

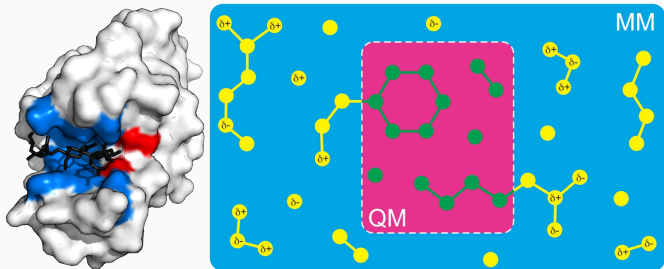
QM/MM APPLICATIONS WITH GROMACS

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2018

Moscow State University, Moscow

SIMULATION OF ENZYMES



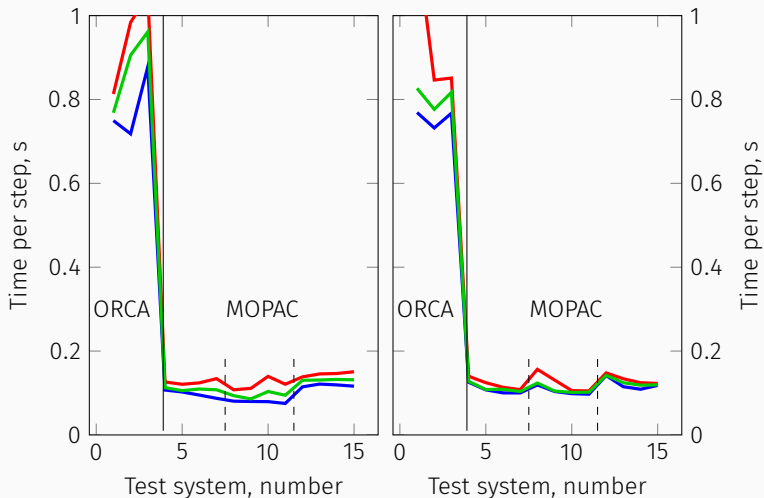
$$E = \frac{k}{2}(b_0 - b)^2$$

$$H\Psi = E\Psi$$

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

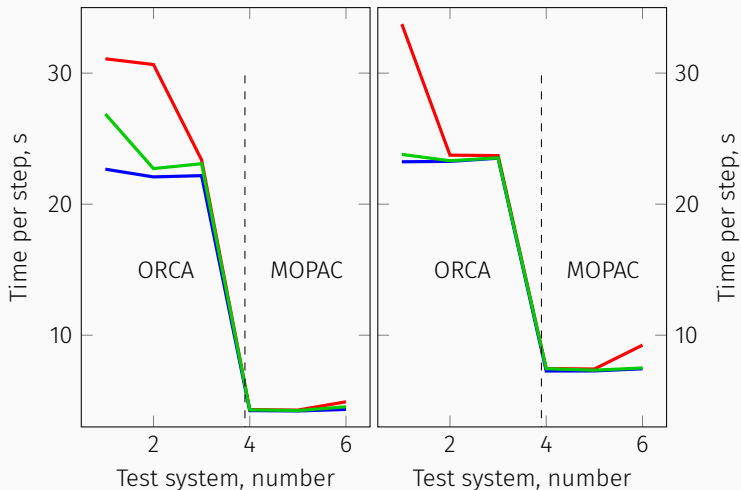
<https://en.wikipedia.org>

PERFORMANCE WITH 64 QM ATOMS



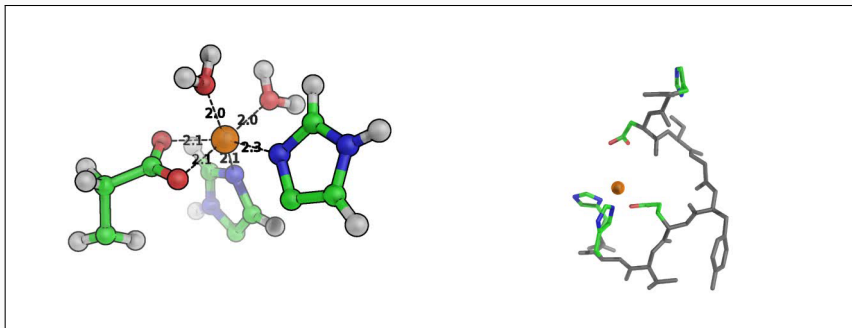
Performance of QM/MM packages for the "small" system on local workstation (left) and supercomputer "Lomonosov-2" wit Lustre filesystem (right).

