NEW QM/MM IMPLEMENTATION OF THE MOPAC2012 IN THE GROMACS

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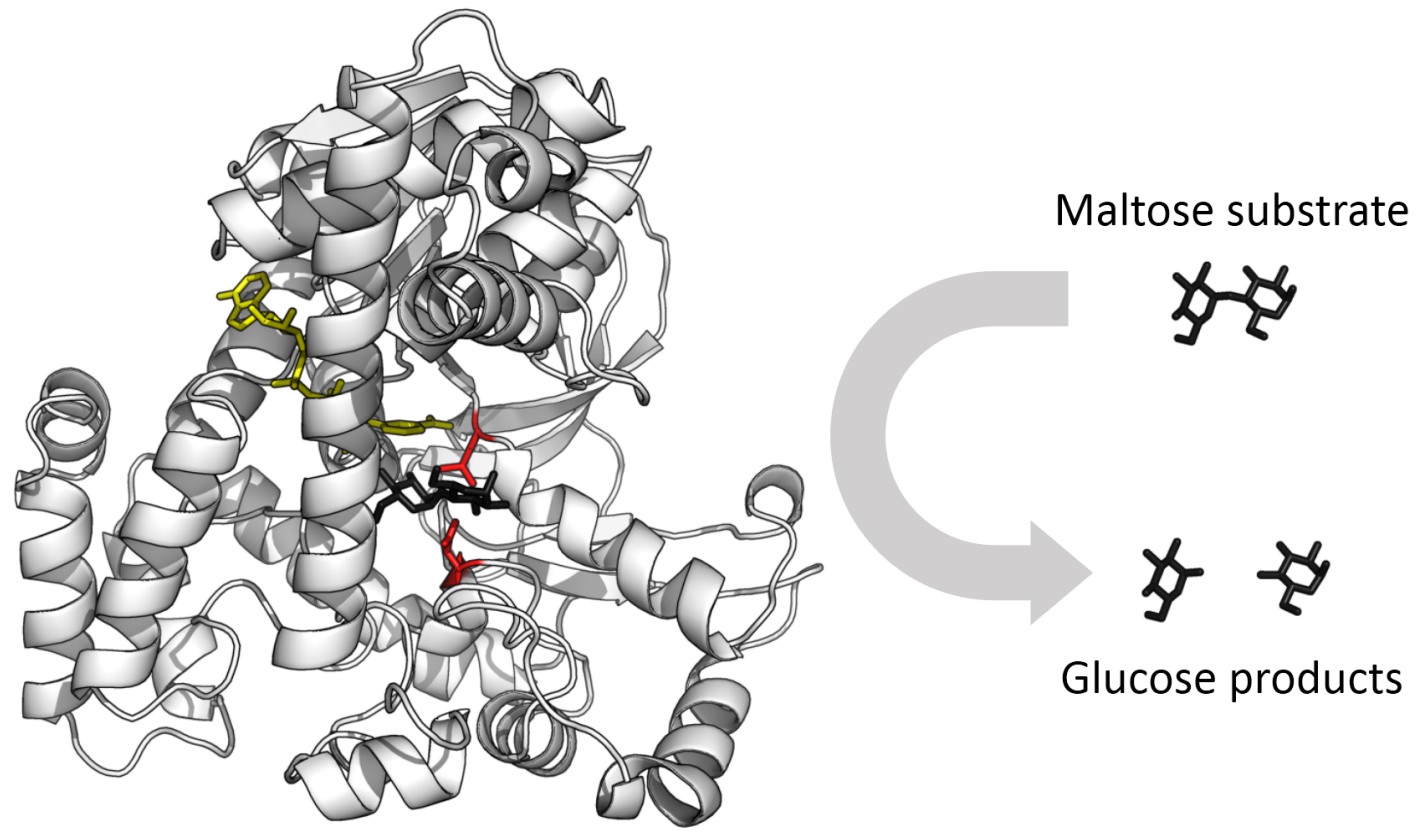
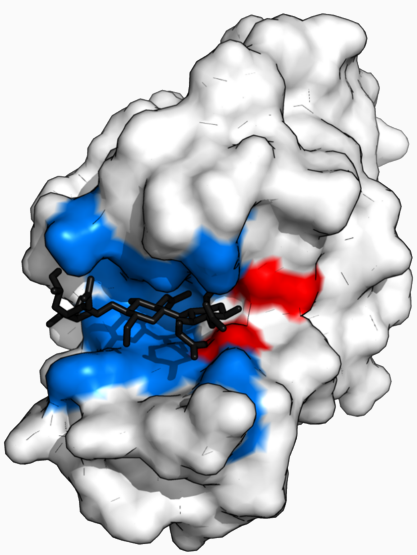
МГУ, Москва

