Potential of Biomolecular Simulations in Drug Design

Vojtěch Spiwok
spiwokv@vscht.cz
Department of Biochemistry and Microbiology
University of Chemistry and Technology, Prague

http://web.vscht.cz/spiwokv/
http://www.metadynamics.cz

Outline:

History

Theory

Sampling Problem

History:

1953: Metropolis Monte Carlo simulation of dense liquid of 2D spheres
Metropolis, Rosenbluth, Rosenbluth, Teller & Teller *Journal of Chemical Physics* 1953, **21**, 1087-1092.

1956: Molecular dynamics simulation of hard spheres
Alder and Wainwright *Journal of Chemical Physics* 1957, **27**, 1208-1209.

1964: Molecular dynamics simulation of liquid argon
Rahman *Physical Reviews* 1964, **136**, A405-A410.

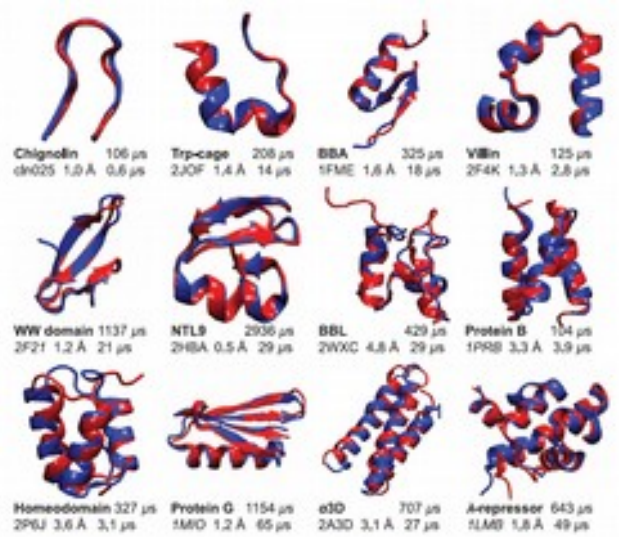
1969: Monte Carlo simulation of water
Barker and Watts *Chemical Physics Letters* 1969, **3**, 144-145.

1971: Molecular dynamics simulation of water
Rahman and Stillinger *Journal of Chemical Physics* 1971, **55**, 3336-3359.

1977: Molecular dynamics simulation of protein
McCammon, Gelin and Karplus *Nature* 1977, **267**, 585-590.

History:

1977: Molecular dynamics simulation of protein
McCammon, Gelin and Karplus *Nature* 1977, **267**, 585-590.
3.2 ps, < 1,000 atoms



2011: Fast-folding protein folding
Lindorff-Larsen, Piana, Dror, Shaw *Science* 2011, **334**, 517-520.
108-2,936 μs, solvated small proteins

2013: Viral capsid simulation
Zhao *et al. Nature* 2013, **497**, 643-646.
100 ns, ~64,000,000 atoms

2013 Nobel Prize in Chemistry:

The Nobel Prize in Chemistry 2013
Martin Karplus, Michael Levitt, Arieh Warshel

Share this: 950

The Nobel Prize in Chemistry 2013

Photo: A. Mahmoud
Martin Karplus
Prize share: 1/3

Photo: A. Mahmoud
Michael Levitt
Prize share: 1/3

Photo: A. Mahmoud
Arieh Warshel
Prize share: 1/3

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel *"for the development of multiscale models for complex chemical systems"*.

Theory:

What we need?

Computer – to run a simulation

Software – to run a simulation

Instructions – to control length of simulation, temperature, pressure etc.

Topology – to define covalent structure in the system,
properties of atoms and bonds

Starting structure

Theory:

$$m_i \frac{\partial^2 \mathbf{r}_i}{\partial t^2} = \mathbf{F}_i$$

$$\mathbf{F}_i = -\frac{\partial V}{\partial \mathbf{r}_i}$$

$$V = \sum_{bonds} \frac{k_b}{2}(r - r_0)^2 + \sum_{angles} \frac{k_a}{2}(\theta - \theta_0)^2$$

$$+ \sum_{torsions} k_t(1 + \cos(n\phi - \phi_S)) + \sum_{pairs} \left[\frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{r_{ij}} + \frac{C_{12}}{r_{ij}^{12}} - \frac{C_6}{r_{ij}^6} \right]$$

Programs:

GROMACS	http://www.gromacs.org
AMBER	http://ambermd.org
CHARMM	https://www.charmm.org
GROMOS	http://www.gromos.net
AceMD	http://www.acellera.com/acemd
Desmond	http://deshawresearch.com/resources.html
NAMD	http://www.ks.uiuc.edu/research/namd/
Tinker	http://dasher.wustl.edu/tinker/

Force fields:

Proteins, nucleic acids, lipids:

AMBER	http://ambermd.org
OPLS	http://zarbi.chem.yale.edu
CHARMM	https://www.charmm.org
GROMOS	http://www.gromos.net

General molecules:
GAFF, OPLS, CHARMM, MM2, MM3, MMFF

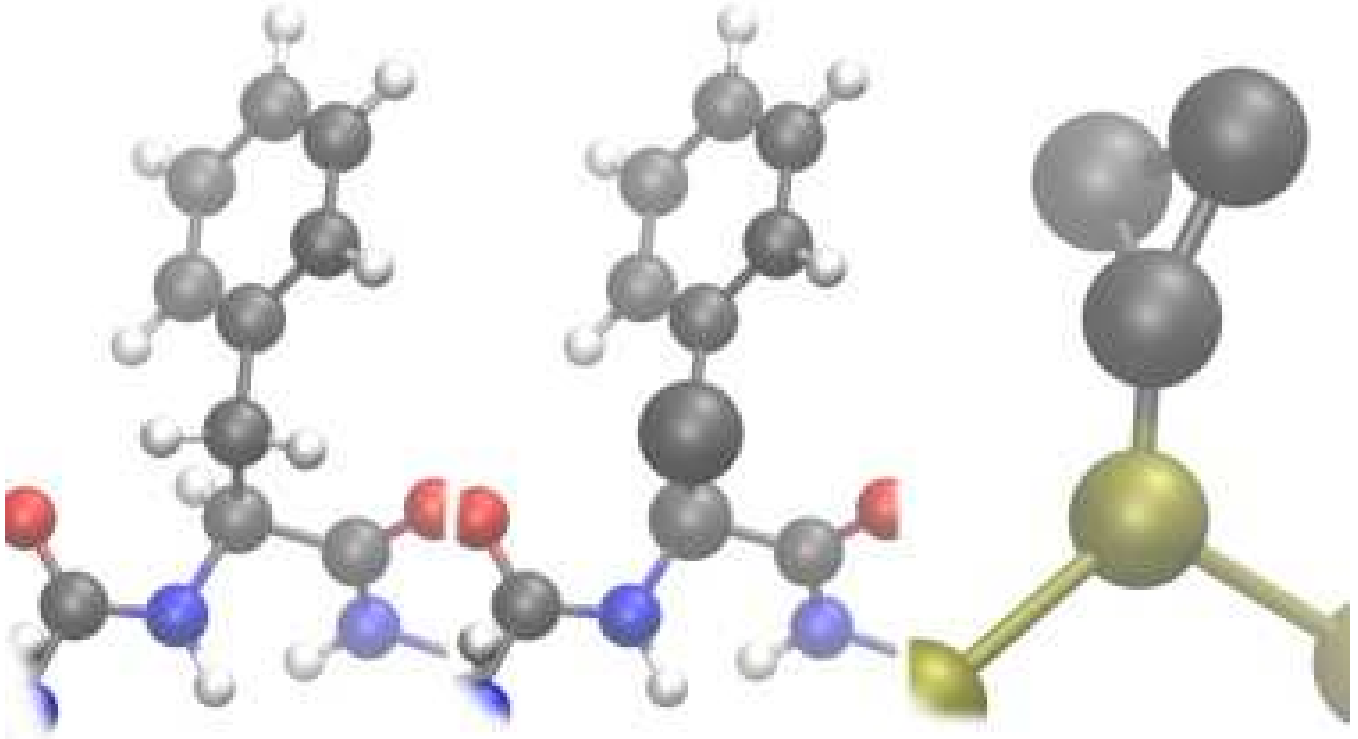
Special:

Glycam (carbohydrates)	http://glycam.org
Martini (coarse grained)	http://md.chem.rug.nl

$$V=\sum_{bonds}\frac{k_b}{2}(r-r_0)^2+\sum_{angles}\frac{k_a}{2}(\theta-\theta_0)^2$$

$$+\sum_{torsions}k_t(1+\cos(n\phi-\phi_S))+\sum_{pairs}\left[\frac{1}{4\pi\epsilon_0}\frac{q_iq_j}{r_{ij}}+\frac{C_{12}}{r_{ij}^{12}}-\frac{C_6}{r_{ij}^6}\right]$$

Force fields:

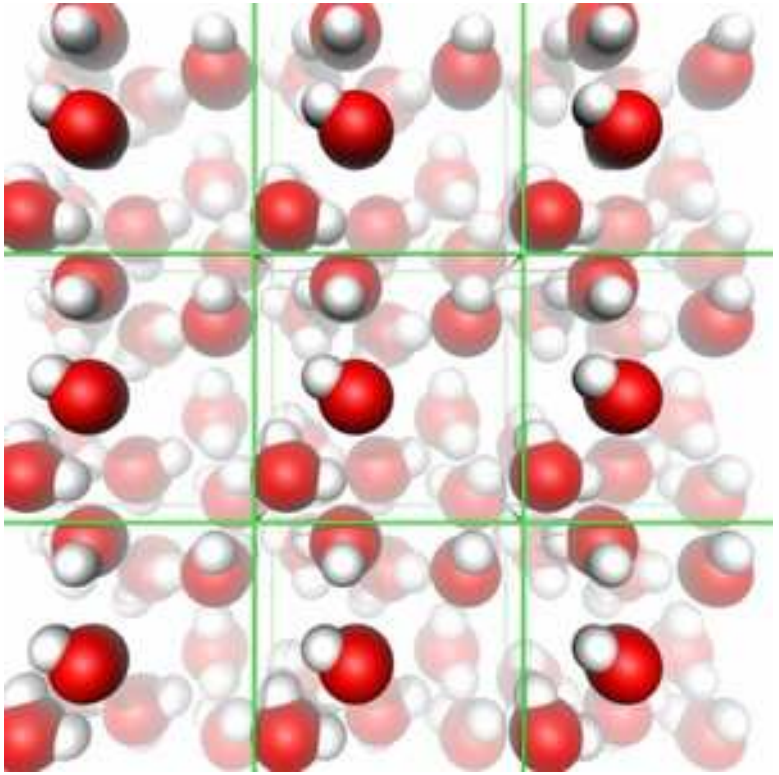


All atom United atom Coarse grained

Which systems we can simulate?