PERFORMANCE WITH 400 QM ATOMS



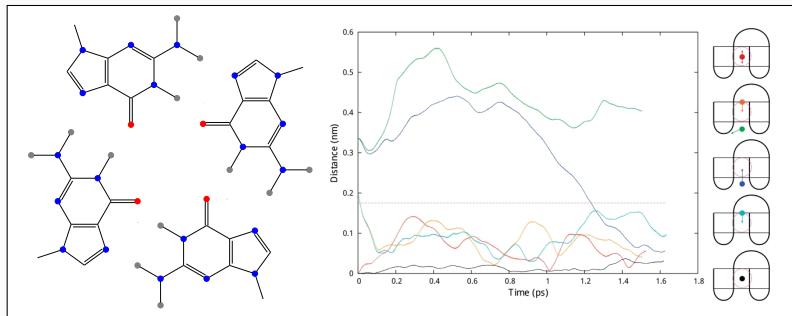
Performance of test systems for the "big" system on local workstation (left) and supercomputer "Lomonosov-2" wit Lustre filesystem.

SIMPLE SYSTEMS, ZN



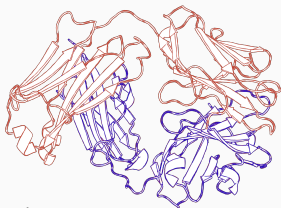
Biophys J. 2010 Nov 17; 99(10): L84–L86.

UNUSUAL DNA, G-QUADRUPLEX

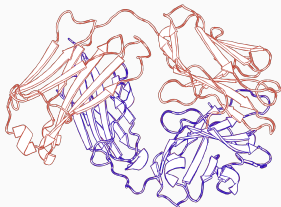


Nucleic Acids Res. 2011 Dec;39(22):9789-802. doi: 10.1093/nar/gkr639.

