

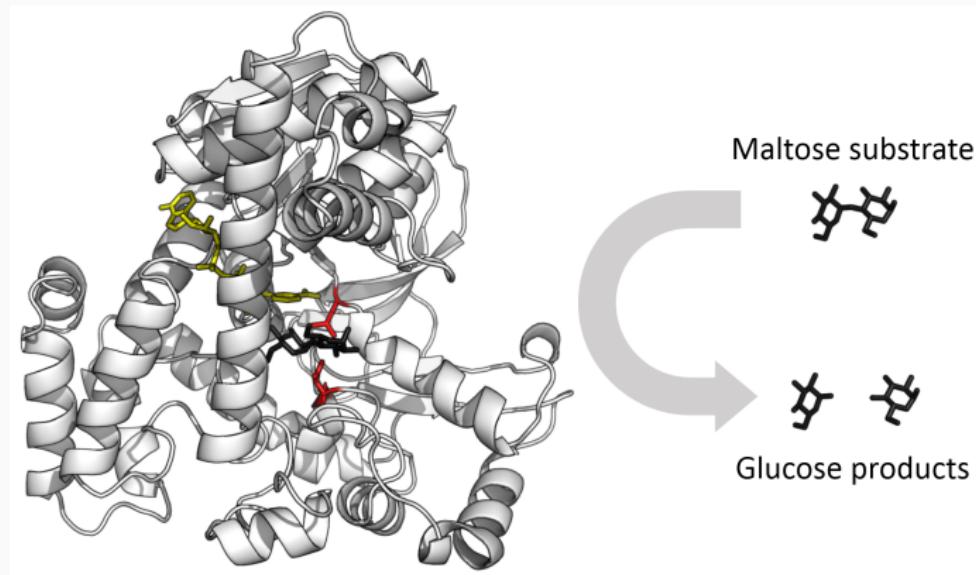
NEW QM/MM IMPLEMENTATION OF THE MOPAC2012 IN THE GROMACS

Андрей Головин, д.х.н., ФББ МГУ

2018

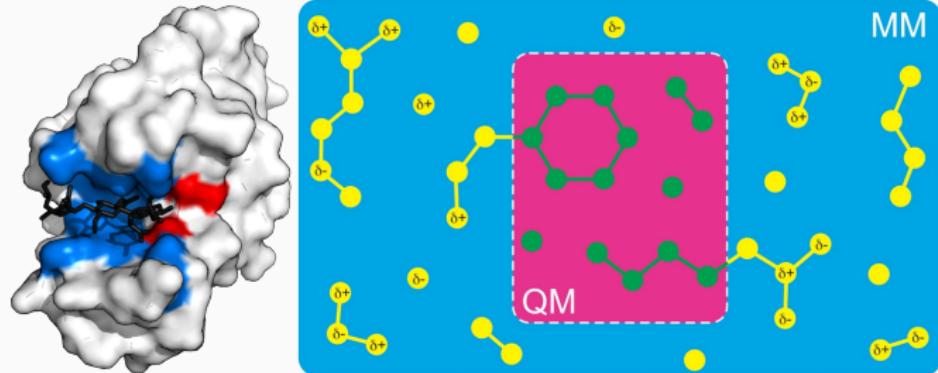
МГУ, Москва

ENZYMES IS LIFE'S KEY MOLECULE



<https://en.wikipedia.org>

SIMULATION OF ENZYMES

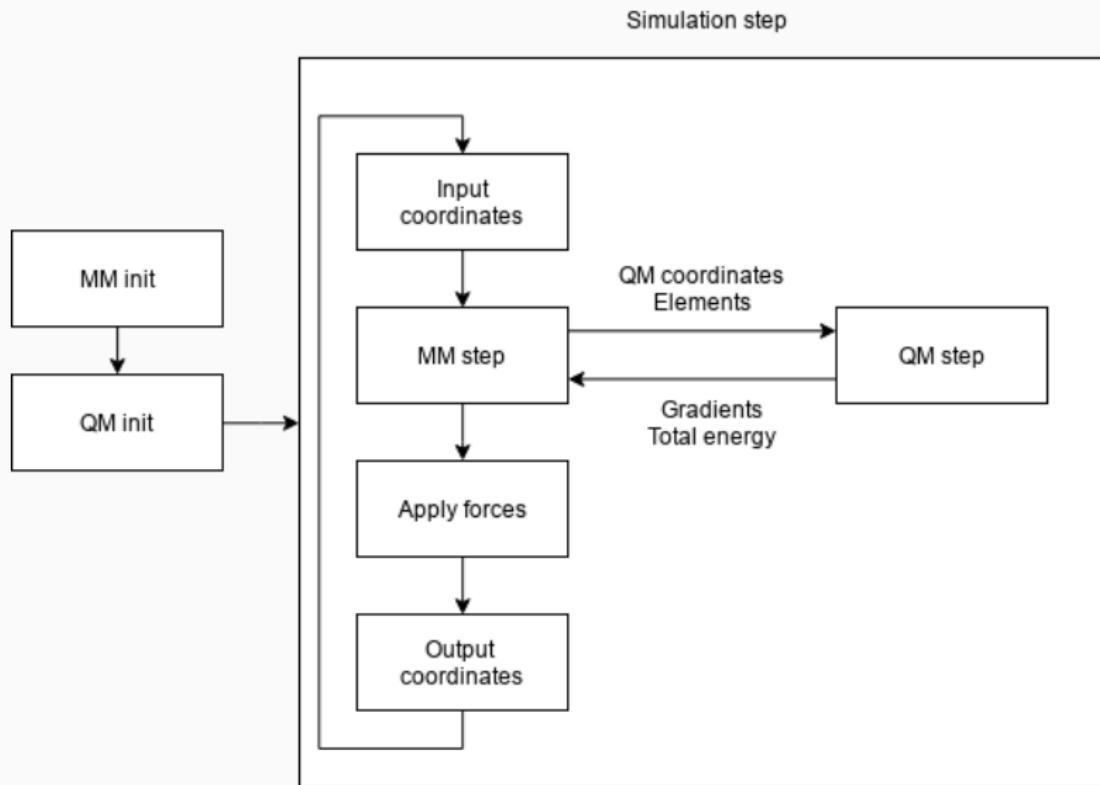


$$E = \frac{k}{2}(b_0 - b)^2$$

$$H\Psi = E\Psi$$

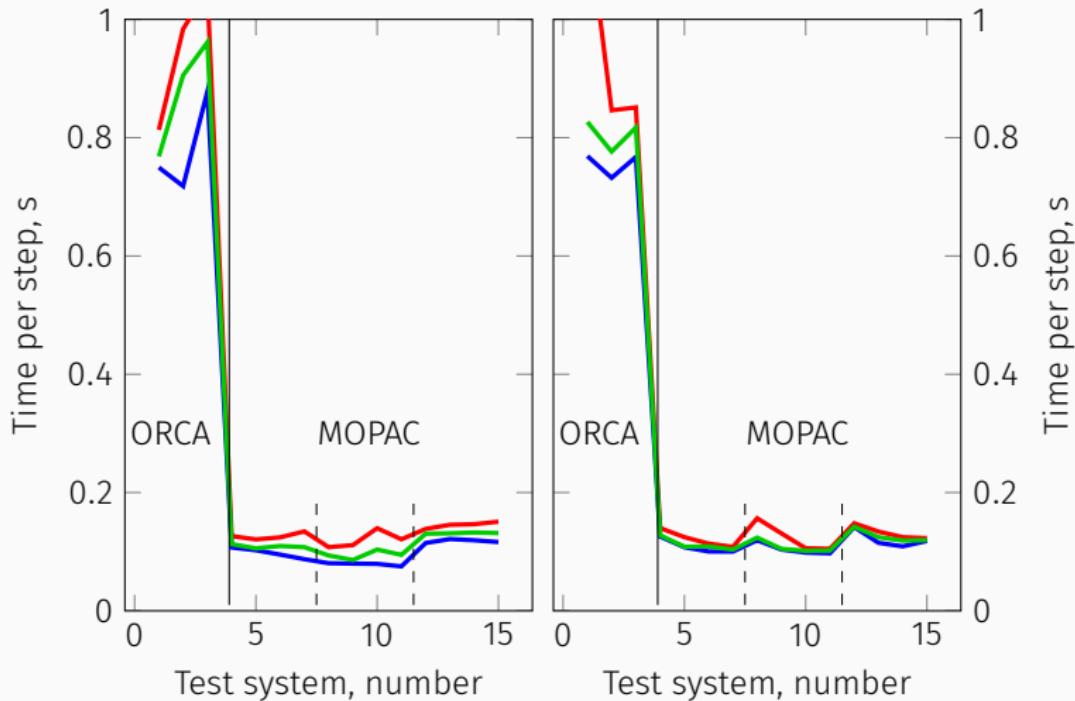
$$E_{tot} = E_I^{QM} + E_{I+II}^{MM} - E_I^{MM} \quad (1)$$

