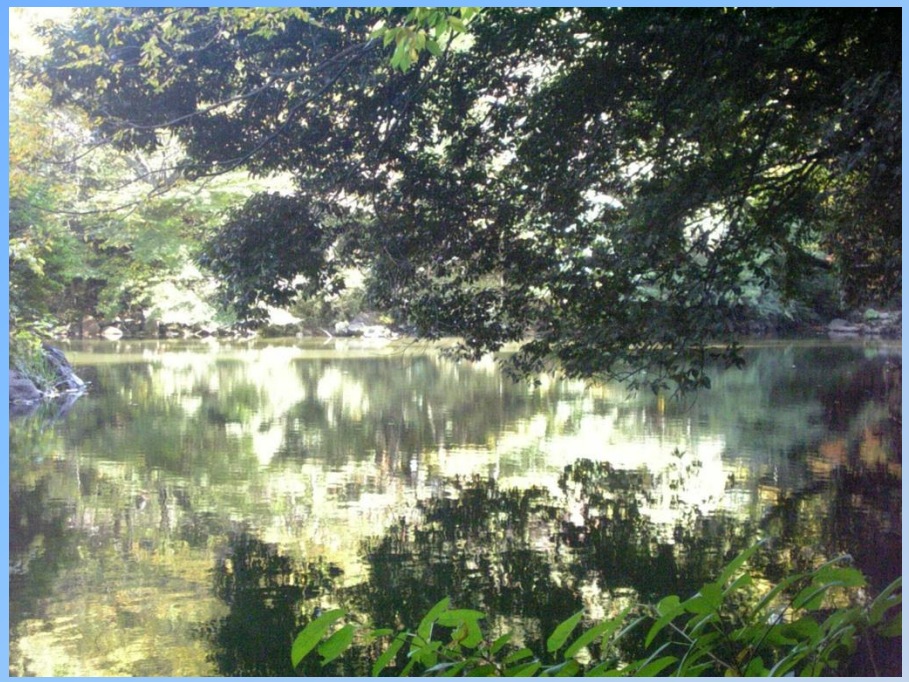
創薬応用シミュレーション



三四郎池

東京大学先端研
藤谷 秀章

How to develop a pharmaceutical

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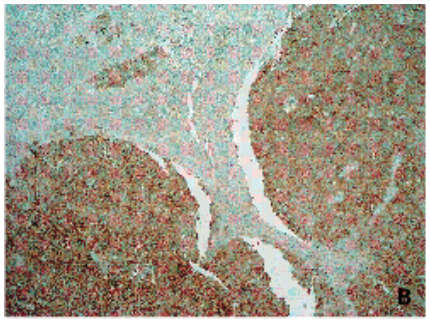
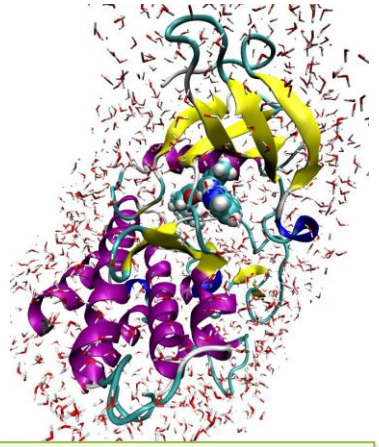
Pathology (tissue, virus)

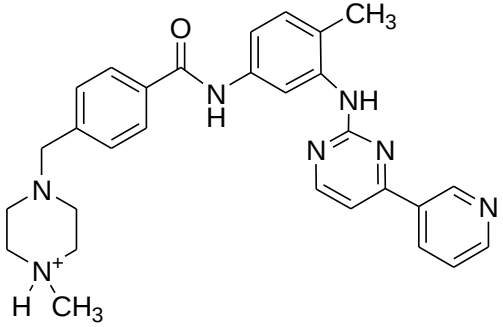


Clinical trial

Animal test

Chemical assay
Cell culture assay





Target protein → Drug design → Chemical synthesis

Critical assessment of docking simulation

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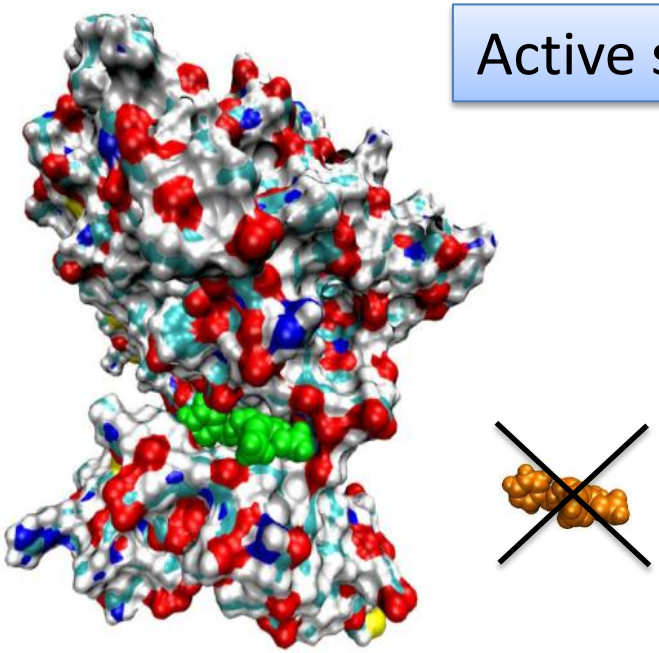
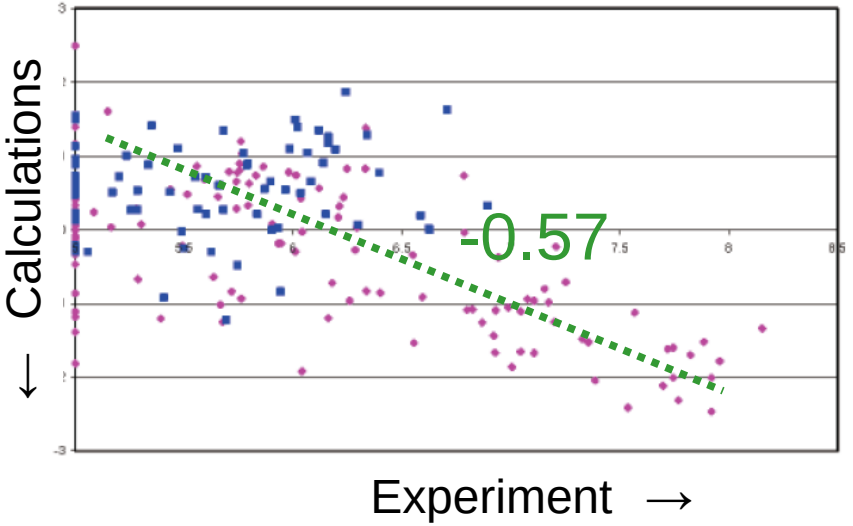
Small molecules fit the binding pocket ?

