

# Biomolekulární Simulace



Historie

Teorie

Problém vzorkování

## Historie:

### 1953: Metropolis Monte Carlo simulace 2D disků

Metropolis, Rosenbluth, Rosenbluth, Teller & Teller *Journal of Chemical Physics* 1953, **21**, 1087-1092.

### 1956: Simulace molekulové dynamiky 2D disků

Alder and Wainwright *Journal of Chemical Physics* 1957, **27**, 1208-1209.

### 1964: Simulace molekulové dynamiky kapalného argonu

Rahman *Physical Reviews* 1964, **136**, A405-A410.

### 1969: Monte Carlo simulace vody

Barker and Watts *Chemical Physics Letters* 1969, **3**, 144-145.

### 1971: Simulace molekulové dynamiky vody

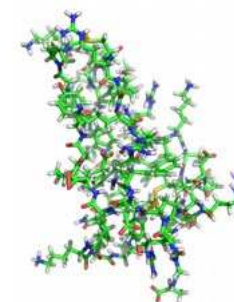
Rahman and Stillinger *Journal of Chemical Physics* 1971, **55**, 3336-3359.

### 1977: Simulace molekulové dynamiky proteinu

McCammon, Gelin and Karplus *Nature* 1977, **267**, 585-590.

Historie:

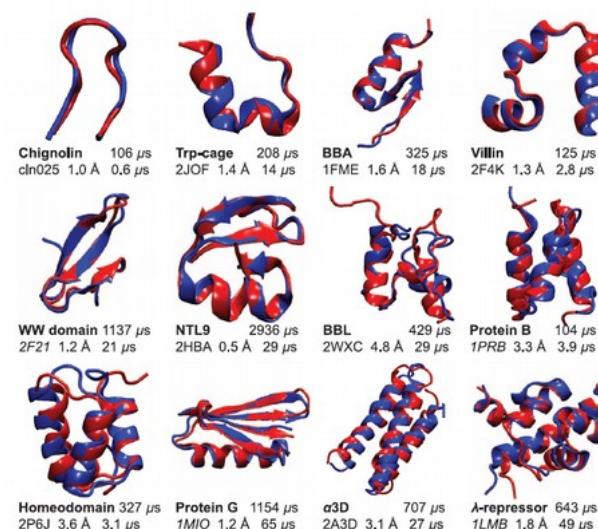
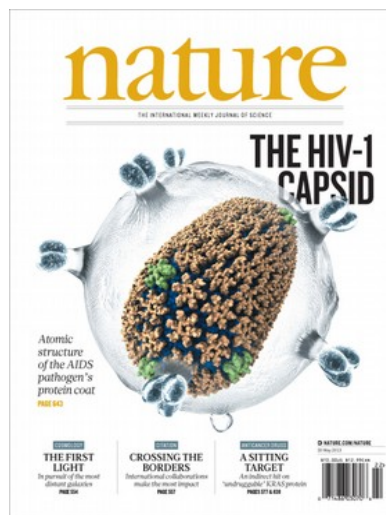
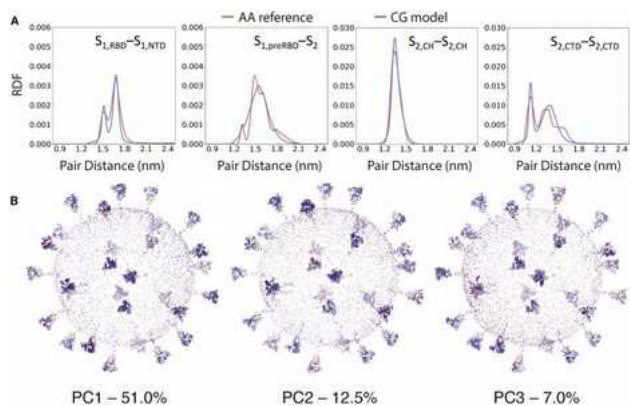
1977: Simulace molekulové dynamiky proteinu  
 McCammon, Gelin and Karplus *Nature* 1977, **267**, 585-590.  
**3.2 ps, < 1,000 atoms**



Lindorff-Larsen, Piana, Dror, Shaw *Science* 2011, **334**, 517-20.  
**108-2,936 μs, solvované miniproteiny**

Zhao *et al. Nature* 2013, **497**, 643-6.  
**100 ns, ~64,000,000 atomů**

Yu *et al. Biophys. J.* 2021, **120**, 1097-104.  
**zhrubený přístup**



## 2013 Nobelova cena za chemii:



The Nobel Prize in Chemistry 2013

Martin Karplus, Michael Levitt, Arieh Warshel

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# 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"*.

Photos: Copyright © The Nobel Foundation

Teorie:

## Co potřebujeme?

Počítač

Software

Instrukce pro software – délka simulace, teplota, tlak atd.

Topologie – definice kovalentní struktury systému a vlastností atomů

Počáteční 3D struktura (i s rychlostmi, pokud jsou k dispozici)

Teorie:

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

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

$$V = \sum_{\text{bonds}} \frac{k_b}{2} (r - r_0)^2 + \sum_{\text{angles}} \frac{k_a}{2} (\theta - \theta_0)^2$$
$$+ \sum_{\text{torsions}} k_t (1 + \cos(n\phi - \phi_s)) + \sum_{\text{pairs}} \left[ \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{r_{ij}} + \frac{C_{12}}{r_{ij}^{12}} - \frac{C_6}{r_{ij}^6} \right]$$

Programy:

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/>



Silová pole (force fields):

**Proteiny, nukleové kyseliny, lipidy:**

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

**Obecné molekuly:**

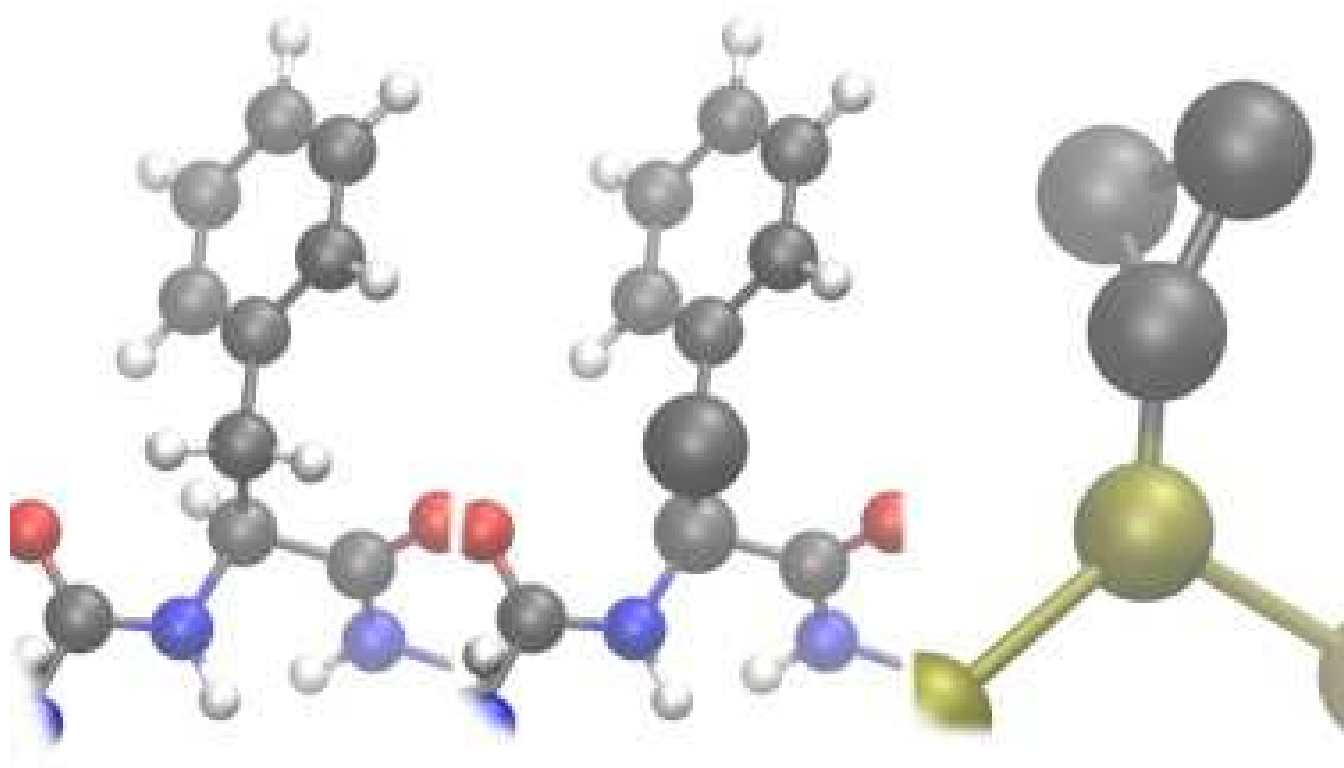
GAFF, OPLS, CHARMM, MM2, MM3, MMFF

**Speciální:**

Glycam (sacharidy) <http://glycam.org>  
Martini (zhrubené) <http://md.chem.rug.nl>

$$V = \sum_{bonds} \frac{k_b}{2} (r - r_0)^2 + \sum_{angles} \frac{k_a}{2} (\theta - \theta_0)^2$$
$$+ \sum_{torsions} k_t (1 + \cos(n\phi - \phi_s)) + \sum_{pairs} \left[ \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{r_{ij}} + \frac{C_{12}}{r_{ij}^{12}} - \frac{C_6}{r_{ij}^6} \right]$$

Silová pole (force fields):