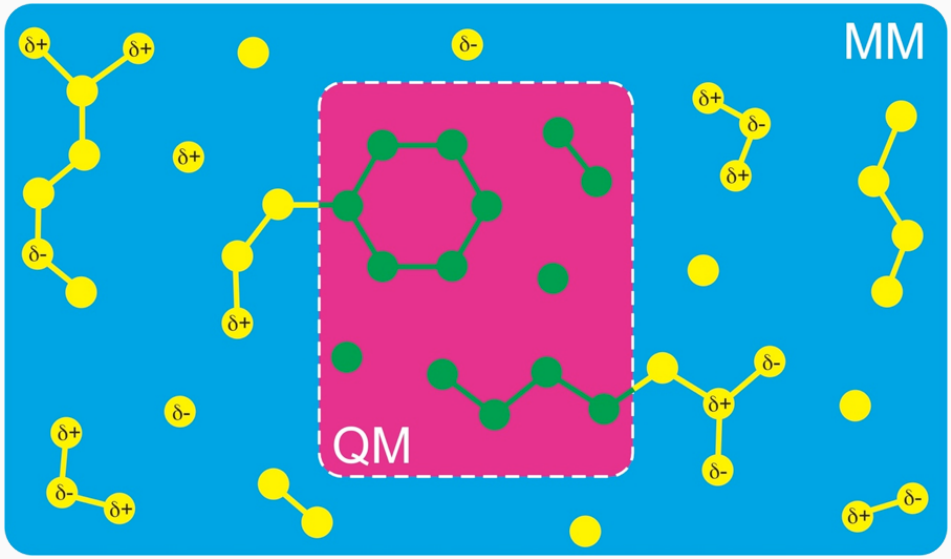
ENZYMES IS LIFE'S KEY MOLECULE



https://en.wikipedia.org

SIMULATION OF ENZYMES

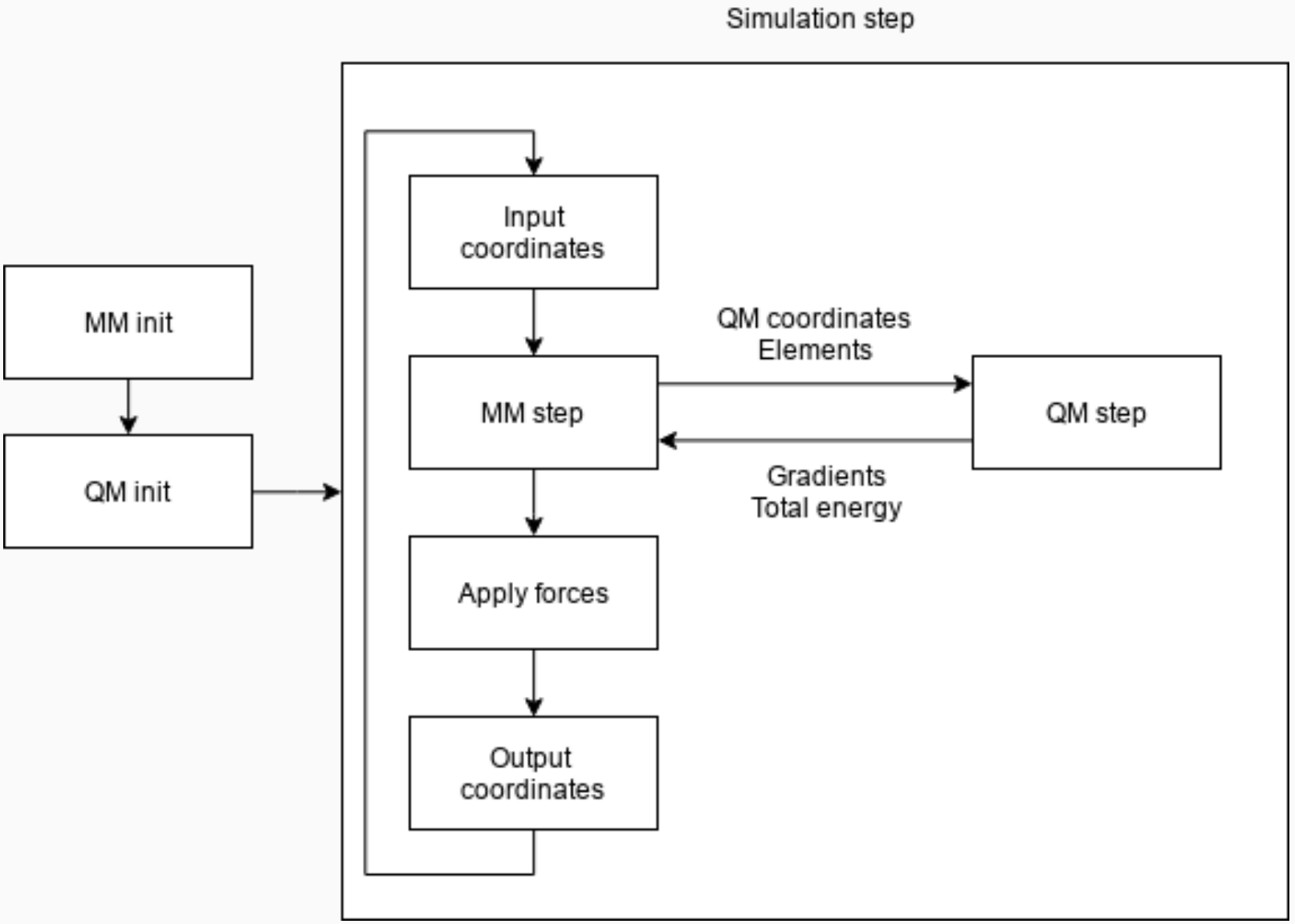




$$E = \frac{k}{2}(b_0 - b)^2 \qquad H\Psi = E\Psi$$

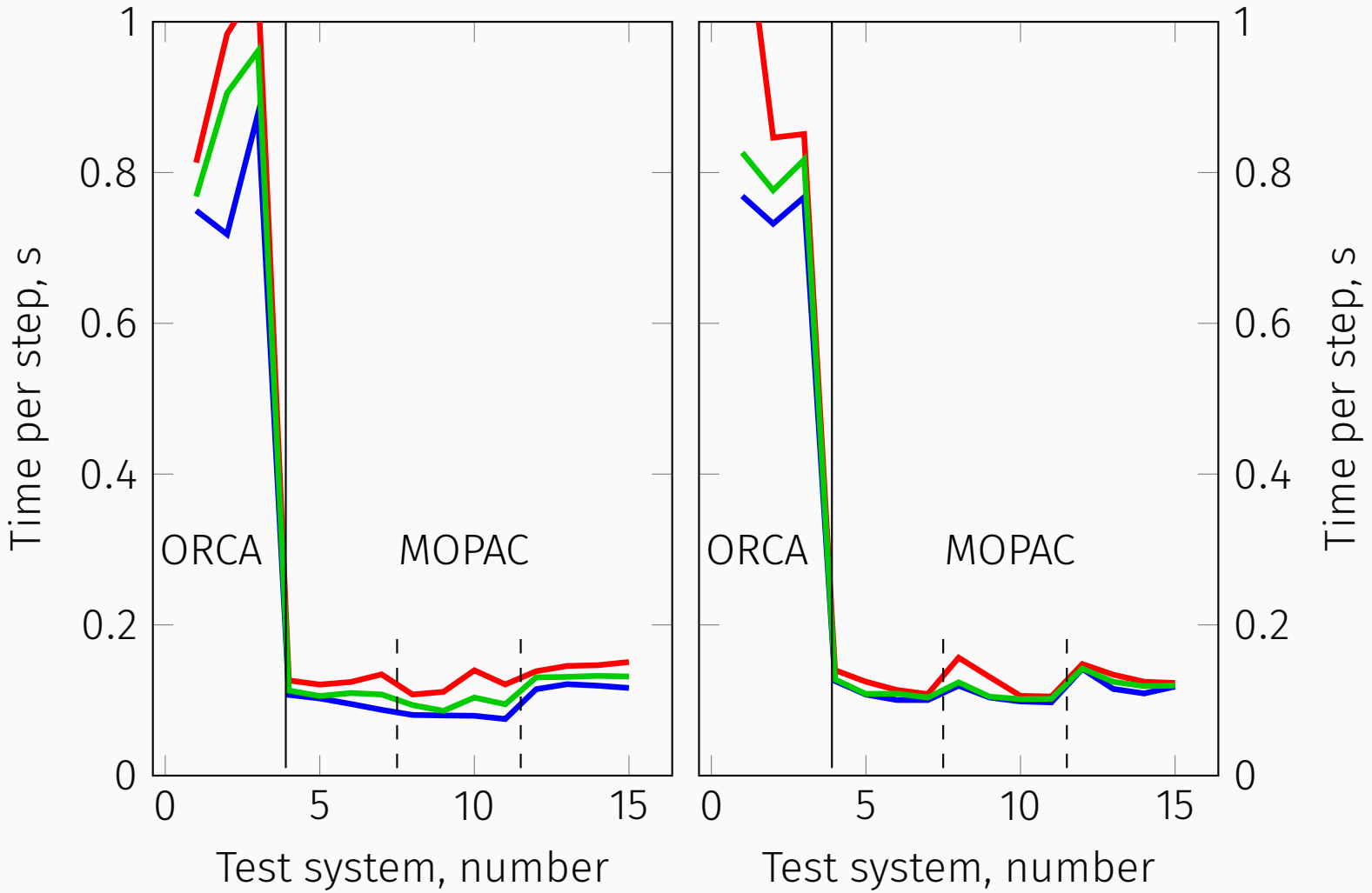
$$E_{tot} = E_I^{QM} + E_{I+II}^{MM} - E_I^{MM} \tag{1}$$