Active site structure ⟺ Molecule



Binding affinity (Activity)

Binding affinity of docking simulations



Warren et al, J Med. Chem., (2006)
GlaxoSmithKline

All atom molecular dynamics

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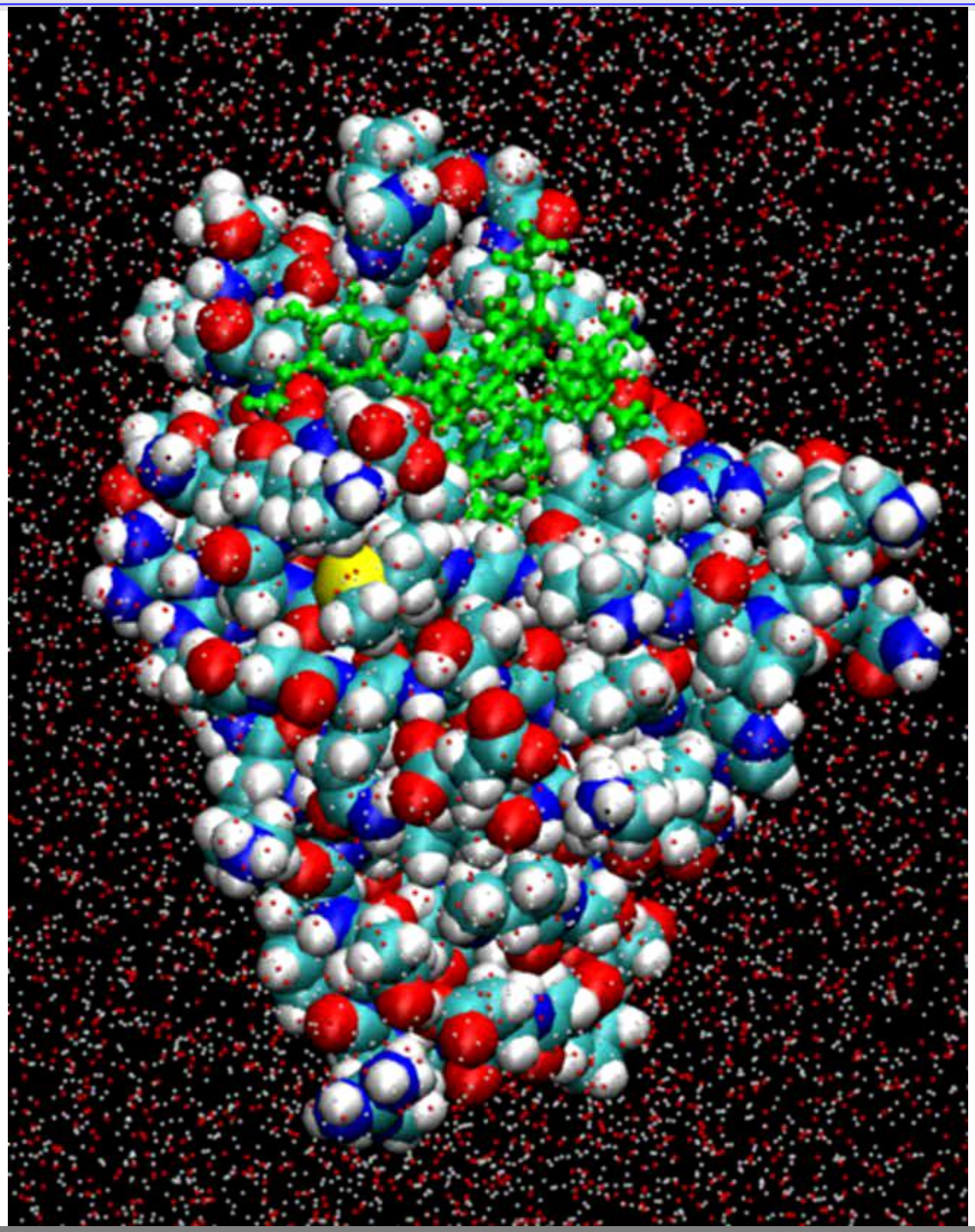

