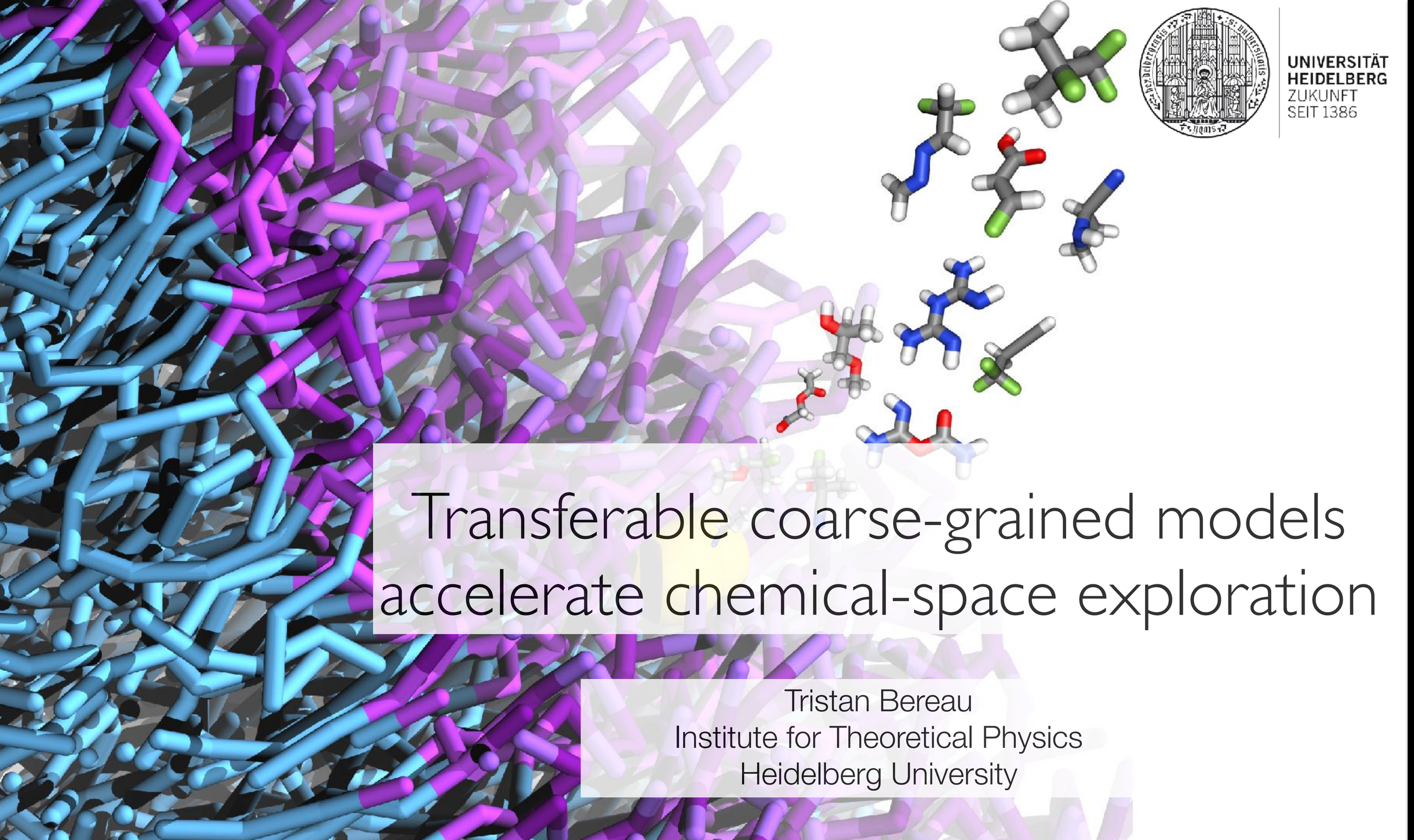

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Transferable coarse-grained models accelerate chemical-space exploration

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Acknowledgments

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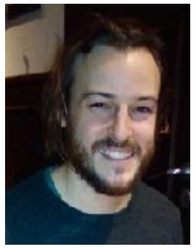
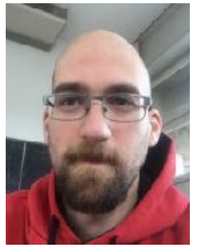

Marc Stieffenhofer


Joseph Rudzinski


Kiran Kanekal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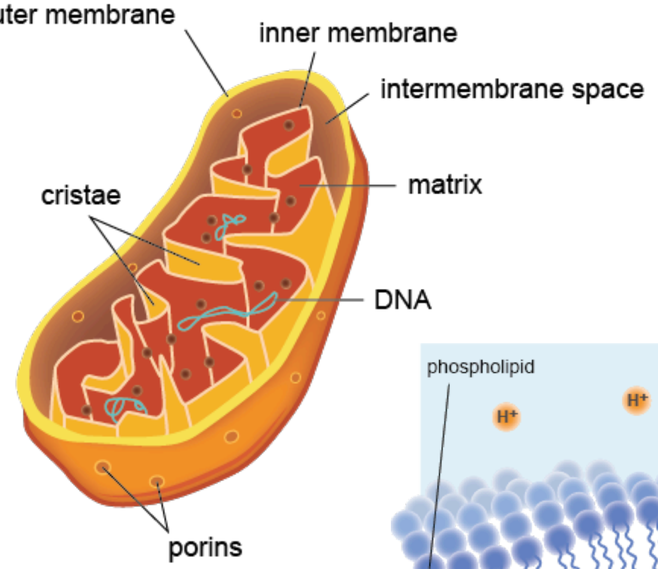
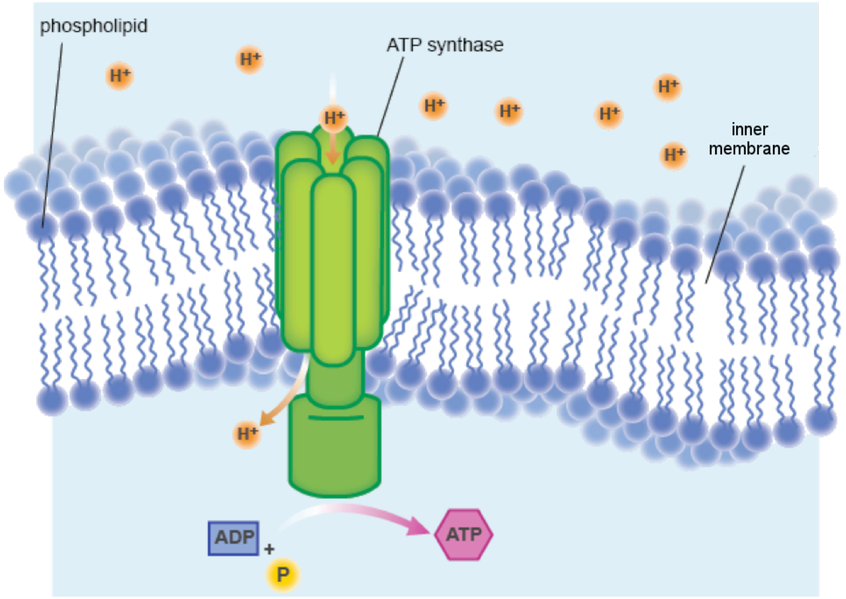
Mitochondria



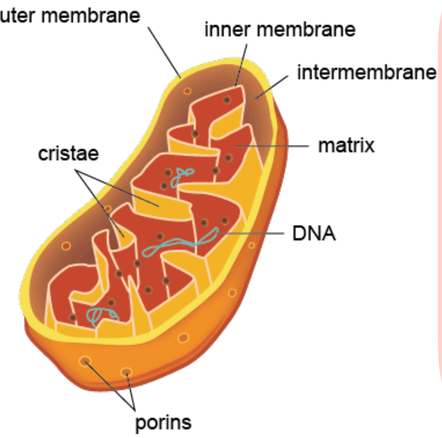


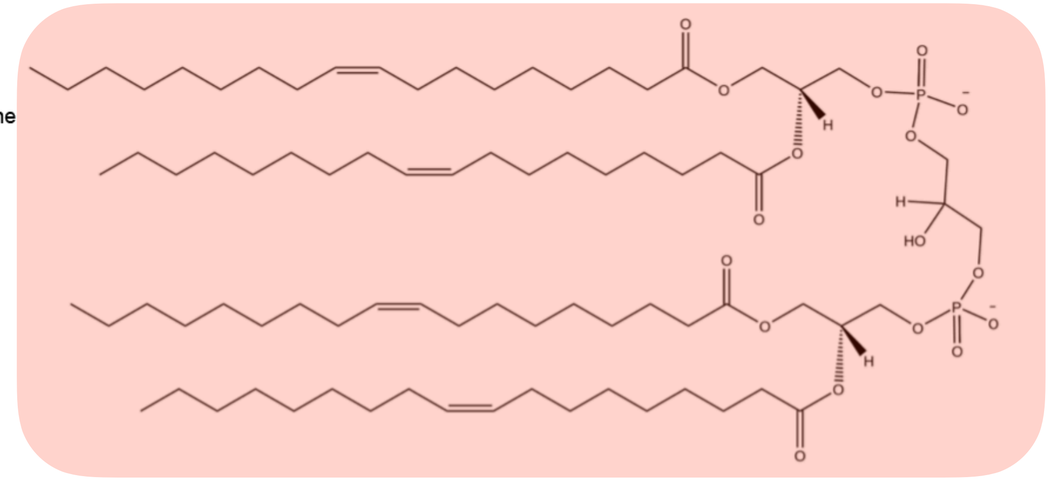
- Produce approx. 64 kg of ATP per day
- Also involved in biogenesis and metabolic cycles

J. Dudek, *Frontiers in Cell and Developmental Biology* **5** (2017)

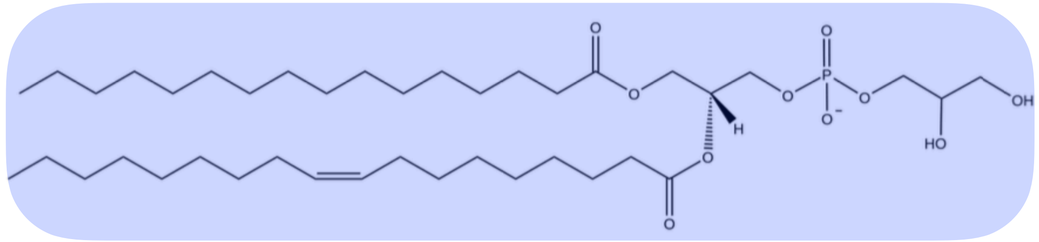
Cardiolipin-linked pathologies

- Inner membrane contains ~20% of cardiolipin (CL)
- Abnormalities in CL composition of IM are linked to Barth syndrome, Tangier disease, heart failure, and neurodegeneration

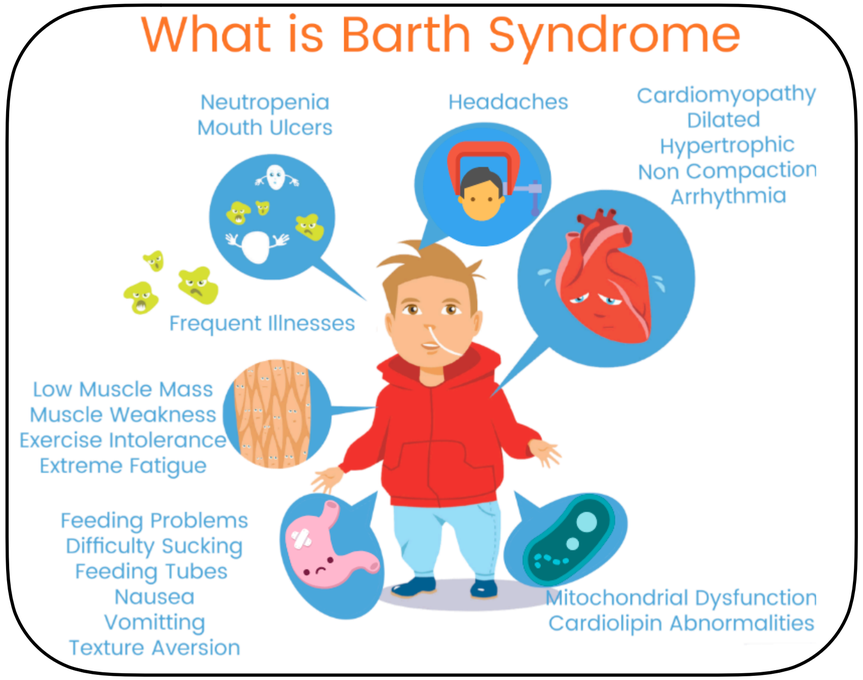




cardiolipin (CL)



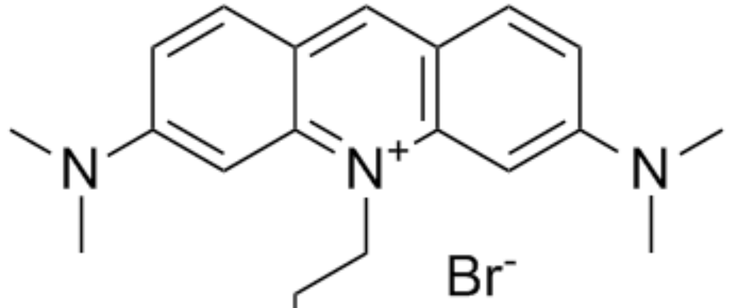
palmitoyloleoyl phosphatidylglycerol (POPG)

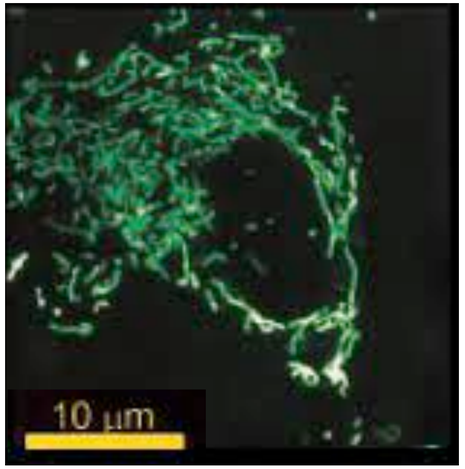


Paradies, Paradies, Ruggiero, Petrosillo, *Cells* **8** (2019)

NAO fluorescent stain

- 10-*N*-nonyl acridine orange (NAO) is a high-affinity probe
- Used as a stain for fluorescent visualization and quantification of IM CL
- Physicochemical basis for specificity is unknown





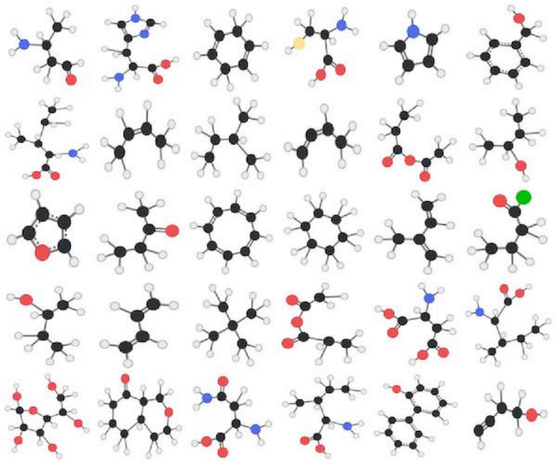
Can we:

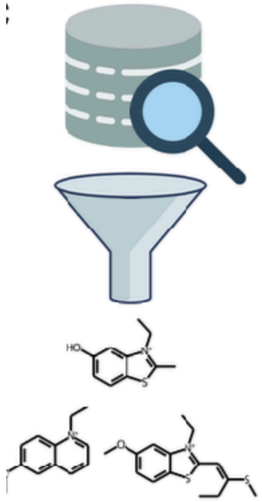
1. **Discover** small organic CL dyes with selectivity superior to NAO?
2. Extract molecular design rules for **mechanism of action**?