<https://en.wikipedia.org>



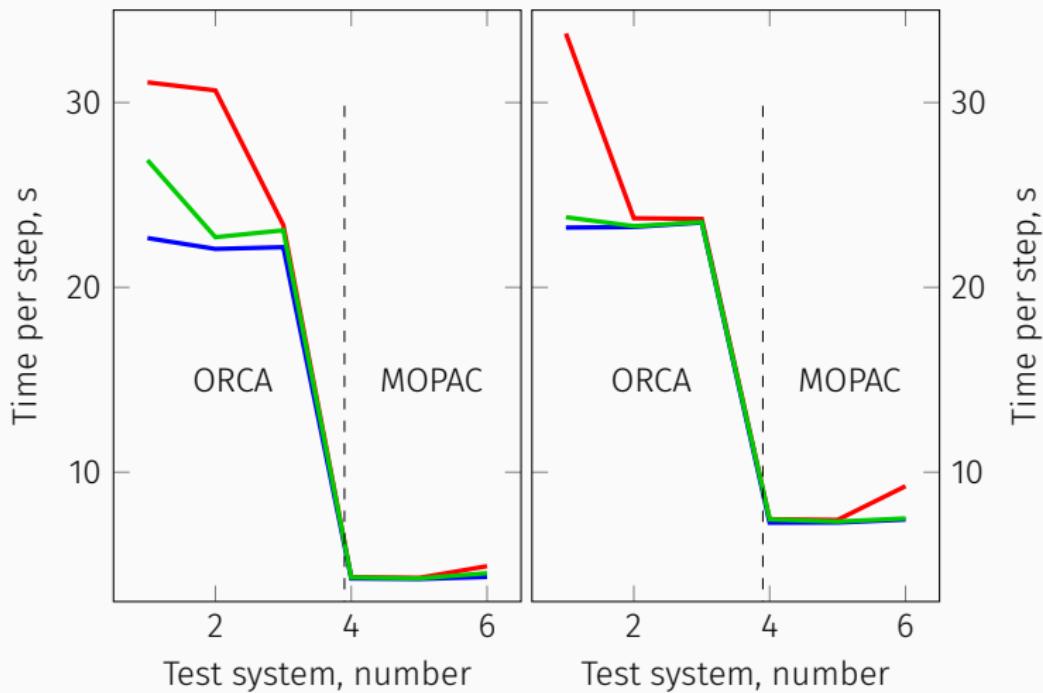
MM Engine = Gromacs, QM Engine = Mopac

PERFOMANCE WITH 64 QM ATOMS



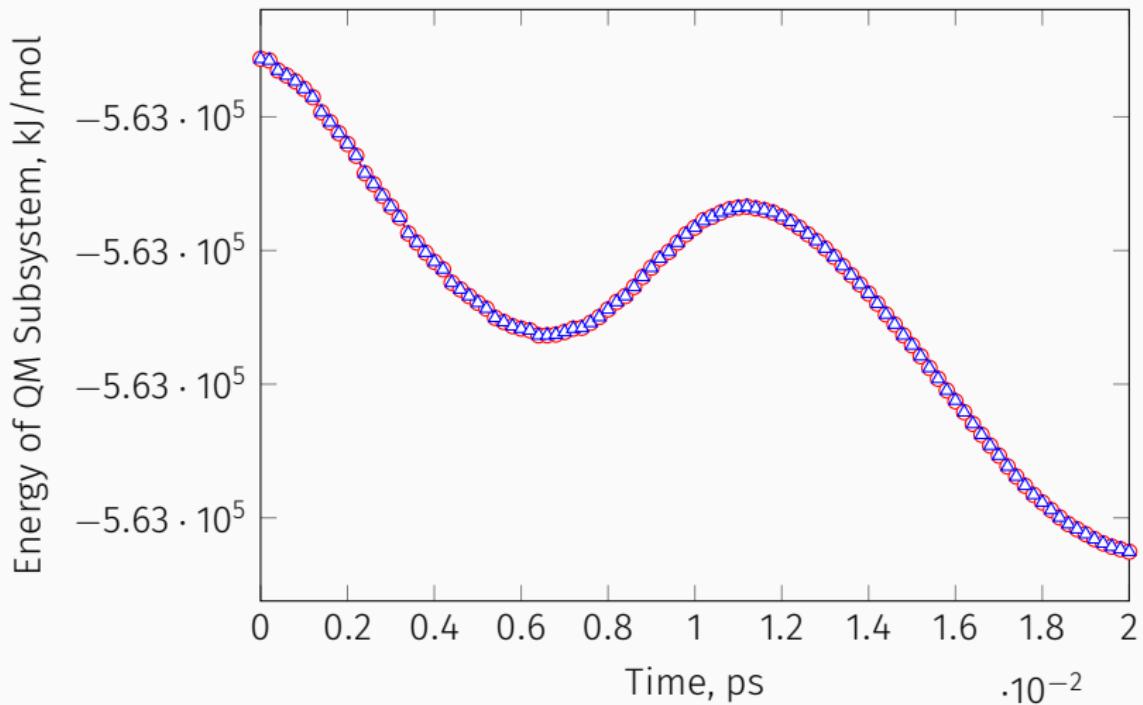
Performance of QM/MM packages for the “small” system on local workstation (left) and supercomputer “Lomonosov-2” wit Lustre filesystem (right).

PERFOMANCE WITH 400 QM ATOMS