- Protein: FKBP
  Small (107 residues)
  Extremely stable

- Ligands: FK506
  Highly potent immunosuppressant activity

- Structure:
  Well-defined hydrophobic pocket

Time scale of protein dynamics

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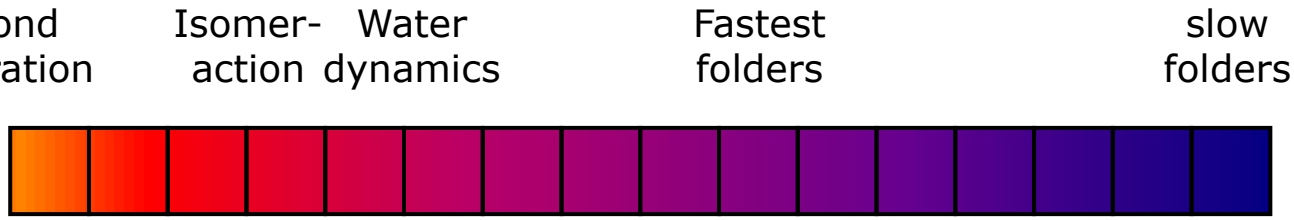
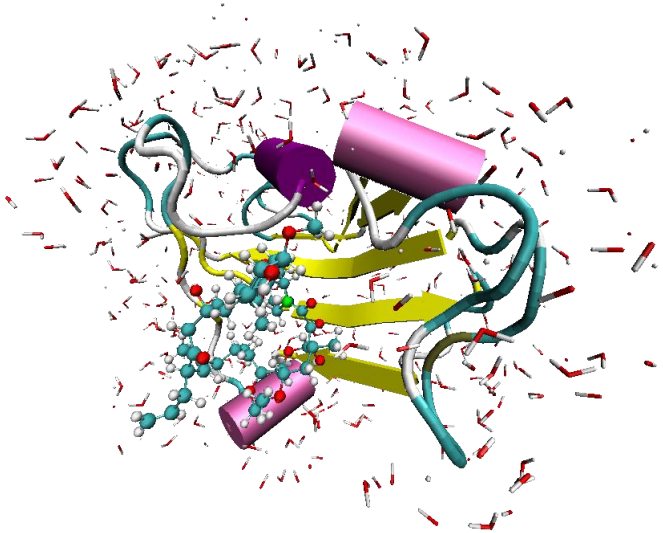


1MD step

Molecular dynamics for protein structure change



1 microsecond (10^{-6}s) → 10^{9} steps
1CPU: 1second/1step → 32 years

High performance computation

Conformation energy difference

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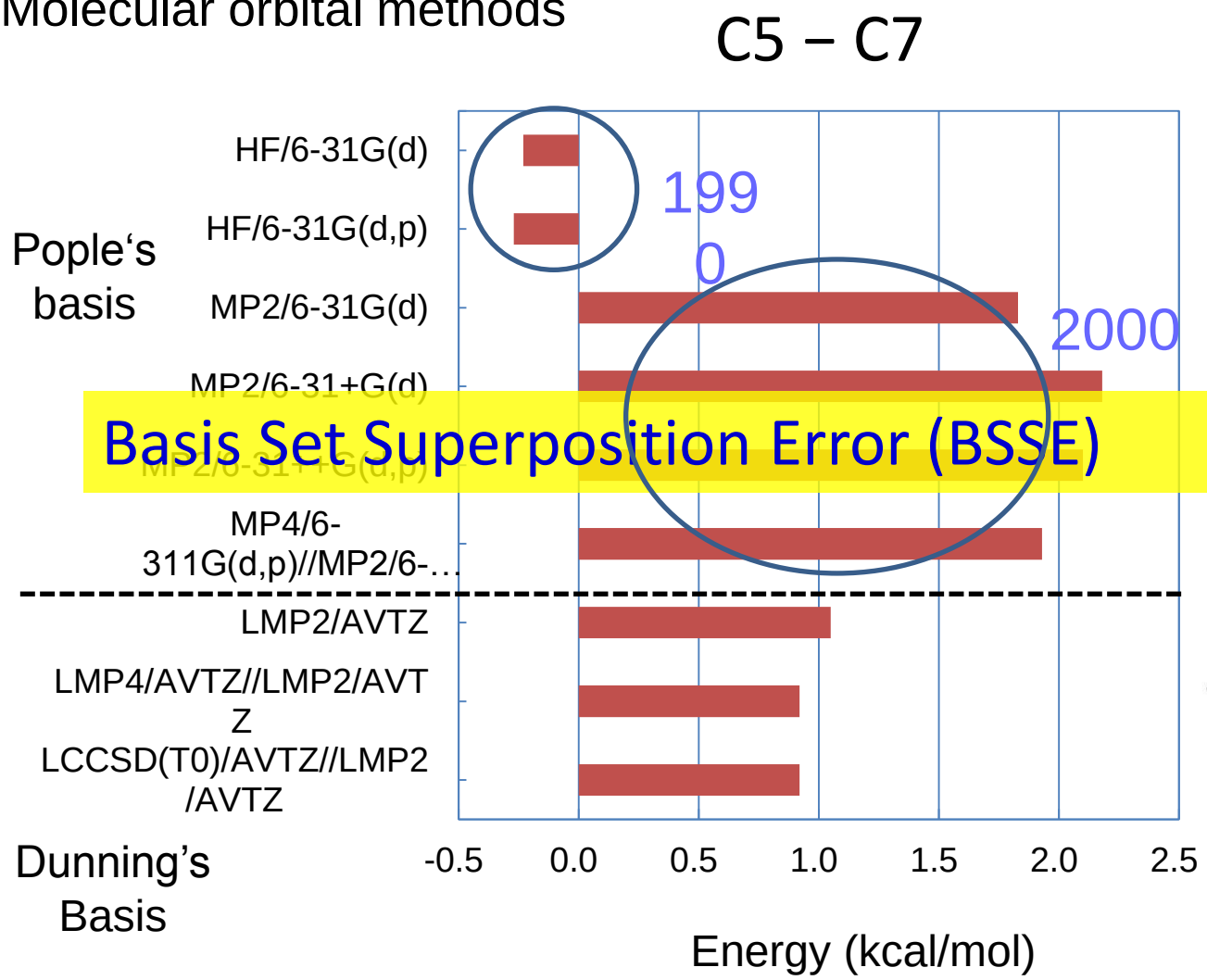
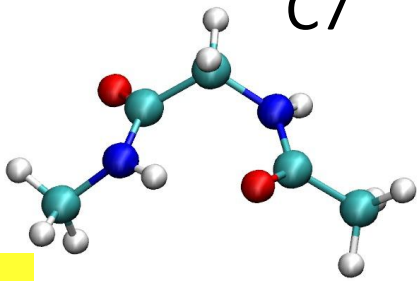
Molecular orbital methods



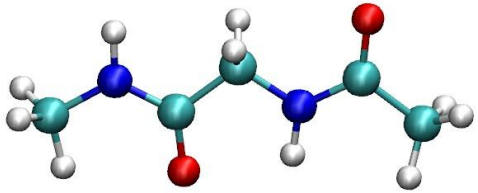
Basis Set Superposition Error (BSSE)