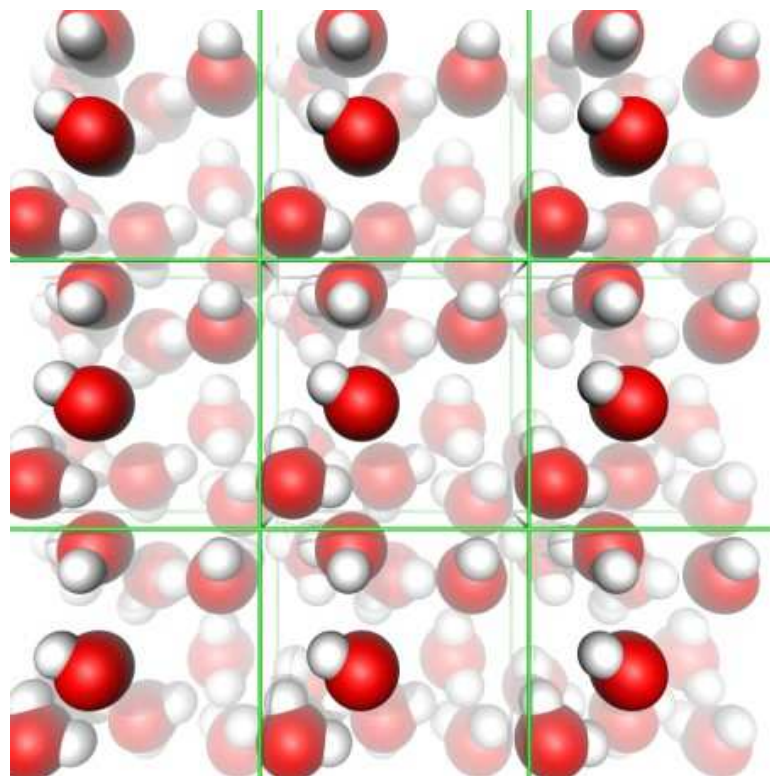


All atom

United atom

Coarse grained

Periodická okrajová podmínka (periodic boundary condition)



Co můžeme ovlivnit?

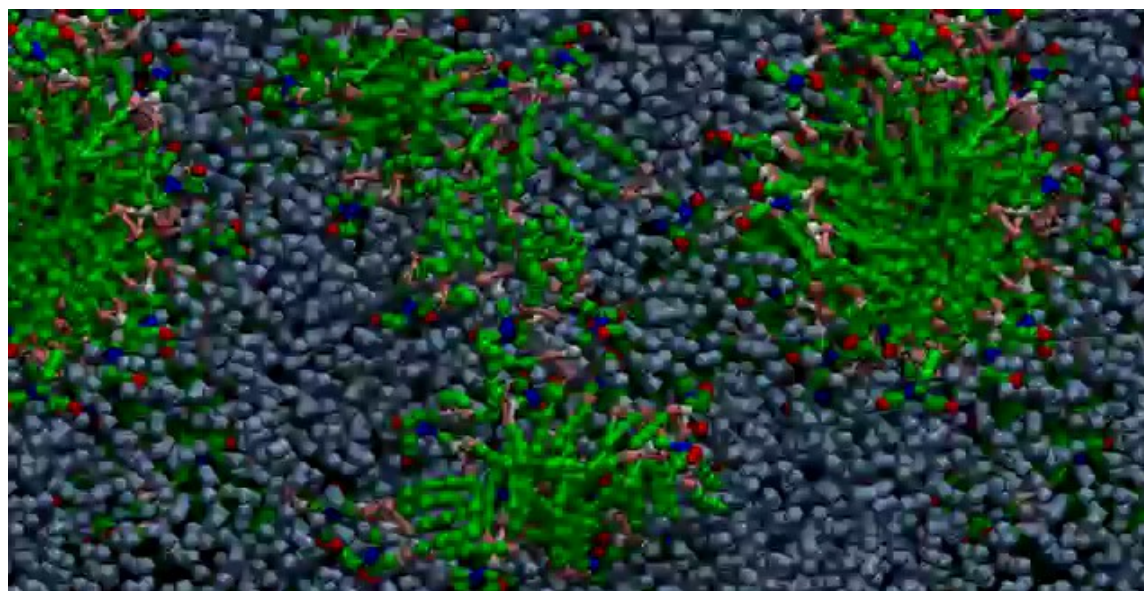
Délku simulace = počet kroků x velikost kroku (1-2 fs)

Teplotu

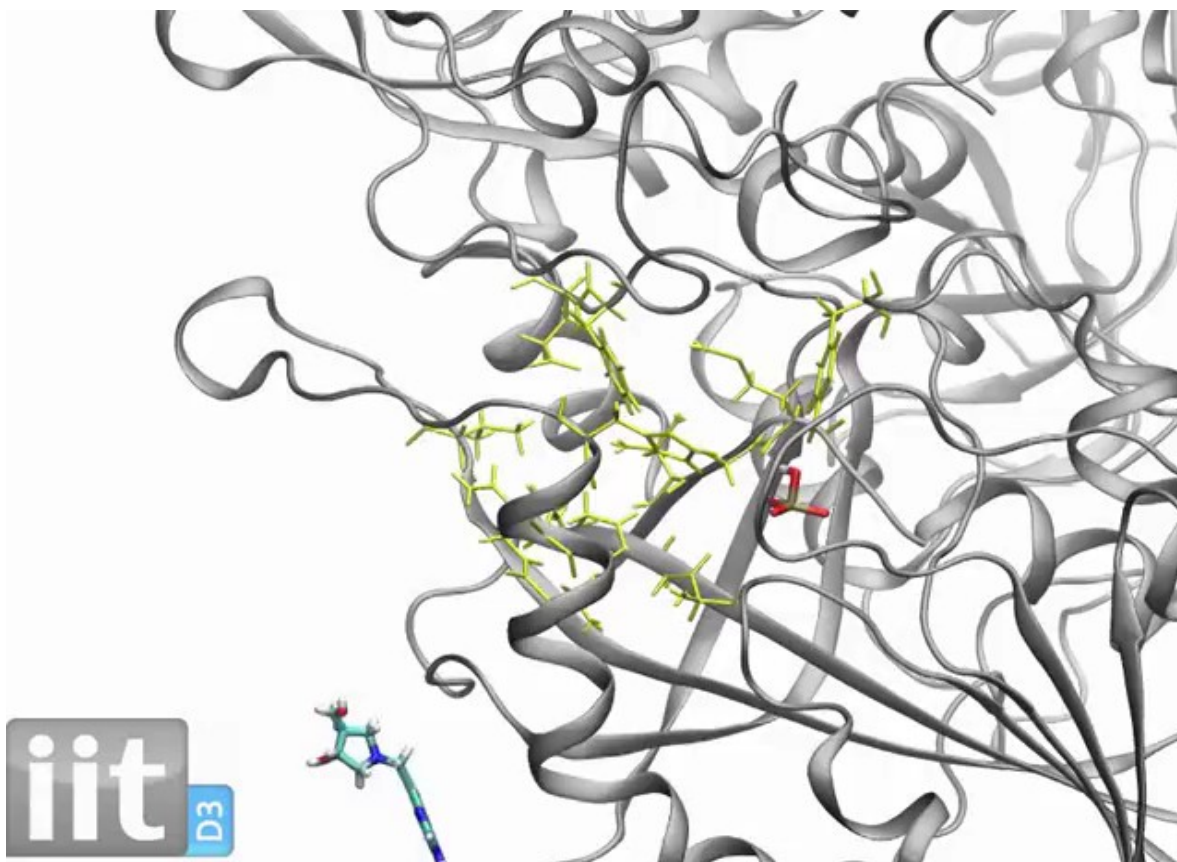
Tlak, povrchové napětí

Další (electrické pole, externí síly, konstantní pH atd.)