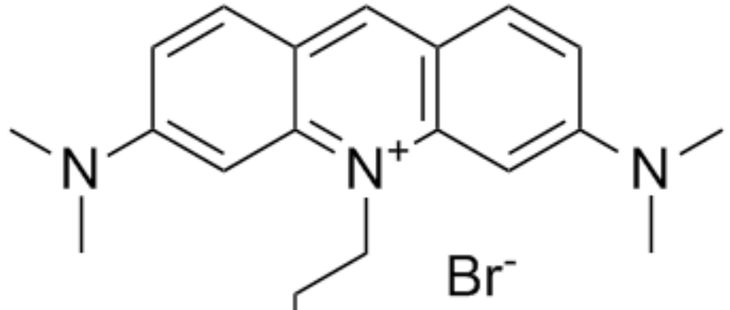
Dirk Schneider
(JGU Mainz)

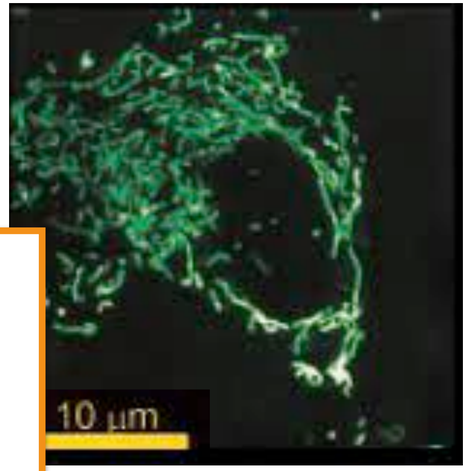
Fernandez, Ceccarelli, Muscatello, *Analytical Biochemistry* **328** (2004); Rodriguez *et al.*, *Mitochondrion* **8** (2008); Horvath, Daum, *Progress in Lipid Research* **52** (2013); Zielonka *et al.*, *Chemical Reviews* **117** (2017); Jacobson *et al.*, *Journal of Neurochemistry* **82** (2002)

Approaches









1. Fit experimental data to machine-learning model

   Little to no c

2. Run all-atom m

   Unbearably

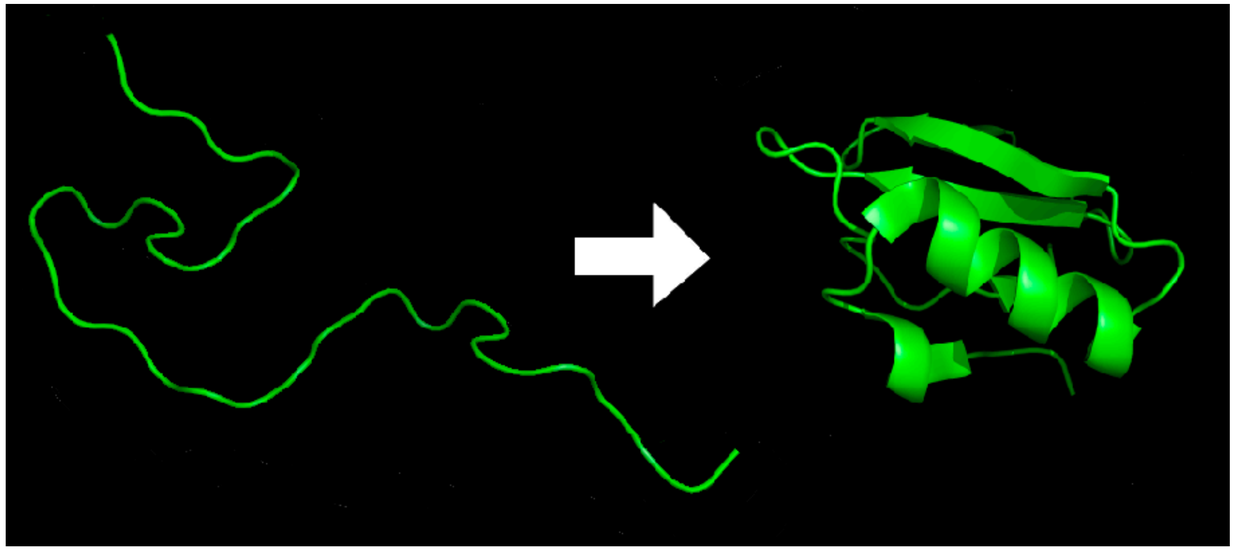
3. Run coarse-grained molecular dynamics simulations

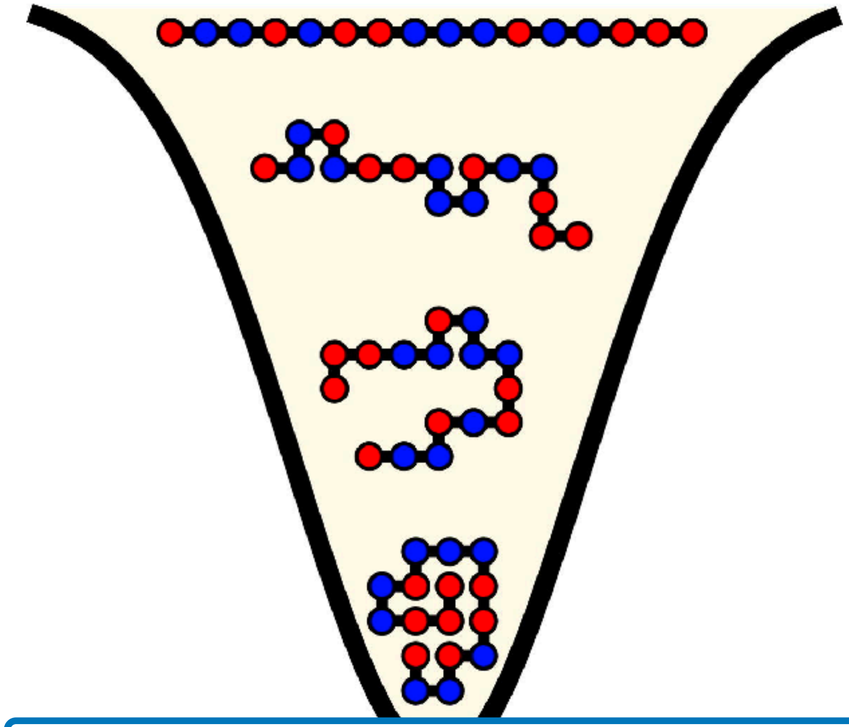
   Precision vs model simplicity?

Challenges

1. Coarse-graining too simplistic?
2. Generate ML training data from computer simulations

HP protein models





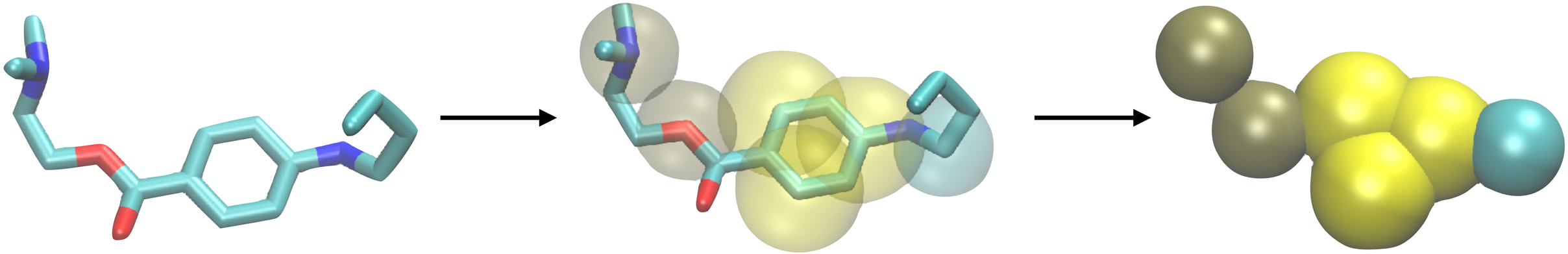
- Recast protein-folding problem as a lattice polymer model
- Discovery of funnel-shaped energy landscape theory
- Map 20 amino acids into binary code: **H**ydrophobic and **P**olar beads

Top-down model with bead types: Martini does something similar (with more chemical fidelity)

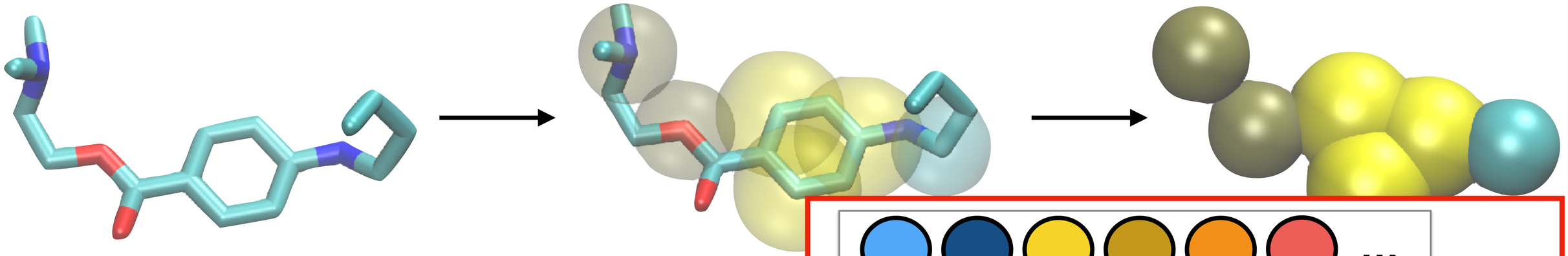
21)

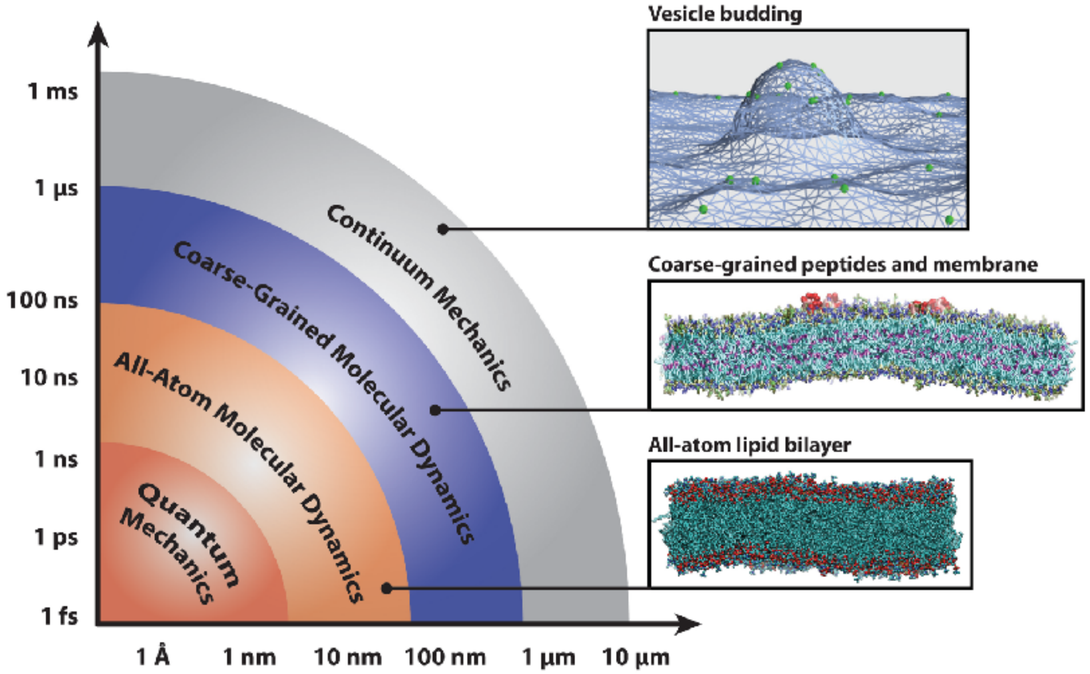
See work from Dill, MacCallum, Wolynes, Chan, Shakhnovich, and many others

Coarse-graining molecules



Short primer on coarse-graining





Bradley and Radhakrishnan, *Polymers* **5** (2013)

Bead types: *chemical fragments*

- **Top-down**: from phenomenological information / large-scale physics

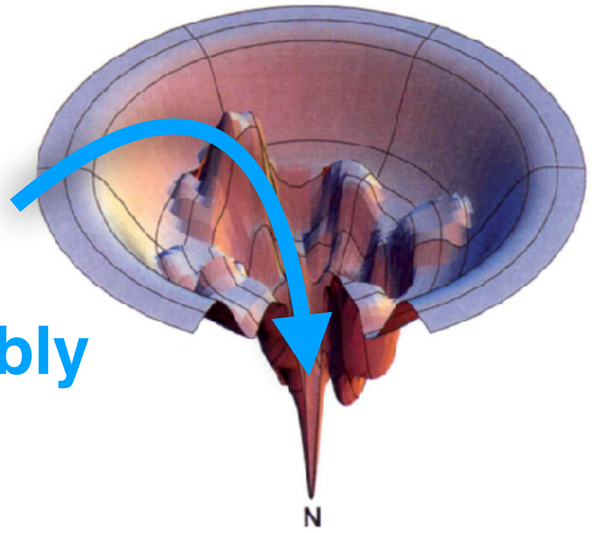
- **Bottom-up**: from microscopic information (e.g., atomistic simulations)

Noid, *J Chem Phys* **139** (2013)