- Solvated (bio)molecules and biomolecular complexes
- Membranes and membrane proteins
- Special systems (crystals, pores etc.)

Periodic boundary condition



What can be controlled?

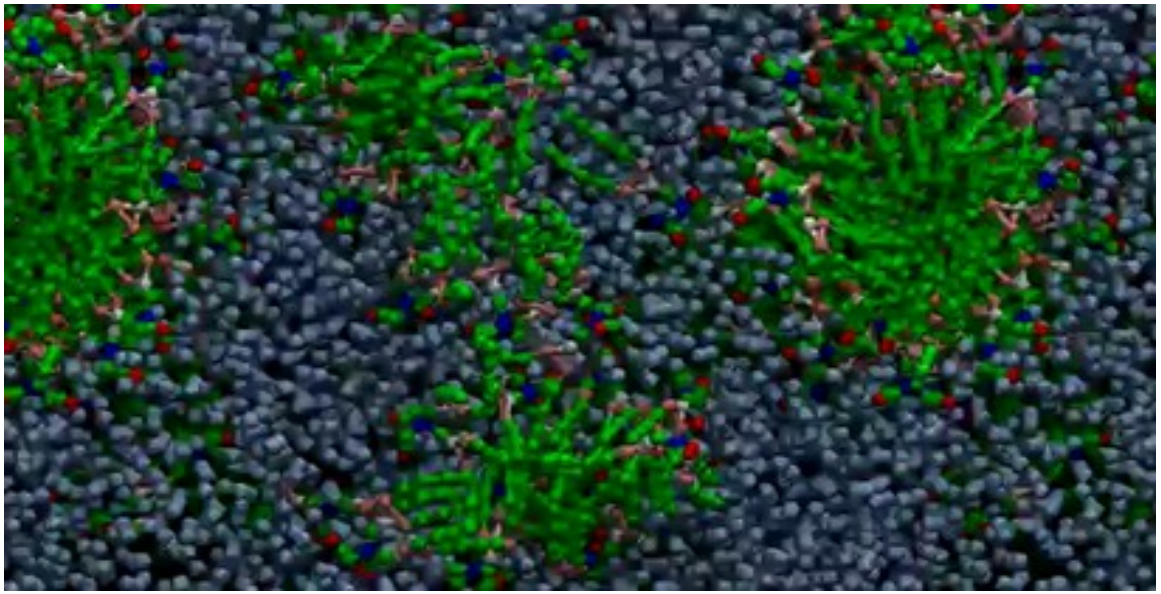
Length of simulation

Temperature

Pressure, surface tension

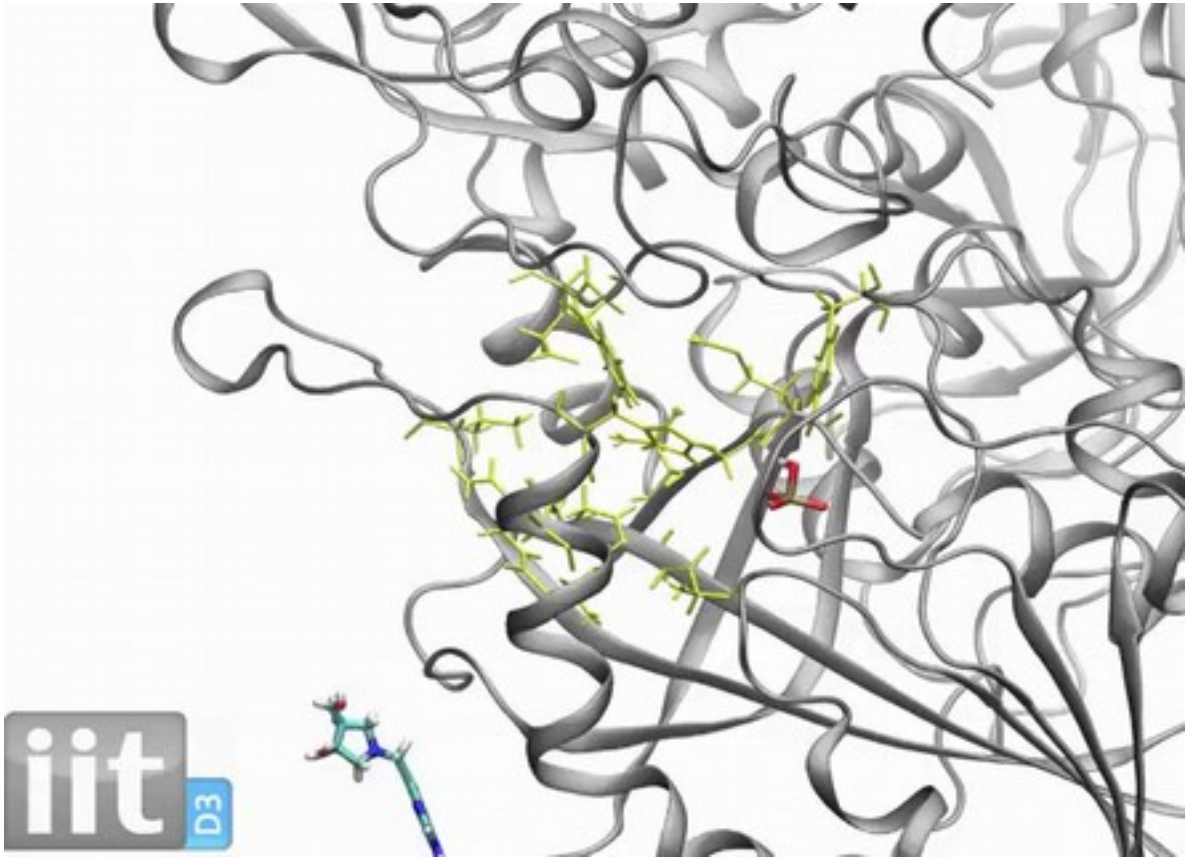
Special topics (electric field, external forces, constant pH etc.)

Predictive simulations
Spontaneous formation of a membrane



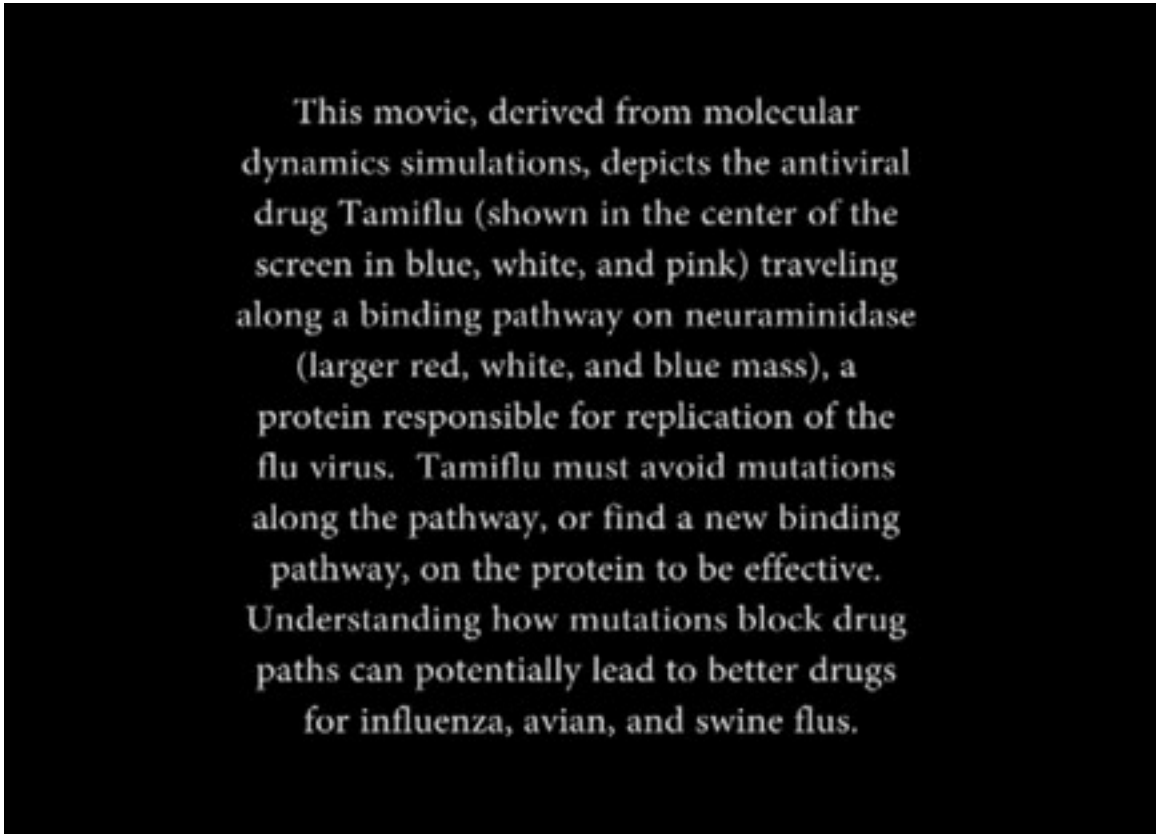
By Axel Kohlmeyer

Predictive simulations
Binding of 4'-deaza-1'-aza-2'-deoxy-1'-(9-methylene)-immucillin-H
to purine nucleoside phosphorylase



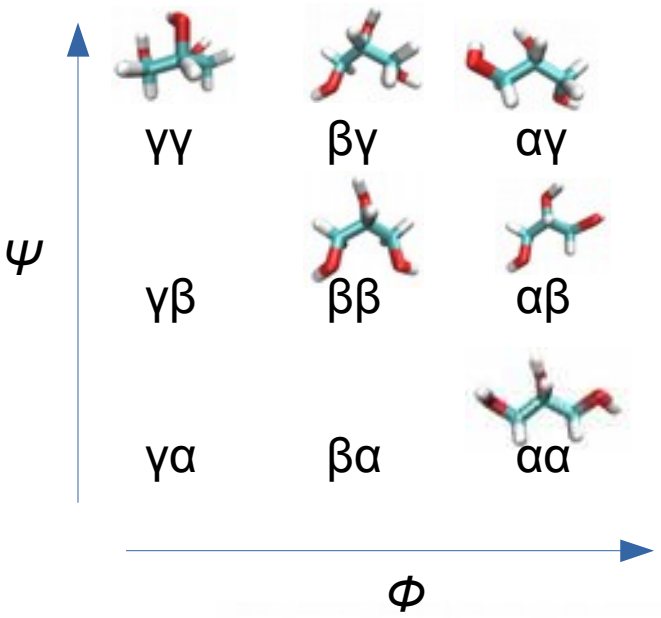
Decherchi S, Berteotti A, Bottegoni A, Rocchia W, Cavalli A *Nature Commun* 2015, **6**, 6155.