## Tvorba membrány



# Vazba 4'-deaza-1'-aza-2'-deoxy-1'-(9-methylene)-immucillin-H Na fosforylasu purinových nukleosidů



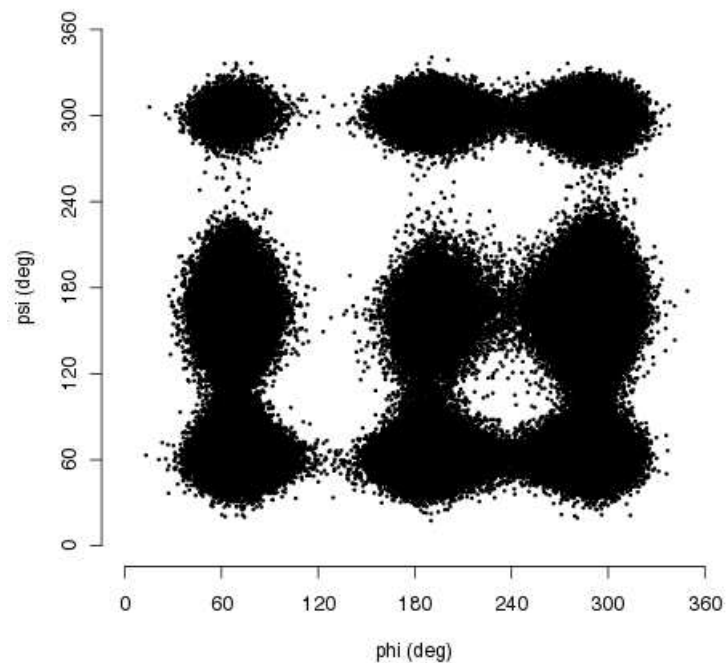
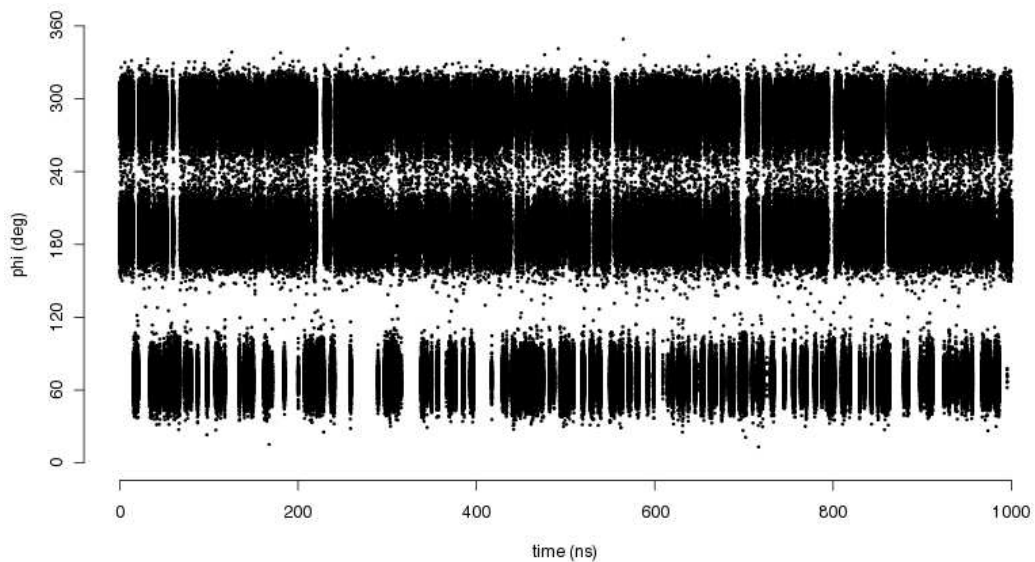
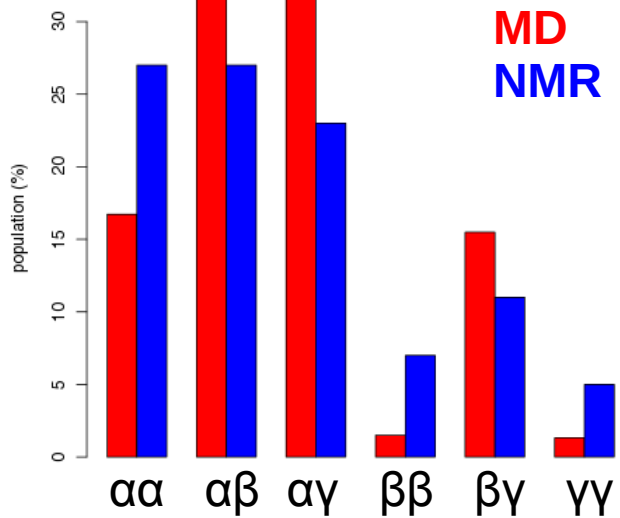
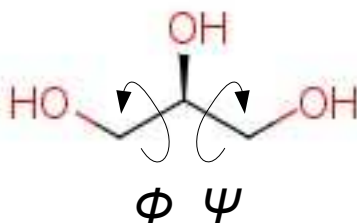
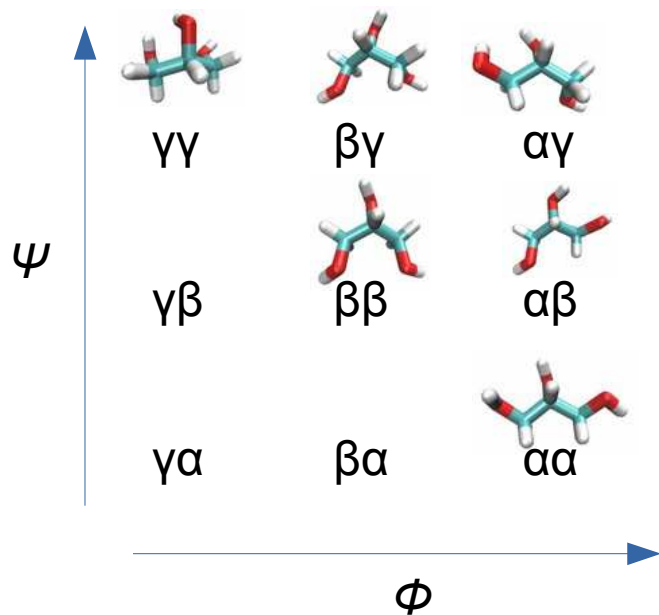
Decherchi S, Berteotti A, Bottegoni A, Rocchia W, Cavalli A *Nature Commun* 2015, **6**, 6155.

## Vazba Tamiflu na chřipkovou neuraminidasu

This movie, derived from molecular dynamics simulations, depicts the antiviral drug Tamiflu (shown in the center of the screen in blue, white, and pink) traveling along a binding pathway on neuraminidase (larger red, white, and blue mass), a protein responsible for replication of the flu virus. Tamiflu must avoid mutations along the pathway, or find a new binding pathway, on the protein to be effective. Understanding how mutations block drug paths can potentially lead to better drugs for influenza, avian, and swine flus.