Compounding challenges in chemical-space exploration

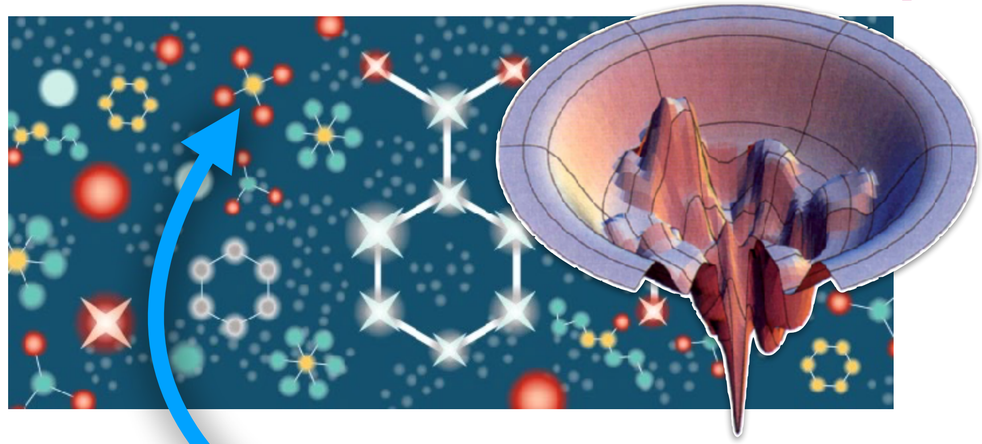
"Compositional landscape"

Free-energy landscape



Voth, *CRC Press* (2008); Noid, *J Chem Phys* **139** (2013)

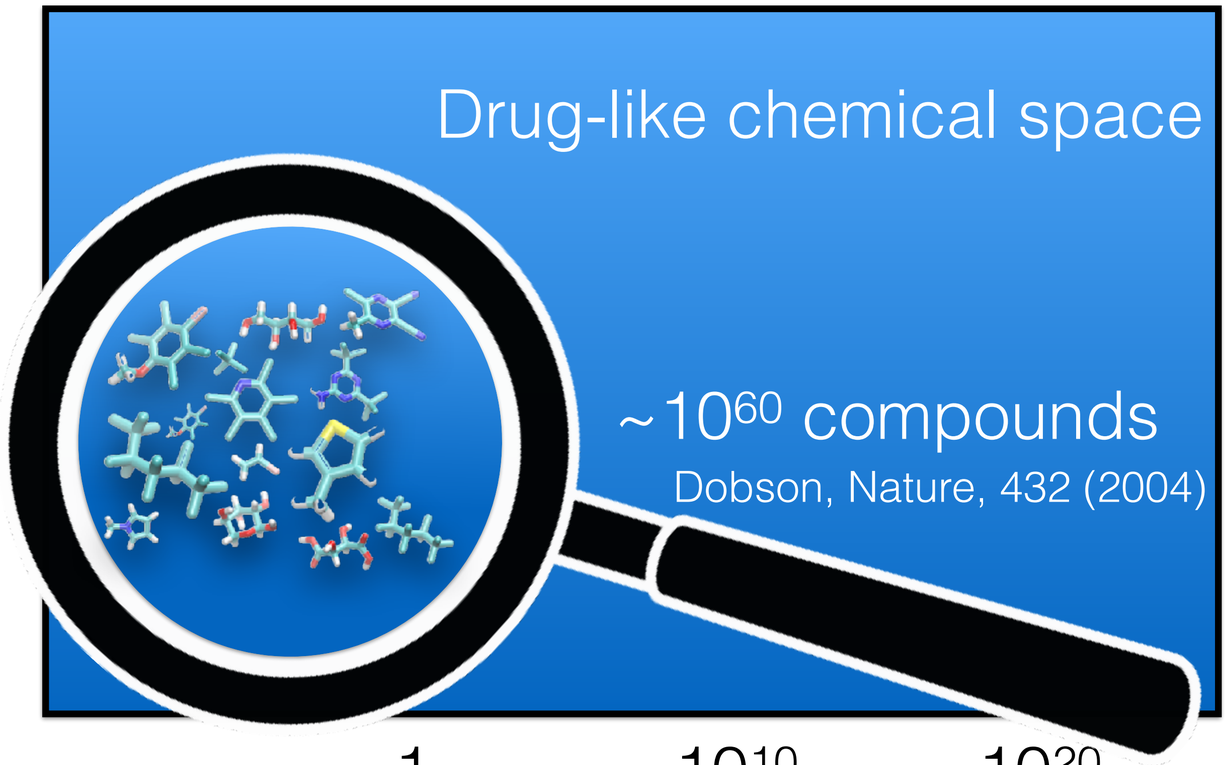
Chemical compound space



Von Lilienfeld *et al.*, *Nat Rev Chem* **4** (2020)

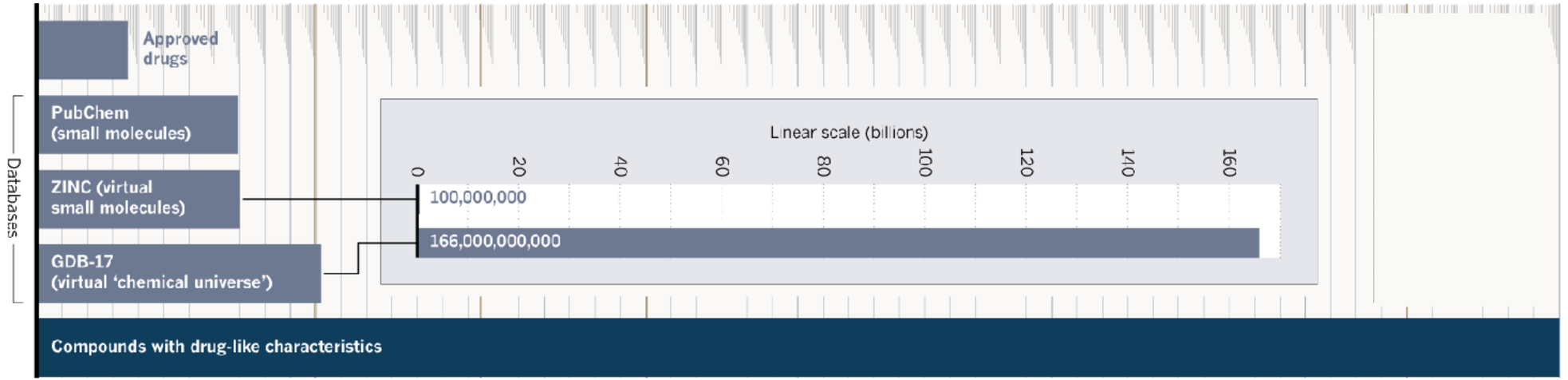
In both cases: Importance-sampling problems!

Chemical space is large



number of carbon atoms in the universe

1 10^{10} 10^{20} 10^{30} 10^{40} 10^{50} 10^{60}

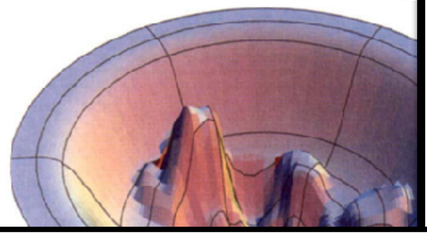


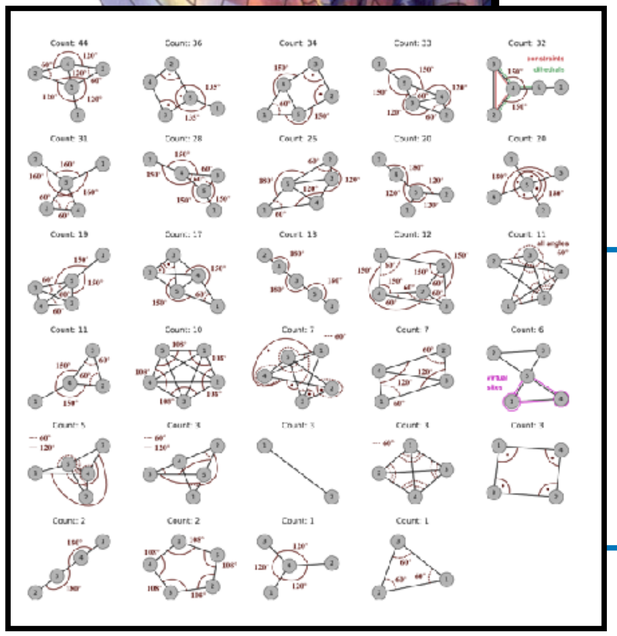
Mullard, Nature, 549 (2017)

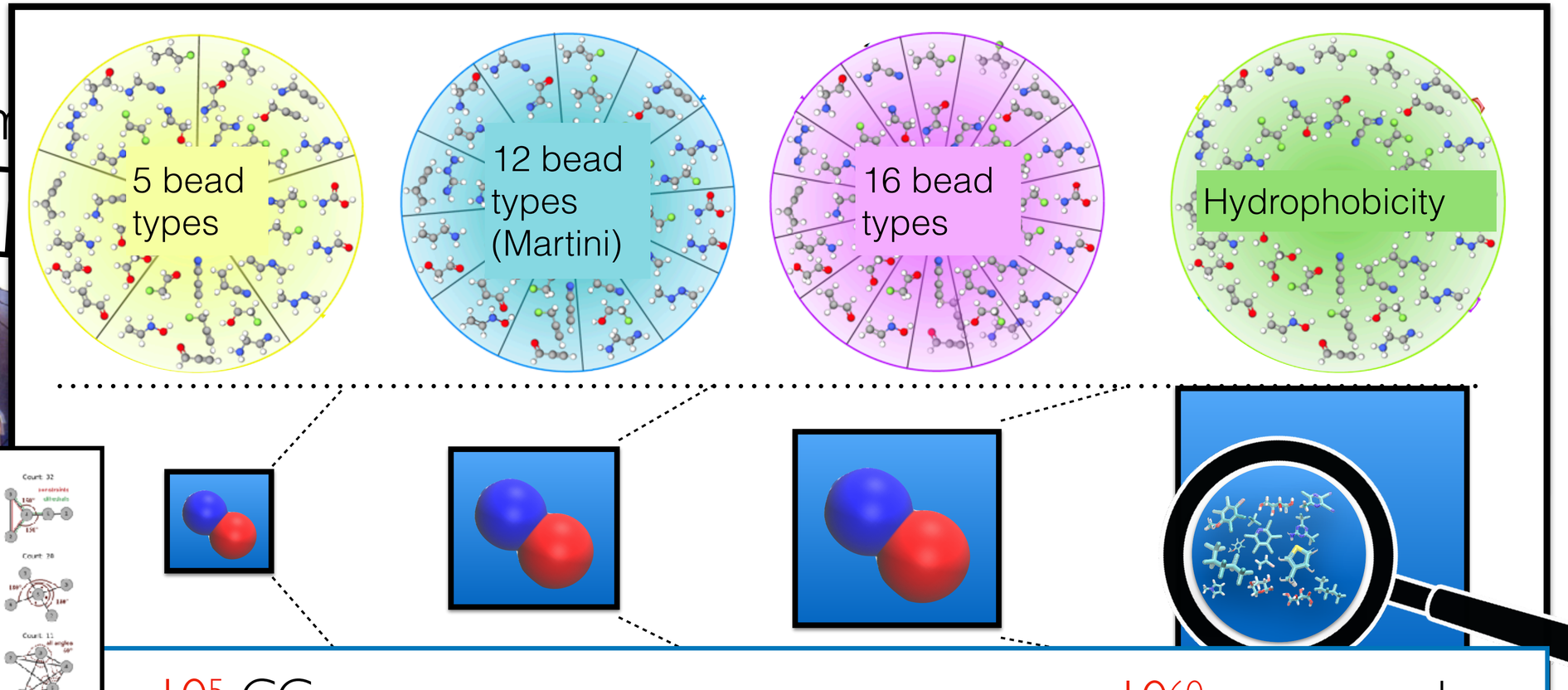
Sampling efficiency of coarse-grained models

Conform

All CG models







~10^5 CG molecules

~10^{60} compounds

Dobson, Nature, 432 (2004)

Drug-like small-molecule chemical space

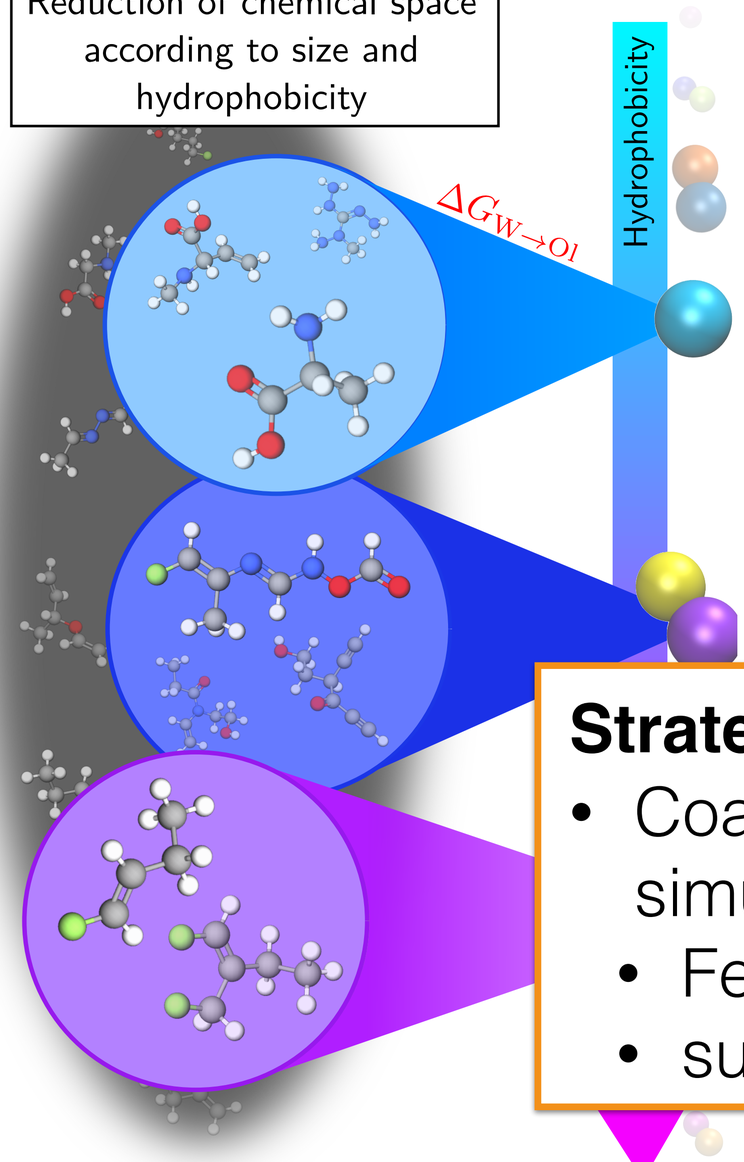
due to finite set of bead types

Work from Voth, Noid, Shell, Kremer, van der Vegt, and others

Kanekal, Bereau, *J Chem Phys* **151** (2019)