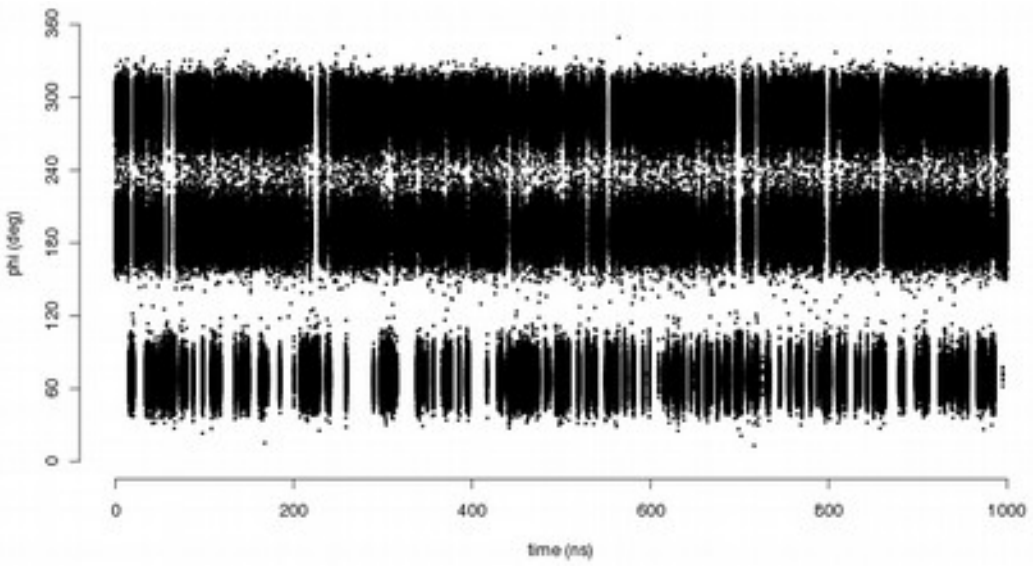
Predictive simulations
Binding of Tamiflu to influenza neuraminidase

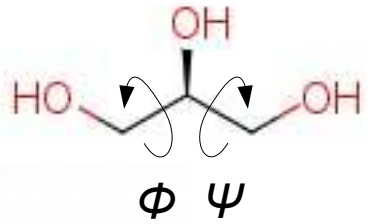


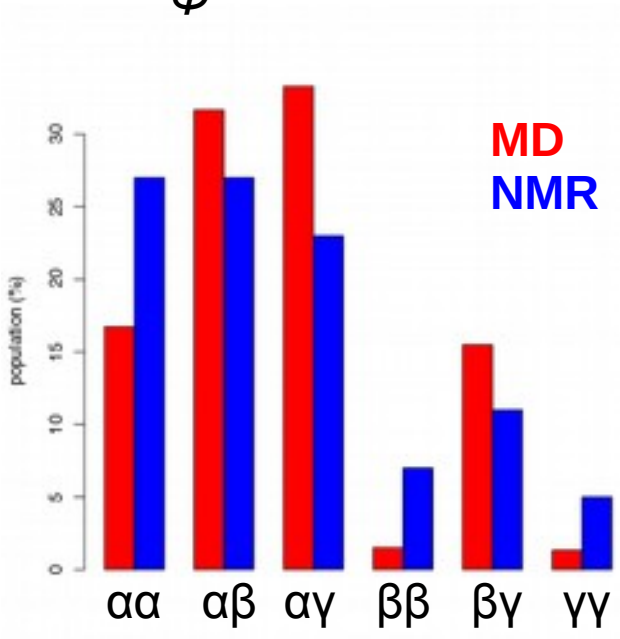
By Klaus Schulten lab

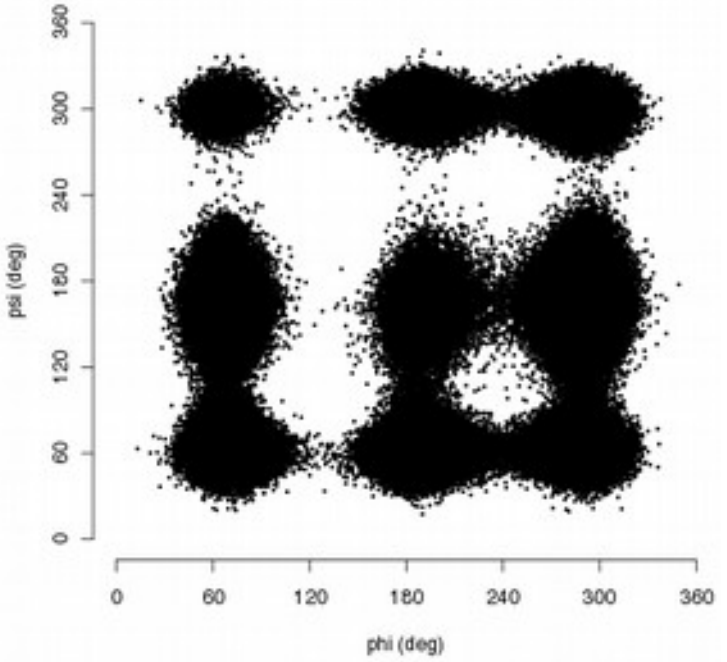
Equilibrium simulations











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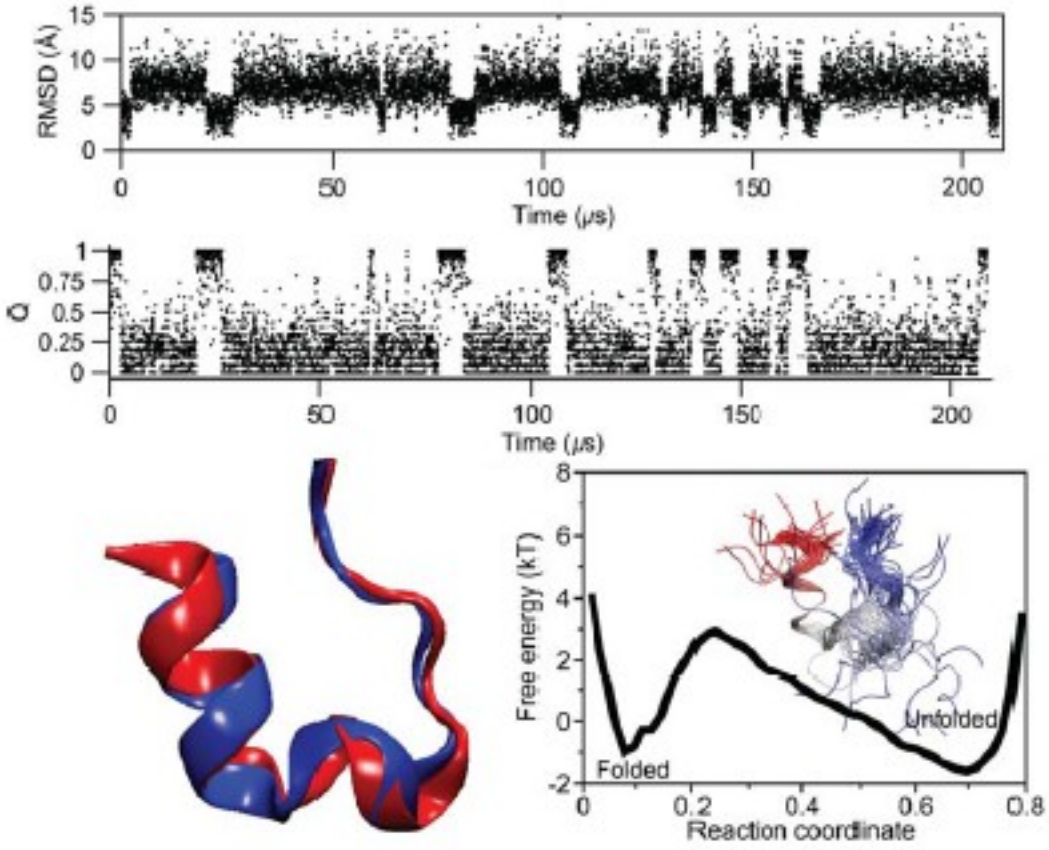
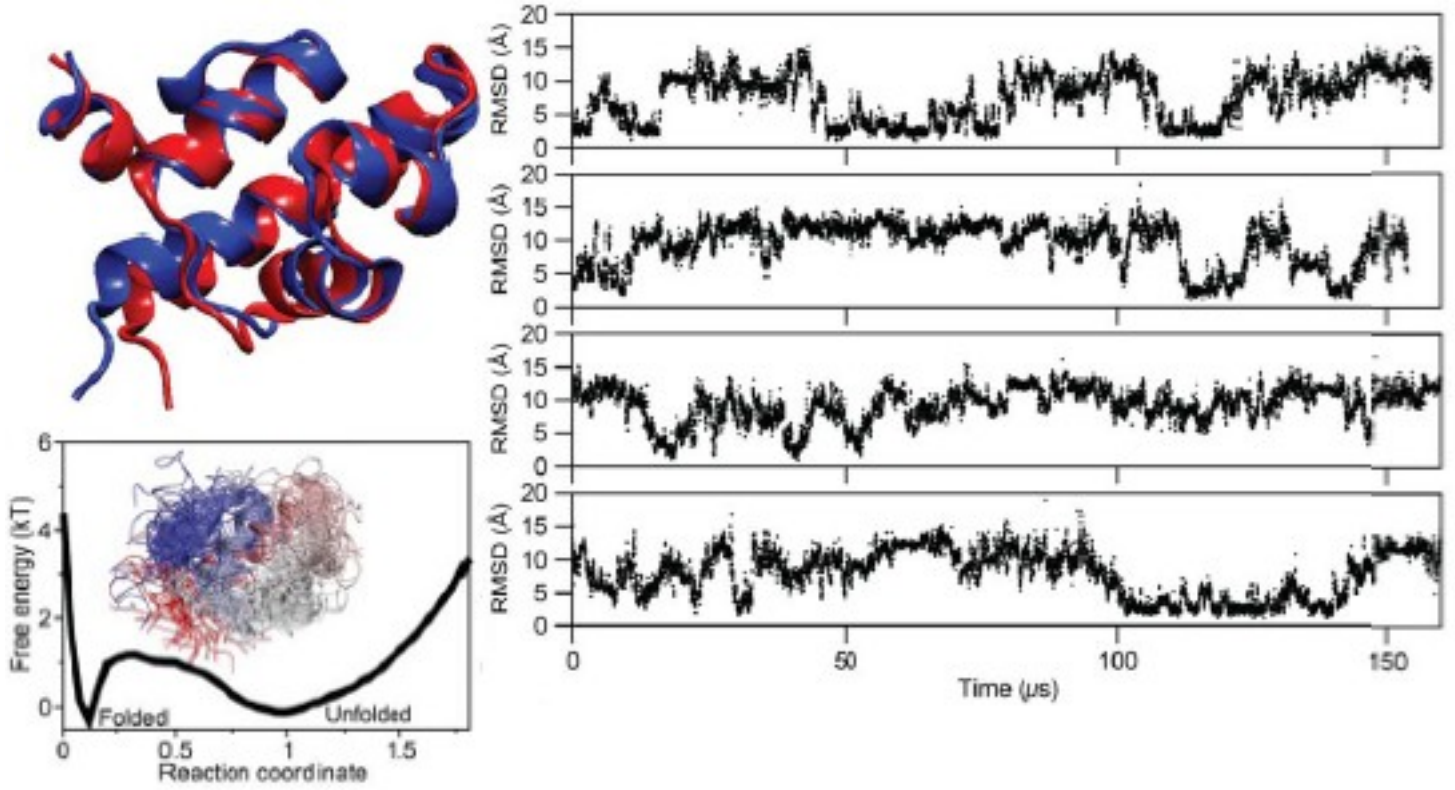
Equilibrium simulations
Trp-cage folding