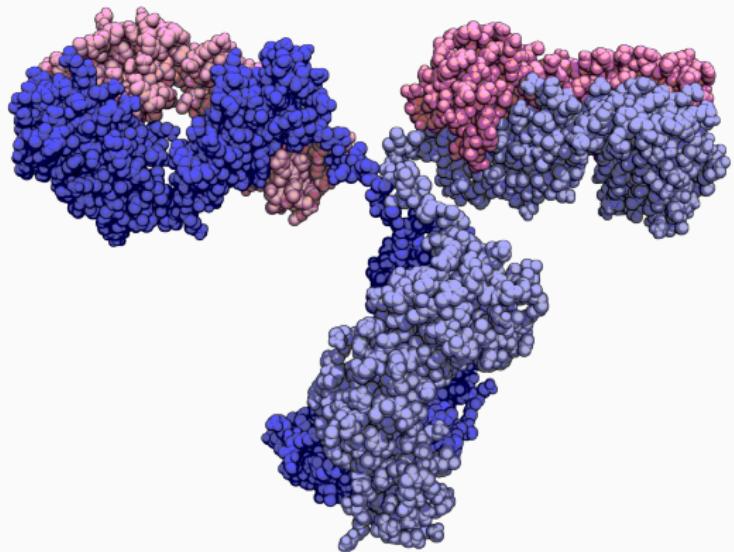
Performance of test systems for the “big” system on local workstation (left) and supercomputer “Lomonosov-2” wit Lustre filesystem.

PRECISION



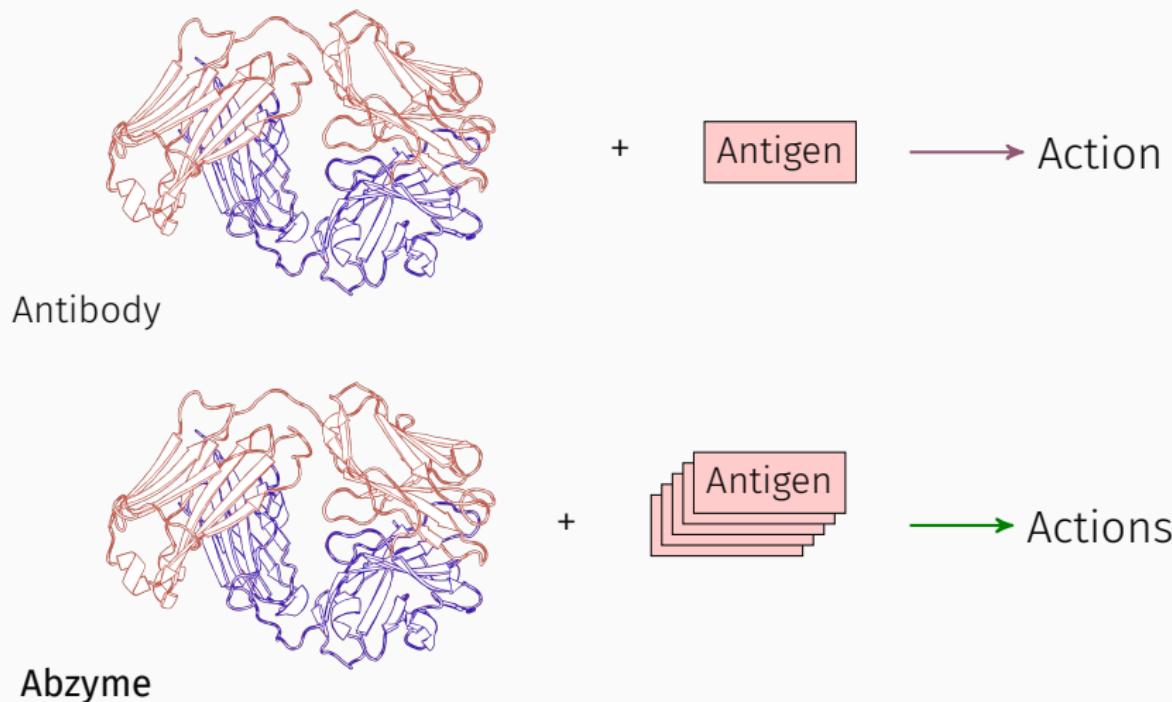
Comparison of energy values for QM subsystem for MOPAC/Gromacs: red circles and ORCA/Gromacs: blue triangles.