High-throughput coarse-graining scheme

Reduction of chemical space according to size and hydrophobicity



Strategy

- Coarse-graining prior to high-throughput simulations
  - Fewer simulations
  - suggests low-dimensional representation

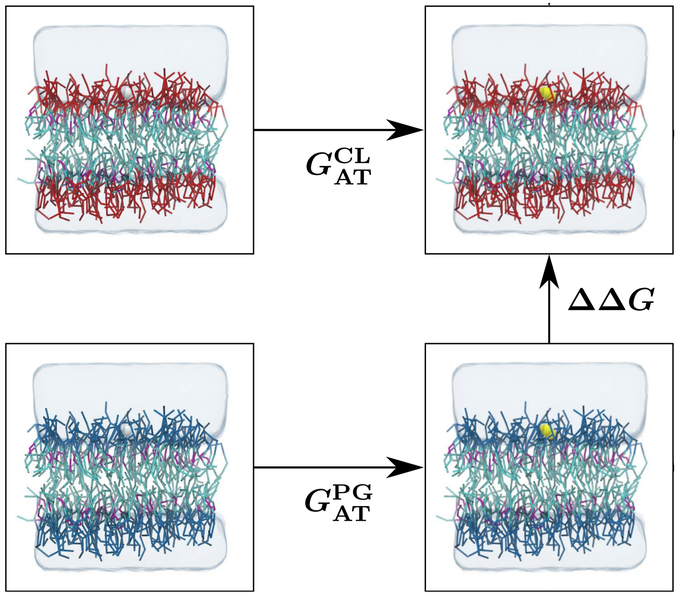
Menichetti, Kanekal, Bereau, *ACS Cent. Sci.* **5** (2019)

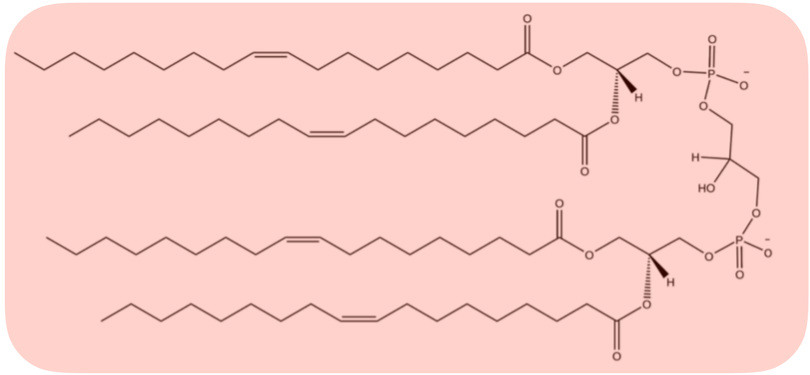
Kiran Kanekal

Roberto Menichetti

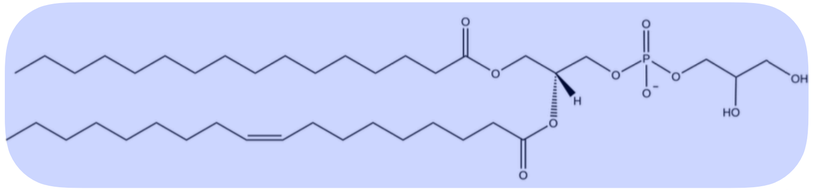
CGMD selectivity measurements

- Compute transfer free energies into CL and POPG membranes using alchemical transformations
- Objective function to maximize CL vs POPG selectivity:





cardiolipin (CL)



palmitoyloleoyl phosphatidylglycerol (POPG)

$$\Delta\Delta G_{\mathrm{POPG}\rightarrow\mathrm{CL}} = \Delta G_{\mathrm{CL}} - \Delta G_{\mathrm{POPG}}$$

Maximize the gap

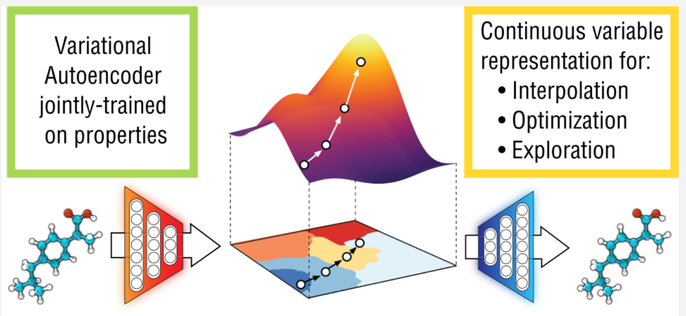
Thermodynamic preference for desired CL membrane

Thermodynamic preference for most chemically similar competitor

High-throughput virtual screening

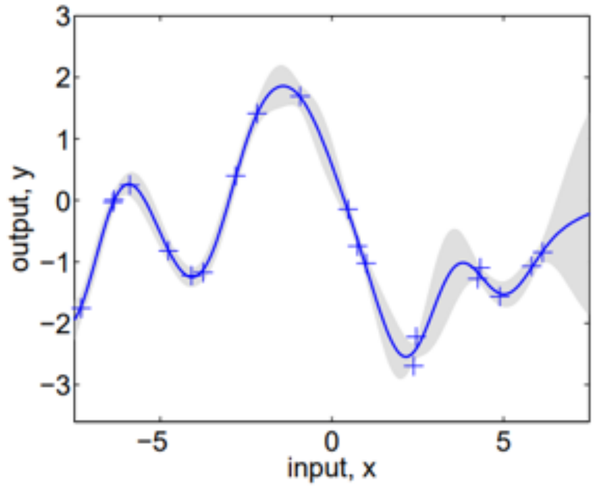
Learn featurization

Unsupervised deep representation learning of chemical space using regularized autoencoders



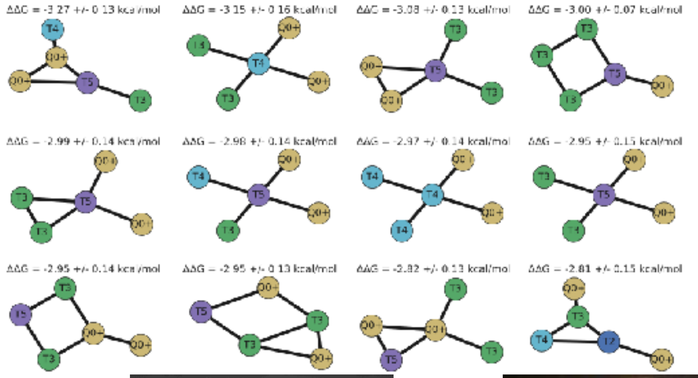
Estimate fitness

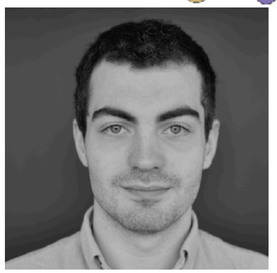
Supervised learning of sequence-selectivity relationship using Gaussian process regression



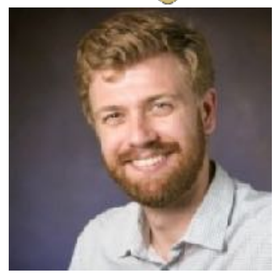
Explore chemical space

Active learning (Bayesian optimization) to optimally deploy coarse-grained molecular dynamics to explore chemical space





Kirill Schmilovich

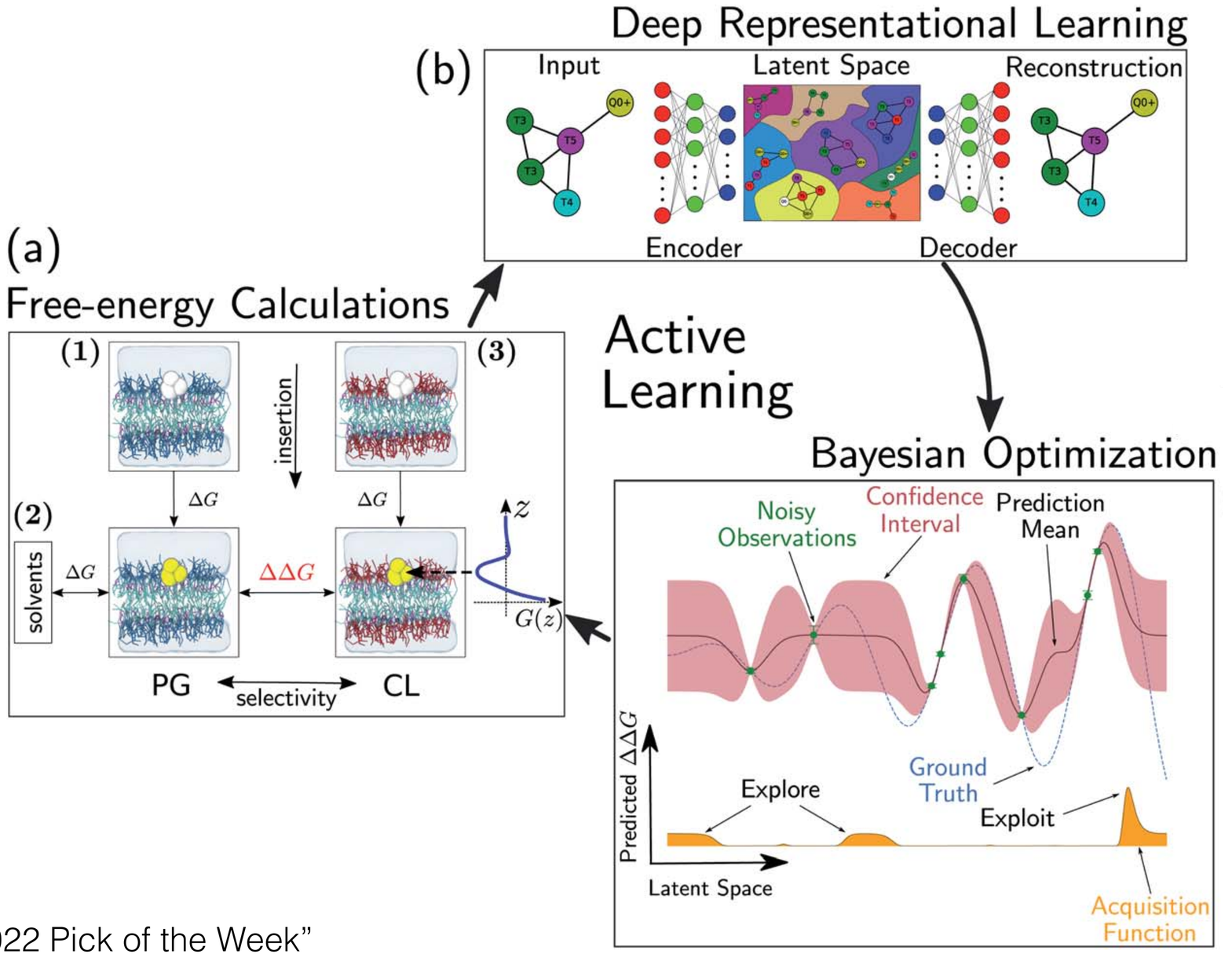


Andrew Ferguson

Gomez-Bombarelli *et al.*, *ACS Central Science* **4** (2018)
Rasmussen "Gaussian processes in machine learning" *Springer*, 2003

Workflow: Multiscale modeling & machine learning

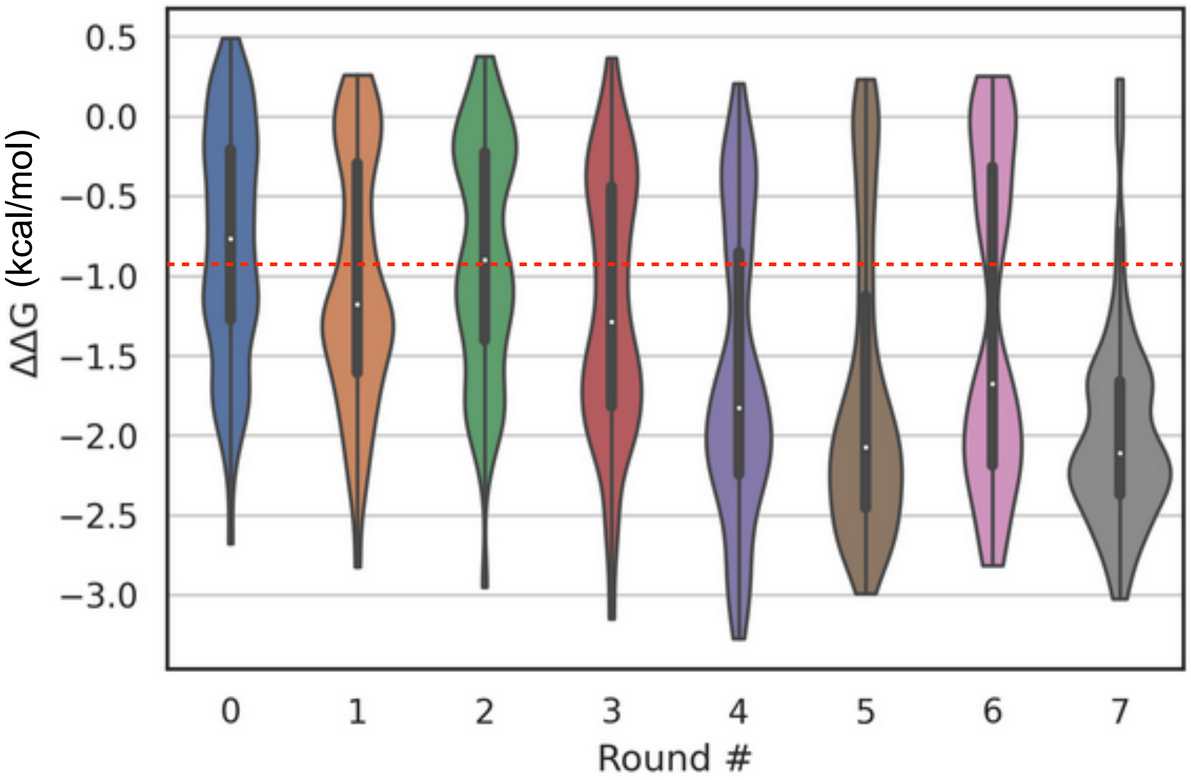
1. Run free-energy calculations for active learning cycle *n*
2. Attach new free energies to augment training of GPR inside the latent space
3. Bayesian optimization selects next compounds to simulate
4. Repeat until convergence