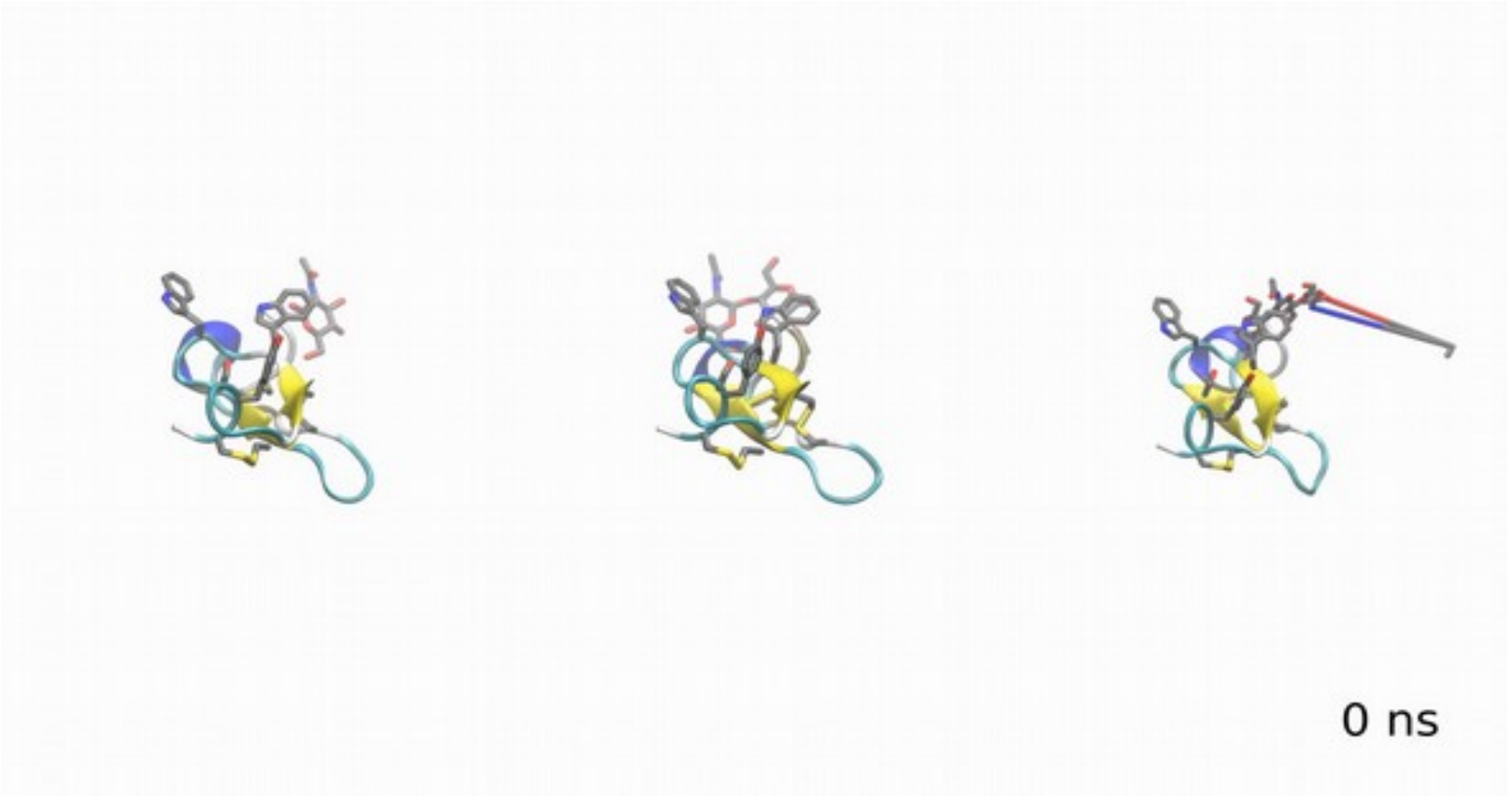
Lindorff-Larsen K, Piana S, Dror RO, Shaw DE *Science* 2011, **334**, 517-520.

Equilibrium simulations
λ-represor folding



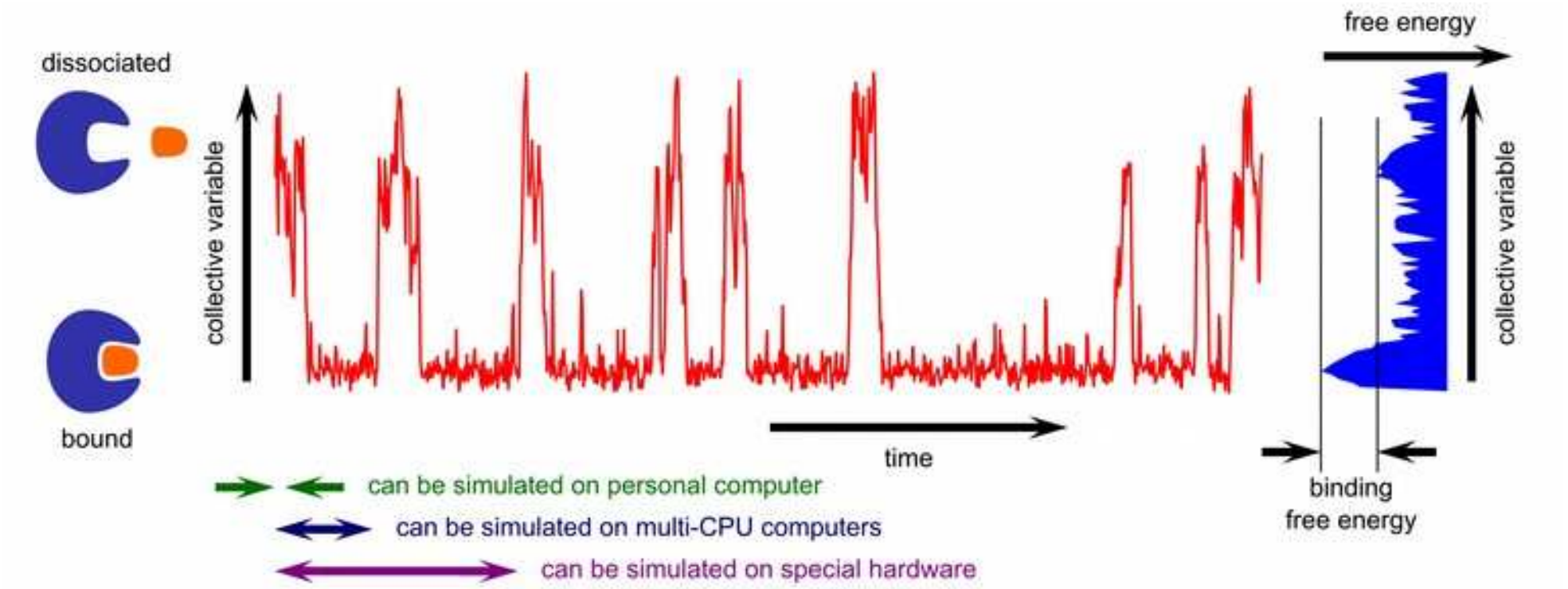
Lindorff-Larsen K, Piana S, Dror RO, Shaw DE *Science* 2011, **334**, 517-520.

What we do
Hevein domain HEV32



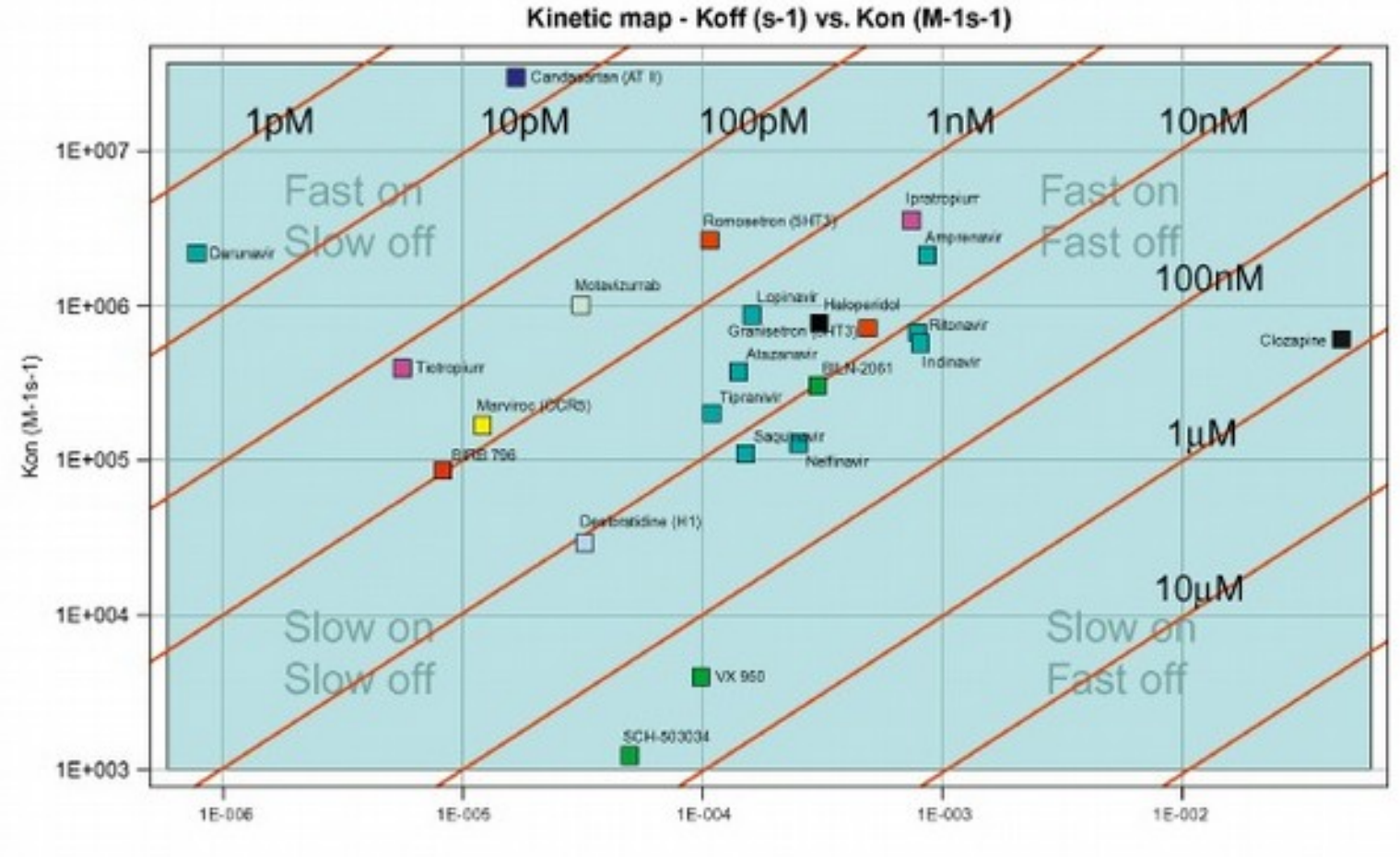
C.O. Solanke *et al. Sci. Rep.* 2019, **9**, 18918.