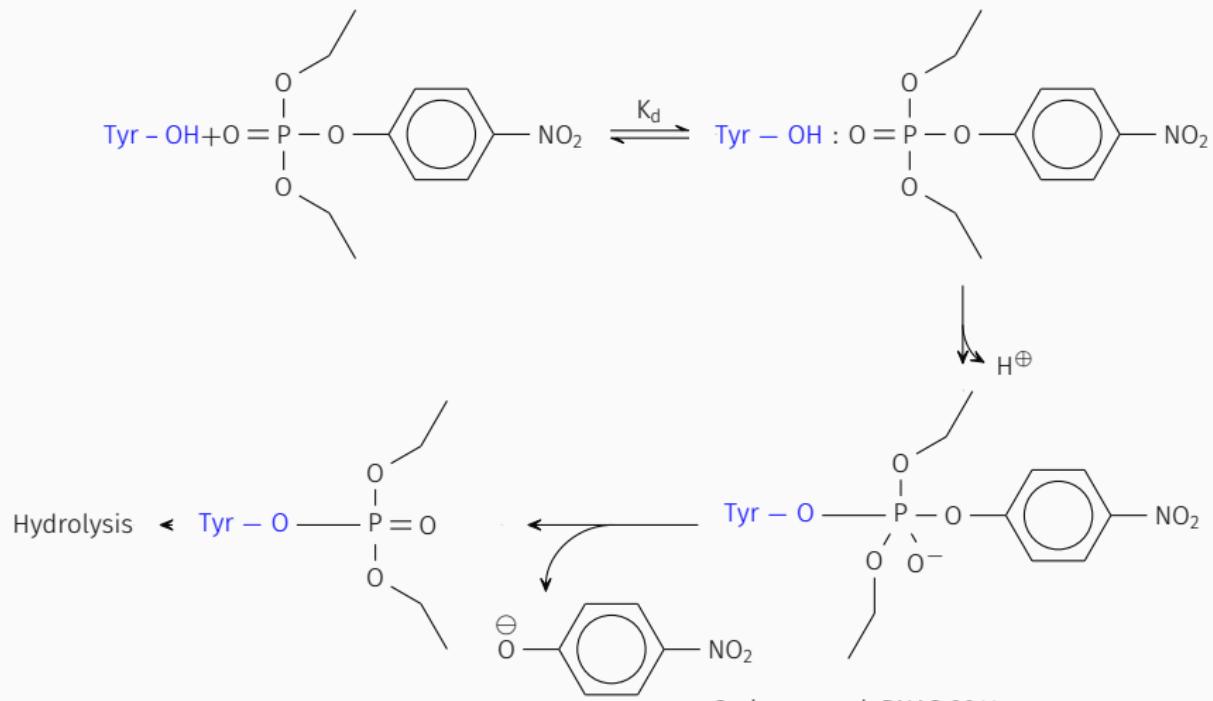
ANTIBODY



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

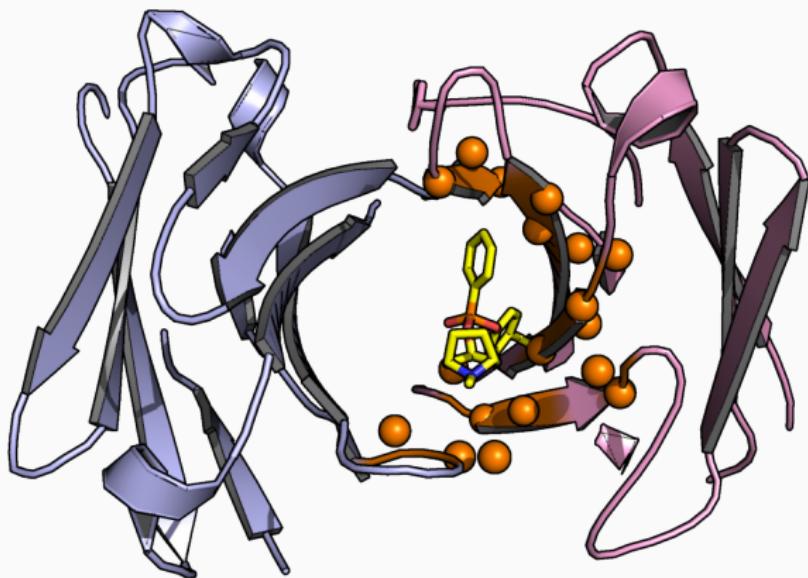
MEDICAL IMPORTANCE





Smirnov et al, PNAS 2011

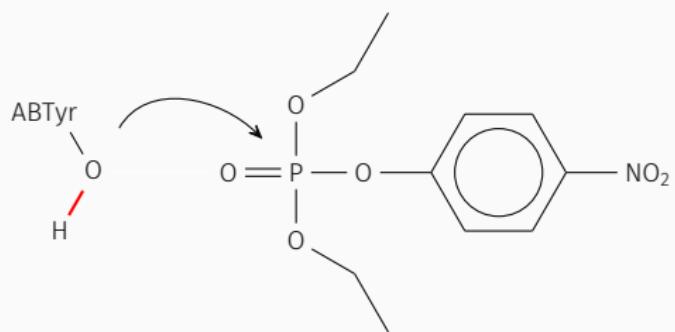
COMBINATORIAL MUTATIONS