Glycine dipeptide

C7



C5



Fujitani et al, JCTC 5, 1155 (2009)

Protein backbone dihedral energy profile

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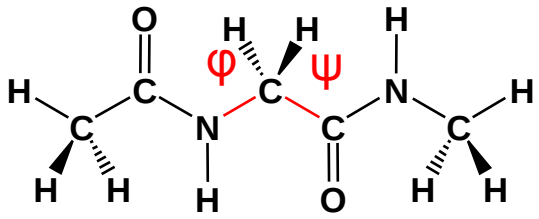
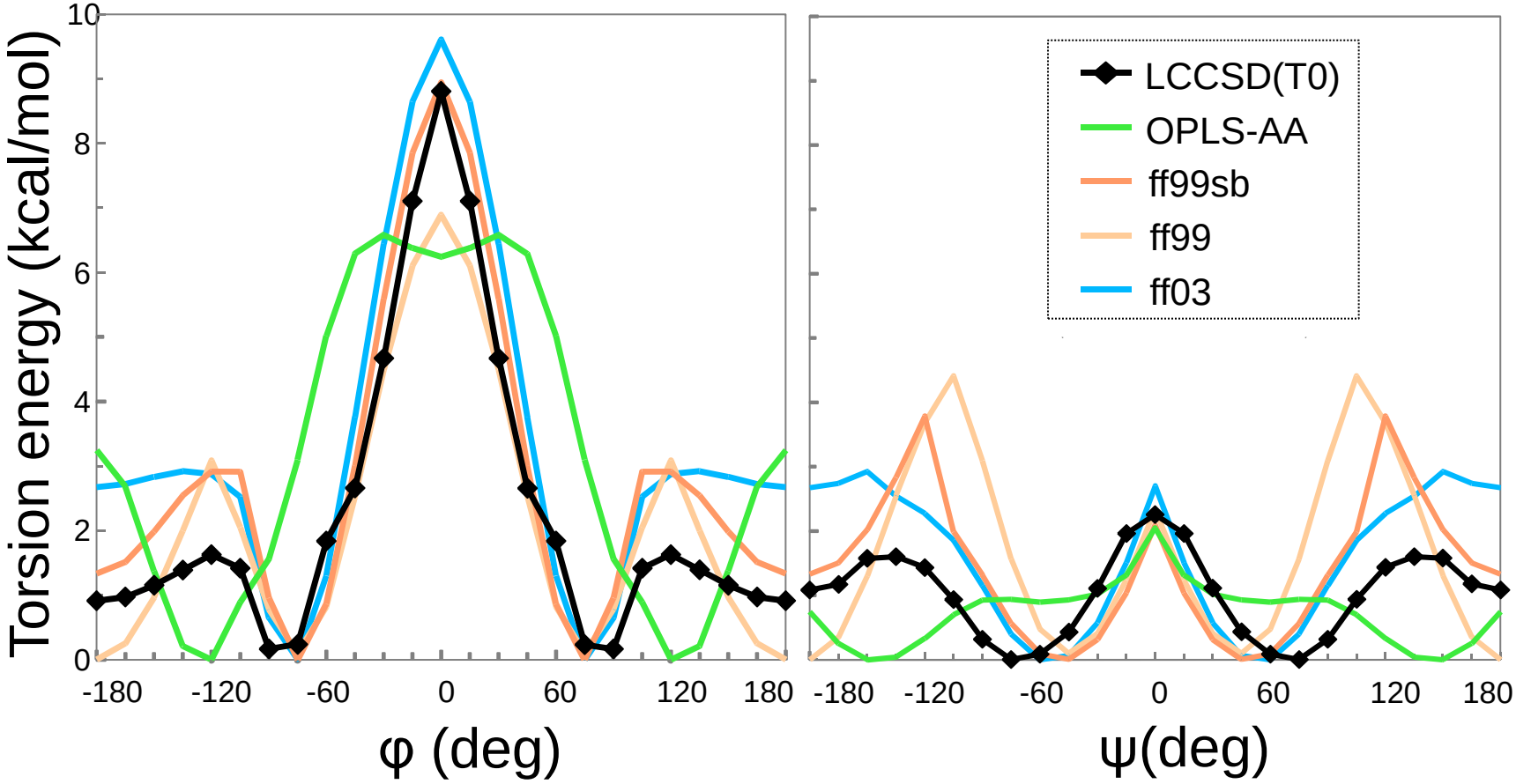


Glycine dipeptide



LCCSD(T0)/AVTZ //LMP2/AVTZ

Fujitani et al, JCTC 5, 1155 (2009)