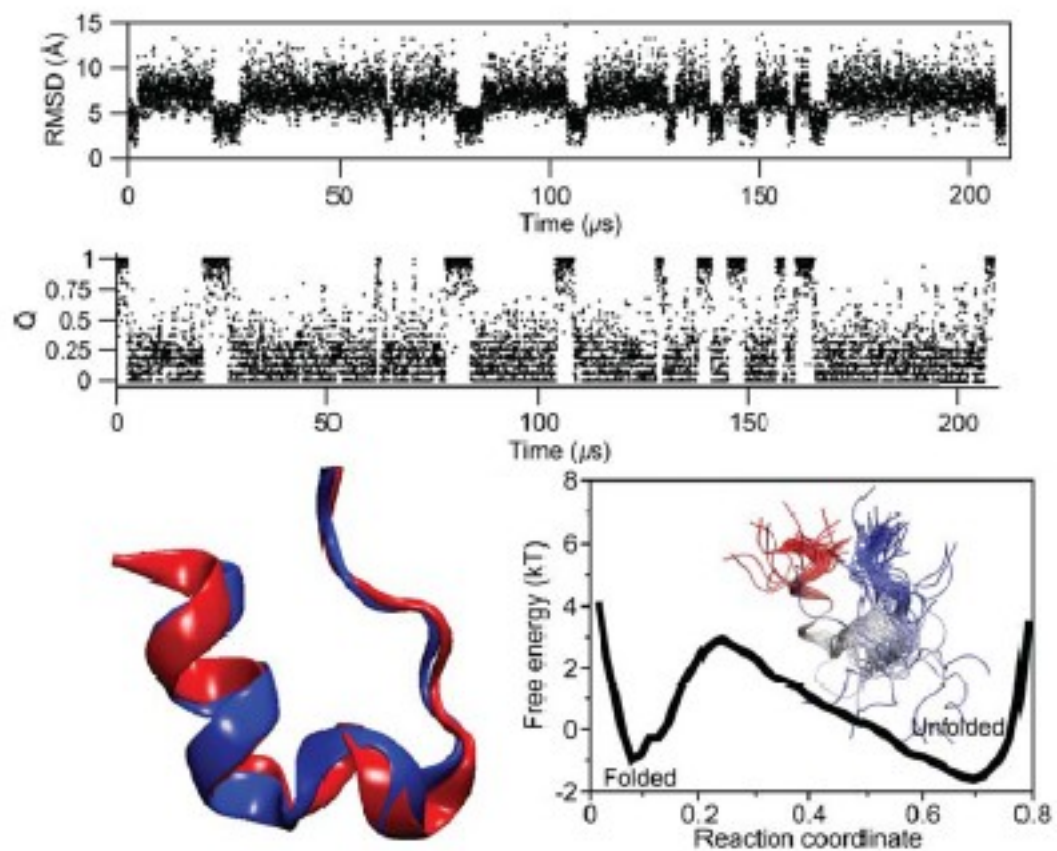
By Klaus Schulten lab

# Glycerol ve vodě



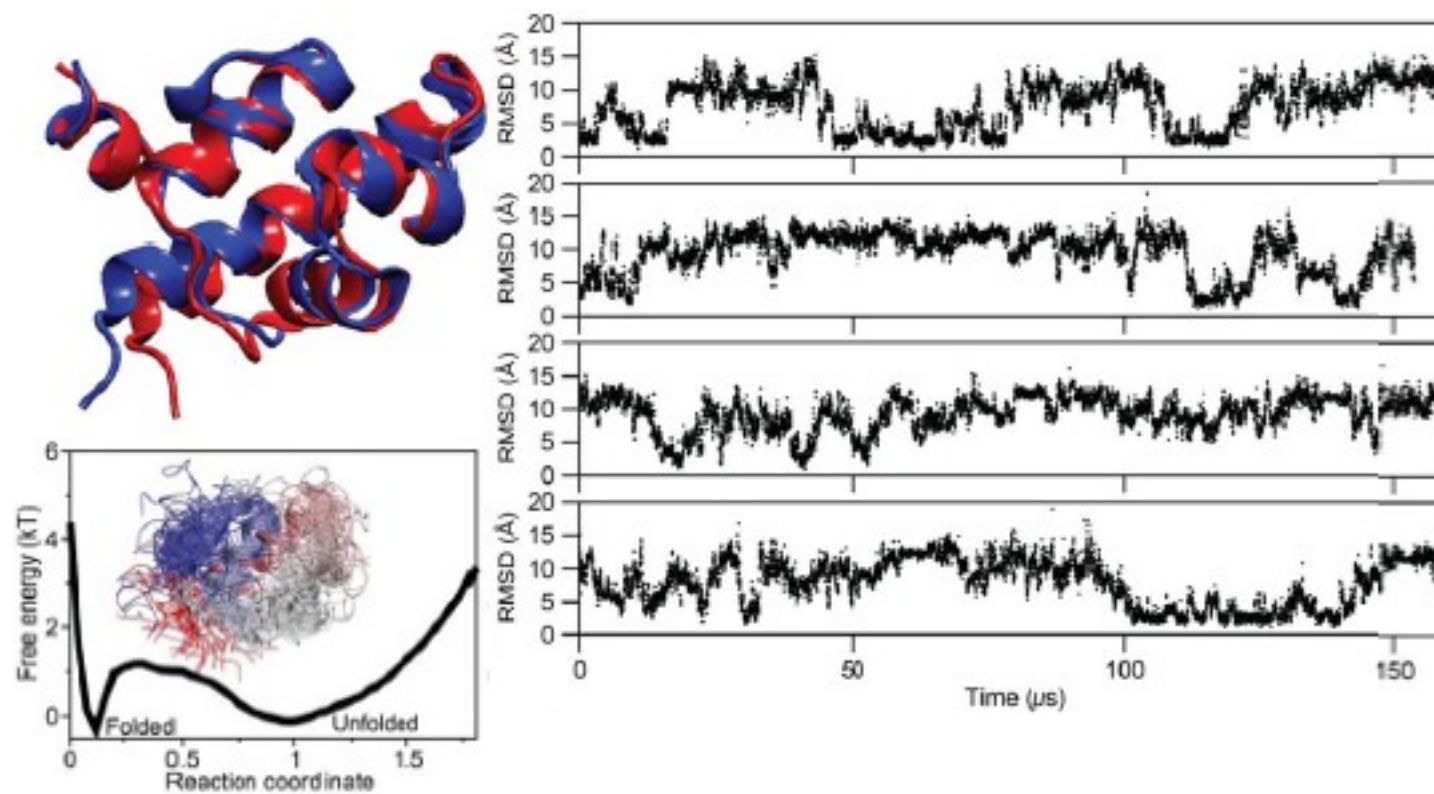


## Trp-cage folding



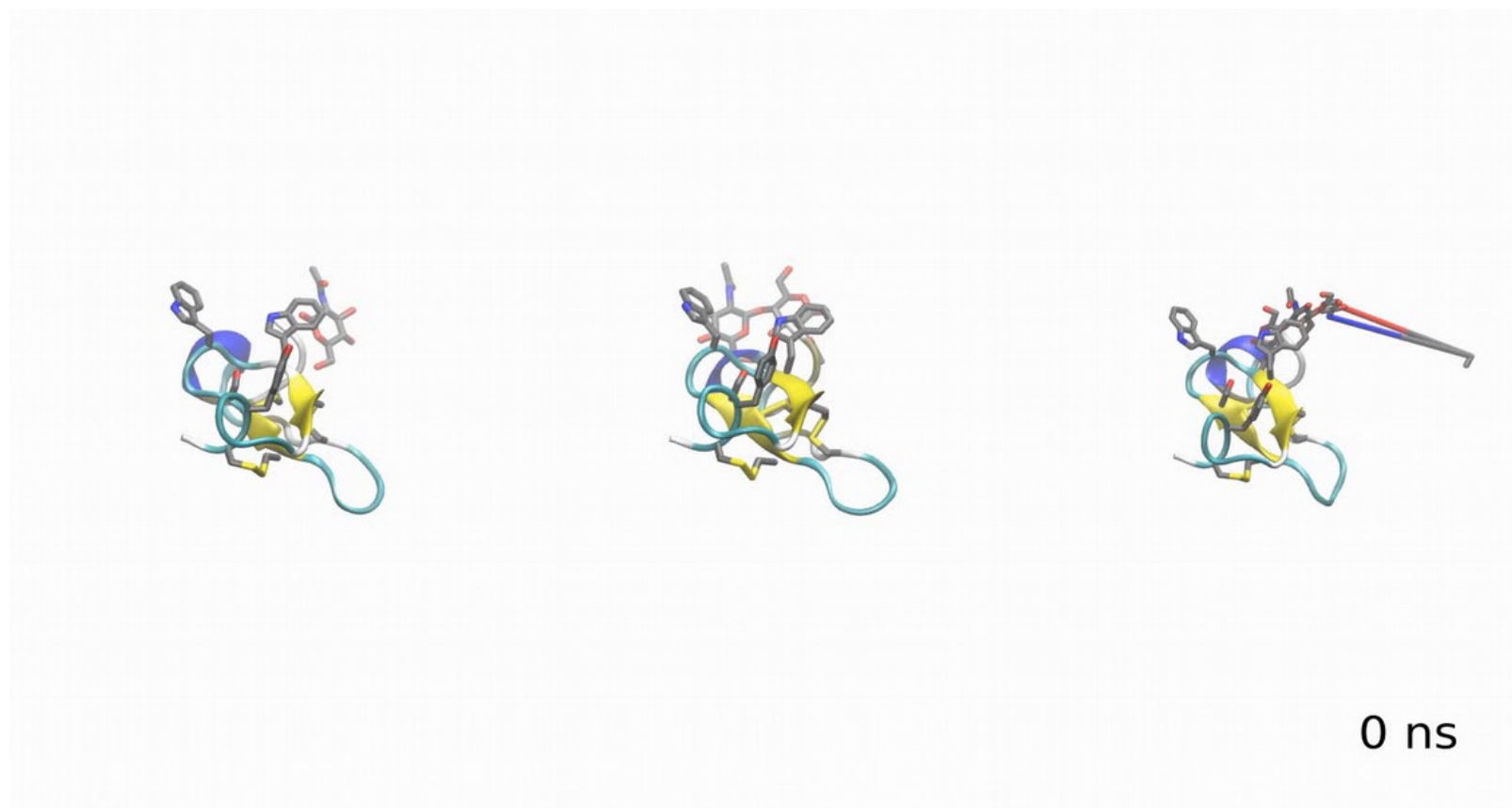
Lindorff-Larsen K, Piana S, Dror RO, Shaw DE *Science* 2011, **334**, 517-520.

## $\lambda$ -repressor folding



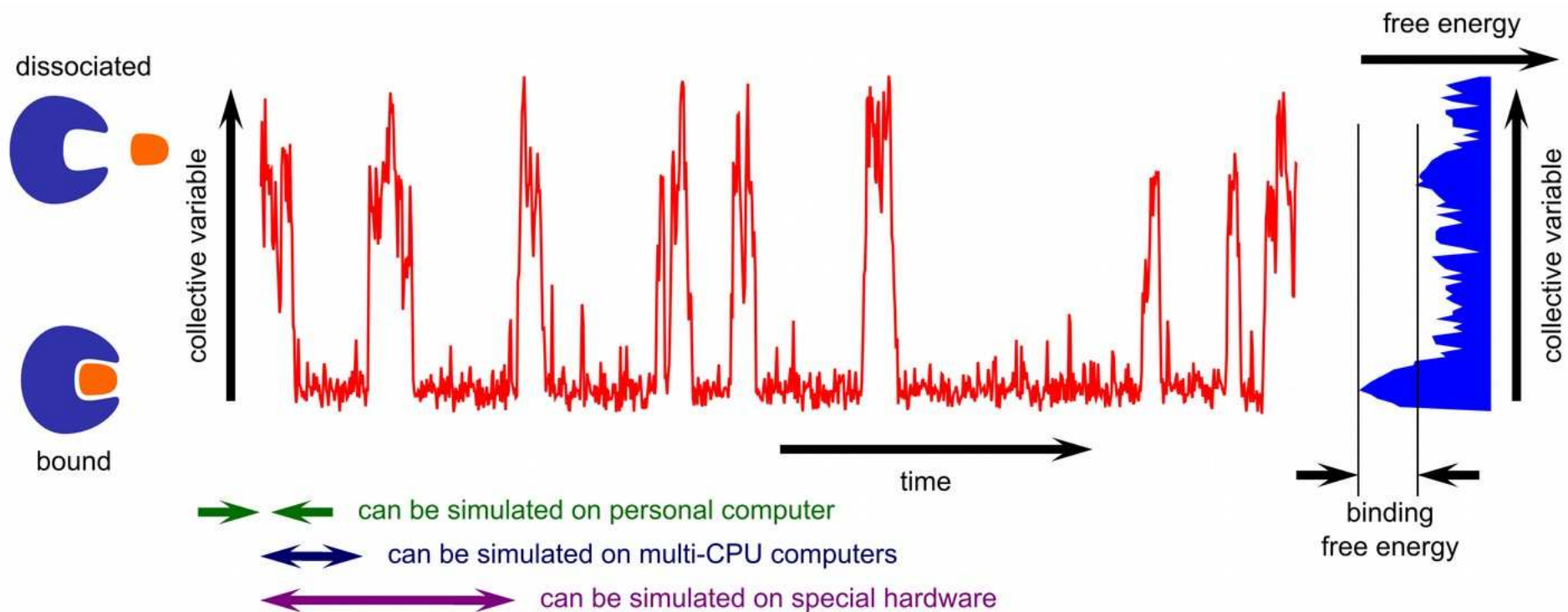
Lindorff-Larsen K, Piana S, Dror RO, Shaw DE *Science* 2011, **334**, 517-520.