17 positions = 20^{17} mutants
We need to reduce sampling

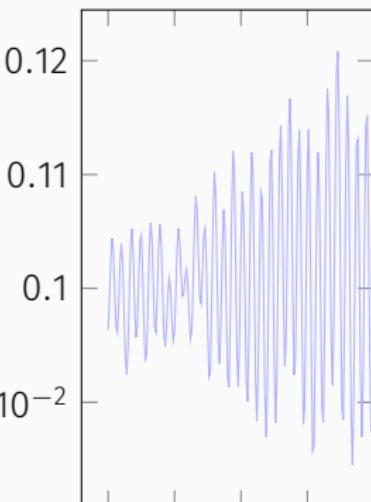
QM/MM METADYNAMICS

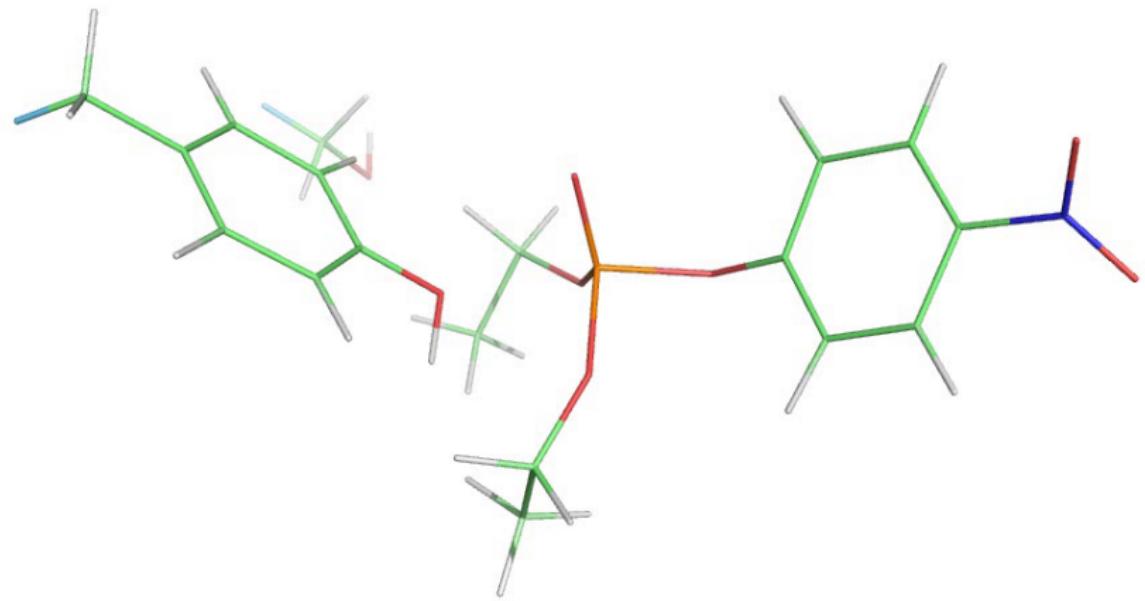
- we «warm up» the bond

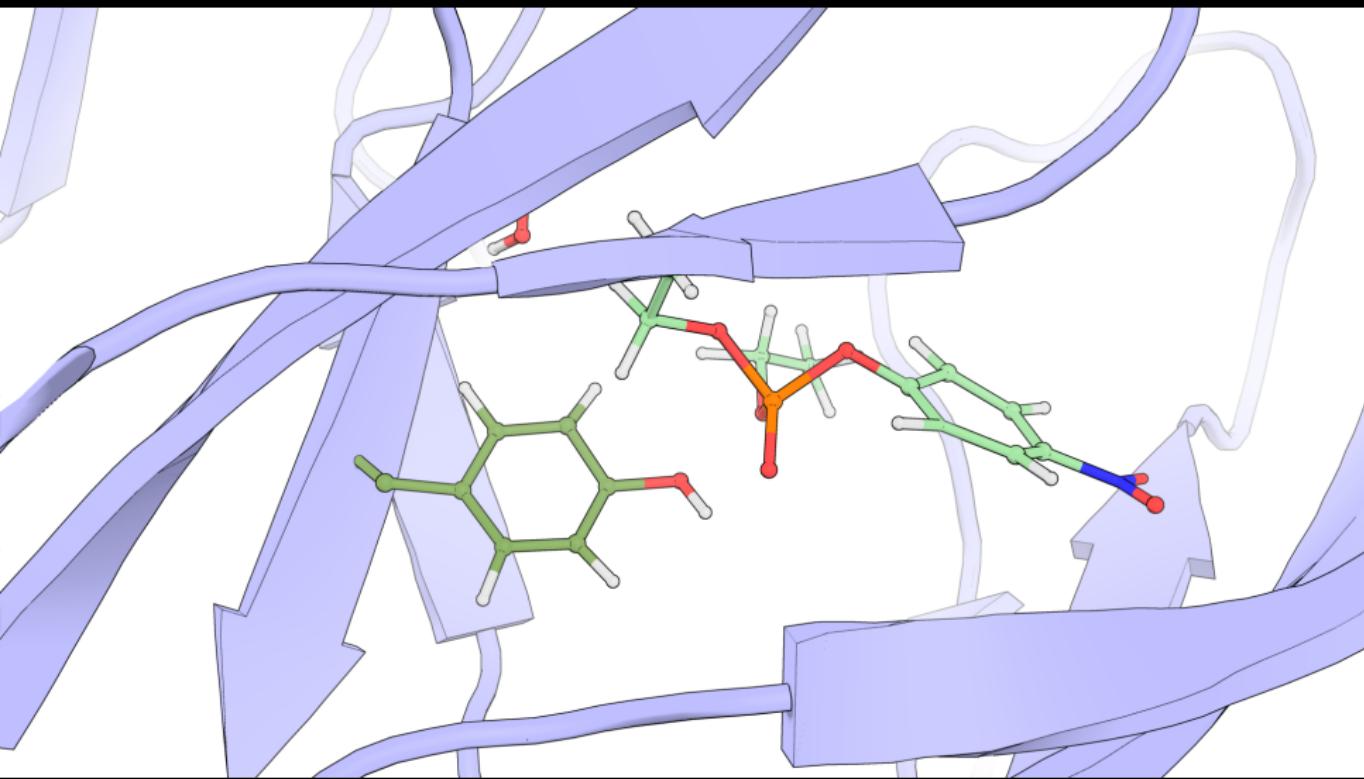


$$V(\vec{s}, t) = \sum_{k\tau < t} W(k\tau) \exp \left(- \sum_{i=1}^d \frac{(s_i - s_i^{(0)}(k\tau))^2}{2\sigma_i^2} \right) 9 \cdot 10^{-2}$$

Liao & Parrinello, 2002

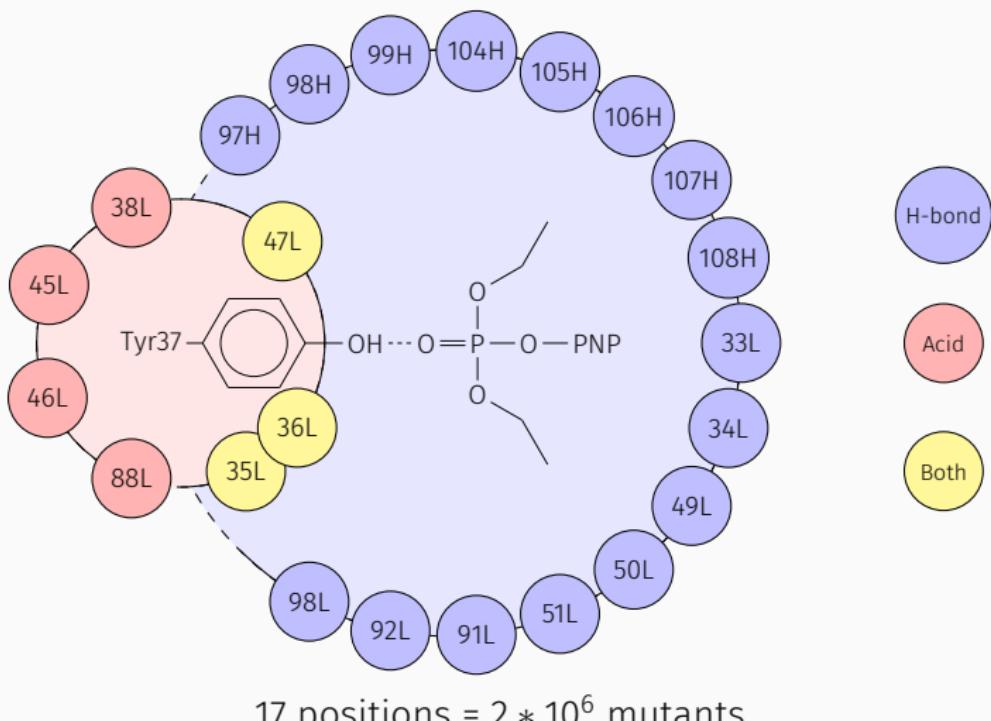






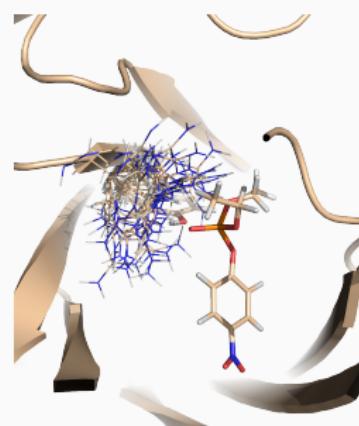
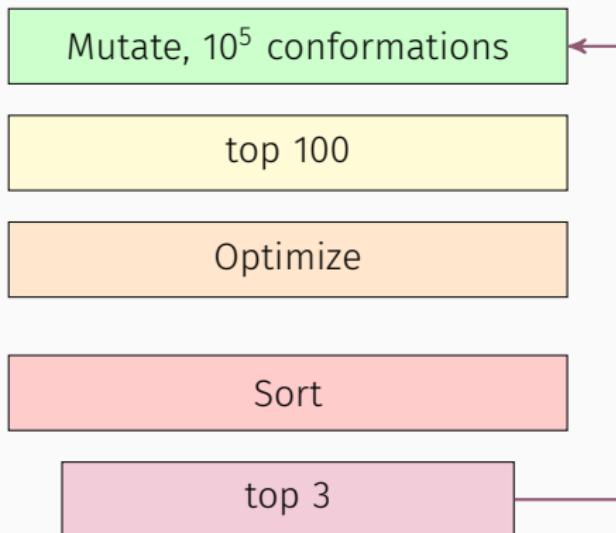
Mechanism