De novo drug design

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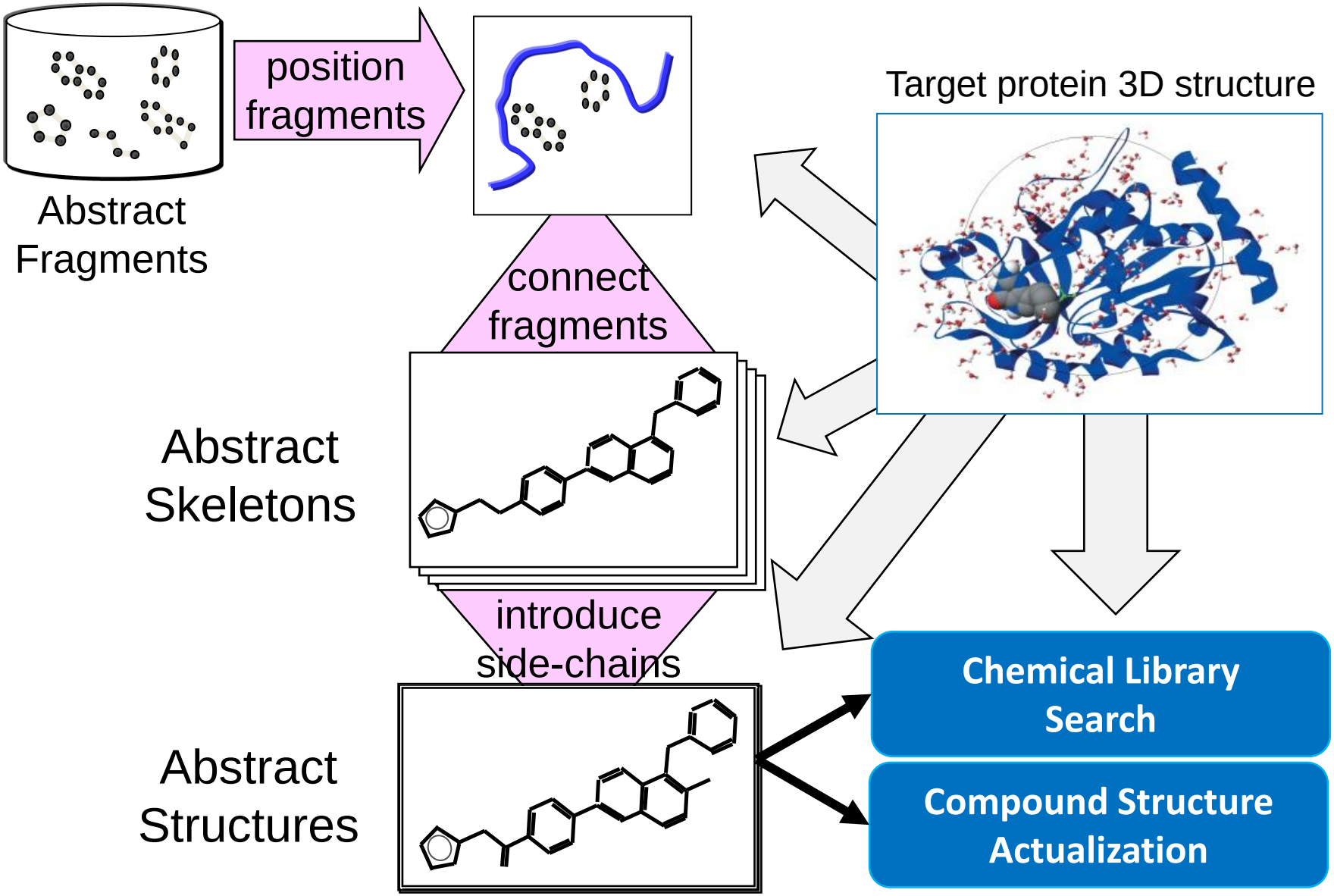

Abstract Fragment based Structuring

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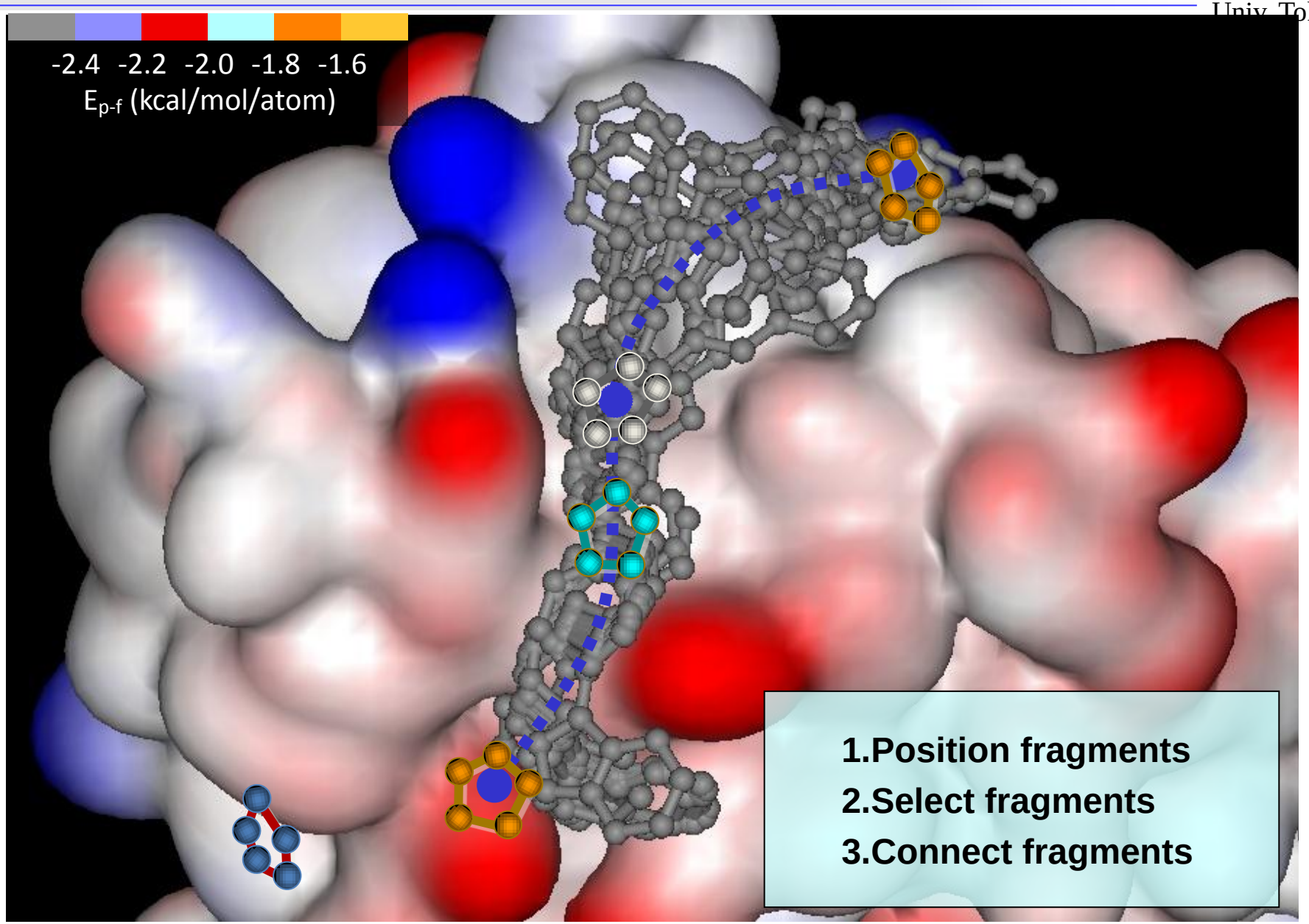