## Hevein domain HEV32



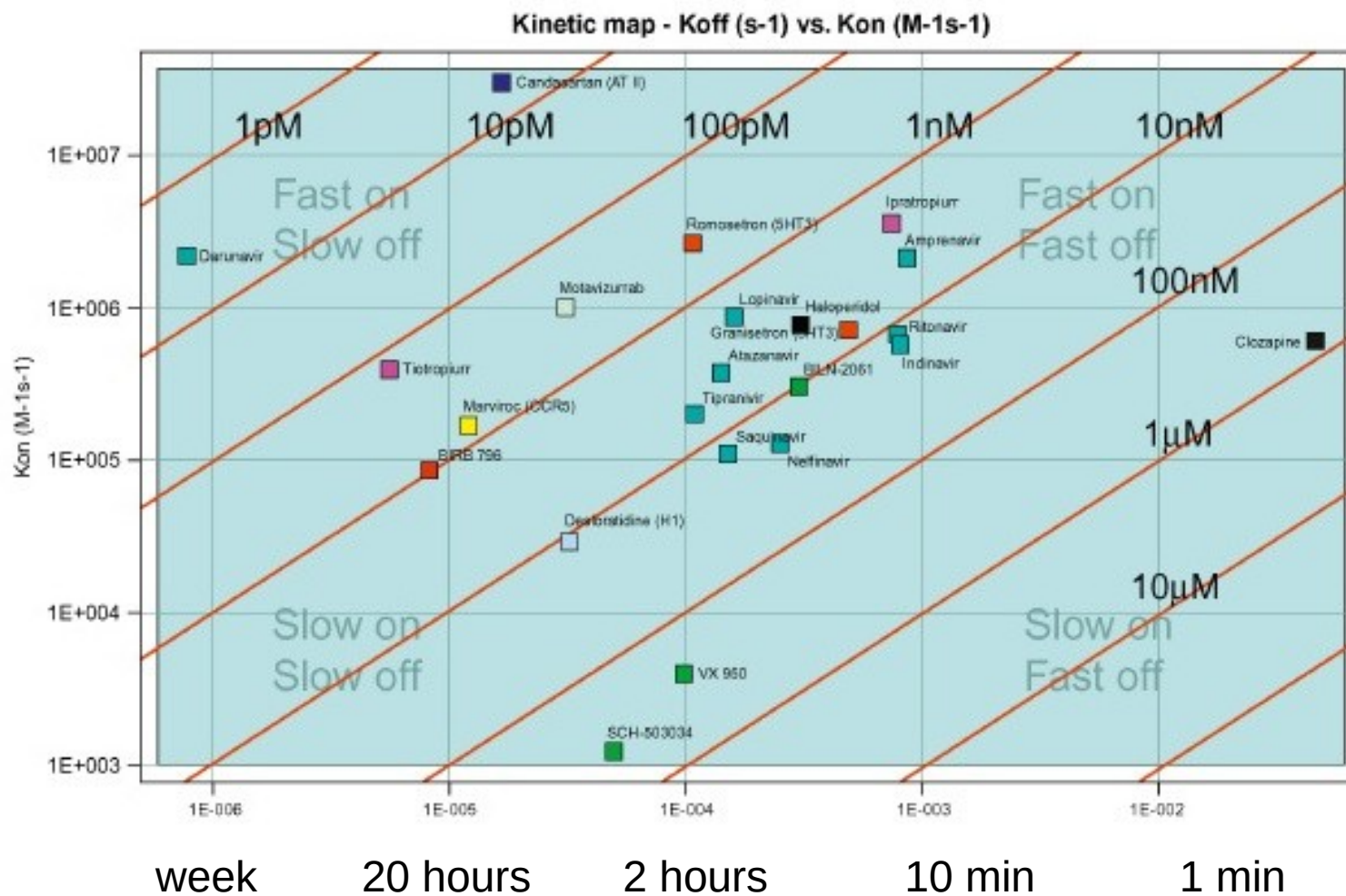
C.O. Solanke *et al.* *Sci. Rep.* 2019, **9**, 18918.

# Vzorkování



# Vzorkování

$$k_{on} - k_{off}$$



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

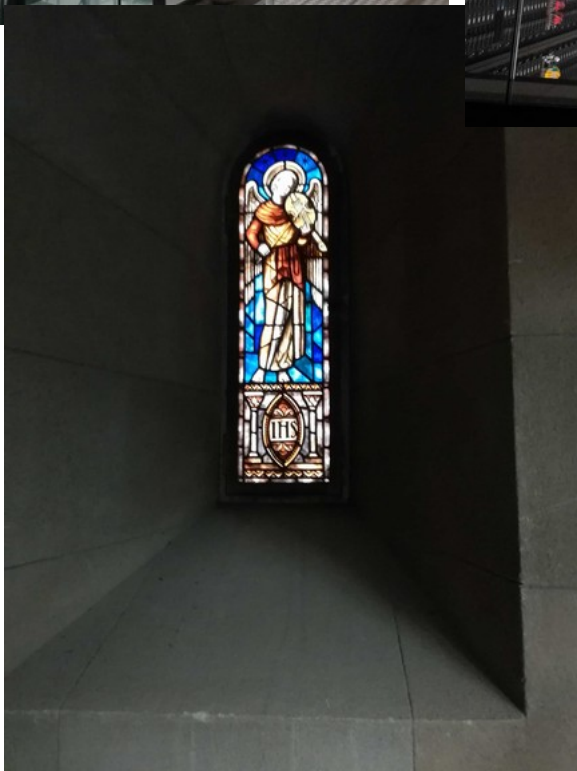
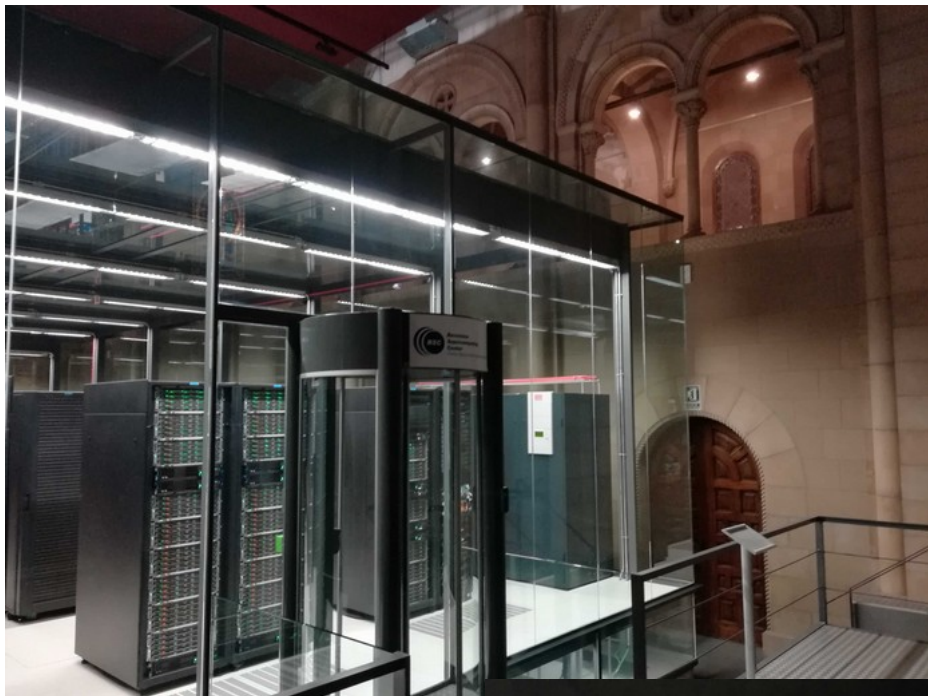
## Vzorkování

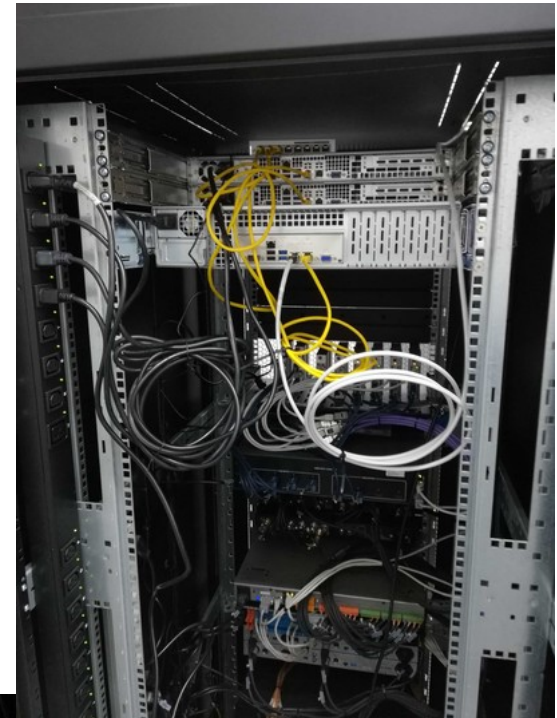
### Silové řešení

|      |   |         |                 |
|------|---|---------|-----------------|
| 1.   | Frontier - DOE/SC/Oak Ridge National Laboratory | USA     | 8 730 112 jader |
| 2.   | Supercomputer Fugaku                            | Japan   | 7 630 848 jader |
| 3.   | LUMI – EuroHPC/CSC                              | Finland | 2 220 288 jader |
| 4.   | Leonardo - EuroHPC/CINECA                       | Italy   | 1 463 616 jader |
| 5.   | Summit - DOE/SC/Oak Ridge National Laboratory   | USA     | 2 414 592 jader |
| ..   |   |         |                 |
| 85.  | Karolina, GPU IT4I                              | Czechia | 71 424 jader    |
| 226. | Karolina, CPU IT4I                              | Czechia | 92 160 jader    |

<http://www.top500.org>









## Speciální hardware

### #200 David Shaw

Founder, D. E. Shaw & Co., L.P.