TYPE OF MUTATIONS



MUTANTS IN 3D

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



375 mutants selected (1125 systems) CPU query on Lomonosov-2

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

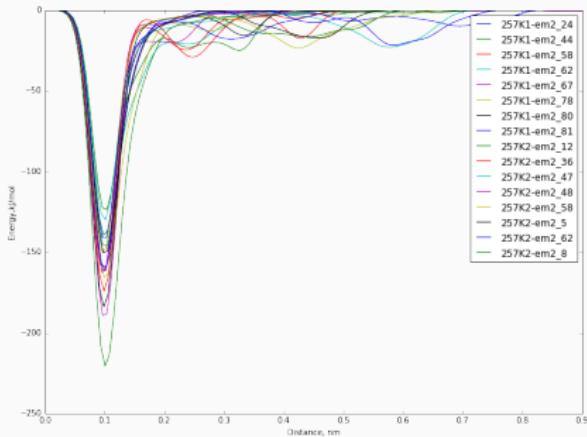
QM/MM SELECTION

375 mutants * 3 replica

Sort on reaction fact

Sort on energy

top 10



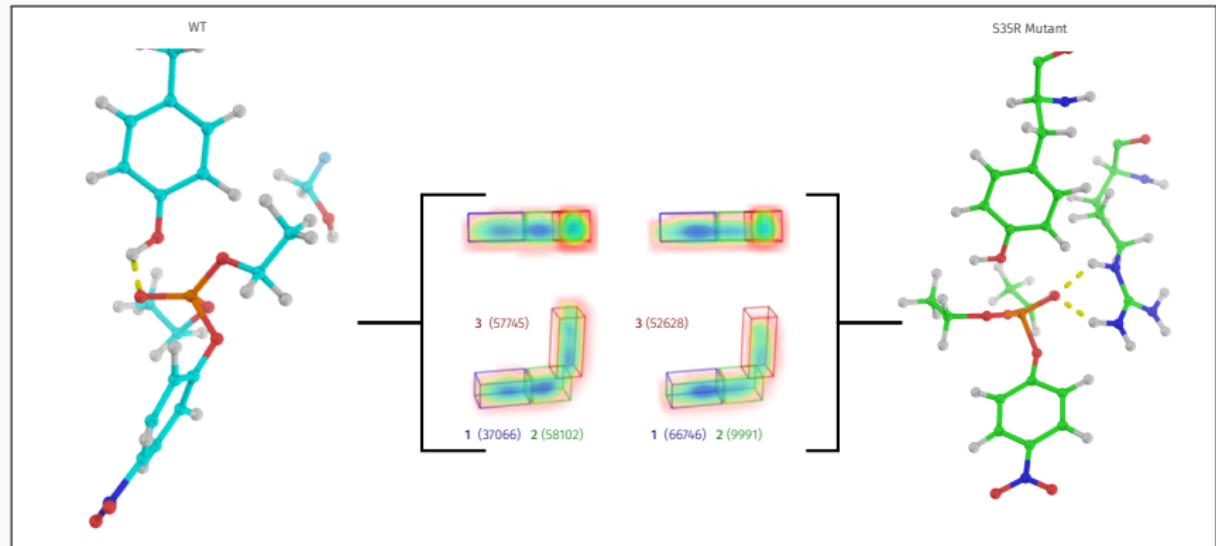
- H-bond donor aminoacids won
- 10 mutants was selected on CPU querry Lomonosov-2

EXPERIMENTAL VALIDATION

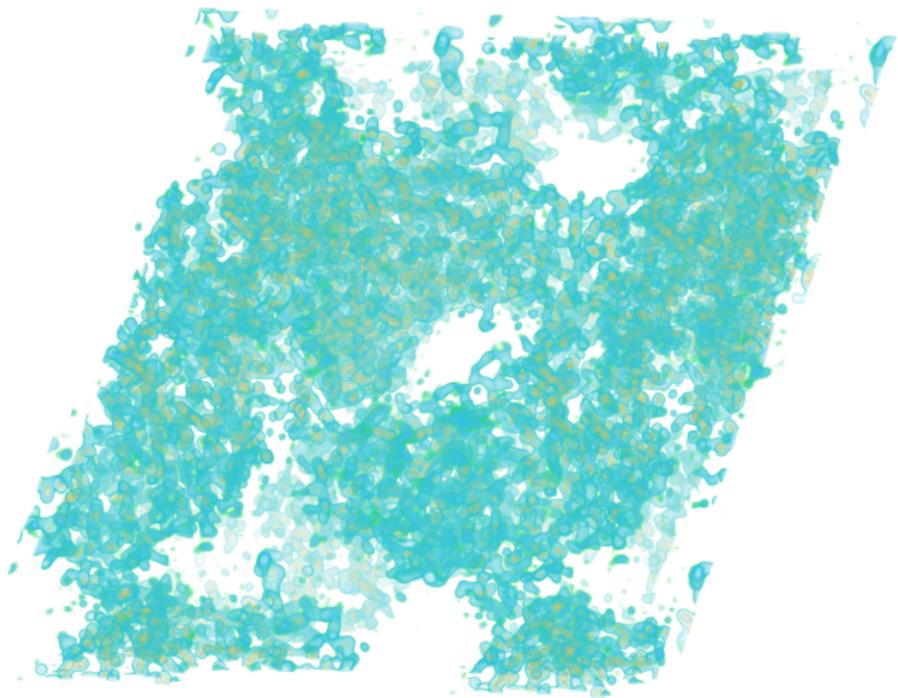
AB	Experiment	Prediction
WT	1	1
S35R	229	14
L47K	333	113
S35E	NA	0

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

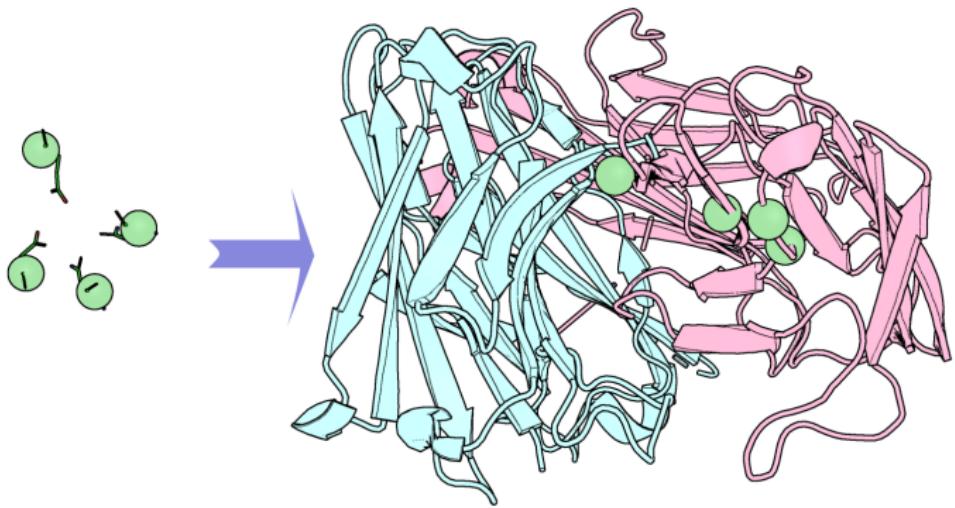
WHY MUTANT IS BETTER?