https://en.wikipedia.org



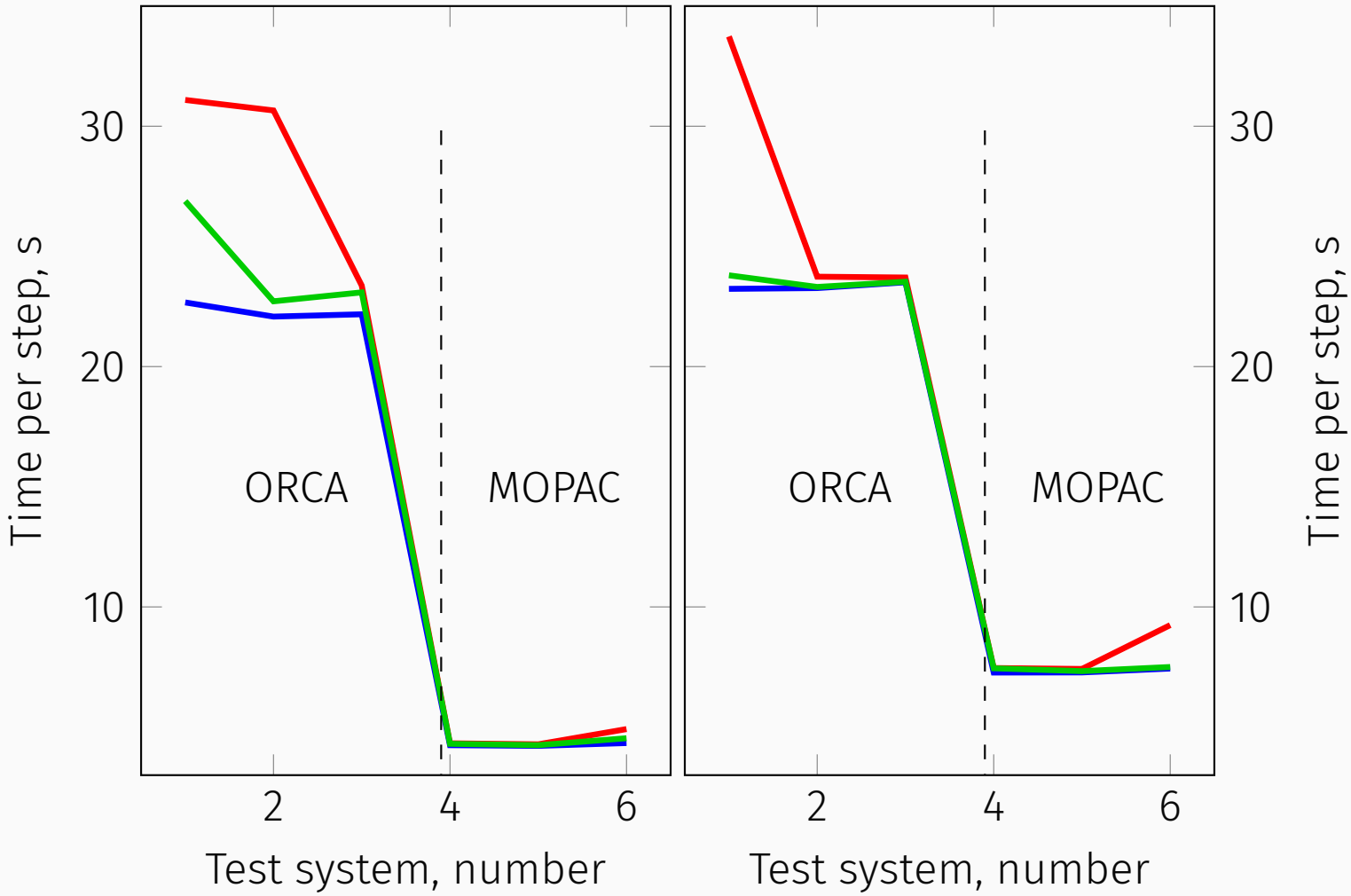
MM Engine = Gromacs, QM Engine = Mopac

PERFOMANCE WITH 64 QM ATOMS



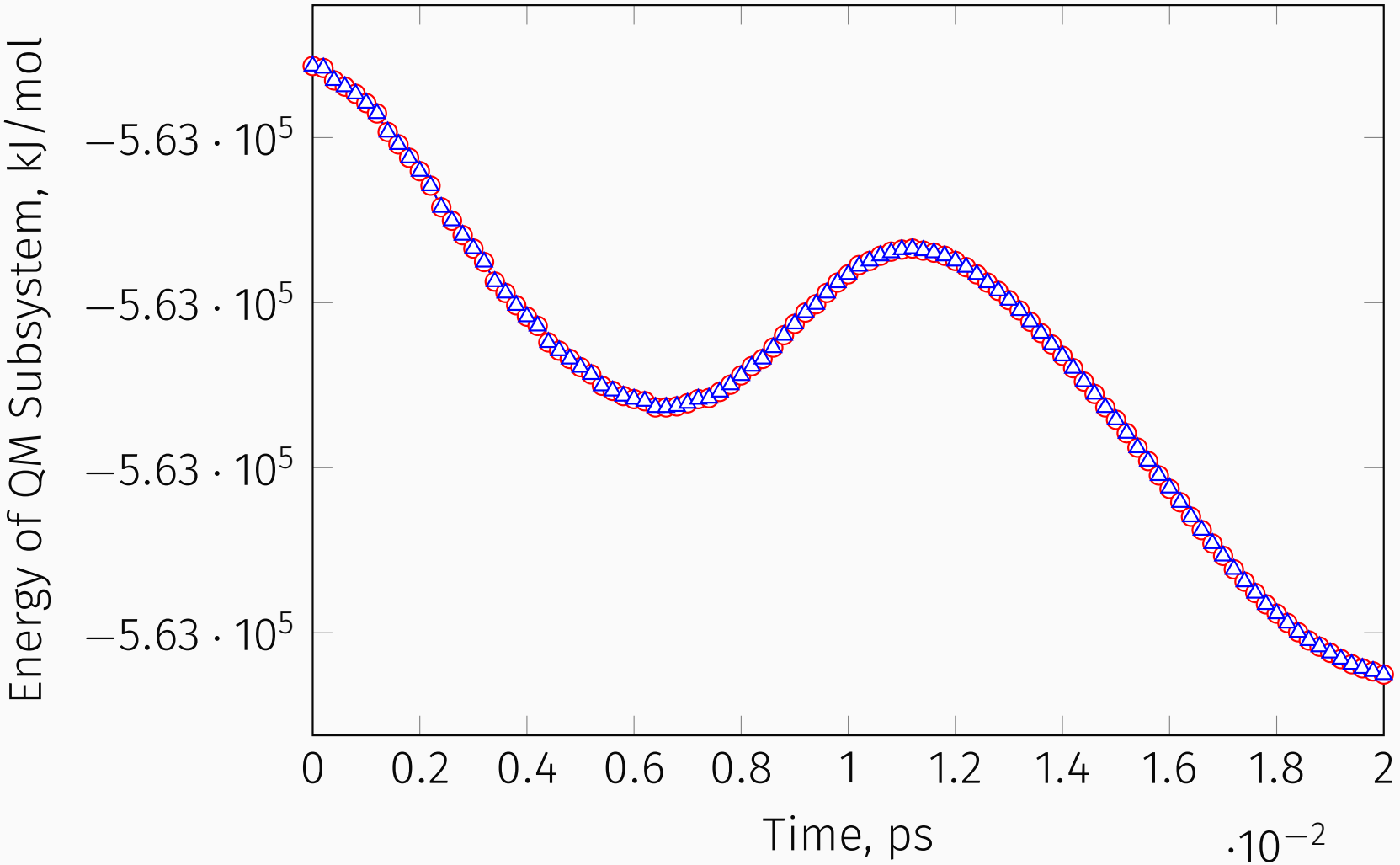
Performance of QM/MM packages for the “small” system on local workstation (left) and supercomputer ”Lomonosov-2” wit Lustre filesystem (right).

PERFOMANCE WITH 400 QM ATOMS



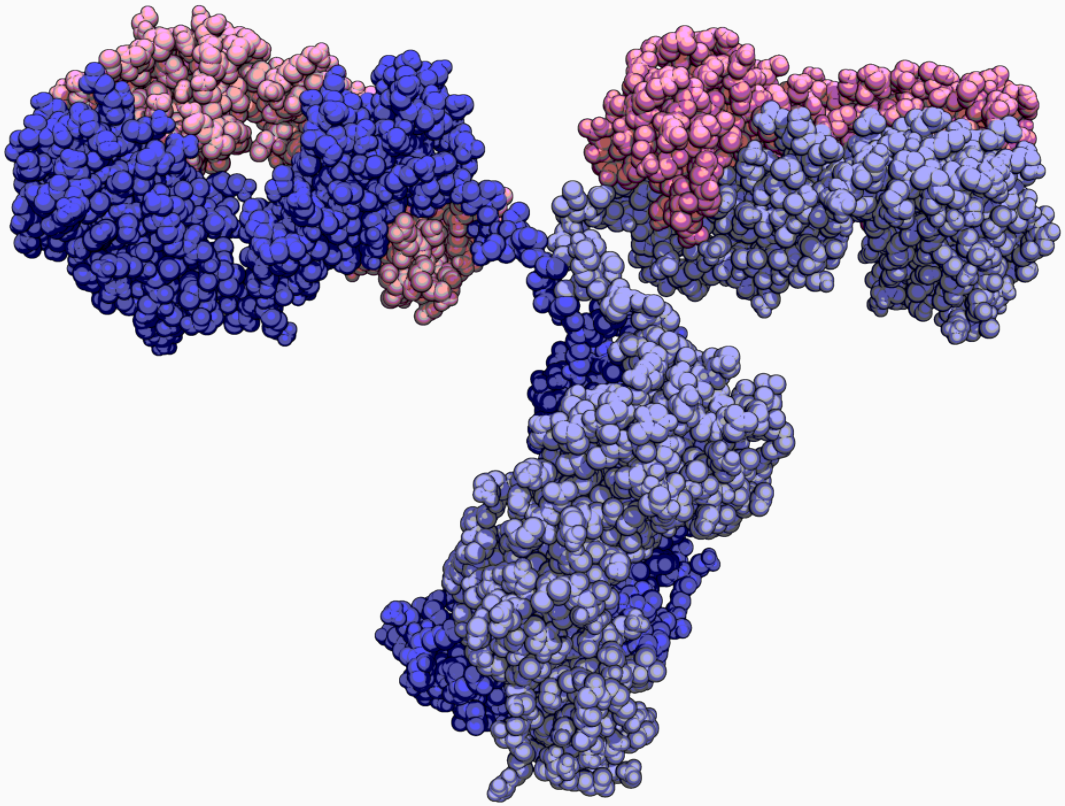
Performance of test systems for the “big” system on local workstation (left) and supercomputer ”Lomonosov-2” wit Lustre filesystem.

PRECISION



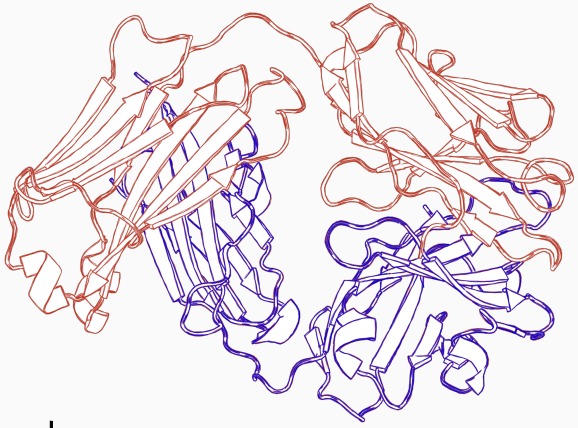
Comparison of energy values for QM subsystem for MOPAC/Gromacs: red circles and ORCA/Gromacs: blue triangles.

