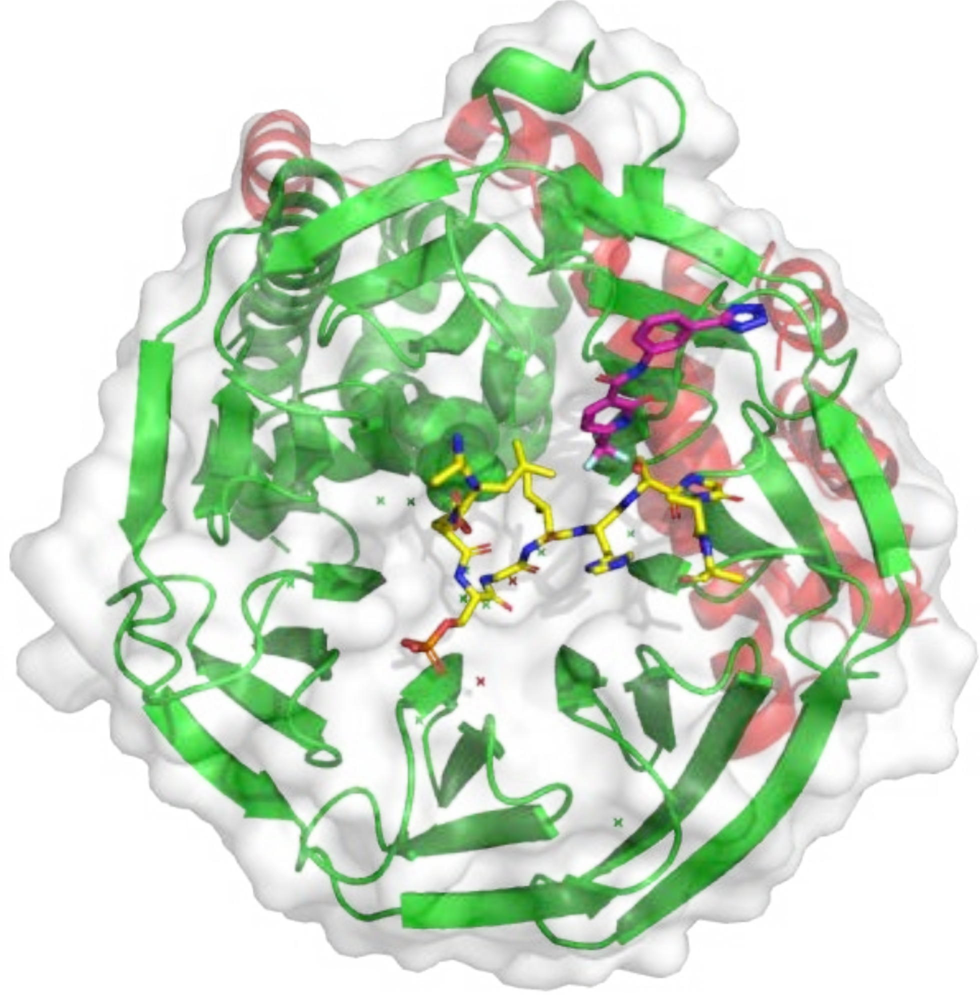
INTERLINE WILL PURSUE A NUMBER OF SELECTIVITY-FOCUSED DESIGN PROBLEMS