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

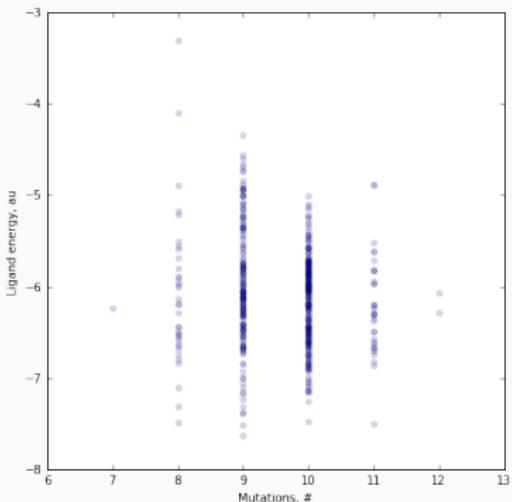
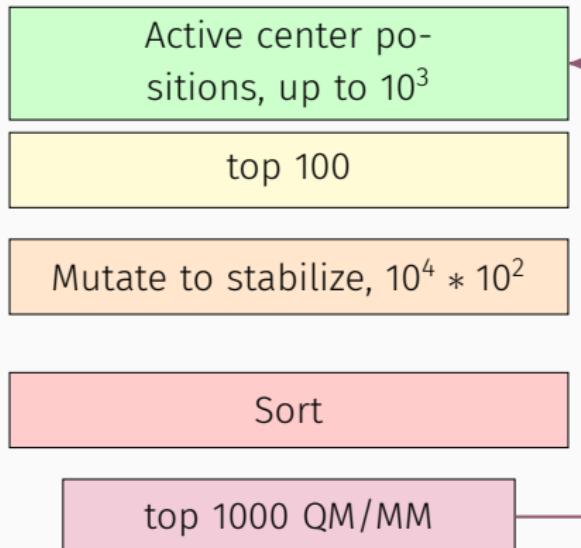


X-ray electron density



ACTIVE CENTER TRANSFER

- 100 ways to accomodate active center
- $5 * 10^4$ mutants PyRosetta



15 mutants selected

Authors

- Artur Zalevsky



- Olga Zolotoreva



Collaborators

- IBCH RAS, Moscow

- Ivan Smirnov

- Alexander Gabibov

- EMBL Hamburg

- Spyros D. Chatziefthimiou

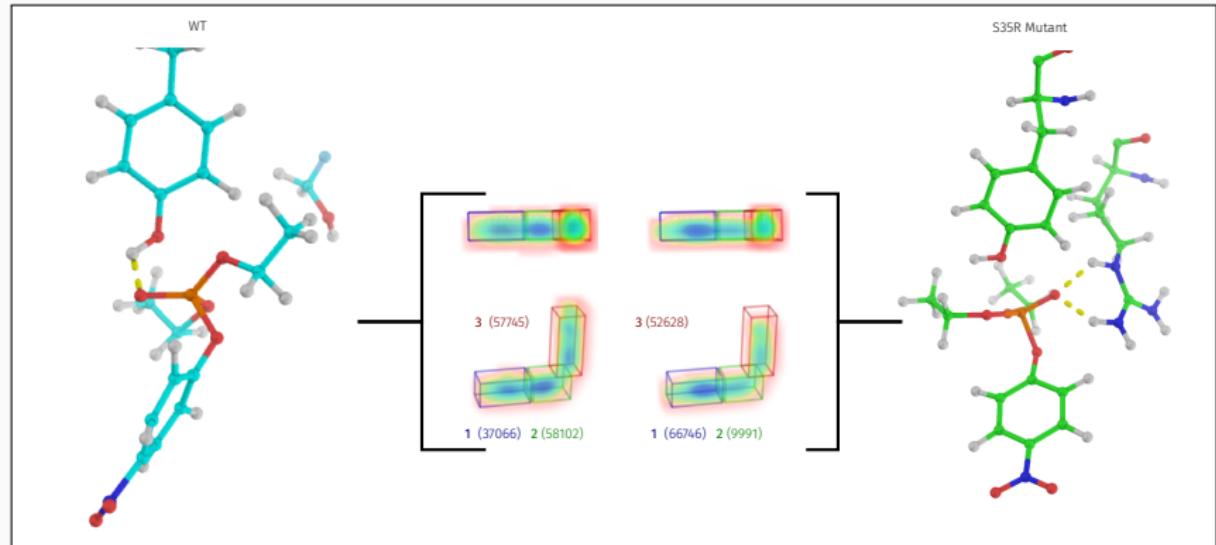
- Krebs Institute, UK

- Michael Blackburn

QM/MM Interface improvement was supported by Russian Ministry of Education and Science, project number RFMEFI57617X0095

The screenshot shows the header of the Science Advances journal website. The main title "Science Advances" is displayed in large white letters on a black background, with the AAAS logo to its right. Below the title is a red navigation bar with links for Home, News, Journals, Topics, and Careers. Underneath the red bar is a secondary navigation bar with links for Science, Science Advances (which is underlined), Science Immunology, Science Robotics, Science Signaling, and Science Translational Medicine. At the bottom of the page, there is a "SHARE" section with social media icons for Facebook, Twitter, and LinkedIn, followed by the article title "Robotic QM/MM-driven maturation of antibody combining sites" and the author list "Ivan V. Smirnov^{1,*}, Andrey V. Golovin^{1,*}, Spyros D. Chatziefthimiou^{2,3}, Anastasiya V. Stepanova^{1,2,4}, Yingji...".

ПОЧЕМУ МУТАНТ ЛУЧШЕ?



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

METHODS

- 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