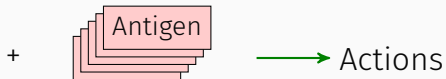
MEDICAL IMPORTANCE

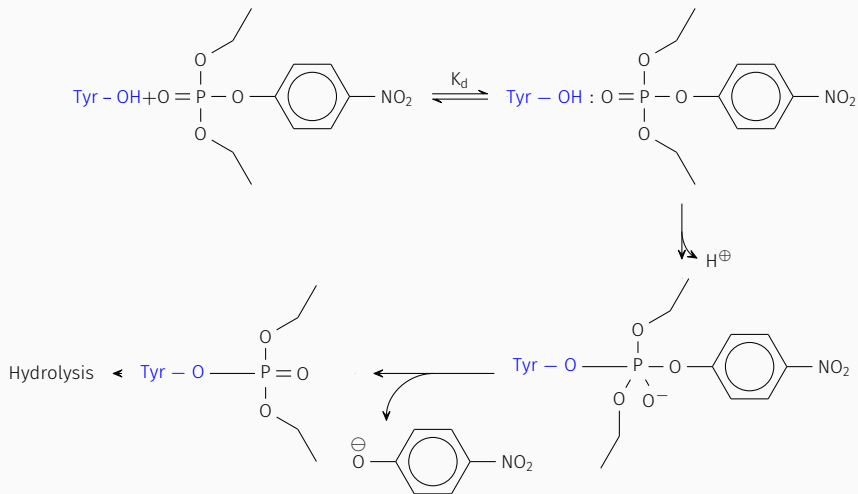


Antibody



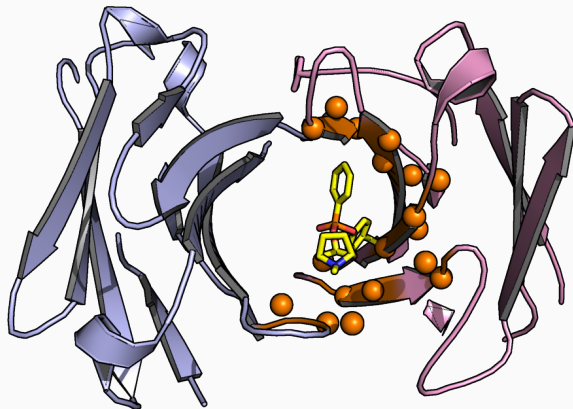
Abzyme





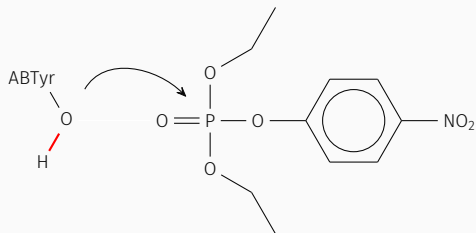
Smirnov et al, PNAS 2011

COMBINATORIAL MUTATIONS

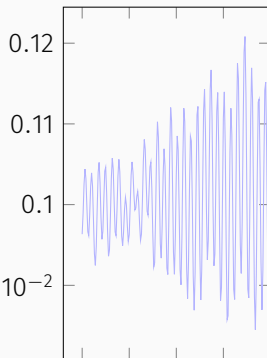


17 positions = 20^{17} mutants
We need to reduce sampling

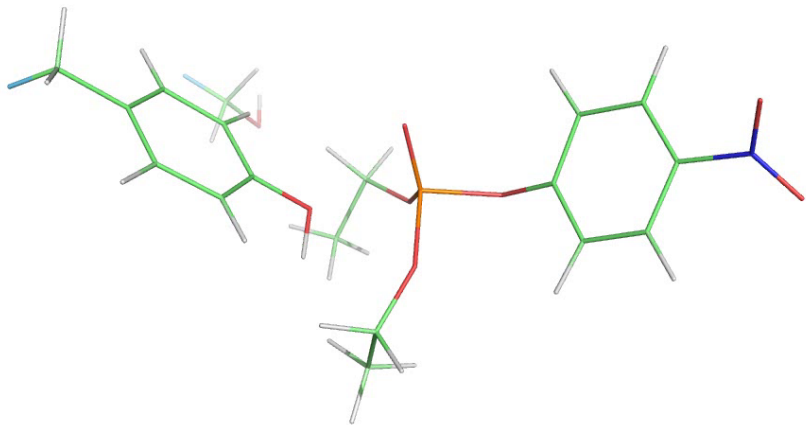
- we «warm up» the bond



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

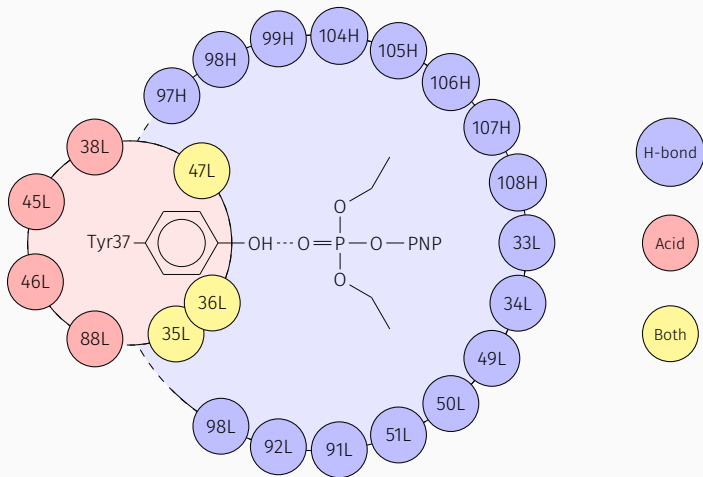


Liao & Parinello, 2002





TYPE OF MUATTIONS



17 positions = $2 * 10^6$ mutants

MUTANTS IN 3D

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

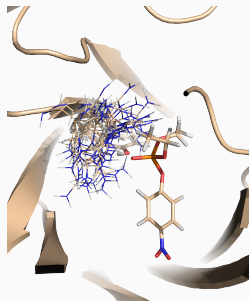
Mutate, 10^5 conformations

top 100

Optimize

Sort

top 3



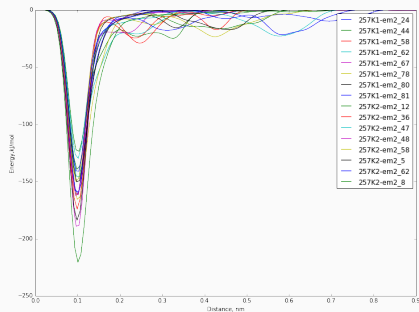
375 mutants selected (1125 systems) CPU query on Lomonosov-2