Sampling problem



Sampling problem

k_{on}-k_{off}



week 20 hours 2 hours 10 min 1 min

Smith G. *Progress in Medicinal Chemistry* 2009, **48**, 1-29.

Sampling problem

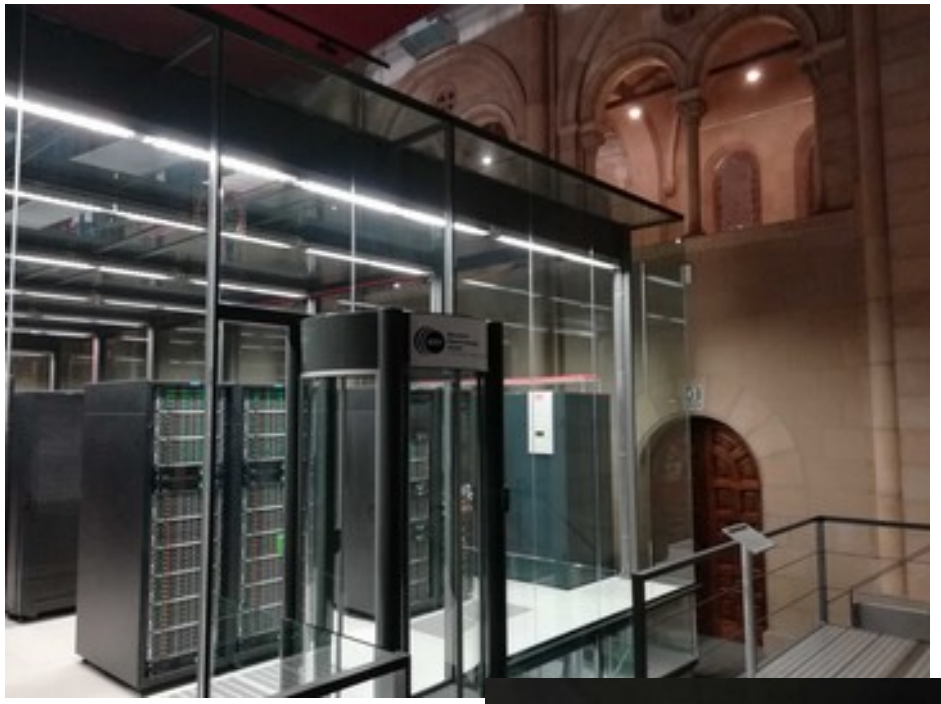
Brute force approach

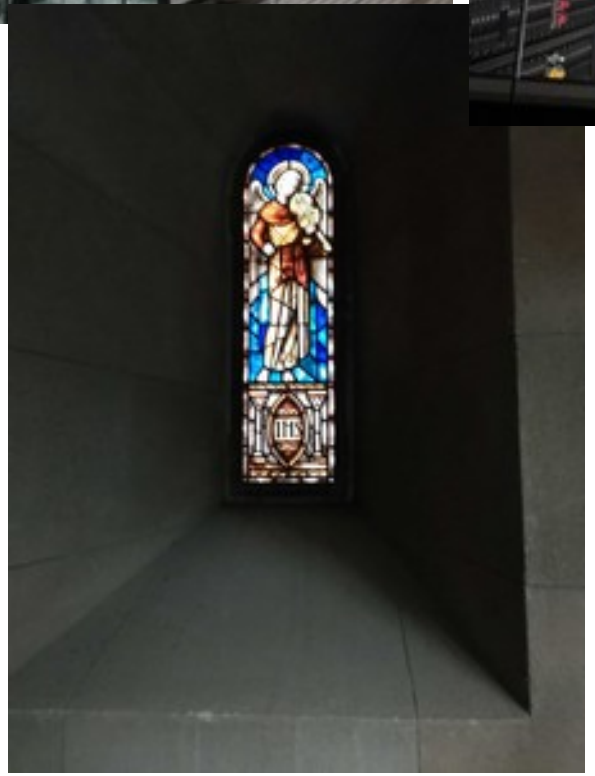
1	Supercomputer Fugaku, Japan	7,299,072
2	Summit - IBM - ORNL, United States	2,414,592
3	Sierra - IBM - DOE/NNSA/LLNL, United States	1,572,480
4	Sunway TaihuLight, China	10,649,600
5	Tianhe-2A, China	4,981,760
6	HPC5, Italy	669,760
7	Selene, NVIDIA, United States	272,800
8	Frontera, United States	448,448
9	Marconi-100 - CINECA, Italy	347,776
10	Piz Daint, Switzerland	387,872
...		
423.	Salomon, CZ	76,895

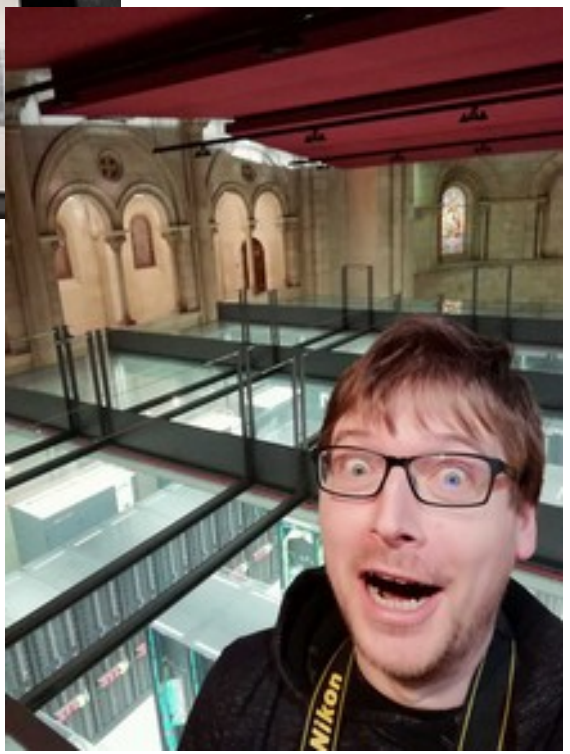
http://www.top500.org

Potential of Biomolecular Simulations in Drug Design

Vojtěch Spiwok







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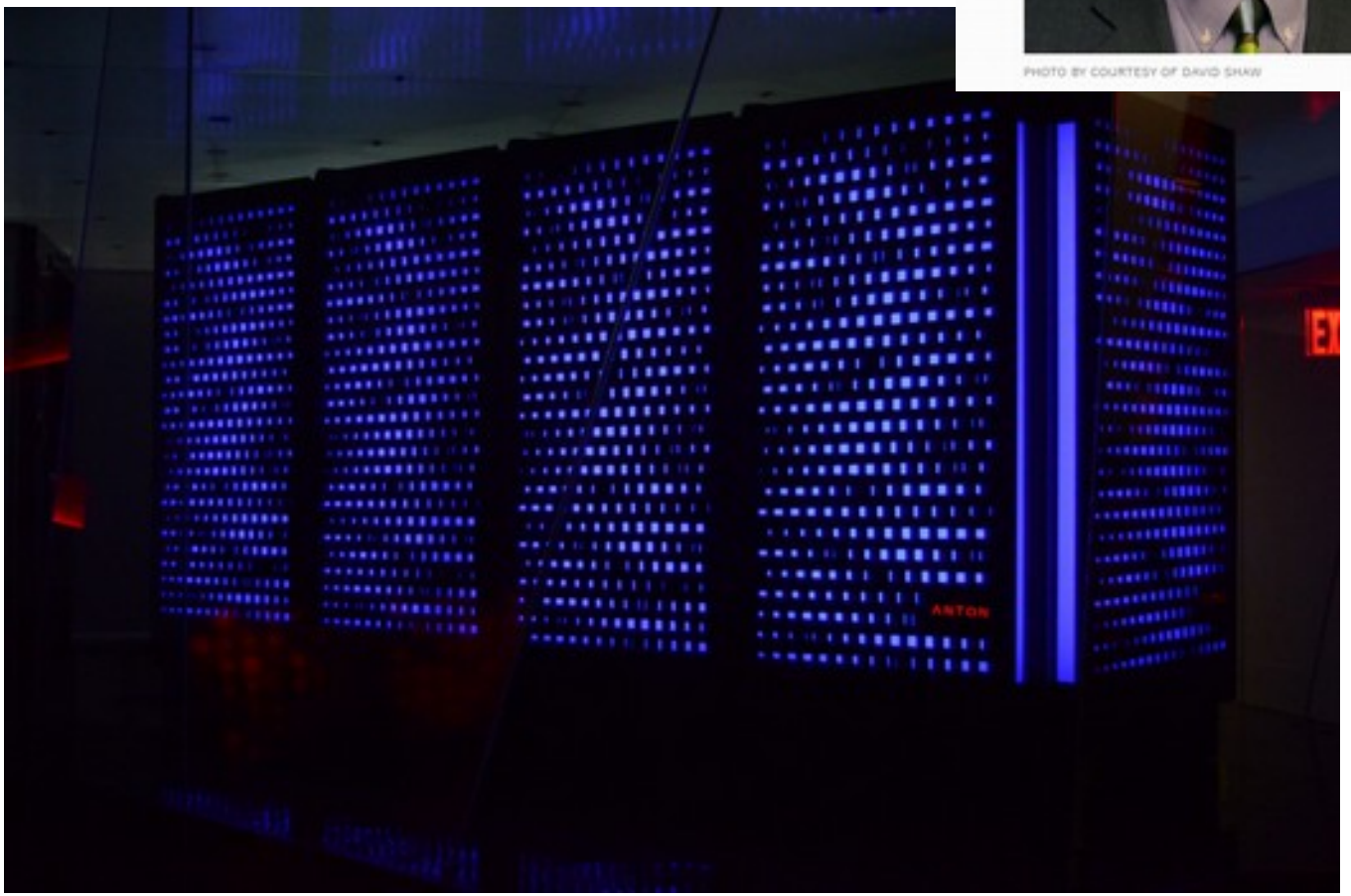
Vojtěch Spiwok