f

t

in



PHOTO BY COURTESY OF DAVID SHAW

#### REAL TIME NET WORTH

as of 9/23/20

**\$6.5B**

#### 2020 BILLIONAIRES NET WORTH

as of 4/7/20

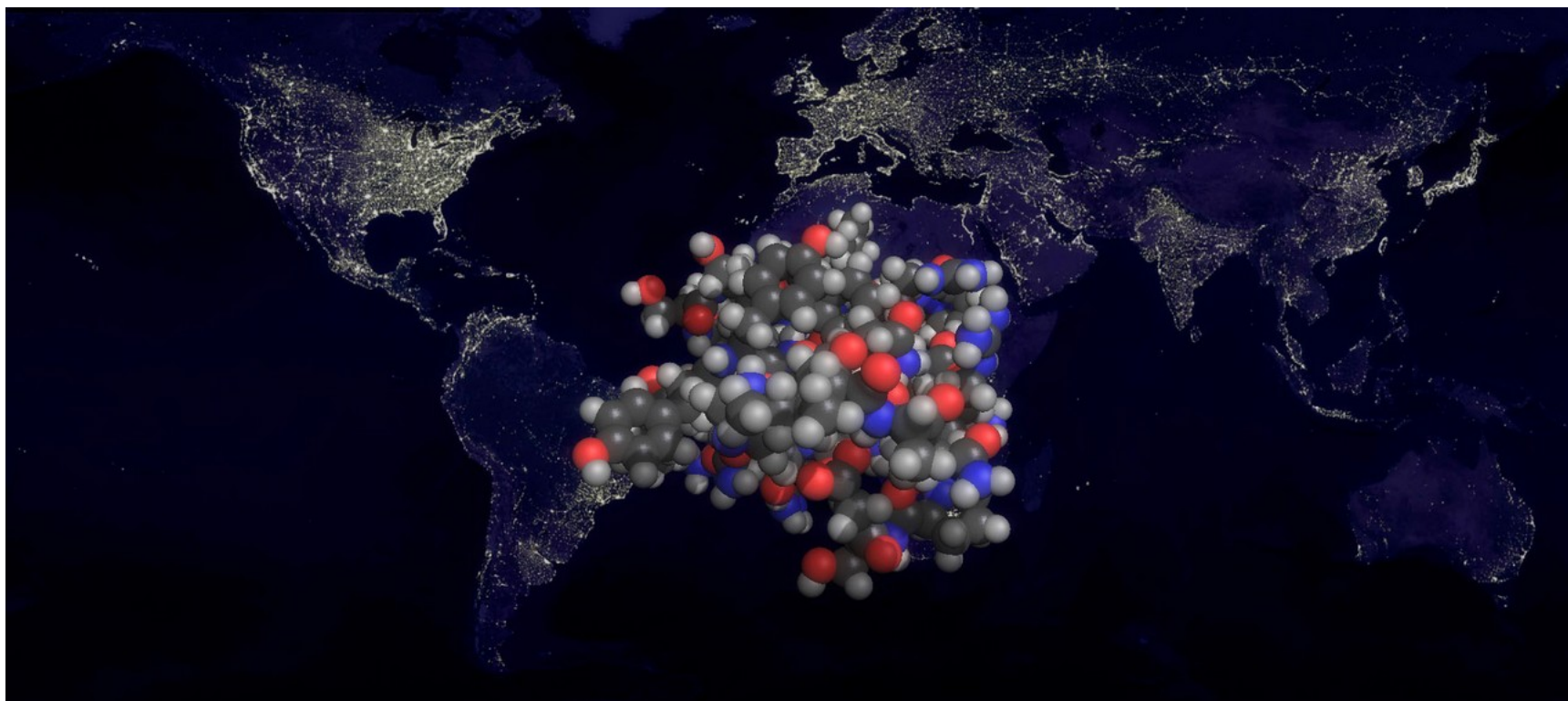
**\$7.3B**



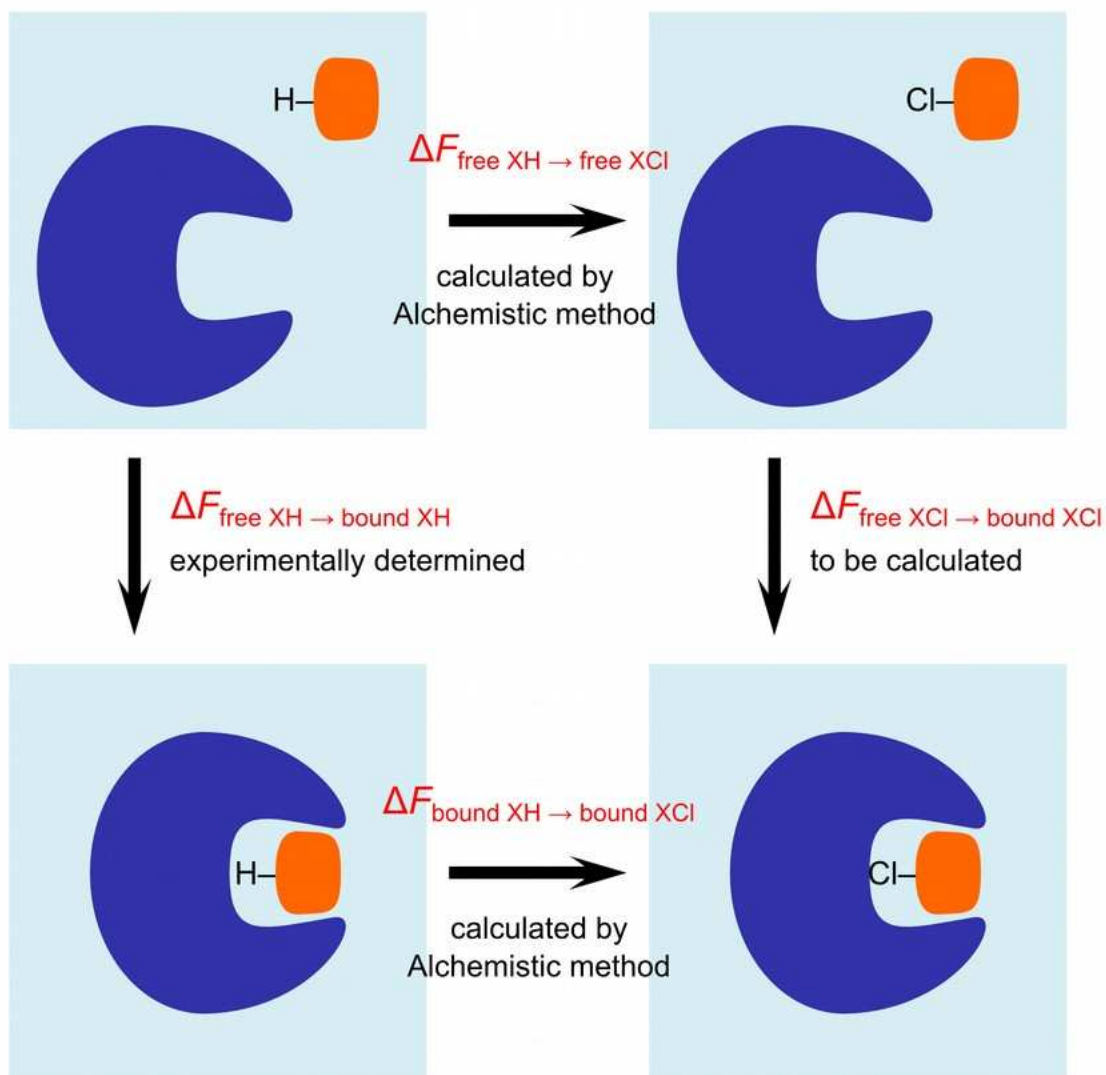
GPU



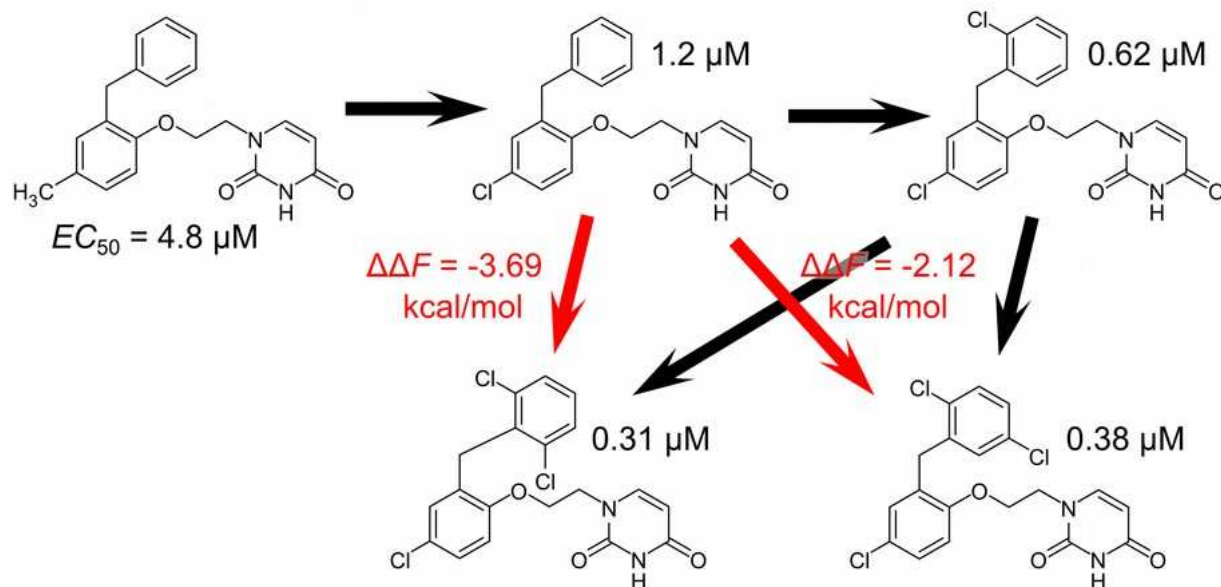
Distributed computing  
<http://folding.stanford.edu>