ANTIBODY

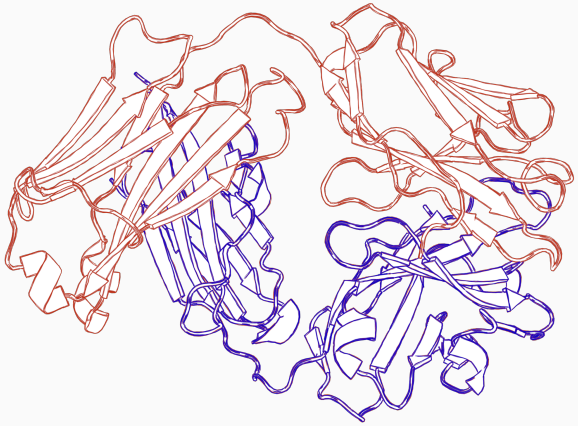


- AB has rigid backbone
- AB is burn to be mutated

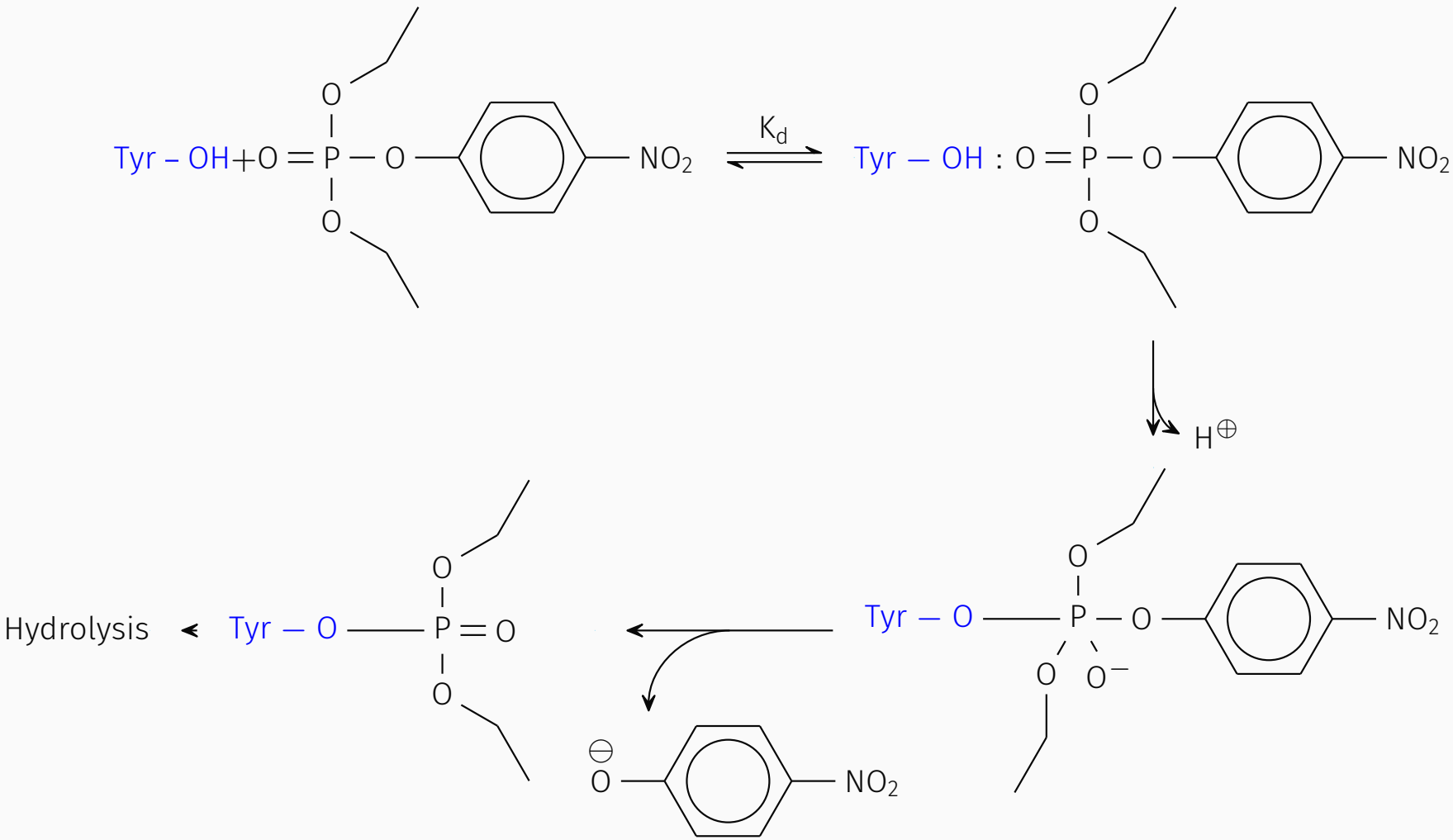
MEDICAL IMPORTANCE



Antibody + Antigen → Action

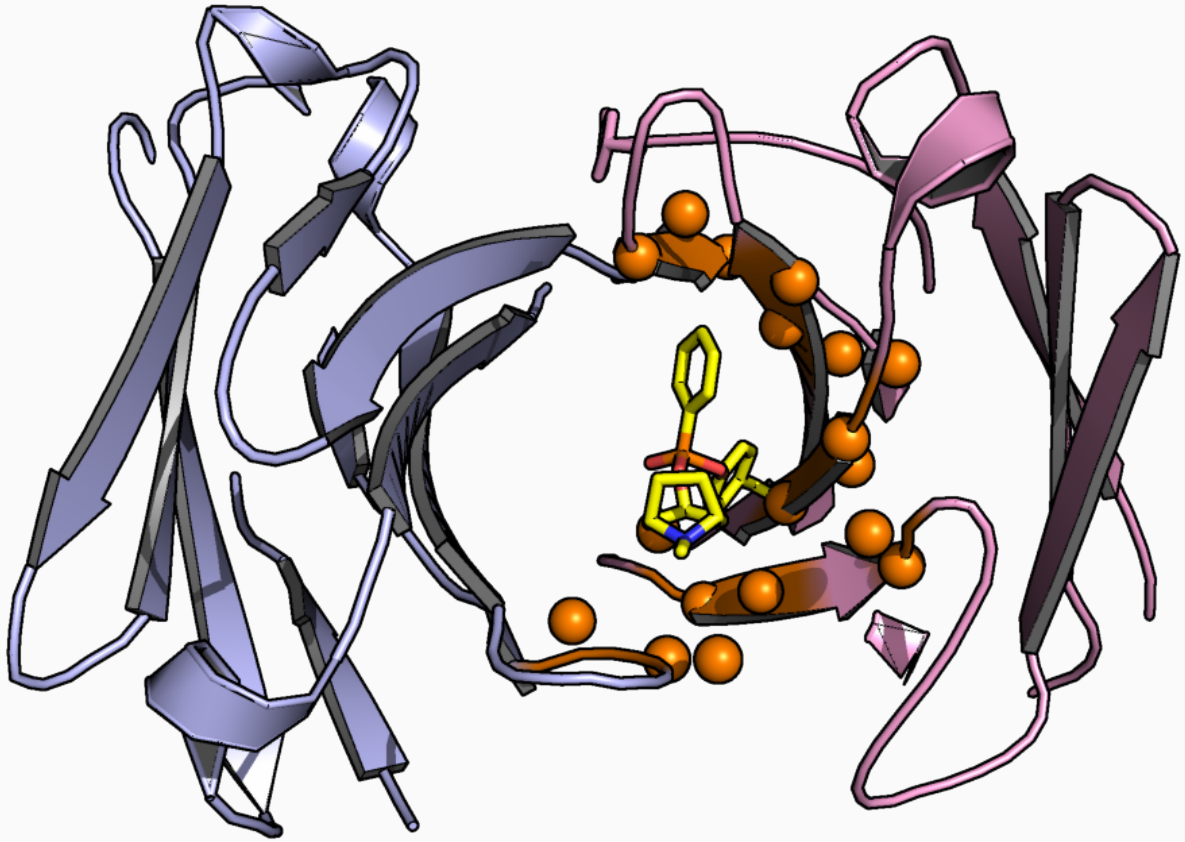


Abzyme + Antigen → Actions



Smirnov et al, PNAS 2011

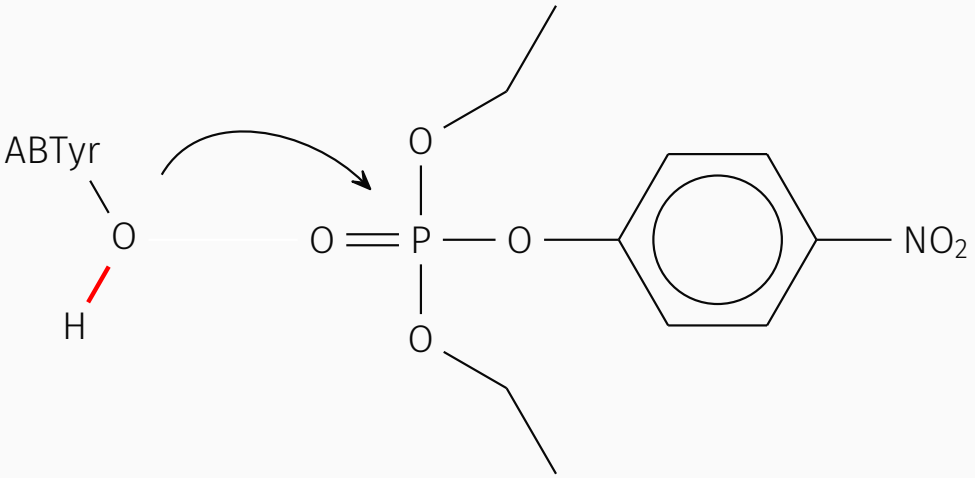