Nonequilibrium equality

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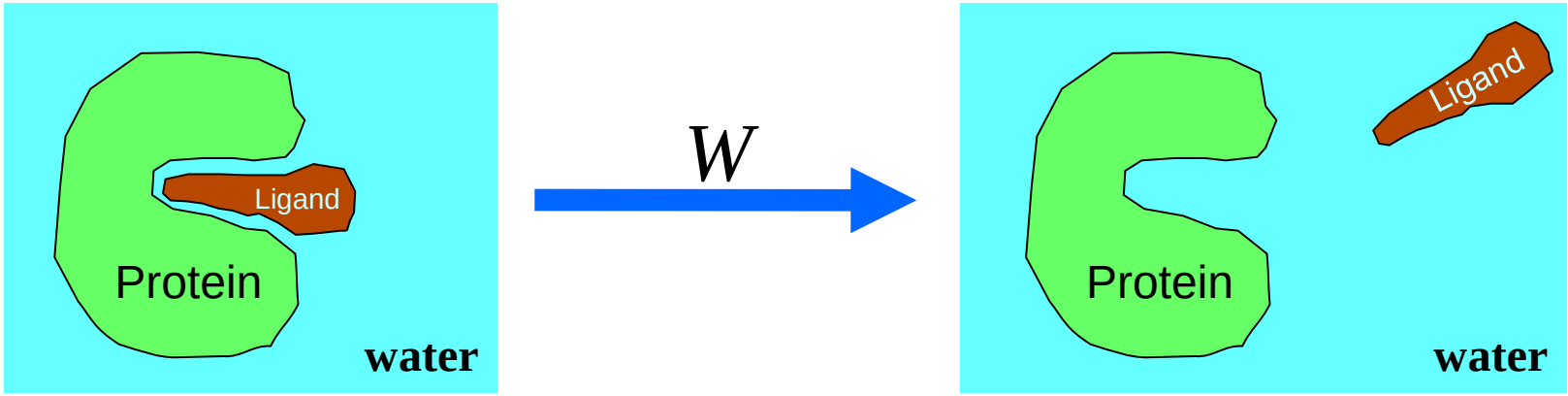
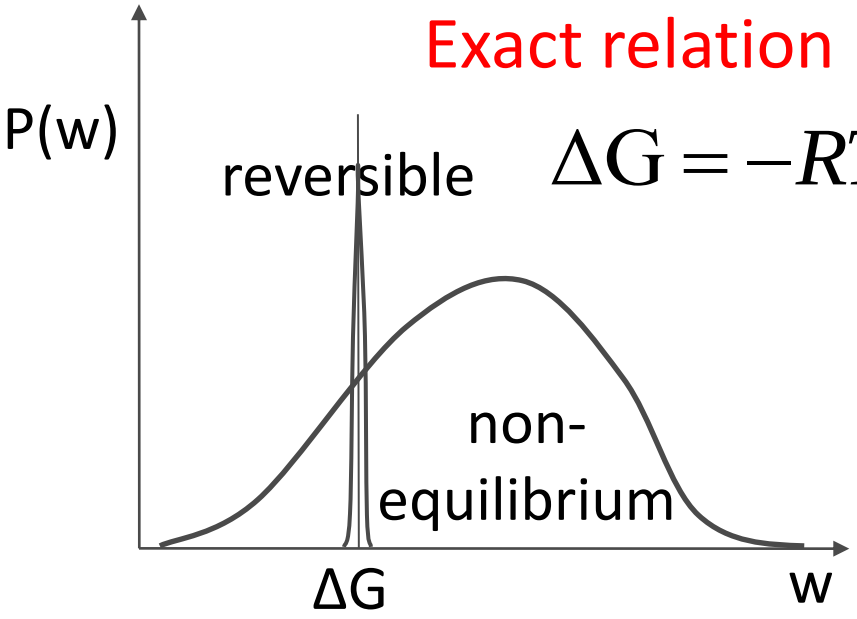


Exact relation but difficult sampling

$$\Delta G = -RT \ln \langle \exp(-W/RT) \rangle$$



Jarzynski (1997)

thermodynamic limit

Cuendet (2006)

Nosé-Hoover thermostat

Irreversible free energy calculation !!