Sampling problem

Brute force approach

Anton



Sampling problem

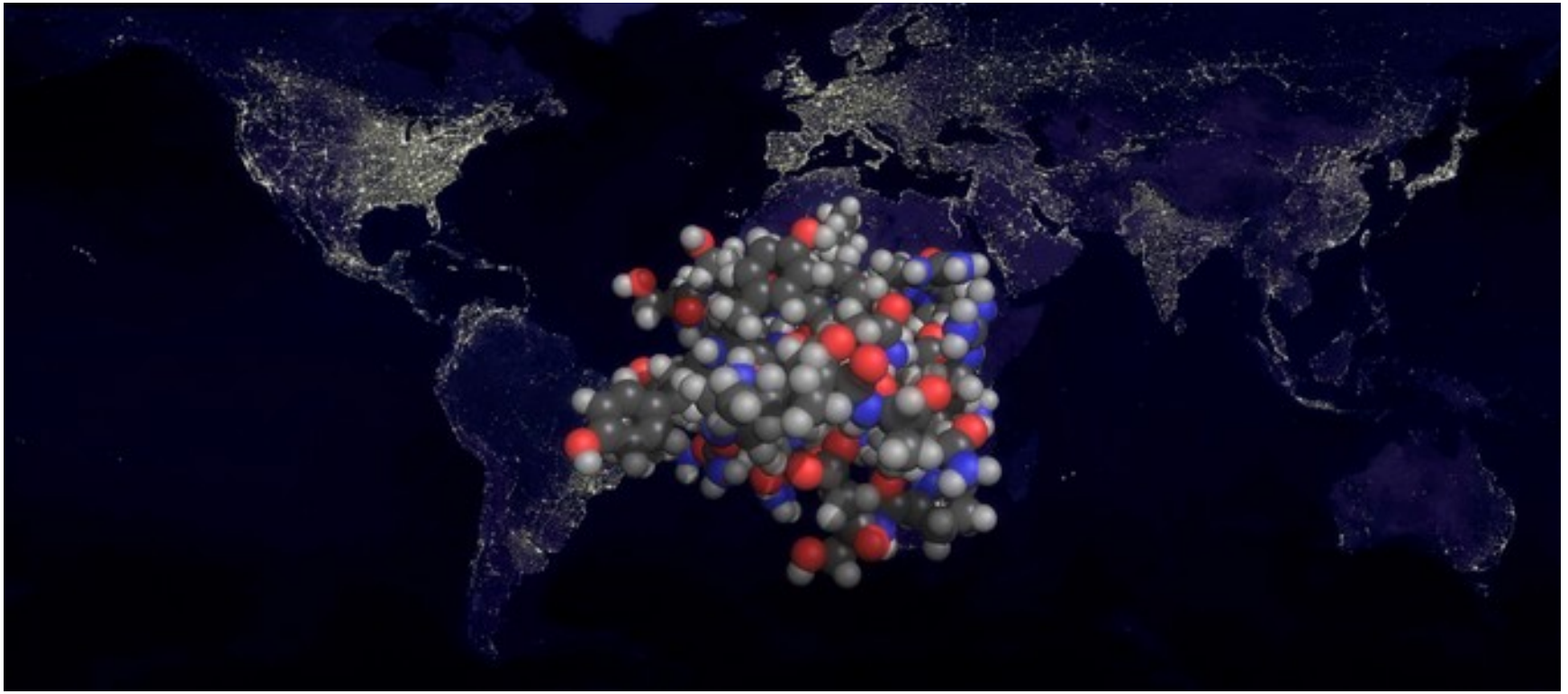
Brute force approach

GPU

Sampling problem

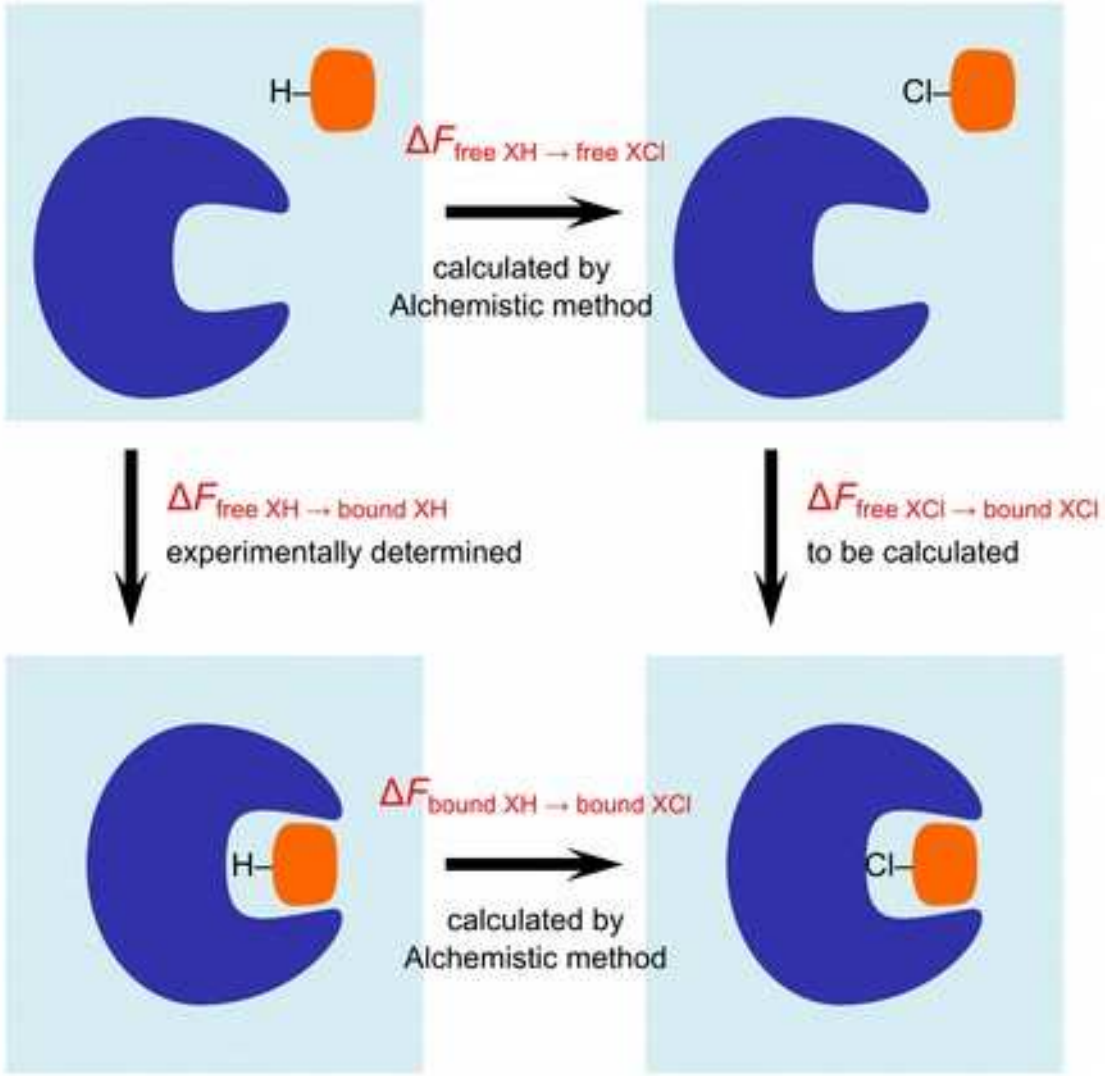
Brute force approach

Distributed computing
http://folding.stanford.edu



Sampling problem

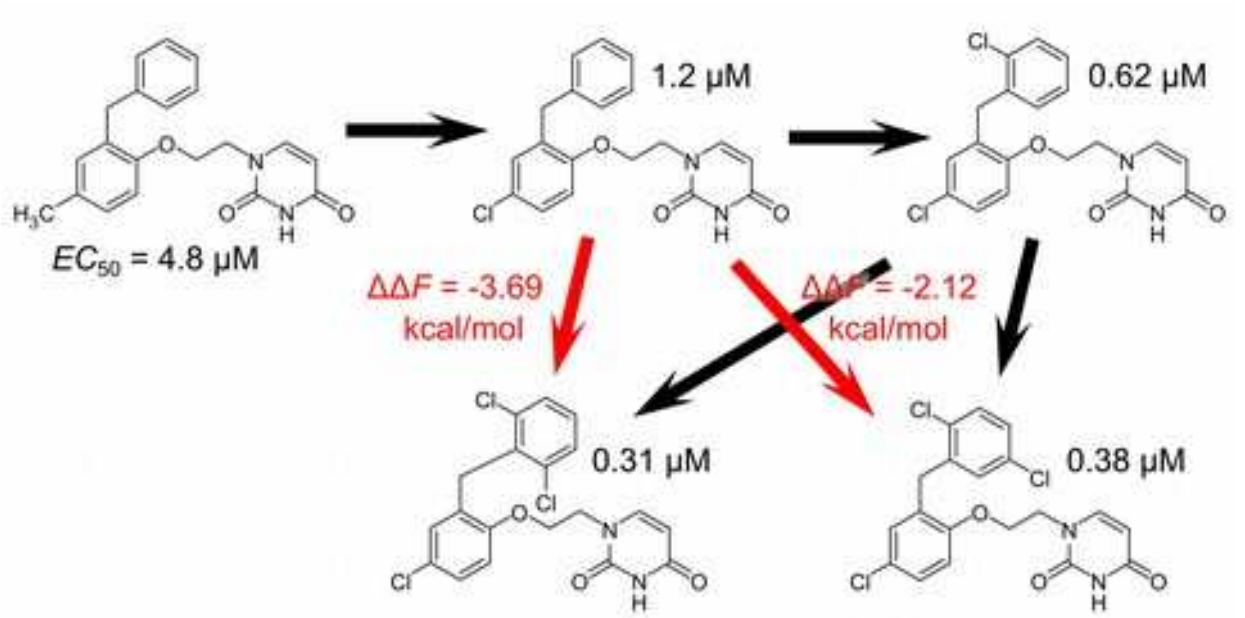
Alchemistic simulations

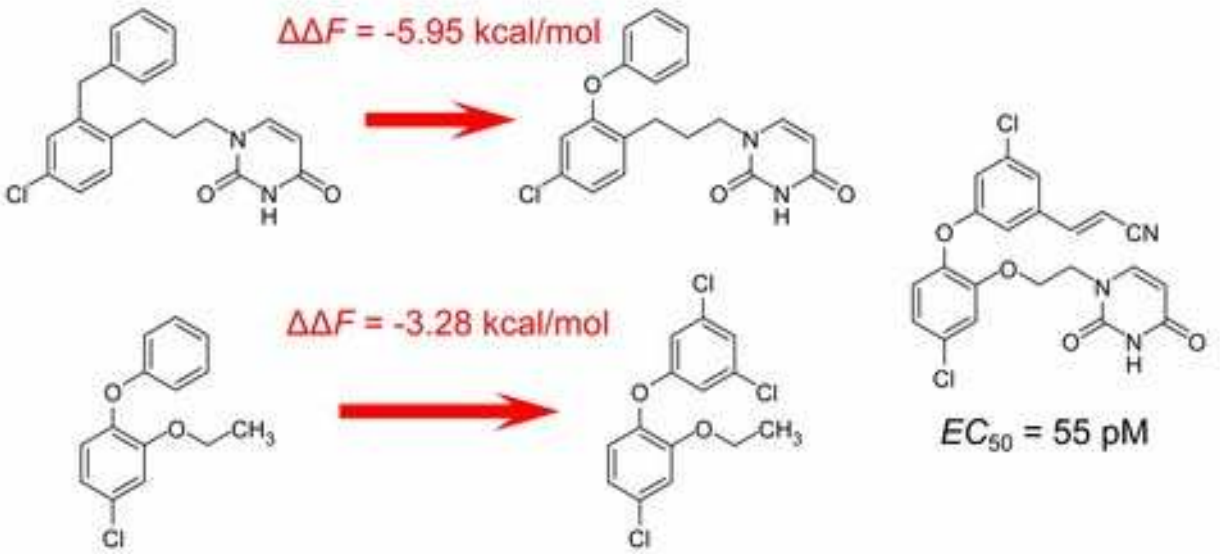


Sampling problem

Alchemistic simulations

Allosteric
HIV reverse transcriptase
inhibitors

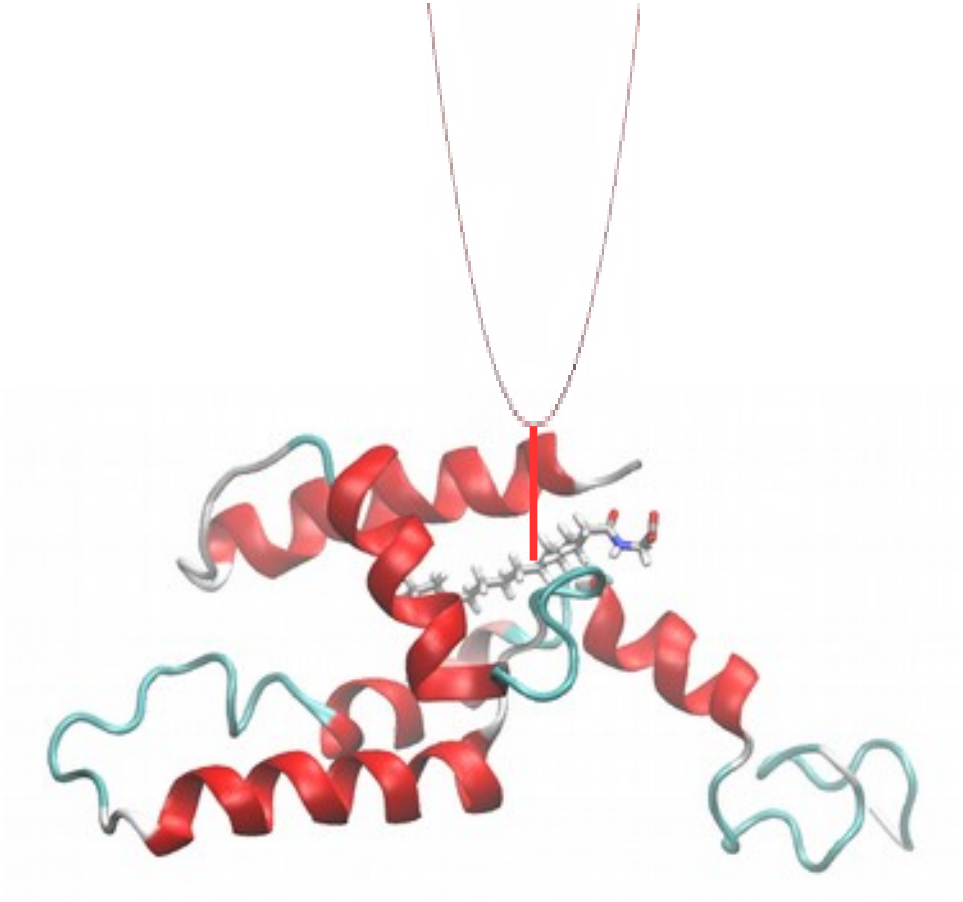




Bollini M, Domaoal RA, Thakur VV, Gallardo-Macias R, Spasov KA, Anderson KA, *et al. J Med Chem* 2011, **54**, 8582-8591.