COMBINATORIAL MUTATIONS



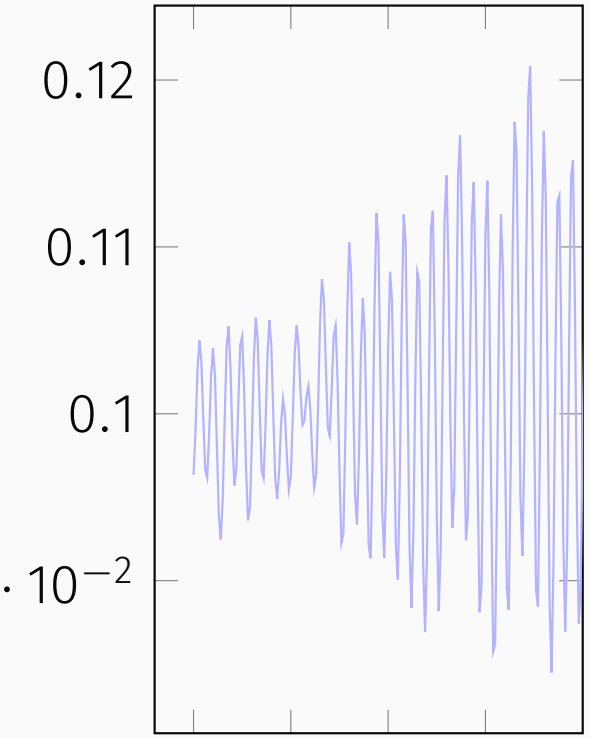
17 positions = 20^{17} mutants

We need to reduce sampling

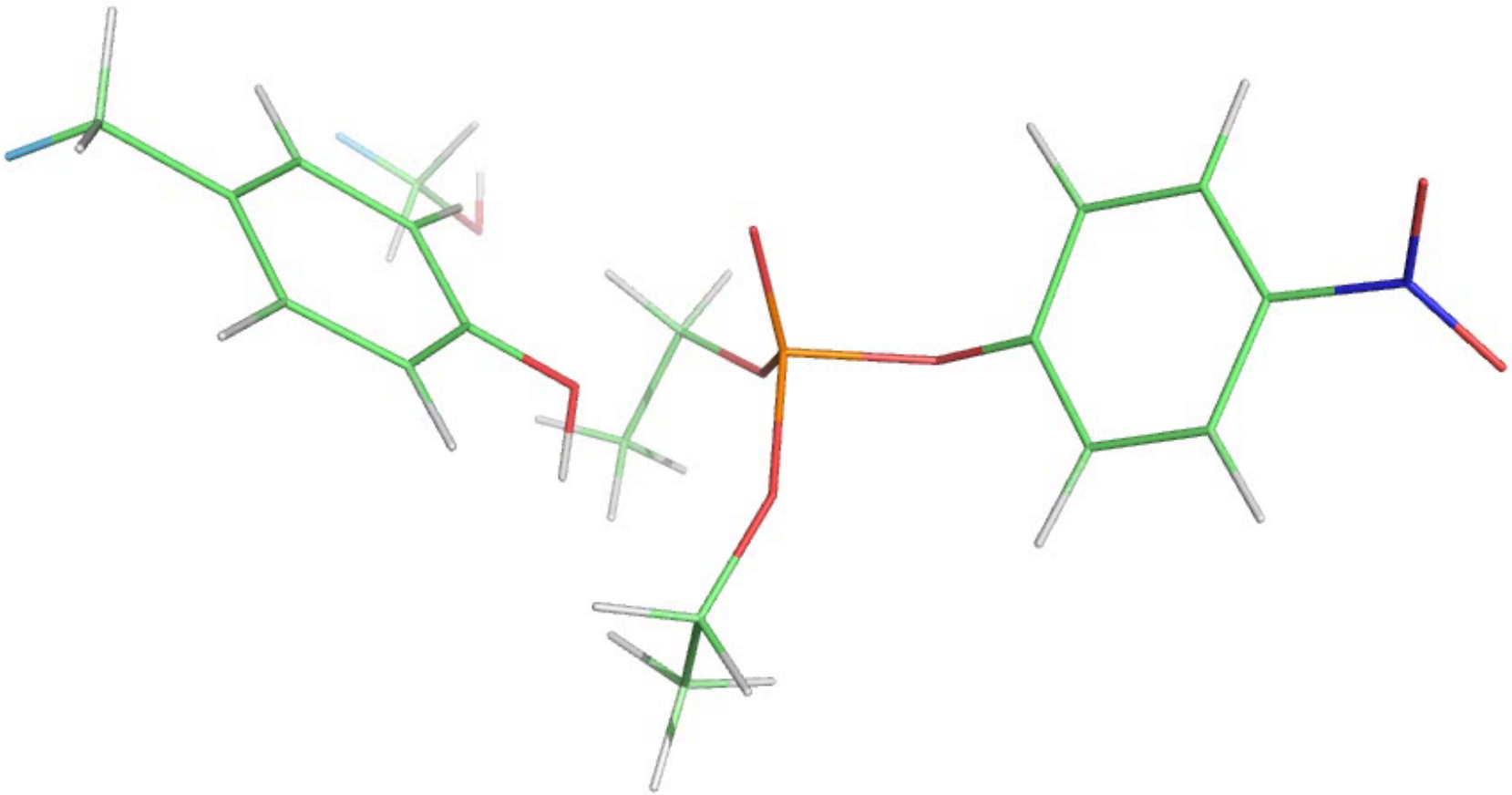
- we «warm up» the bond

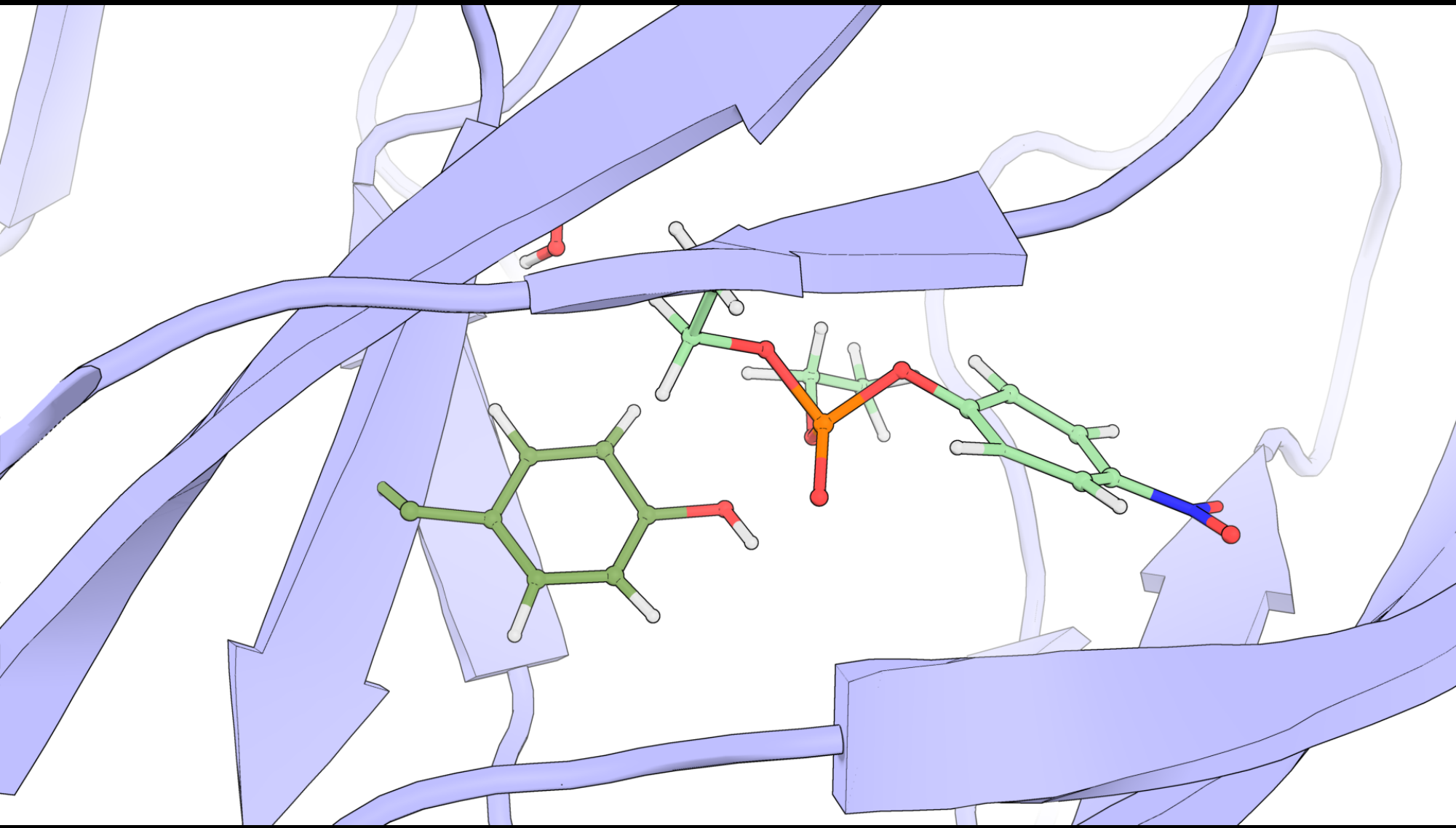


$$V(\vec{s},t) = \sum_{k\tau<t} W(k\tau) \exp\left(-\sum_{i=1}^{d} \frac{(s_i - s_i^{(0)}(k\tau))^2}{2\sigma_i^2}\right)$$