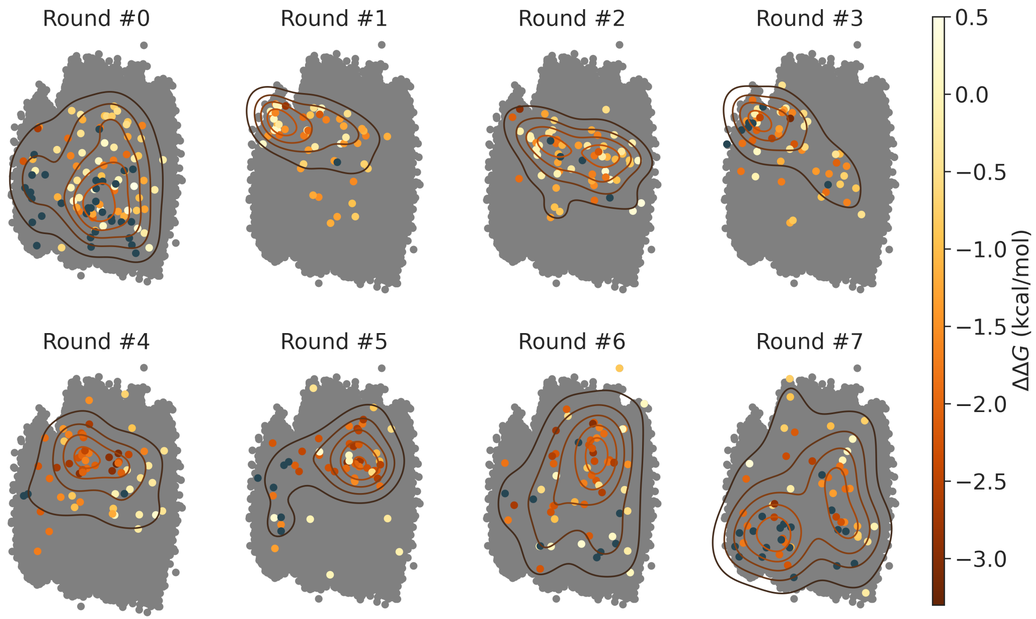


Mohr *et al.*, *Chemical Science* (2022); "2022 Pick of the Week"

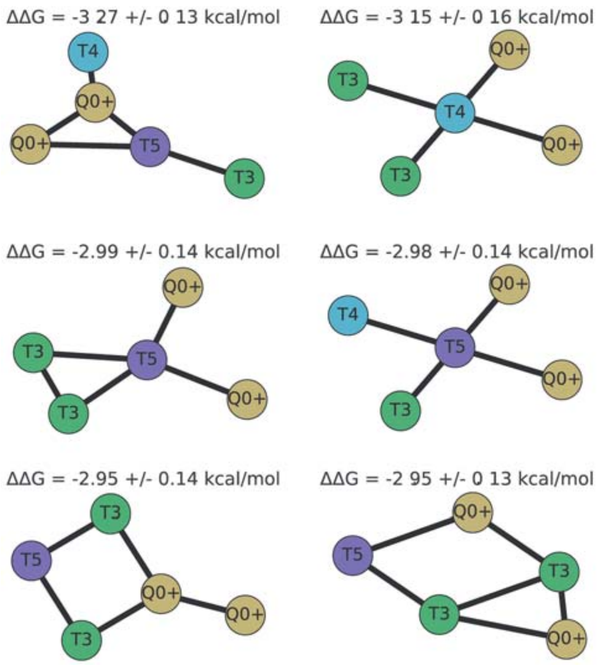
Screening results

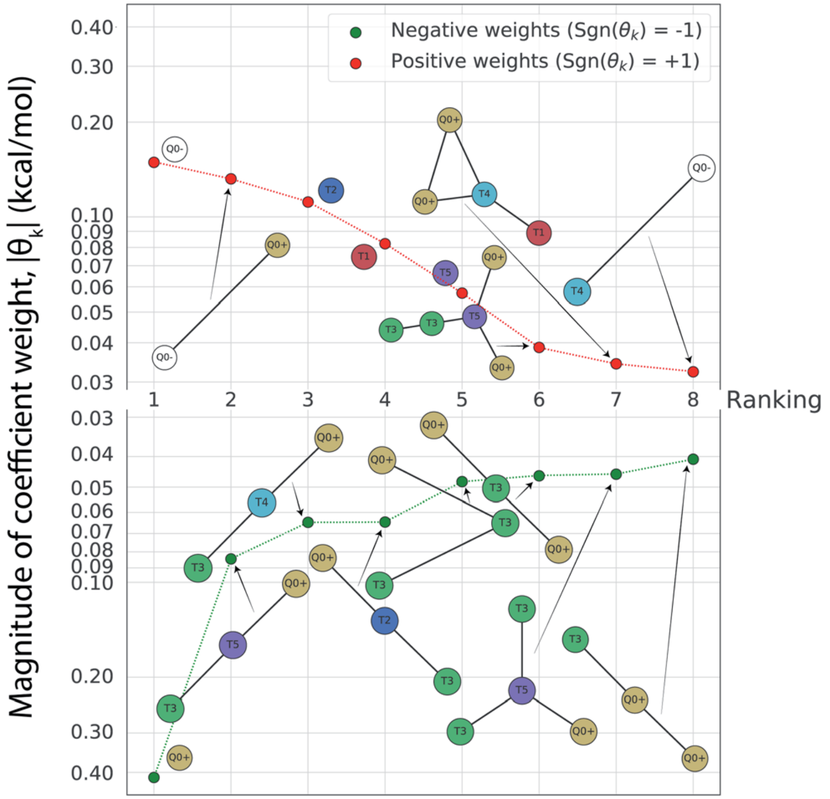
- Performed 7 rounds of screening with 60 candidates per round
- Discover optimal candidate after 4 rounds with $\Delta\Delta G = -3.27$ kcal/mol
  - Sampled only **0.42%** of molecular candidate space
  - **720 GPU-days** of computation
  - **180x selectivity increase** over NAO

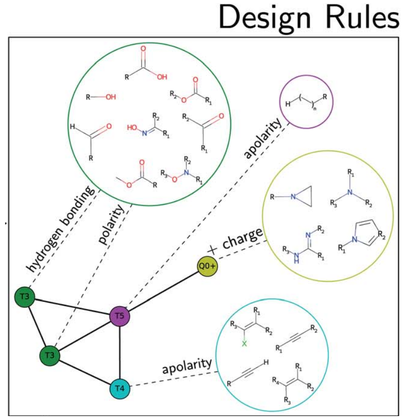




Results: From CG representations to design rules







In silico discovery of design rules

- **Positive charge** (lipid's polar head)
- (coarse-grained) Hbonds
- **Hydrophobicity** (stabilizes in membrane)

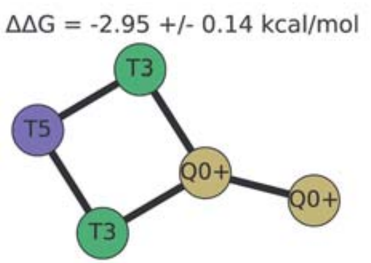
Top coarse-grained compounds

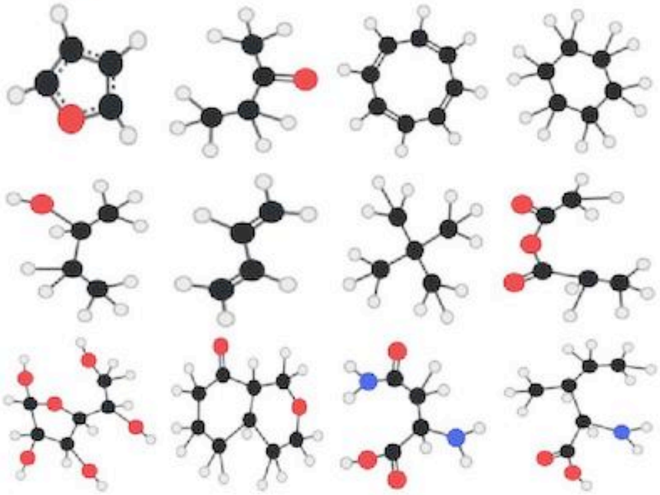
LASSO regression to identify best/worst subgraphs

Design rules

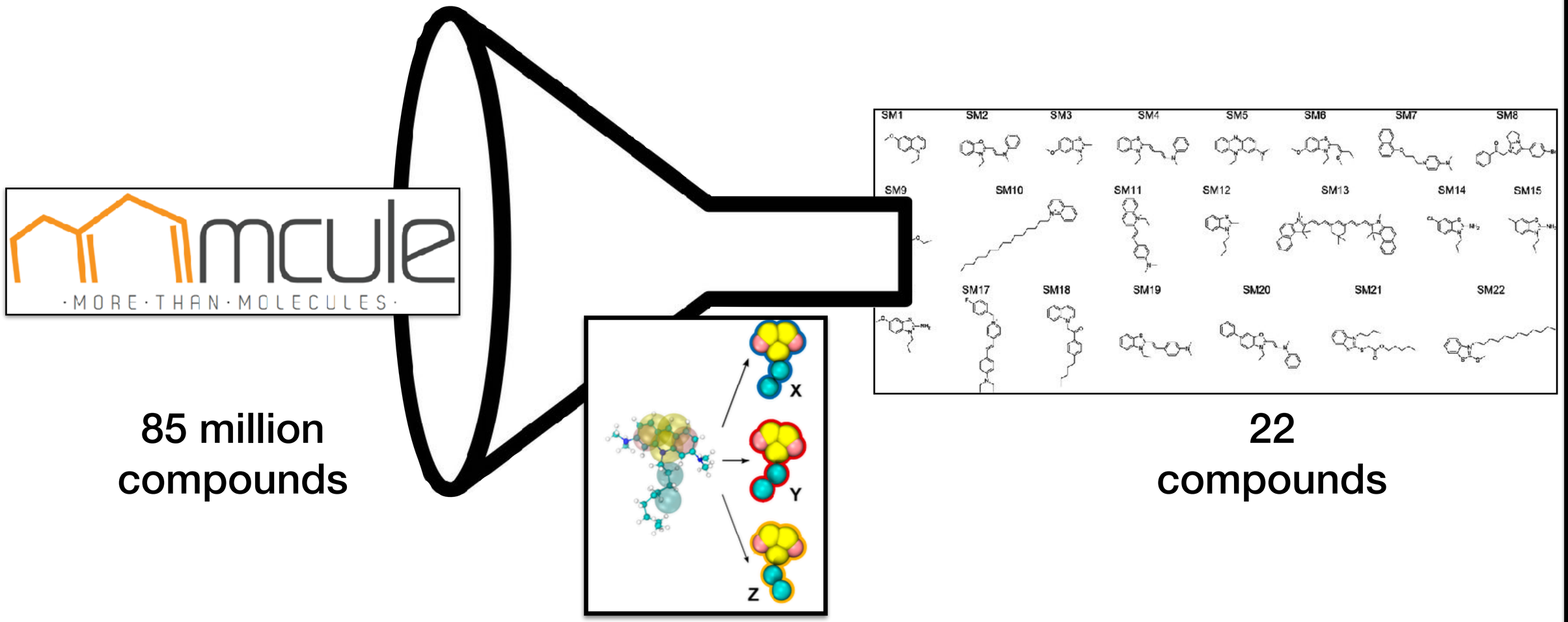
Mohr *et al.*, *Chemical Science* (2022); "2022 Pick of the Week"

How do we translate CG design rules to chemical structures?





Filter vendor databases against design rules



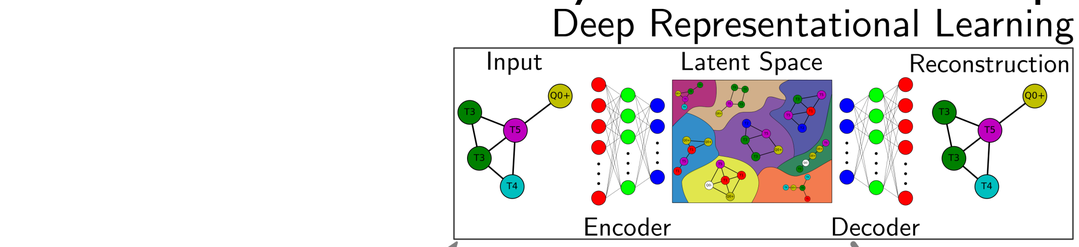
85 million compounds

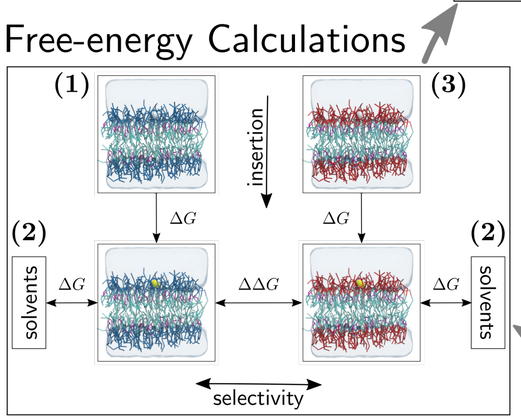
CG design rules

22 compounds

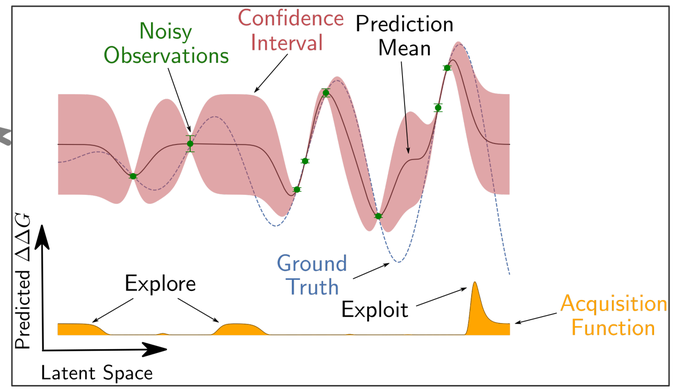
Kleinwächter *et al.*, *RSC Chemical Biology* (2022)

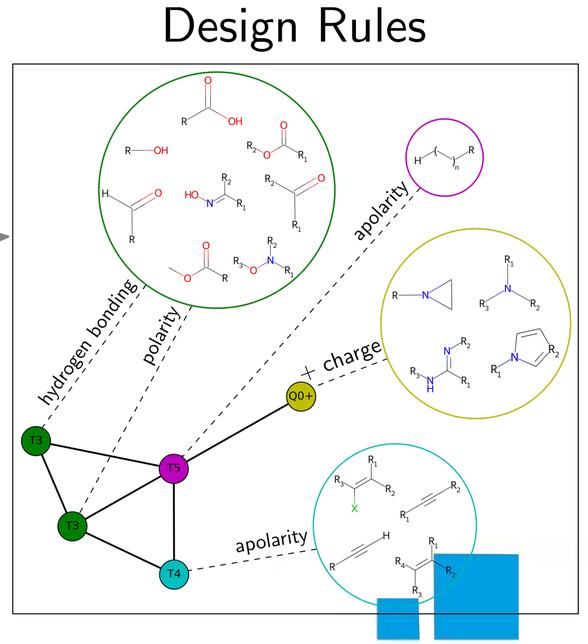
Data-driven discovery of cardiolipin-selective small molecules