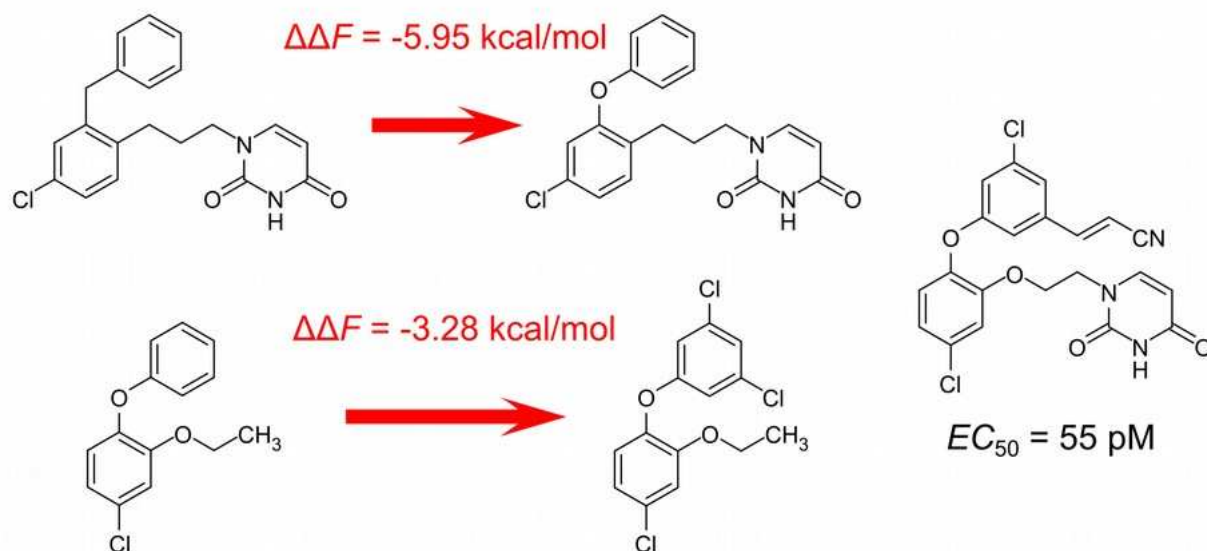
# Alchimistické simulace



## Alchimistické simulace

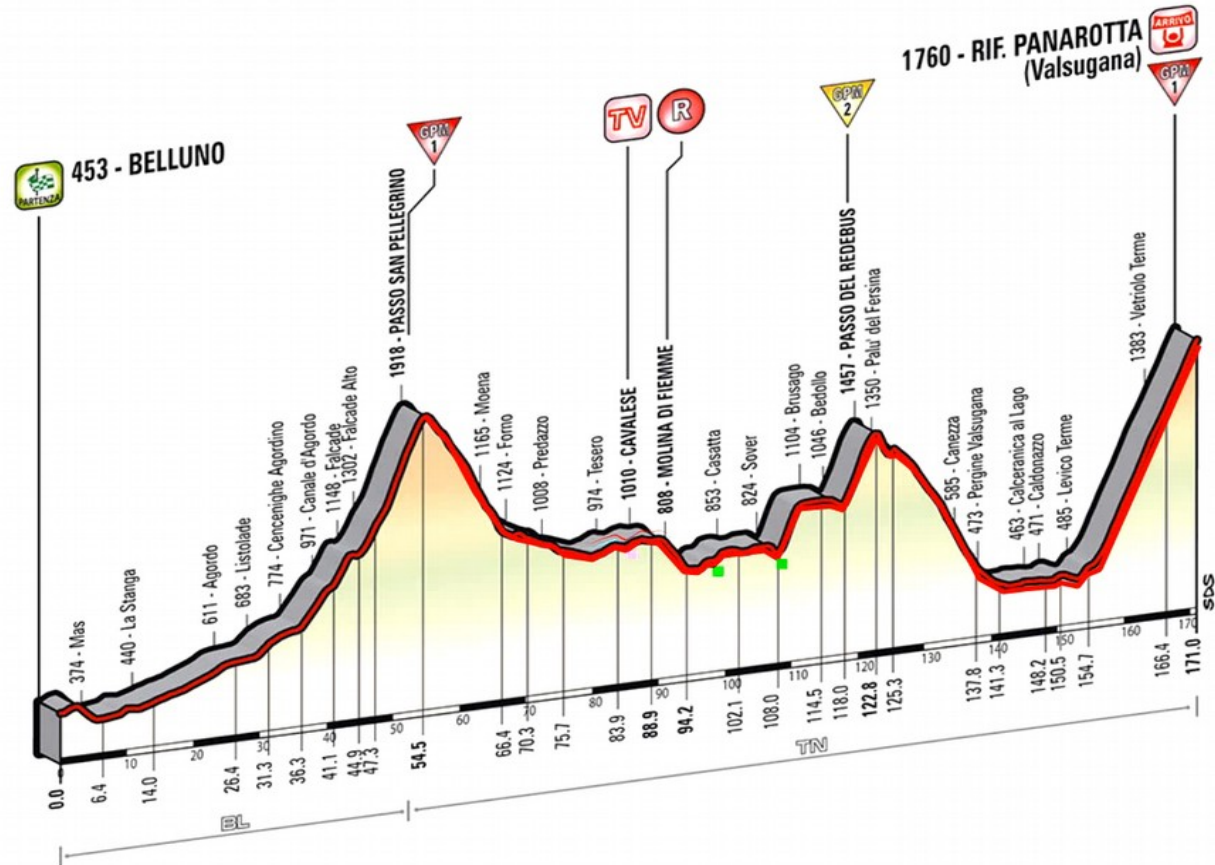


## Allosterické inhibitory HIV reversní transkriptasy



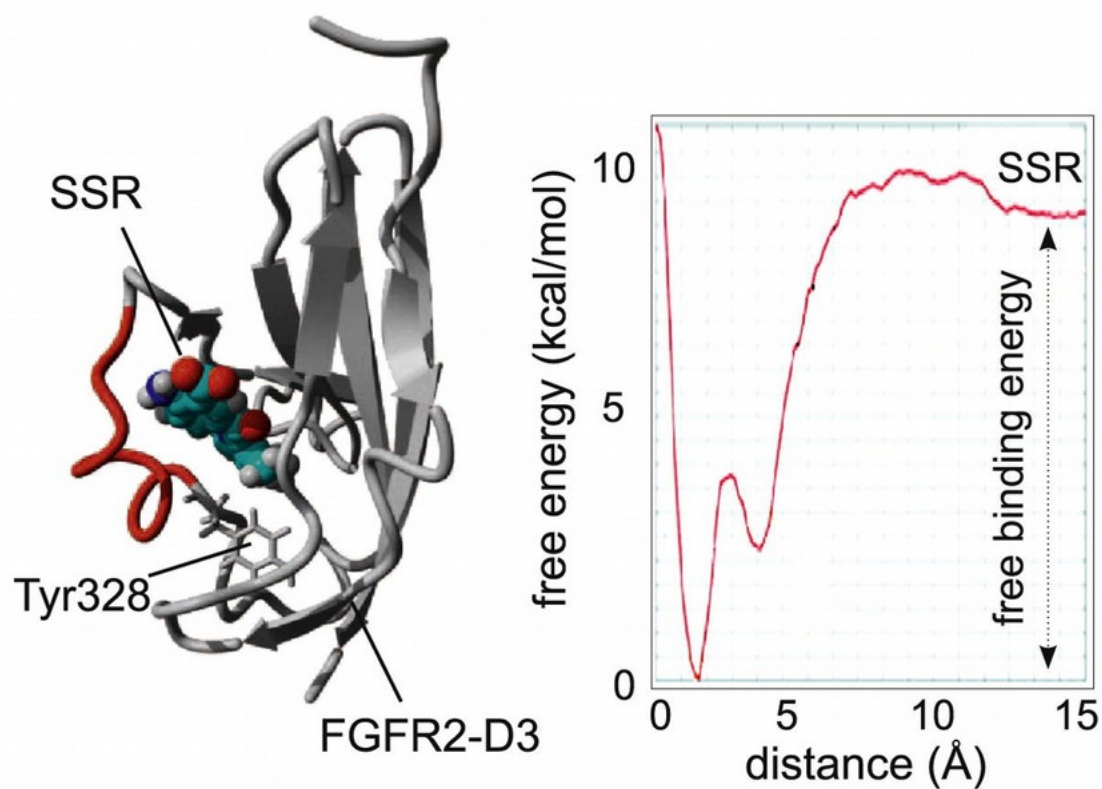
Bollini M, Domaal RA, Thakur VV, Gallardo-Macias R, Spasov KA, Anderson KA, *et al.* *J Med Chem* 2011, **54**, 8582-8591.