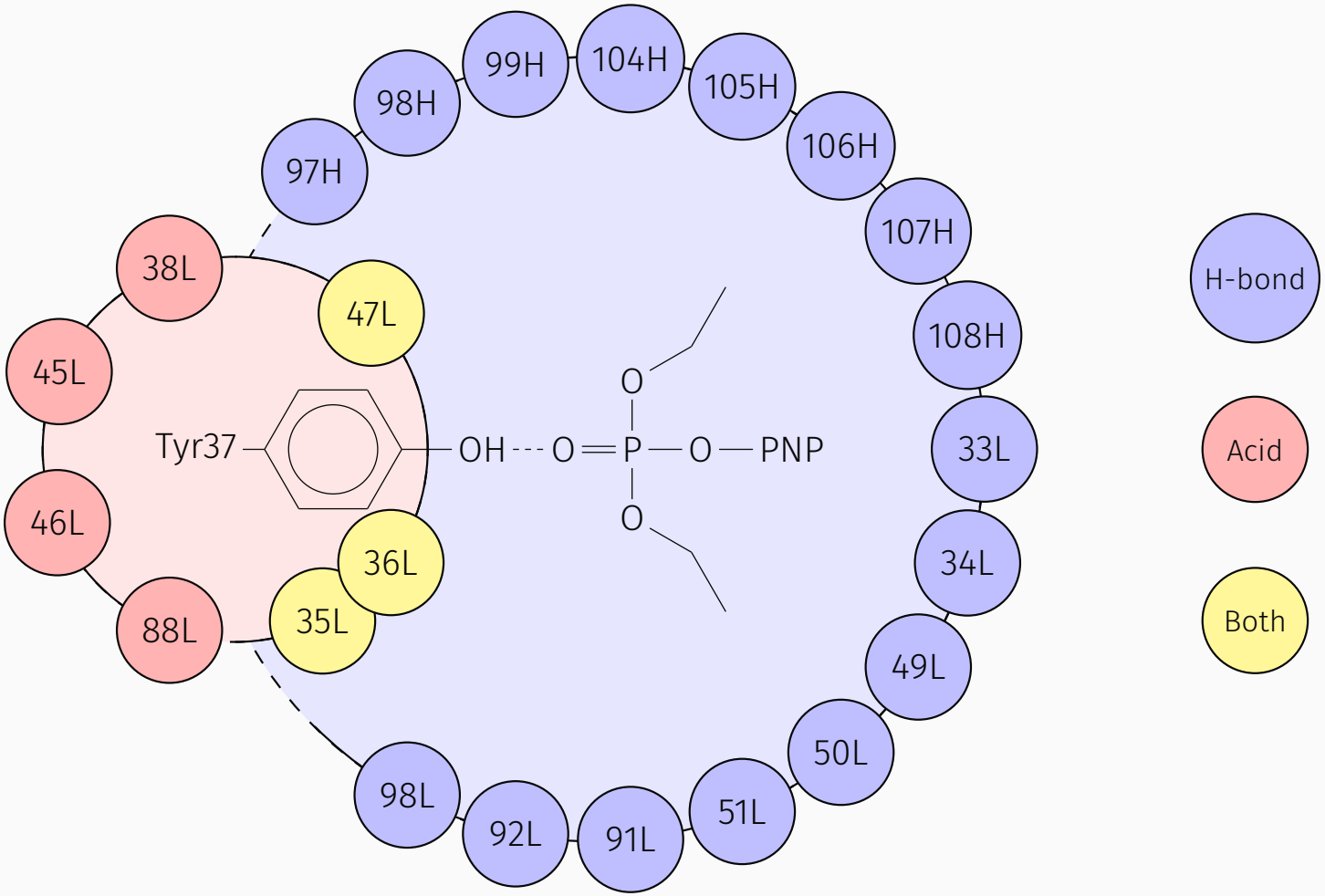
Liao & Parinello, 2002





Mechanism

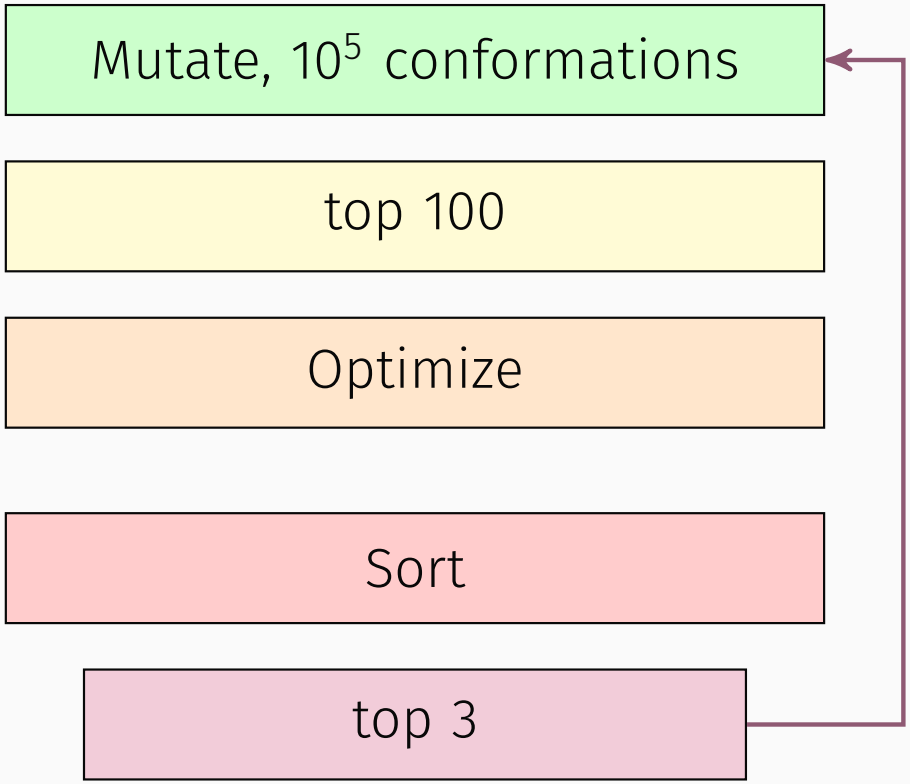
TYPE OF MUATTIONS

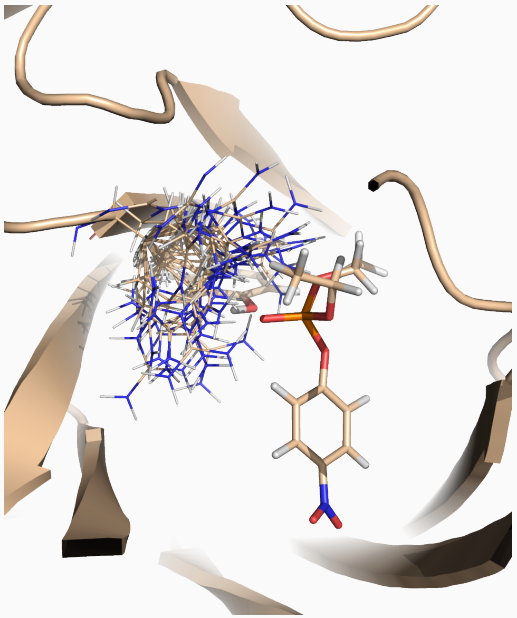


17 positions = $2 * 10^6$ mutants

MUTANTS IN 3D

- $2 * 10^6$ mutants
- PyRosseta framework





375 mutants selected (1125 ssytems) CPU querry on Lomonosov-2

Smirnov, Golovin et al. Sci. Adv. 2016; 2:e1501695

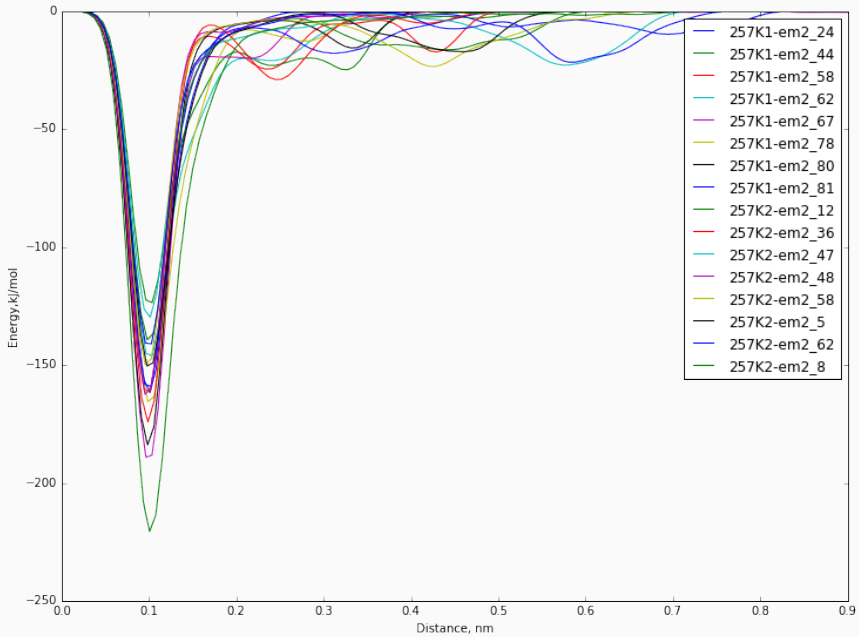
QM/MM SLECTION

375 mutants * 3 replica

Sort on reaction fact

Sort on energy

top 10



- H-bond donor aminoacids won
- 10 muatnts was selected on CPU querry Lomonosov-2

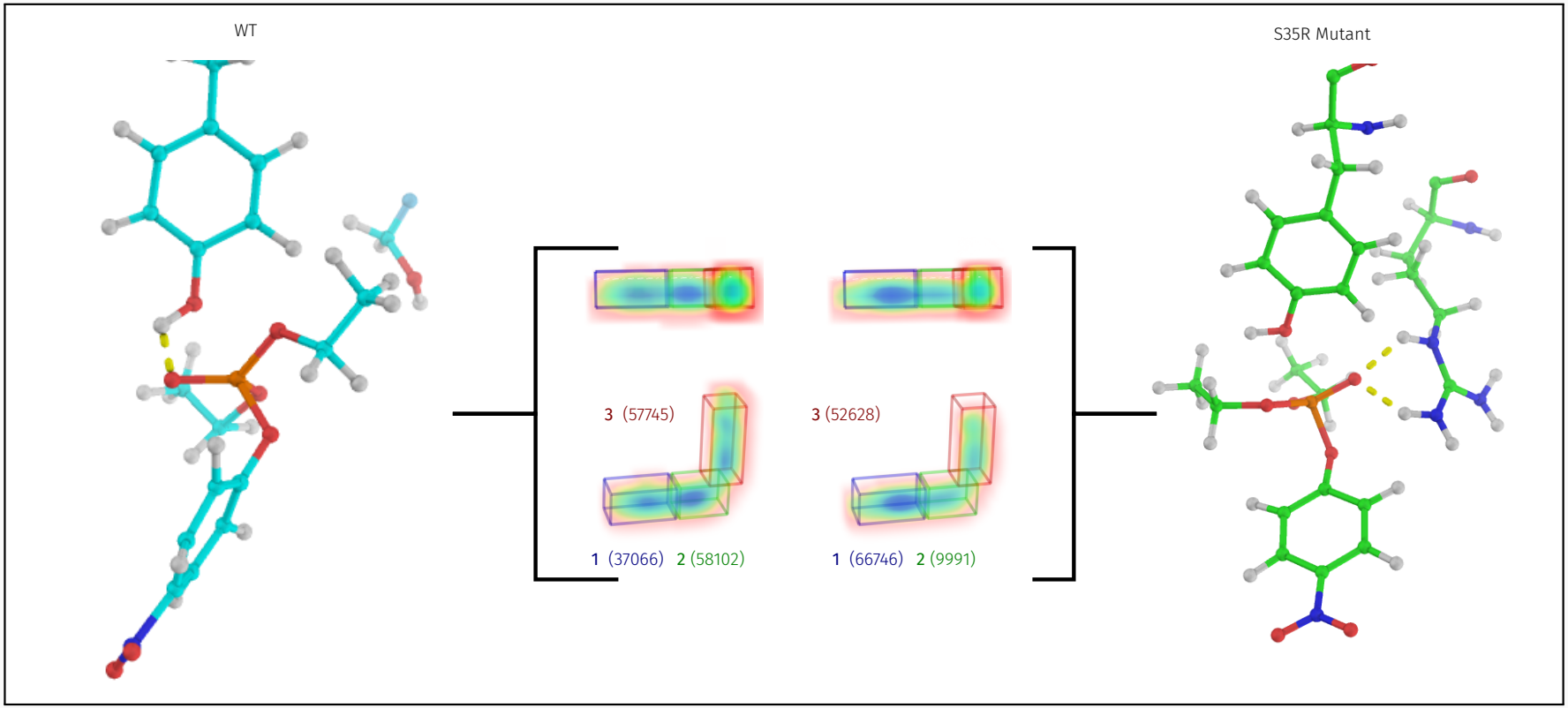
Smirnov, Golovin et al. Sci. Adv. 2016; 2:e1501695