375 mutants * 3 replica

Sort on reaction fact

Sort on energy

top 10

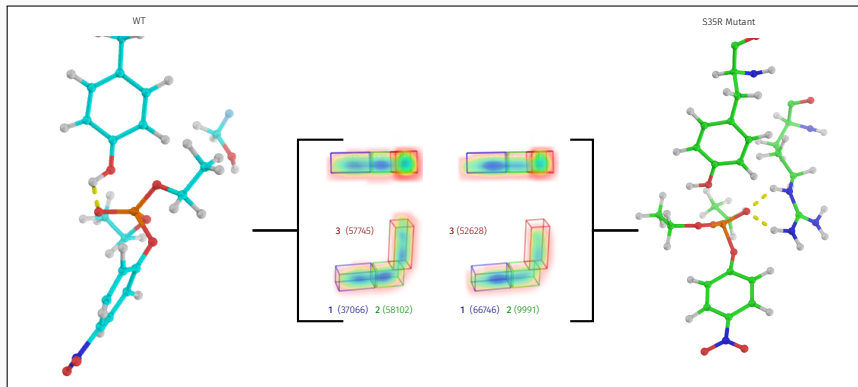


- H-bond donor aminoacids won
- 10 mutants was selected on CPU query Lomonosov-2

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

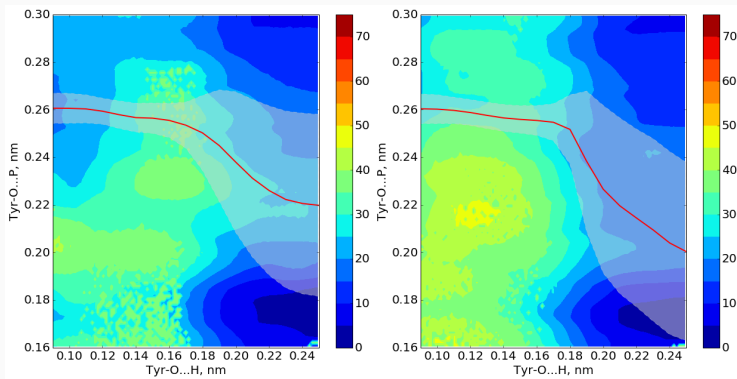
Smirnov, Golovin et al. Sci. Adv. 2016; 2:e1501695

WHY MUTANT1 IS BETTER?

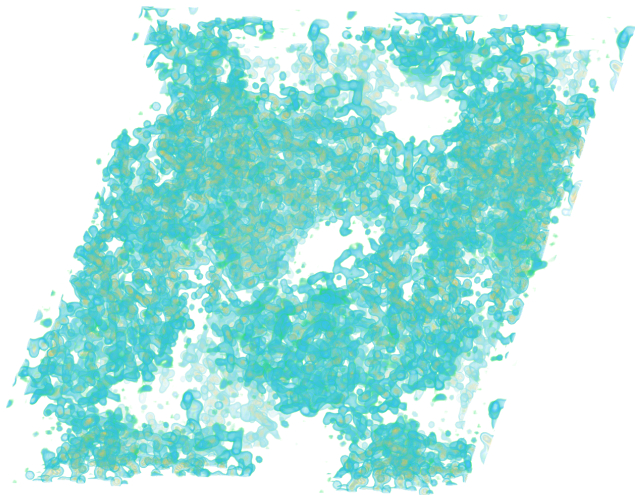


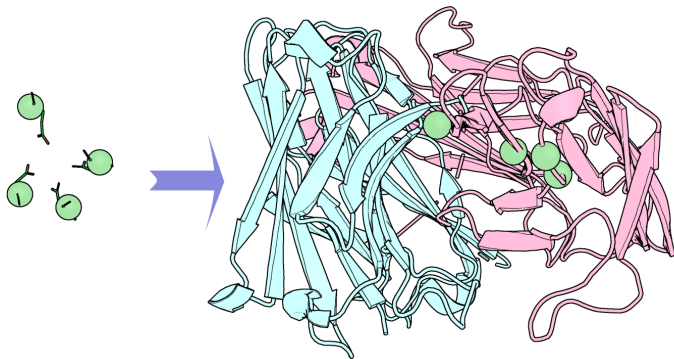
Smirnov, Golovin et al. *Sci. Adv.* 2016; 2:e1501695