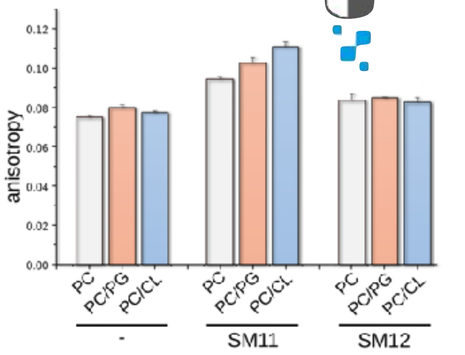


Active Learning





1. Use a *minimal set* of computer simulations to discover **design rules**
2. Suggested 20 compounds for experiments, of which 3 show selectivity *in vitro*, 1 *in vivo*



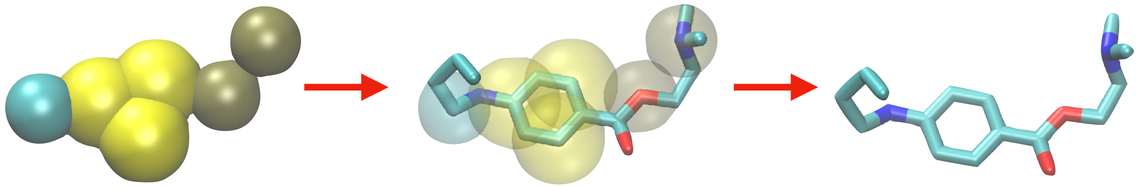
Bernadette Mohr

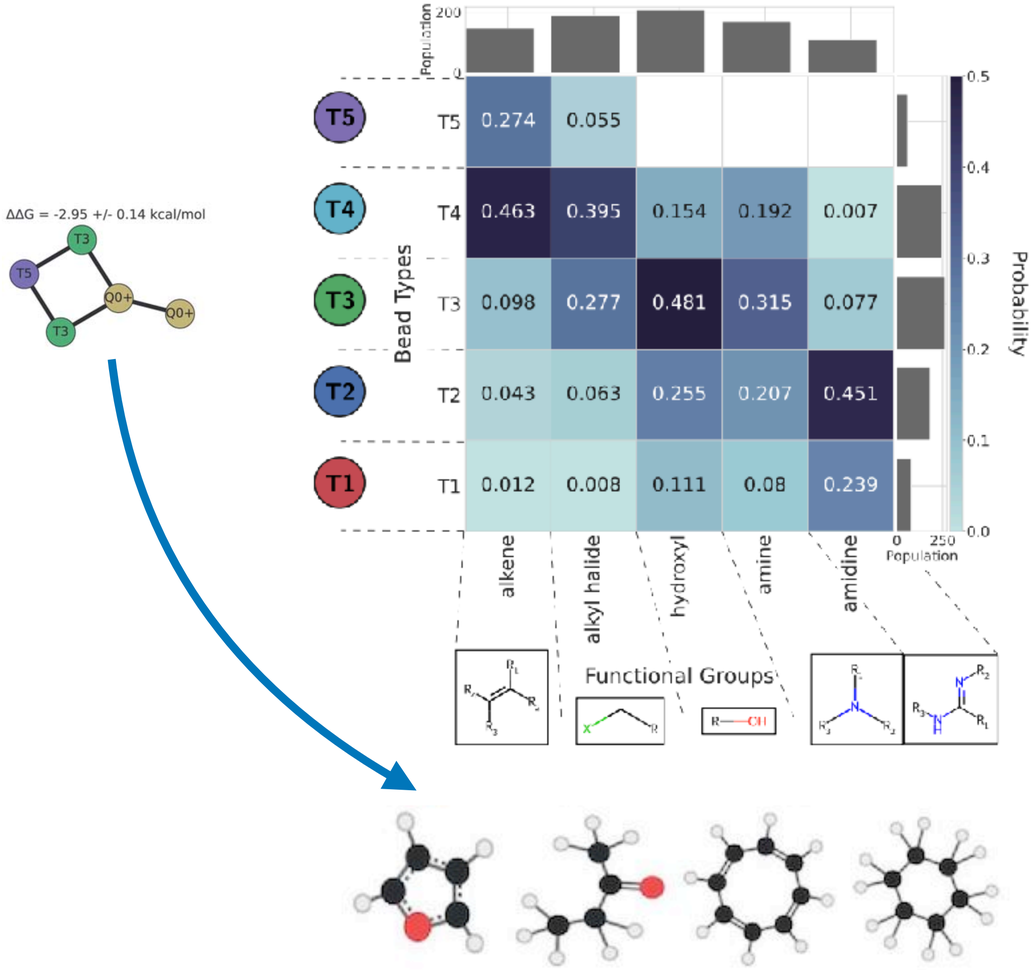
Dirk Schneider

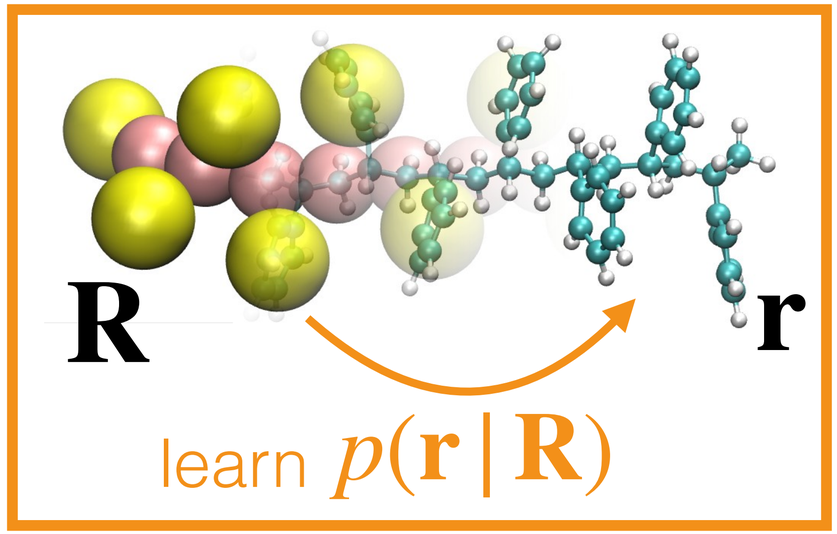
Andrew Ferguson

Mohr *et al.*, *Chemical Science* (2022); "2022 Pick of the Week"
Kleinwächter *et al.*, *RSC Chemical Biology* (2022)

Outlook: reconstructing chemical details

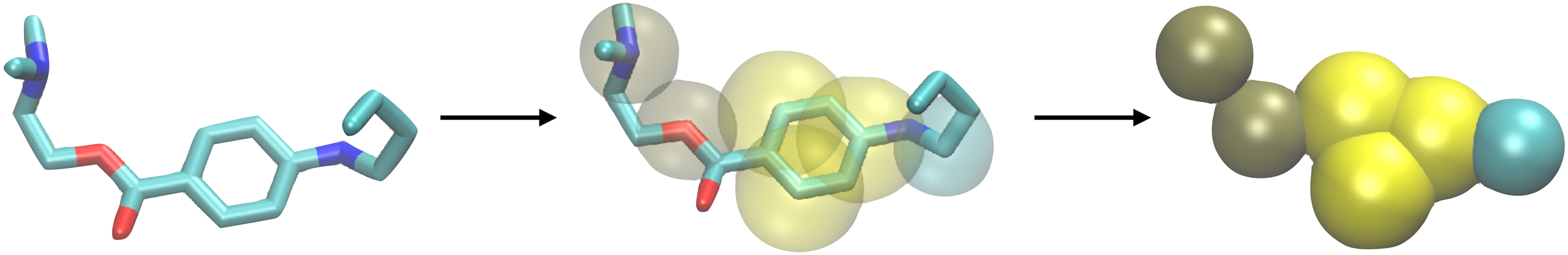






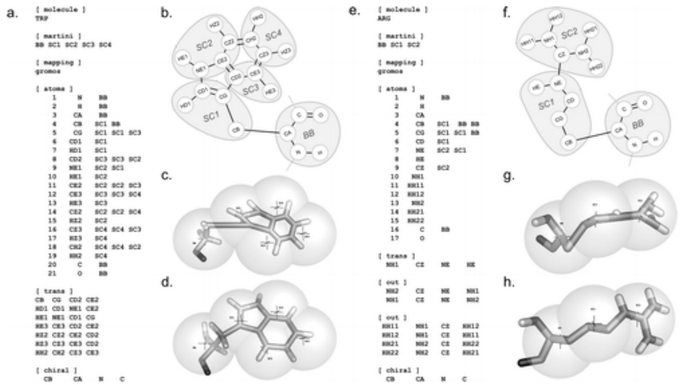
Bernadette Mohr, *PhD thesis*

Fine-graining?



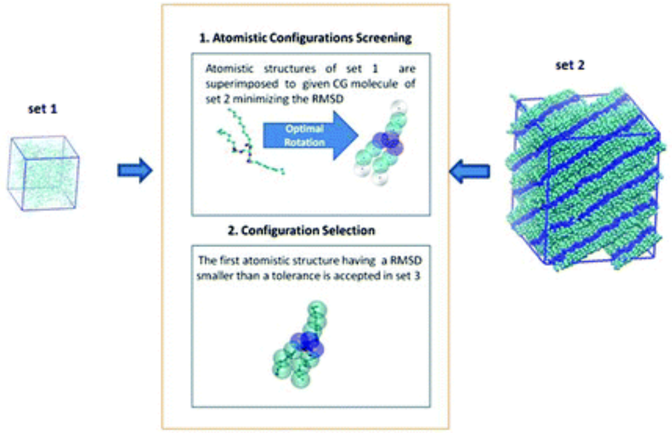
- Going right is straightforward: define a mapping
- **Going left?**

Energy minimization



Wassenaar *et al.*, *JCTC* **10** (2014)

Structural libraries

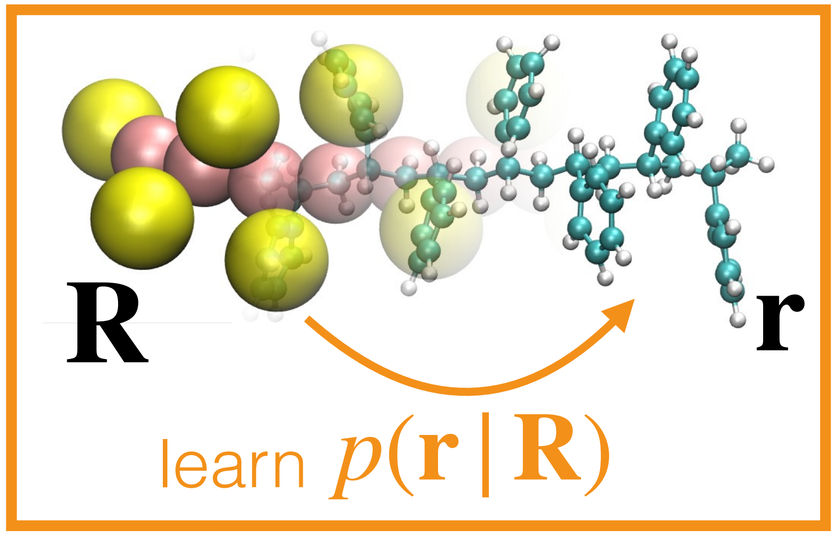


Brasiello *et al.*, *Faraday Disc* **158** (2012)

Generative models

Goodfellow *et al.* NIPS (2014);
Karras et al., *arXiv*:1812.04948 …

Generative adversarial networks: architecture



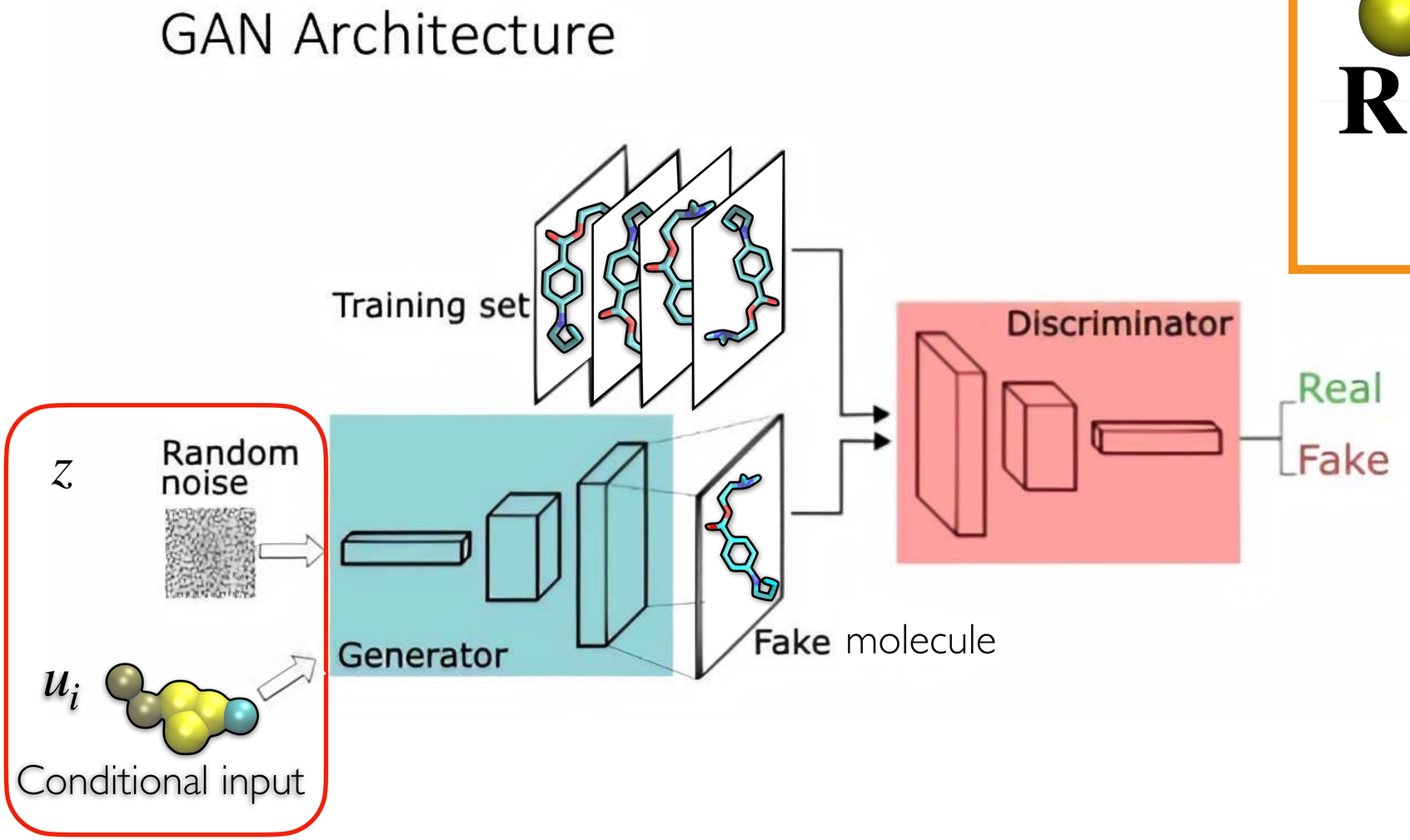
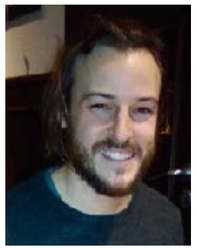
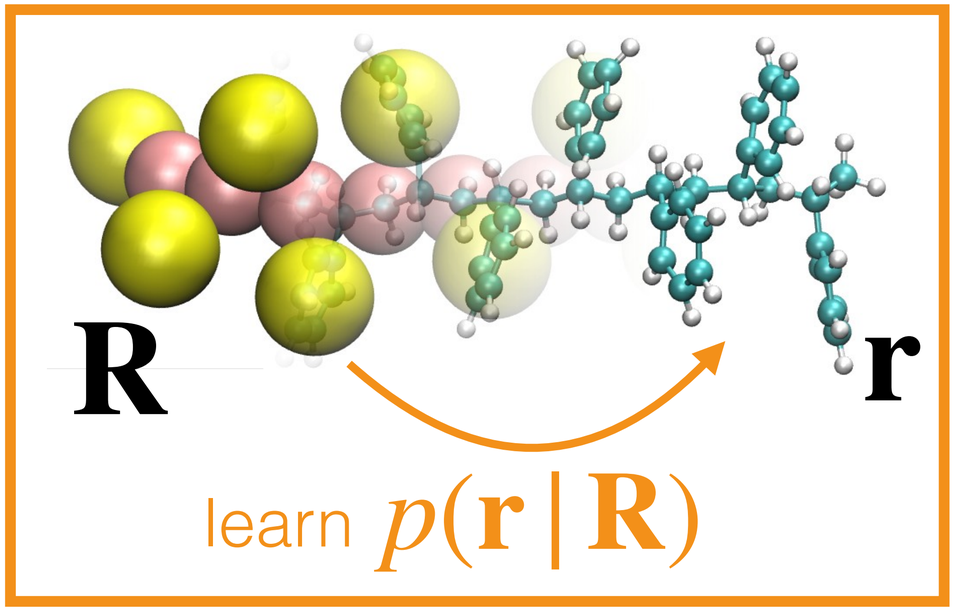