EXPERIMENTAL VALIDATION

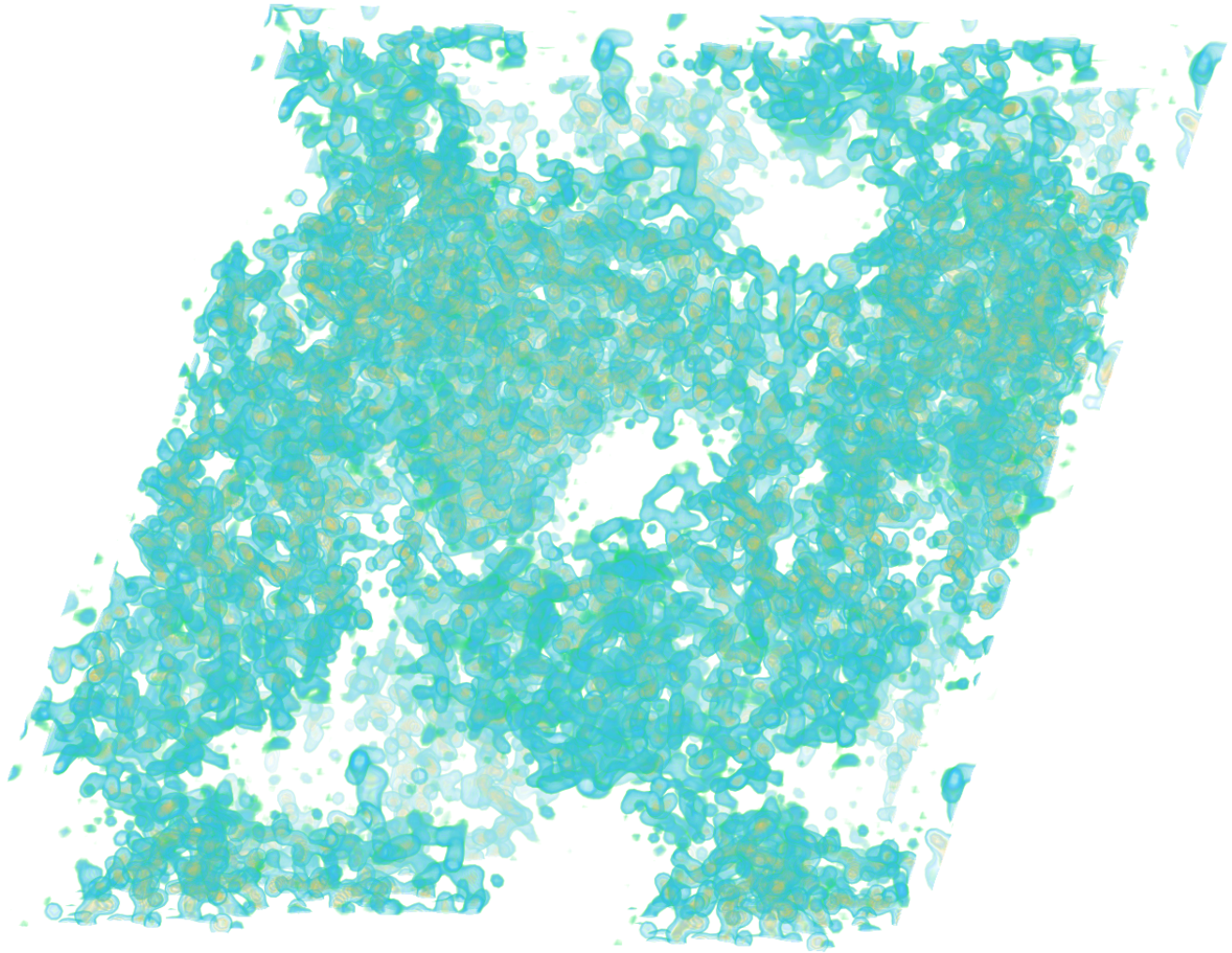
AB	Experiment	Prediction
WT	1	1
S35R	229	14
L47K	333	113
S35E	NA	0

Smirnov, Golovin et al. Sci. Adv. 2016; 2:e1501695

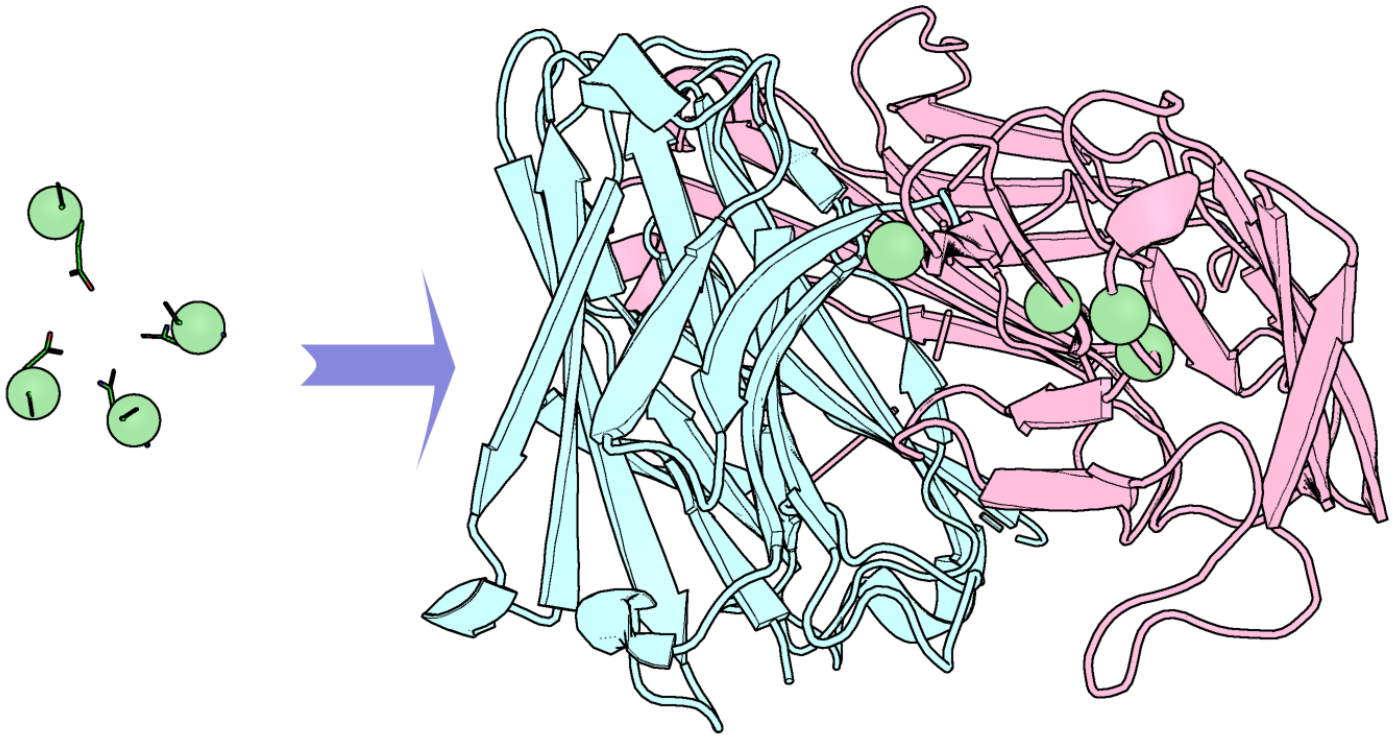
WHY MUTANT IS BETTER?



Smirnov, Golovin et al. Sci. Adv. 2016; 2:e1501695



X-ray electron density



Поиск места для внедрения сайта

ACTIVE CENTER TRANSFER

- 100 ways to acomodate active center
- $5 * 10^4$ mutants PyRosseta

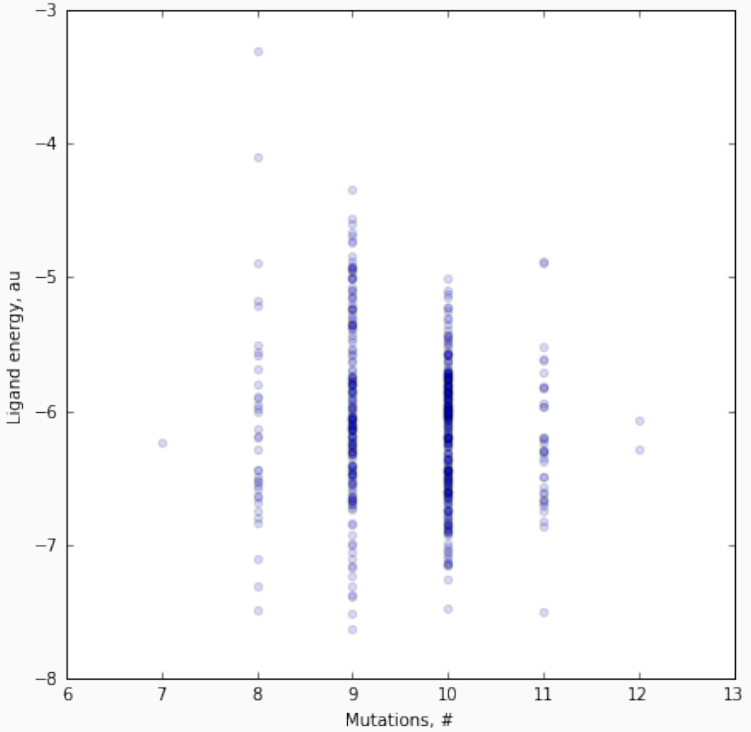
Active center positions, up to 10^3

top 100

Mutate to stabilize, $10^4 * 10^2$

Sort

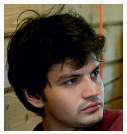
top 1000 QM/MM



15 mutants selected

Authors

- Artur Zalevsky



- Olga Zolotoreva

Collaborators

- IBCH RAS, Moscow
  - Ivan Smirnov
  - Alexander Gabibov
- EMBL Hamburg
  Spyros D. Chatziefthimiou
- Krebs Institute, UK
  Michael Blackburn