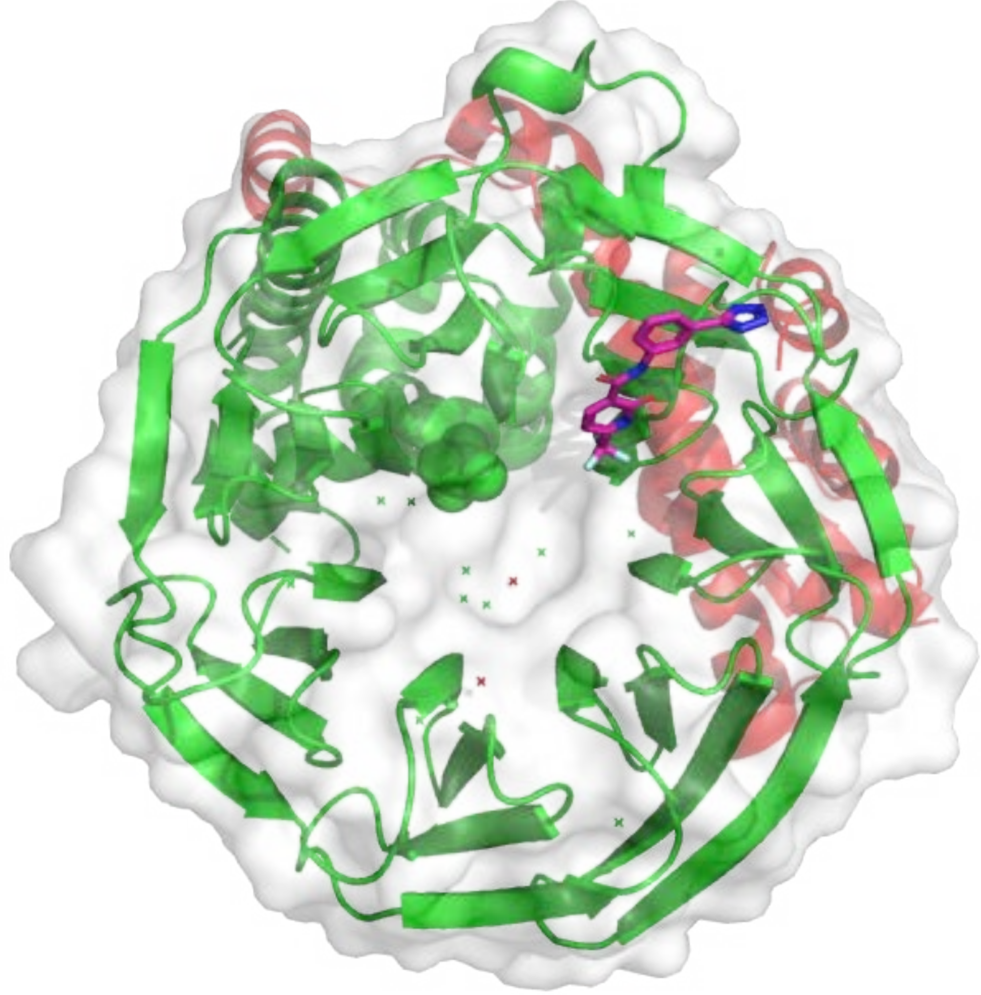
target
(promotes downstream activity)

antitarget
(inhibits downstream activity)