Parallel phase space sampling

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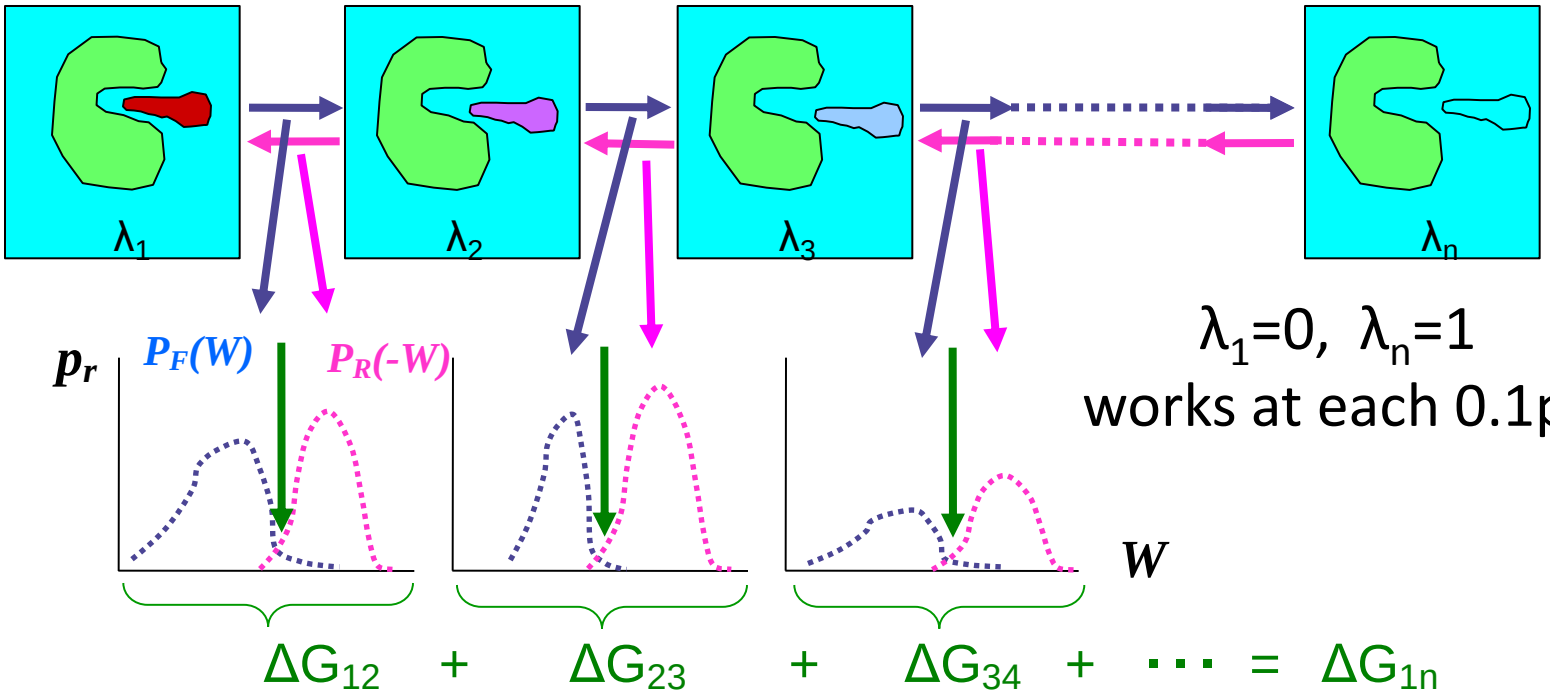
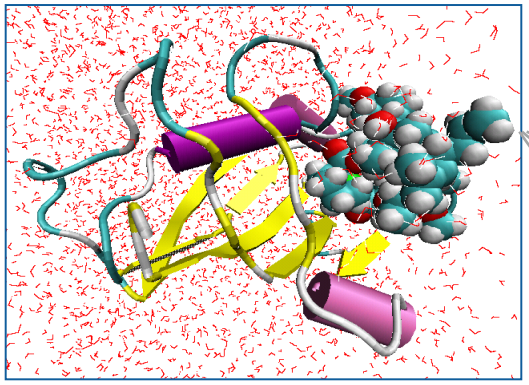
Annihilate interaction strength of ligand to other molecules: λ_i



Interaction strength		Trajectories	Total
32 λ points	X	12	= 384

Fujitani et al, JCP (2005)

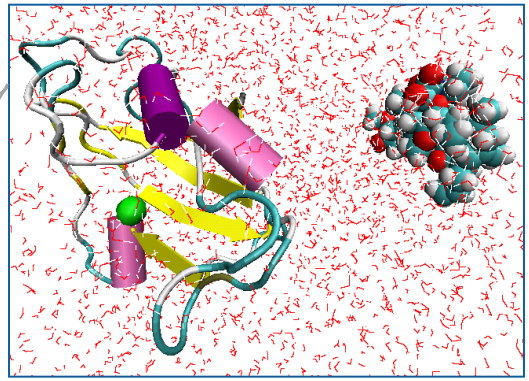
Massively Parallel Computation of Absolute binding FrEe Energy



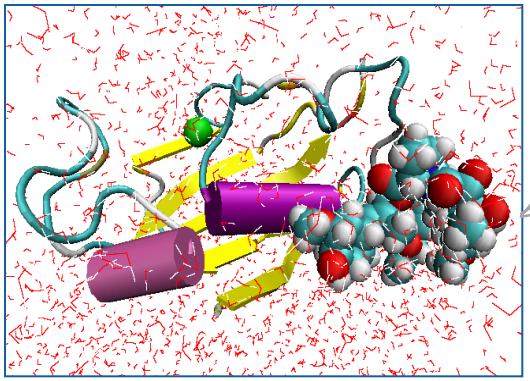
$\lambda = \lambda_1$

MD_{11}
MD_{12}
MD_{13}
:

MD_{n1}
MD_{n2}
MD_{n3}
:



$\lambda = \lambda_n$



$\lambda = \lambda_i$

MD_{i1}
MD_{i2}
MD_{i3}
:

$$||\mathbf{MD}|| = ||\lambda|| \times ||\mathbf{trajectories}|| \times ||\mathbf{annihilation}||$$

Affinity of FKBP ligands

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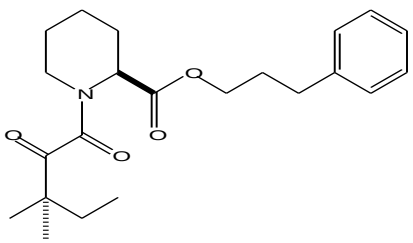