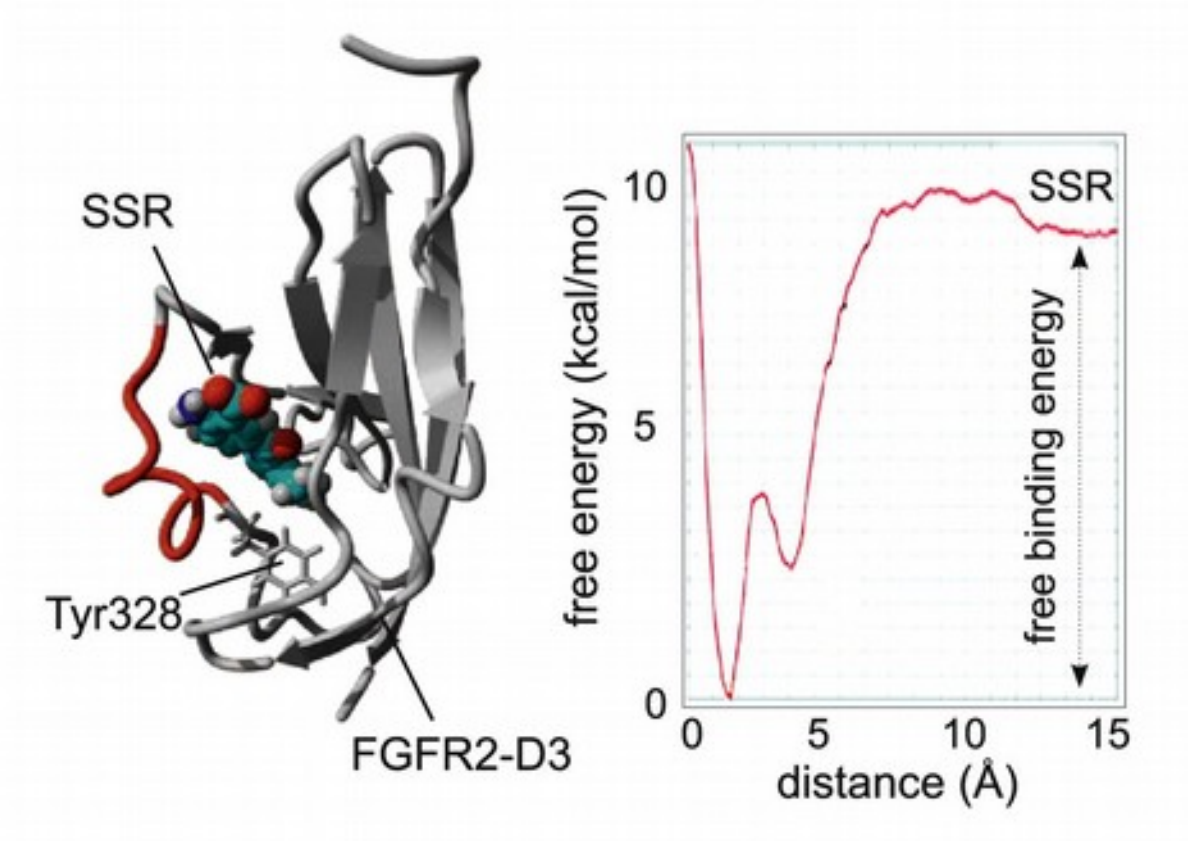
Sampling problem
Umbrella sampling

Sampling problem
Umbrella sampling



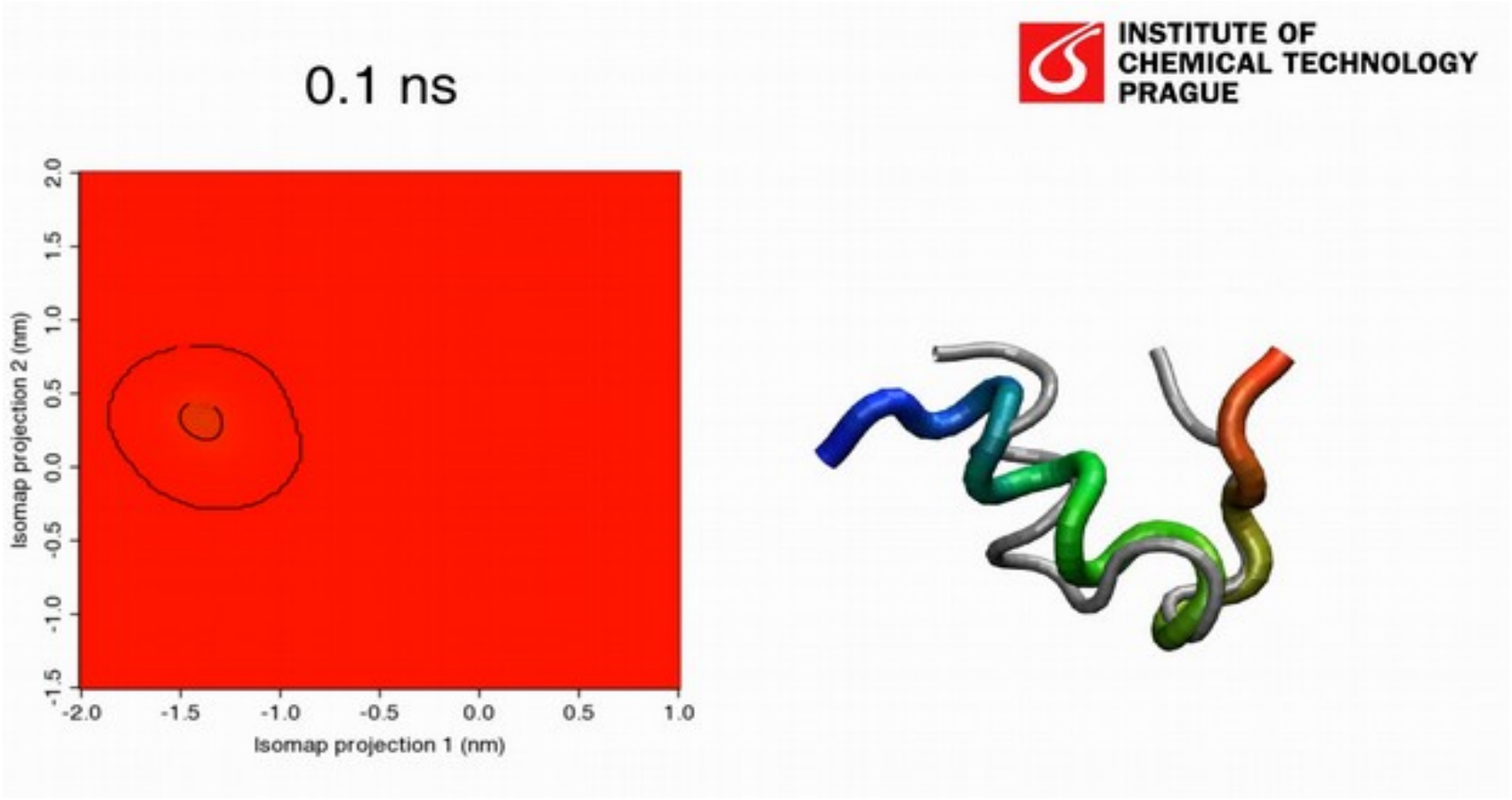
Sampling problem
Metadynamics

Sampling problem
Metadynamics
Allosteric inhibition of fibroblast growth factor by SSR128129E



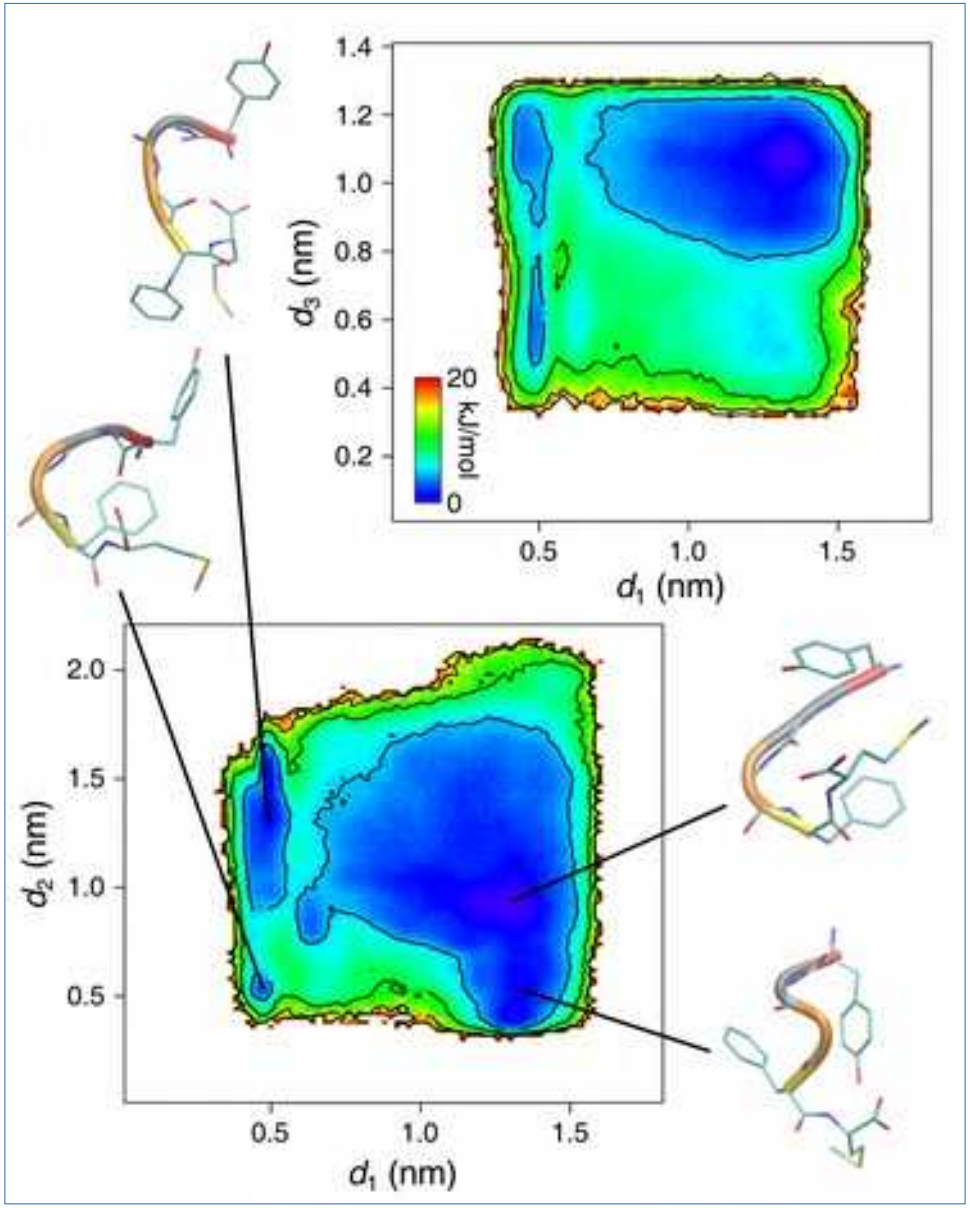
Herbert C *et al. Cancer Cell* 2013, **23**, 489-501.

What we do