selective (de)stabilization of target conformations



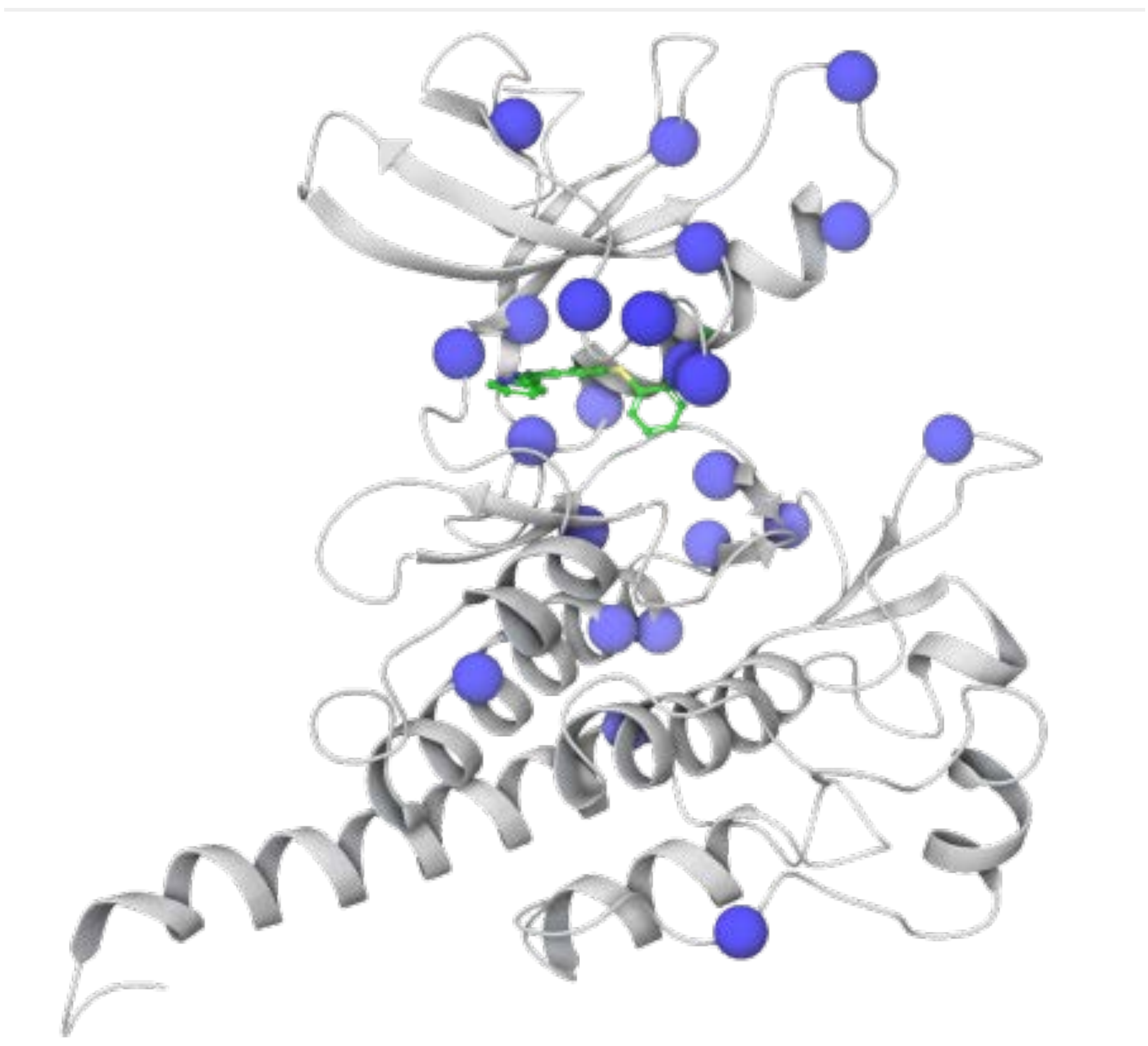
target
(complex to be stabilized)



antitarget
(individual binding partners)