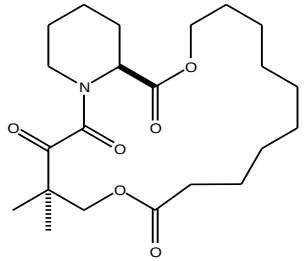

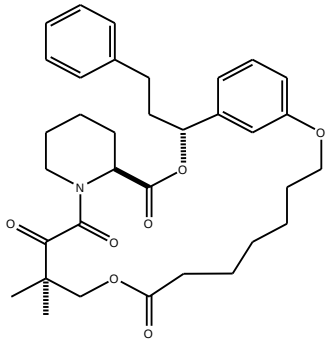

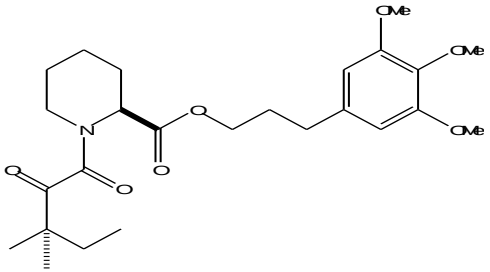

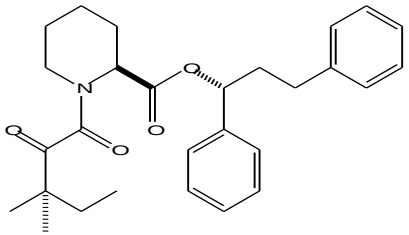

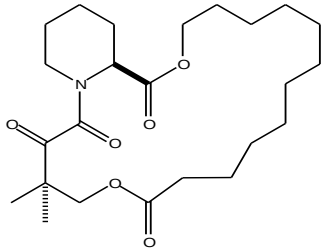

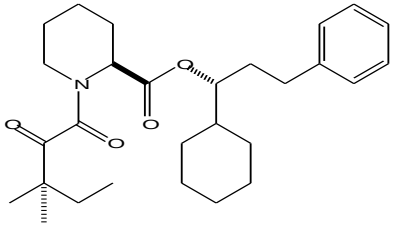

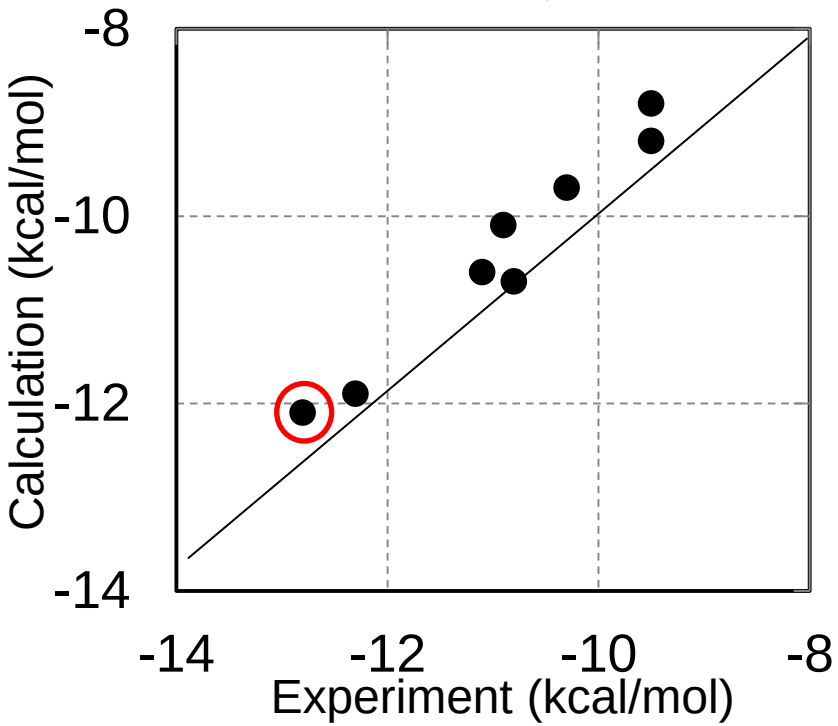

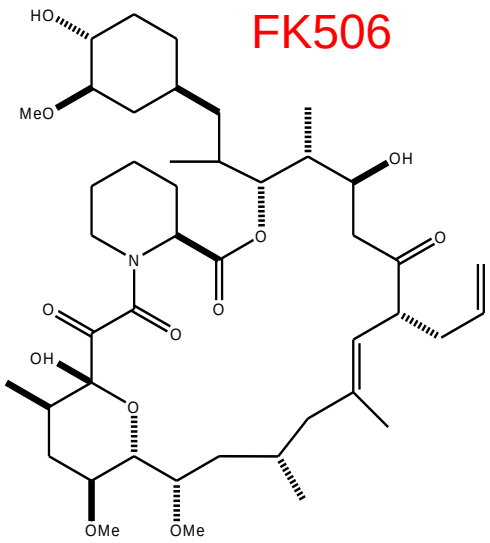

Fujitani et al, PRE (2009)

Highly optimized GROMACS to K computer

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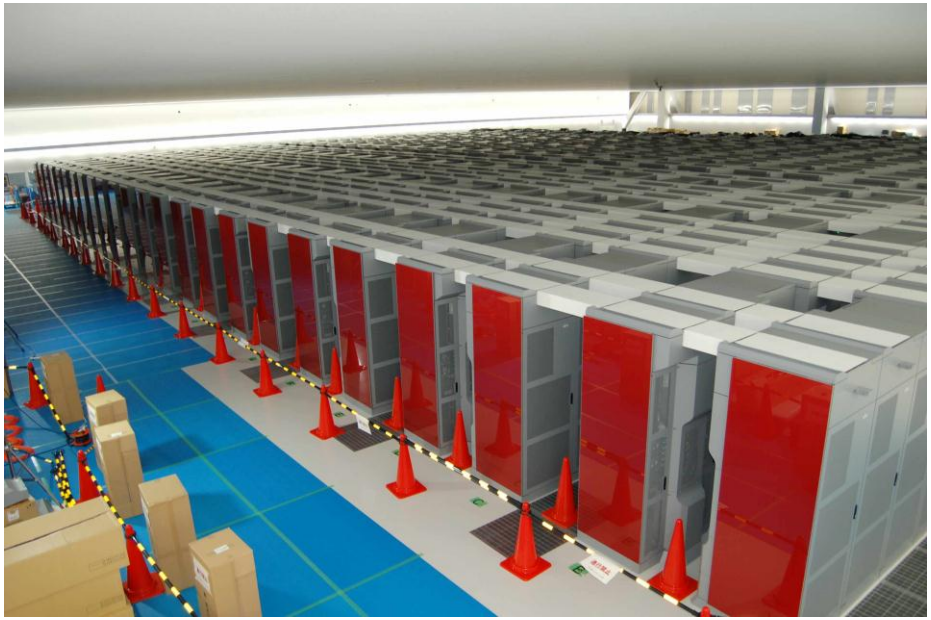
Linpack:10.51 peta flops (2011)



CPU: SPARC64viiifx (8 cores)
88,128 CPU x 8 = 705,024 cores

H. Fujitani, E. Akhmatskaya, E. Lindahl, V. Pande

- Hybrid parallelization (OpenMP & MPI)
- Assembler codes