# Metodynamika



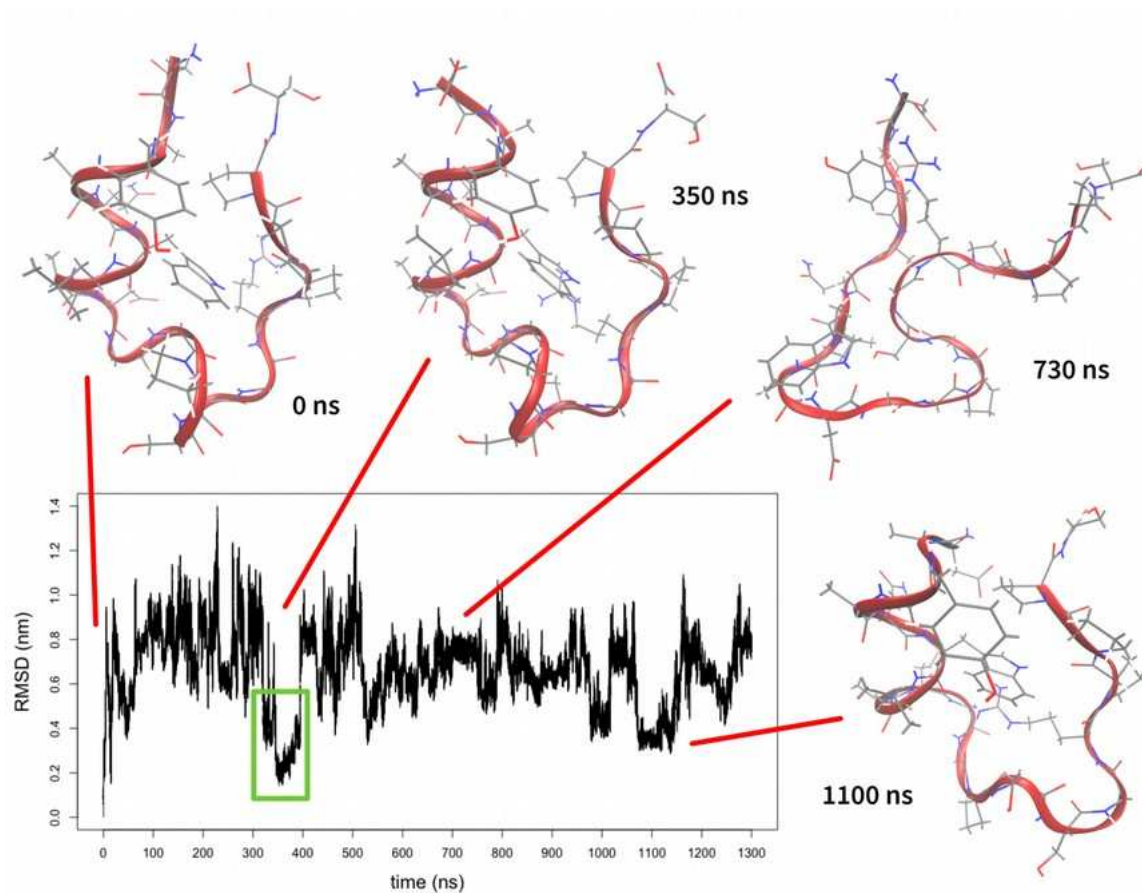
## Metadynamika

### Allosteric inhibition of fibroblast growth factor by SSR128129E



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

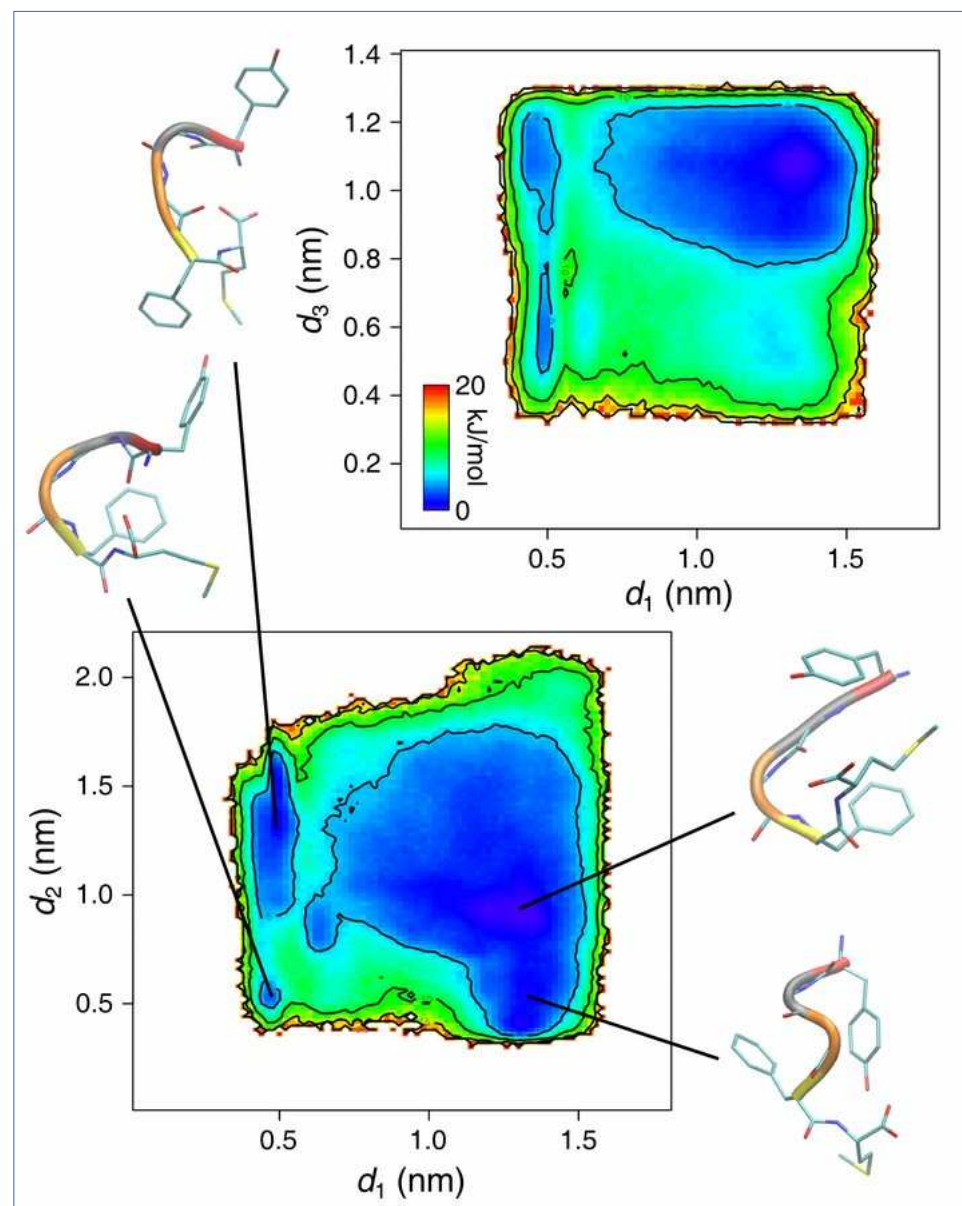
# Metadynamika Sbalování miniproteinů Trp-cage



Helena Hradiská – diplomová práce 2023

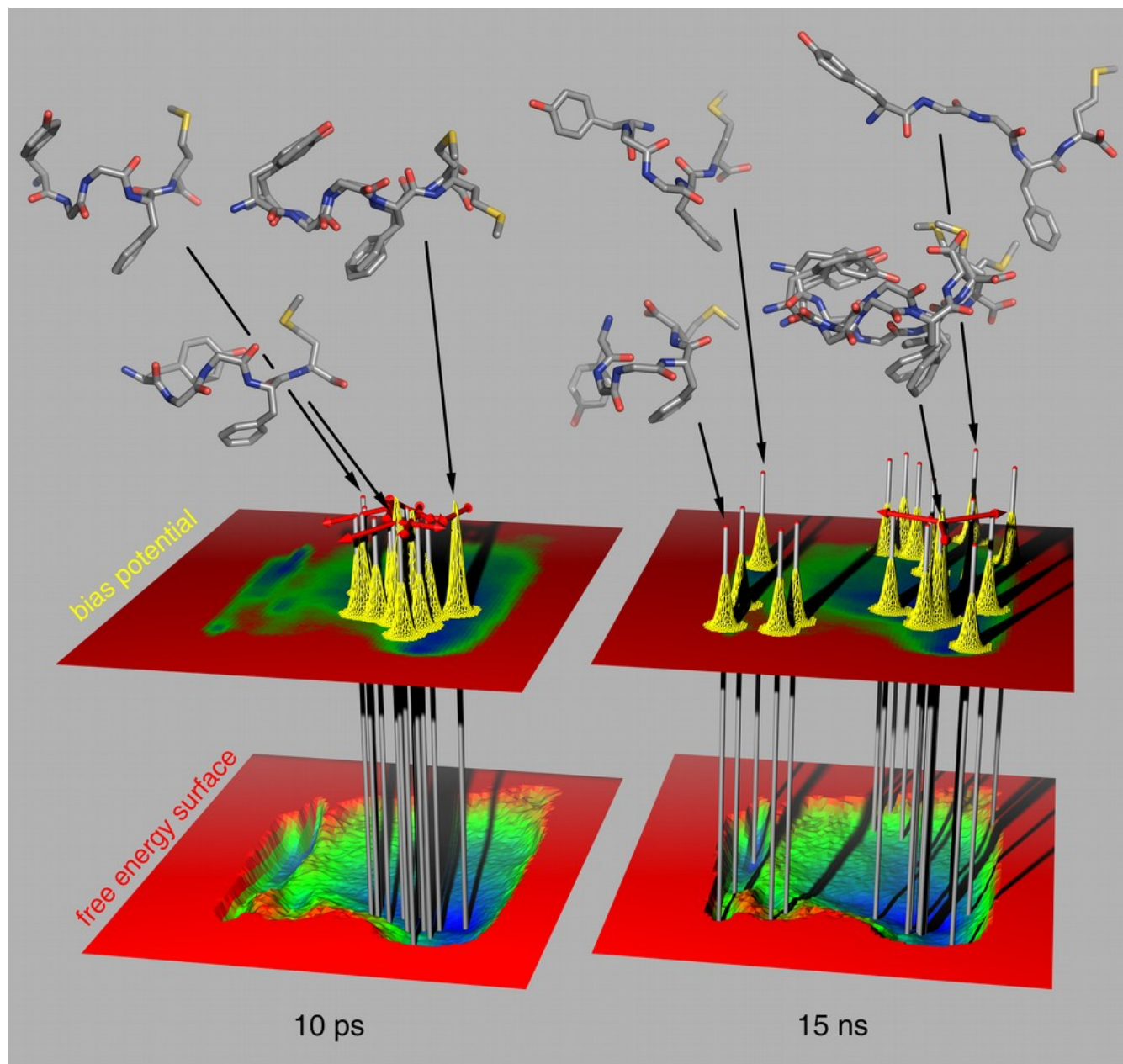


# Metoda létajících Gaussiánů



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

# Metoda létajících Gaussiánů



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