Metadynamics with machine learning



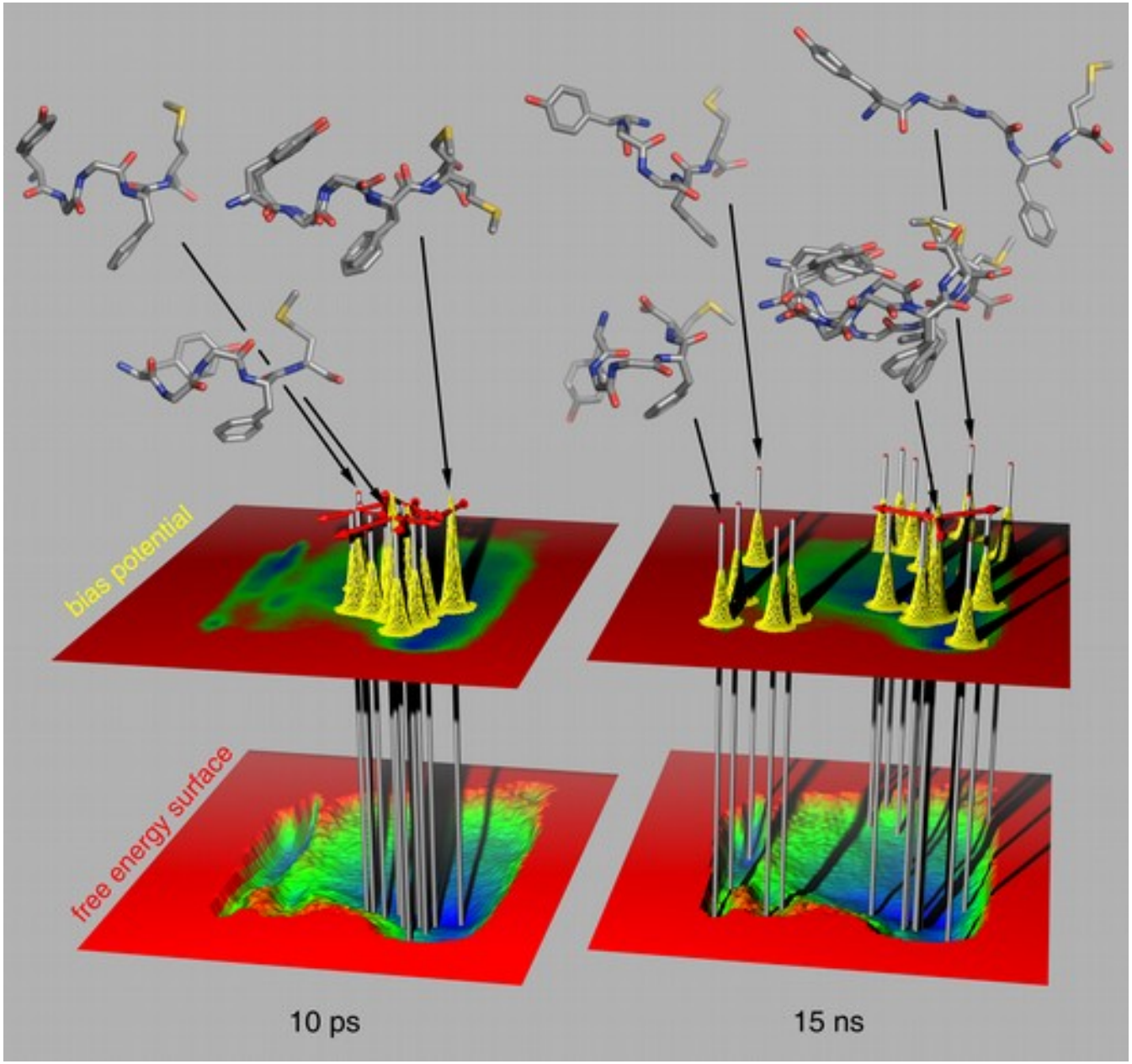
Spiwok V, Oborský P, Pazúriková J, Křenek A, Králová B *J Chem Phys* 2015, **142**, 115101.

What we do
Flying Gaussian method



Šućur Z, Spiwok V *J Chem Theory Comput* 2016, **12**(9) 4644-4650.

What we do
Flying Gaussian method



Šućur Z, Spiwok V *J Chem Theory Comput* 2016, **12**(9) 4644-4650.