selective (de)stabilization of complexes

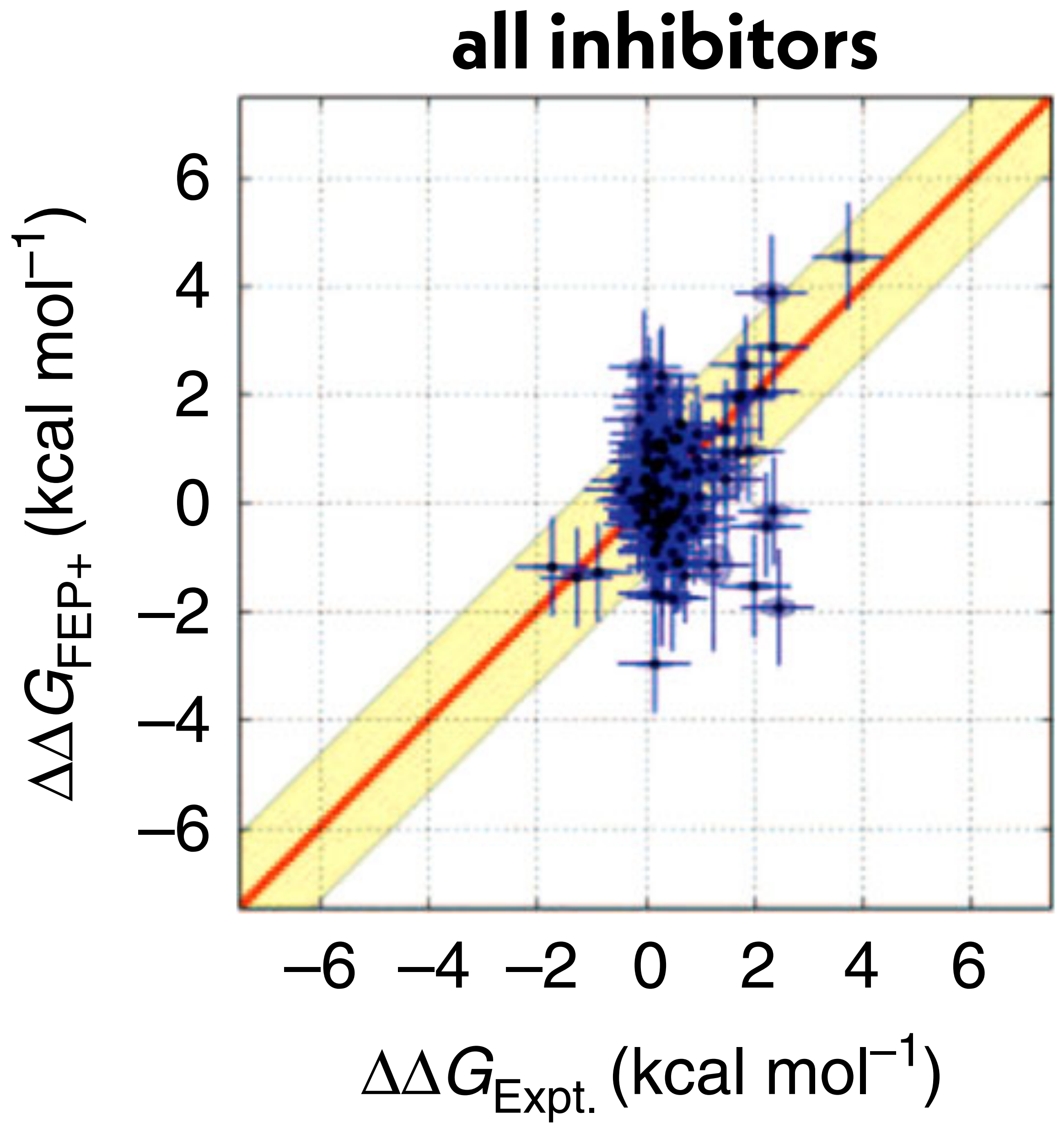
ALCHEMICAL FREE ENERGY CALCULATIONS CAN PREDICT THE IMPACT OF MUTATIONS ON LIGAND BINDING OR PROTEIN-PROTEIN INTERACTIONS



TKI	***N***	***R***	***S***
Axitinib	26	0	26
Bosutinib	21	4	17
Dasatinib	21	5	16
Imatinib	21	5	16
Nilotinib	21	4	17
Ponatinib	21	0	21
Subtotal	131	18	113
Erlotinib	7	1	6
Gefitinib	6	0	6
Total	144	19	125

N_{mut} Total number of mutants for which $\Delta\mathrm{pIC}_{50}$ data was available
Number of **R**esistant, **S**usceptible mutants using 10-fold affinity change threshold

all inhibitors



RMSE (kcal mol^{-1})	0.99	1.15 0.85

		Prediction	
		S	r
Experiment	S	105	8
	r	9	9

Accuracy	0.89	0.92 0.86
Specificity	0.91	0.94 0.89
Sensitivity	0.69	1.00 0.46

KEVIN HAUSER
SCHRÖDINGER (NOW AT RUBRYC)

Hauser, Negron, Albanese, Ray, Steinbrecher, Abel, **Chodera**, Wang. Communications Biology 1:70, 2018