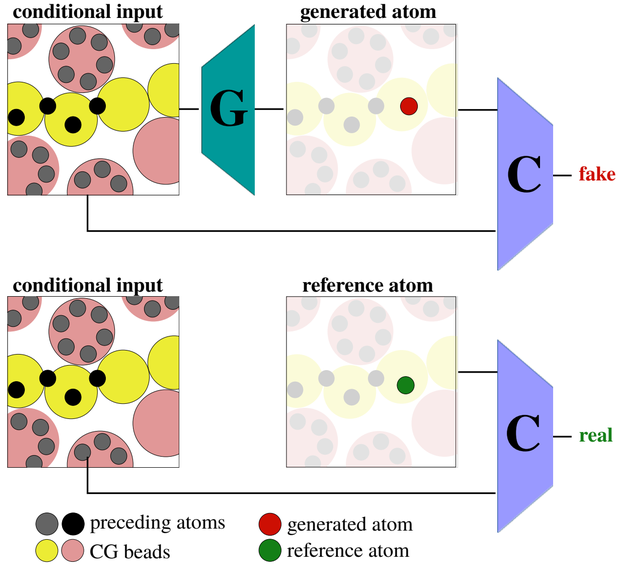
Image adapted from A. Jarda, Medium

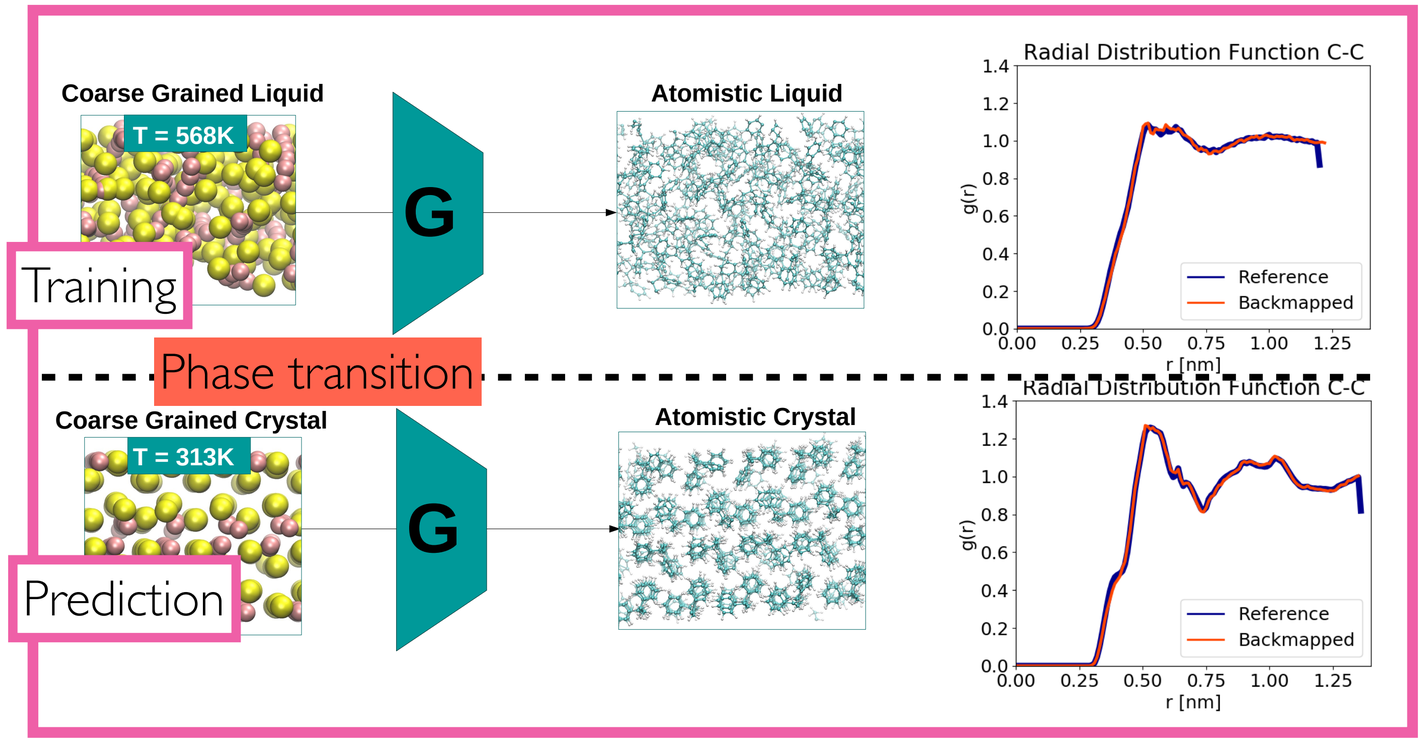


Marc Stieffenhofer

Adversarial backmapping of equilibrated molecular structures





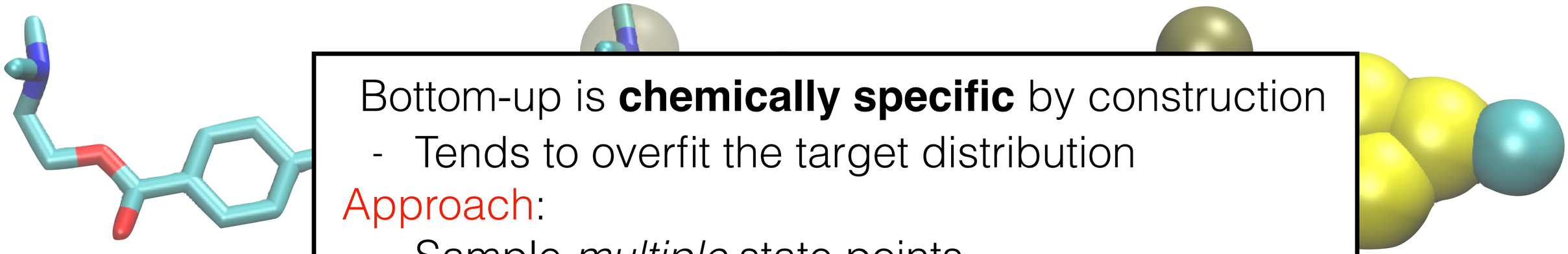


Features

- Loss function incorporates physical priors
- Learns the Boltzmann distribution beyond pairwise statistics
- Temperature transf. from crystal to melt

Stieffenhofer, Wand, Bereau, *Machine Learn Sci Tech* **1** (2020)

Short primer on coarse-graining



Bottom-up is **chemically specific** by construction

- Tends to overfit the target distribution

Approach:

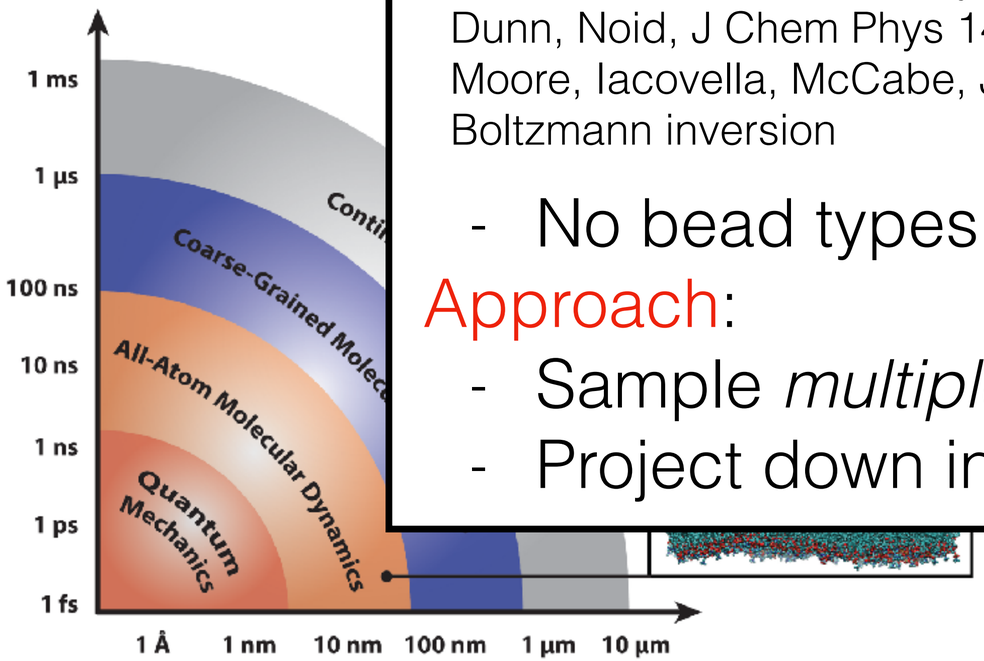
- Sample *multiple* state points

Mullinax, Noid, J Chem Phys 131 (2009): Extended ensemble force matching
Dunn, Noid, J Chem Phys 144 (2016): Ext. ensemble with pressure matching
Moore, Iacovella, McCabe, J Chem Phys 140 (2014): Multistate iterative Boltzmann inversion

- No bead types

Approach:

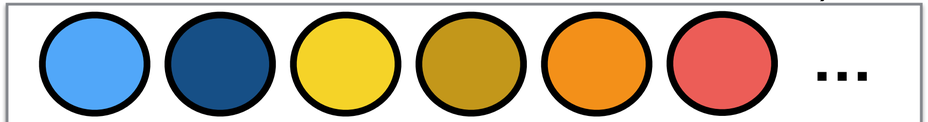
- Sample *multiple* state points + chemistries
- Project down interactions onto bead types



Bradley and Radhakrishnan, *Polymers* **5** (2013)
Noid, *J Chem Phys* **139** (2013)

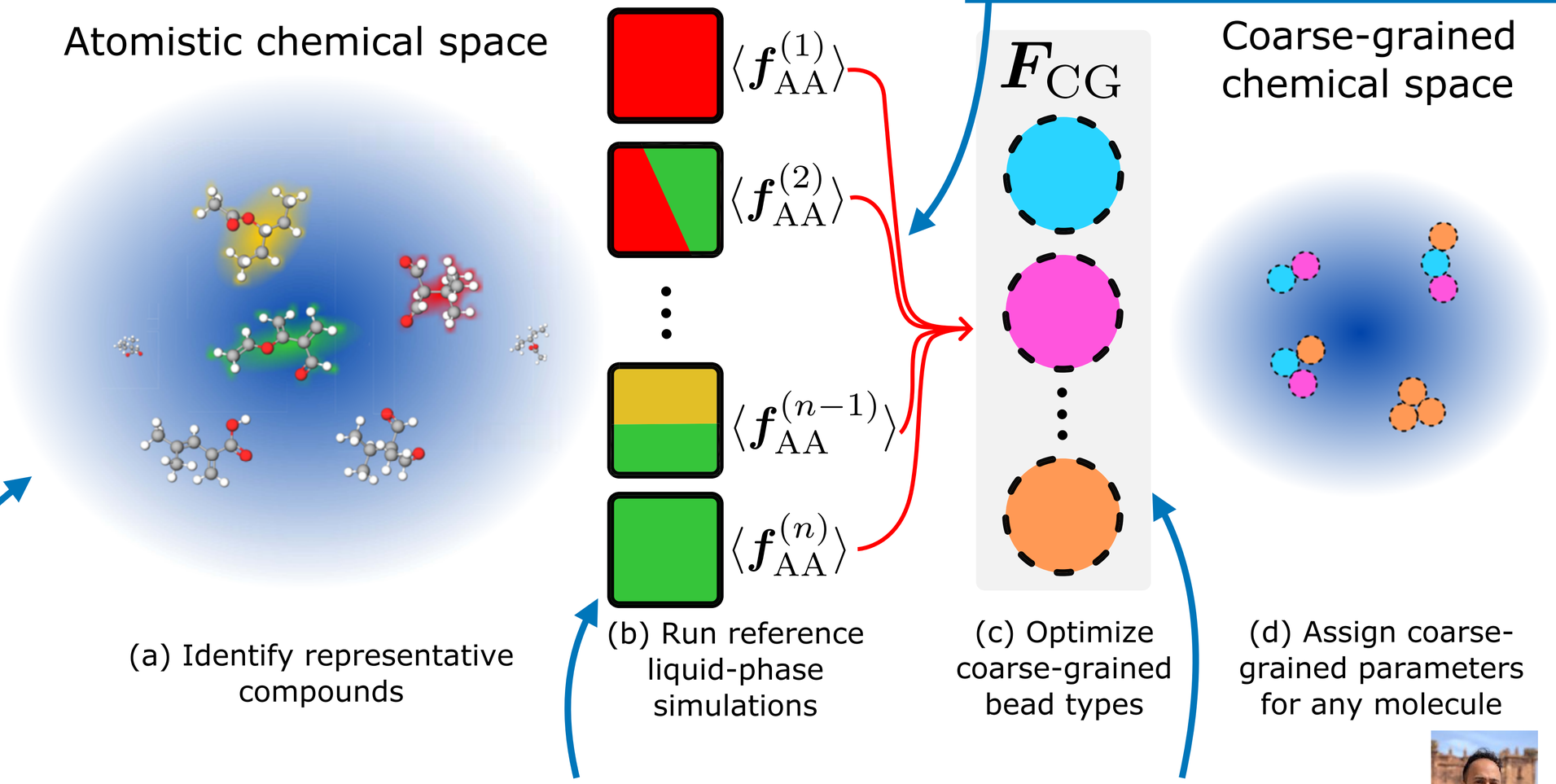
scale physics

ation (e.g., atomistic simulations)