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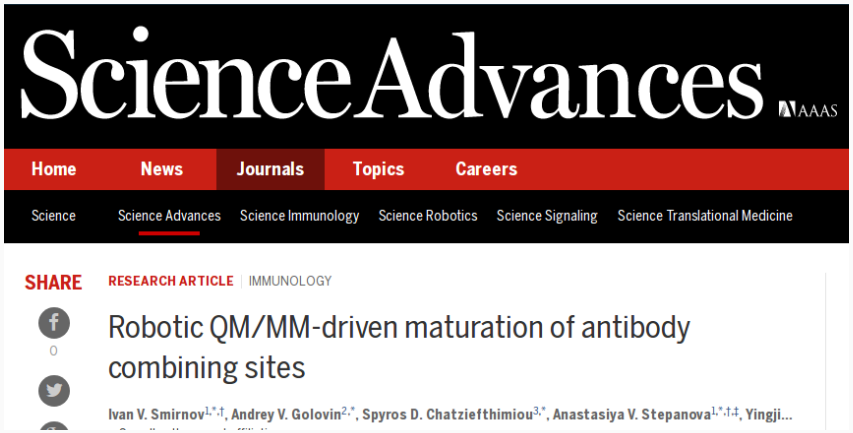
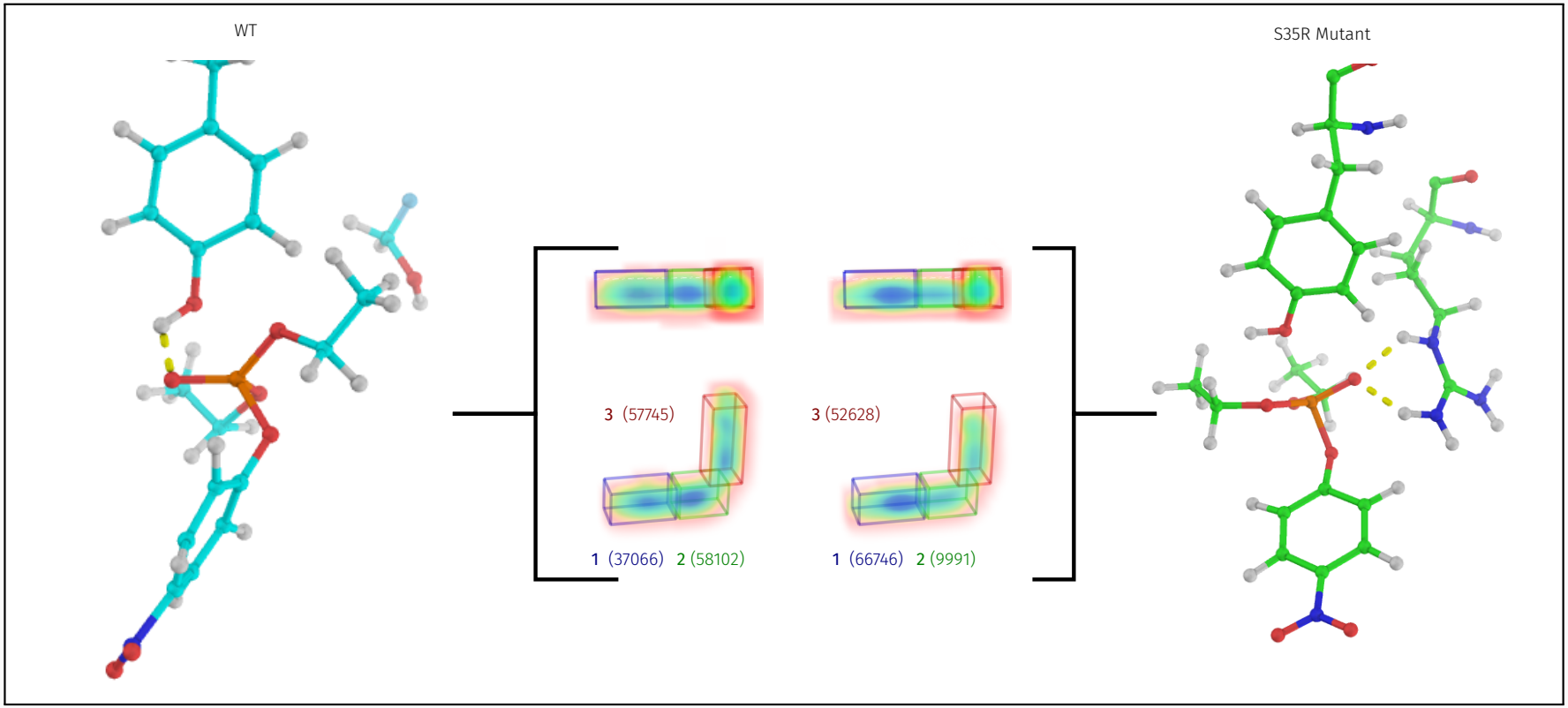


ПОЧЕМУ МУТАНТ ЛУЧШЕ?



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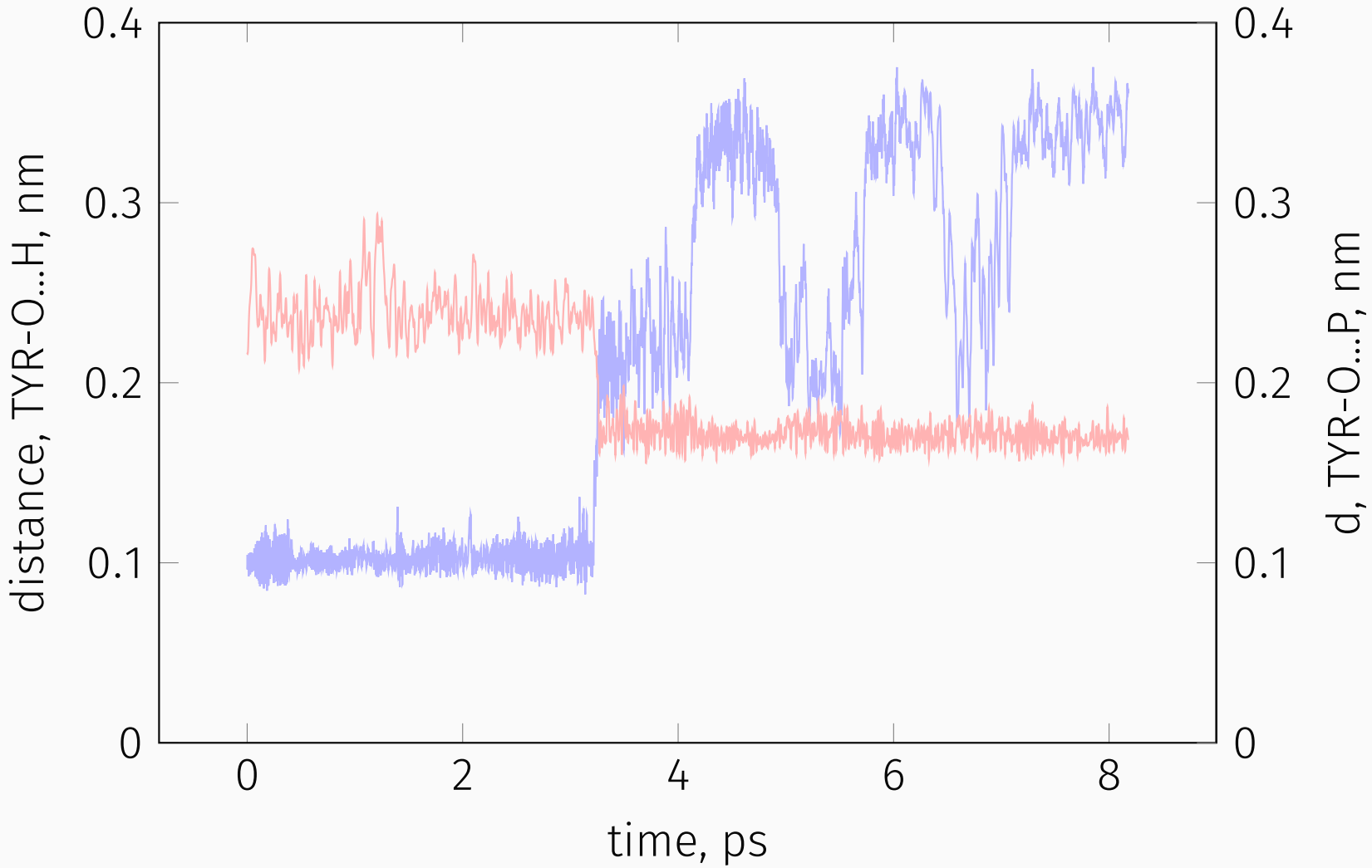
- Gromacs with Plumed, MOPAC2012 as lib
- PM6-D3H4, Hamiltonian with h-bond corrections or DFTb-D3.
- Metadynamics with 0.2 fs step
- Run multiple replicas with stochastic thermostat

TIME-RESOLVED ATTACK



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