DIFFERENT MUTANTS, DIFFERENT MECHANISMS



VFEP, UWHAM, WHAM-2D to be published ASAP





ACTIVE CENTER TRANSFER

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

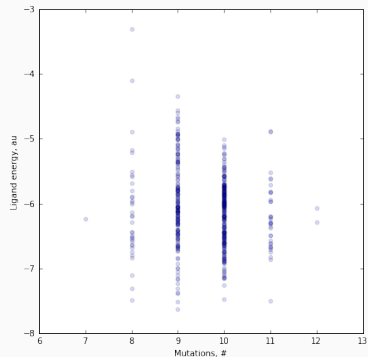
Active center positions, up to 10^3

top 100

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

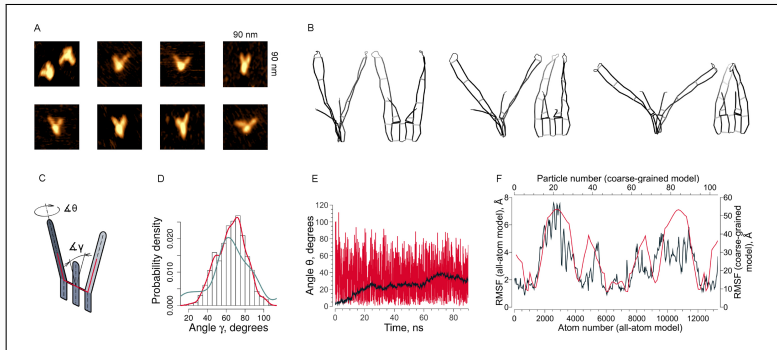
Sort

top 1000 QM/MM



15 mutants selected

UNNATURAL DNA, DNA-ORIGAMI



Nucleic Acids Res. 2018 Feb 16; 46(3): 1102–1112.

Authors

- Artur Zalevsky



- Olga Zolotoreva

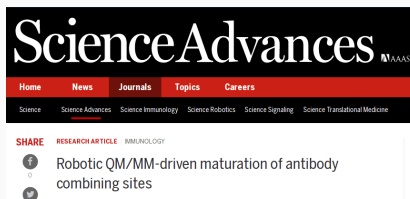


- Alexander Zlobin
- Valentina Maslova
- Andrei Demkiv

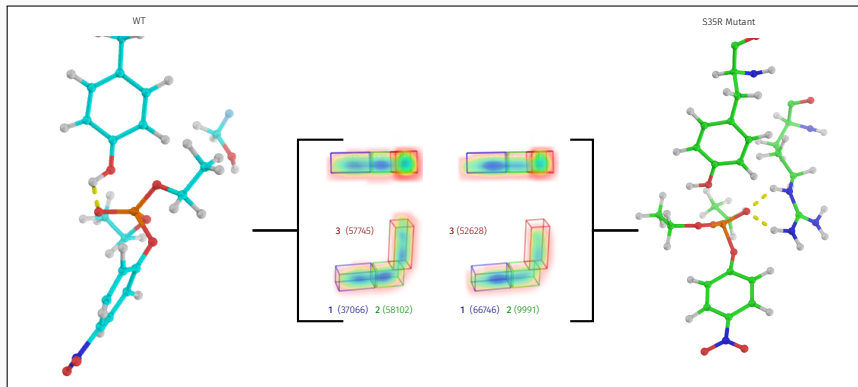
Collaborators

- IBCH RAS, Moscow
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- Krebs Institute, UK
Michael Blackburn

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ПОЧЕМУ МУТАНТ ЛУЧШЕ?



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

- 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