Structure-based and chemically-transferable CG model

Extended-ensemble force matching
Mullinax, Noid, *J Chem Phys* **131** (2009)



3,441 C_7O_2 isomers

703 state points

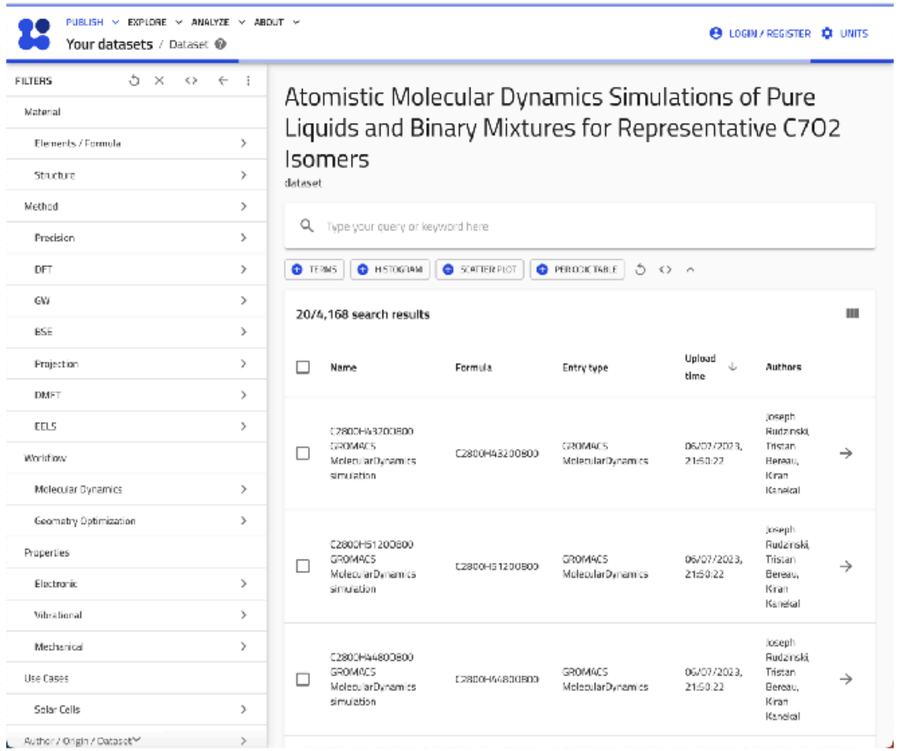
14 CG bead types

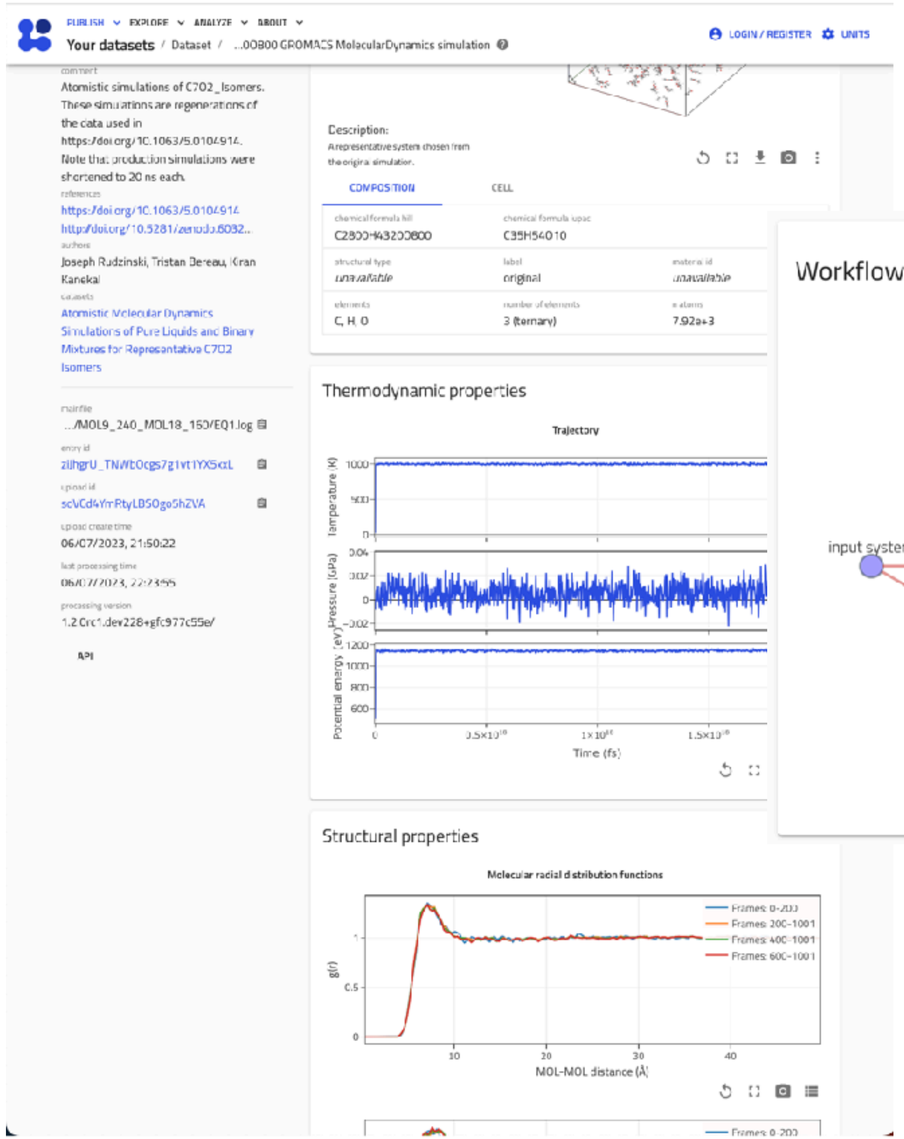
Kanekal, Rudzinski, Bereau, *J Chem Phys* **157** (2022)

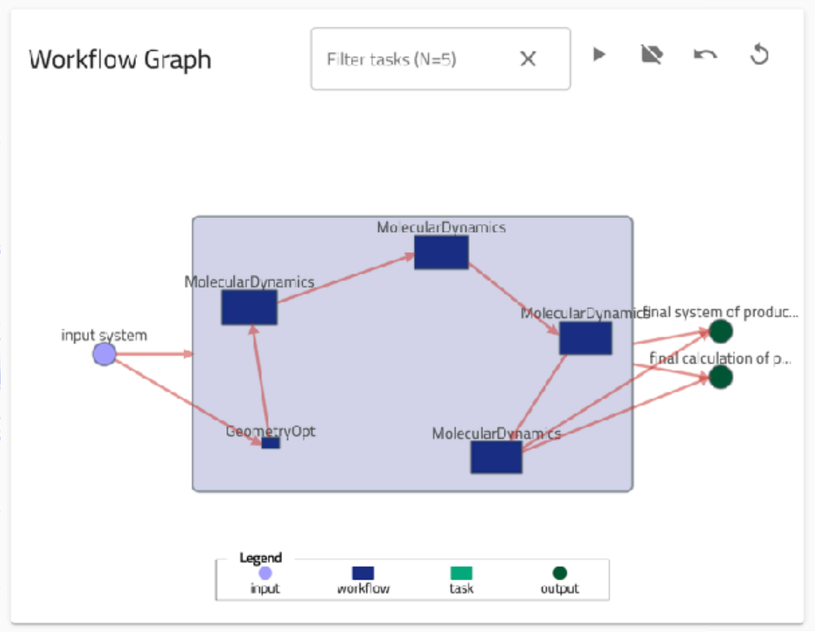

Kiran Kanekal


Joseph Rudzinski

Atomistic MD simulations available on NOMAD





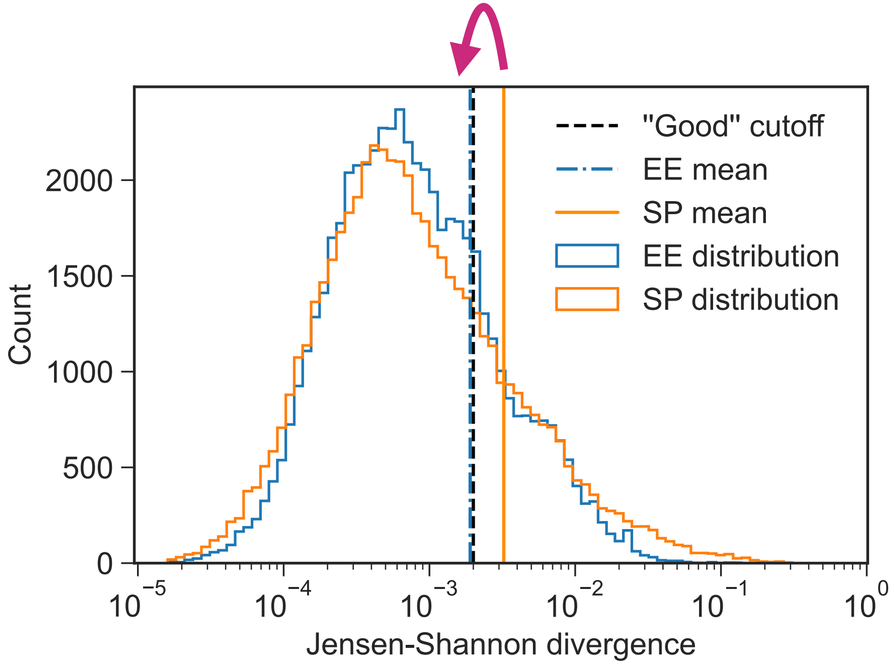


https://nomad-lab.eu/prod/v1/gui/user/datasets/dataset/id/k0FIIN93TDqcDatfaBWpXQ

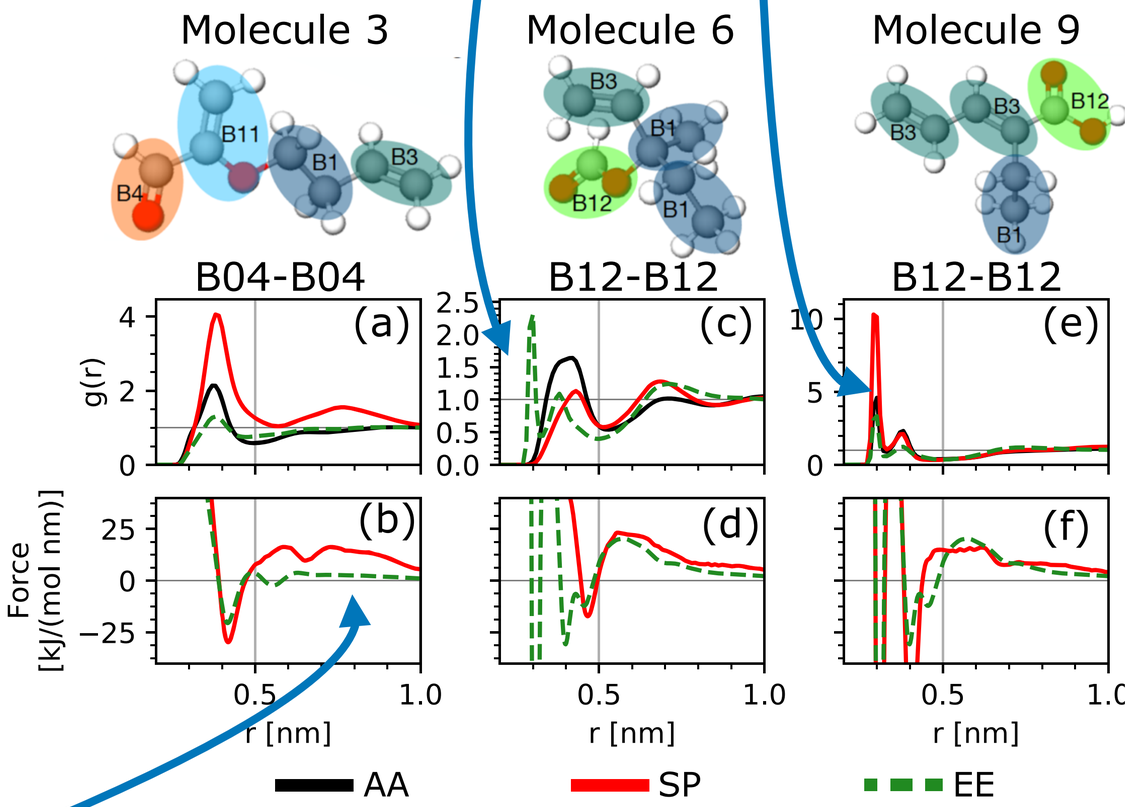
Extended ensemble more accurate than state-point specific models

Extended ensemble models are **more accurate**!

Regularization effect



Same bead type: Averaging smoothens sharp features



Smoothening removes long-range features

Dunn, Noid, *J Chem Phys* **144** (2016)

Kanekal, Rudzinski, Bereau, *J Chem Phys* **157** (2022)

Kiran Kanekal

Joseph Rudzinski

Outlook

Chemical-space perspective

New perspective: Parametrize, calculate, analyze simulations *across* chemical space

Multiscale modeling to explore chemical space

Multiscale description of chemical space exploits scale separation. Accelerates search for structure-property relationships, compound discovery