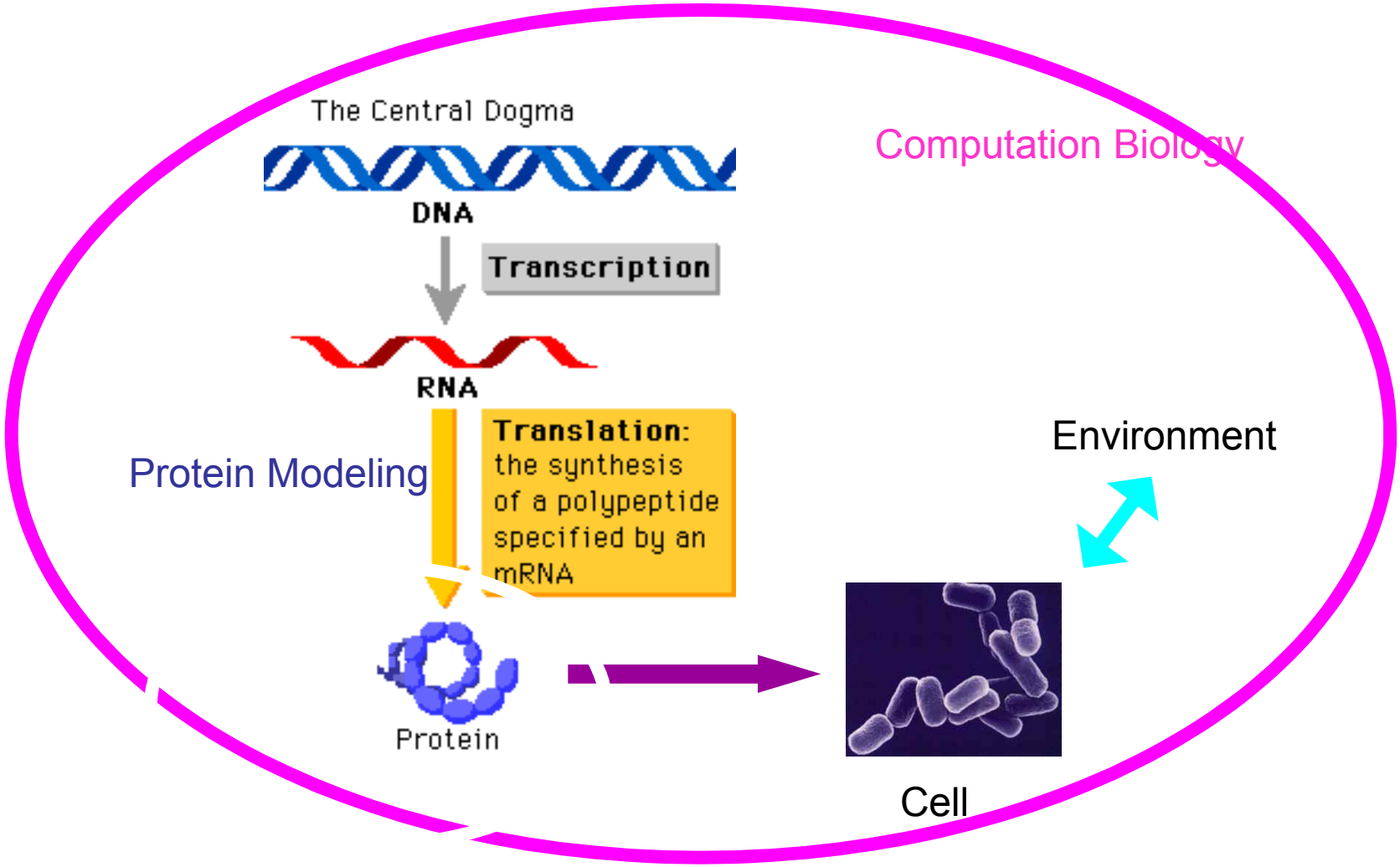
Enzyme Engineering

10. Softwares for protein engineering

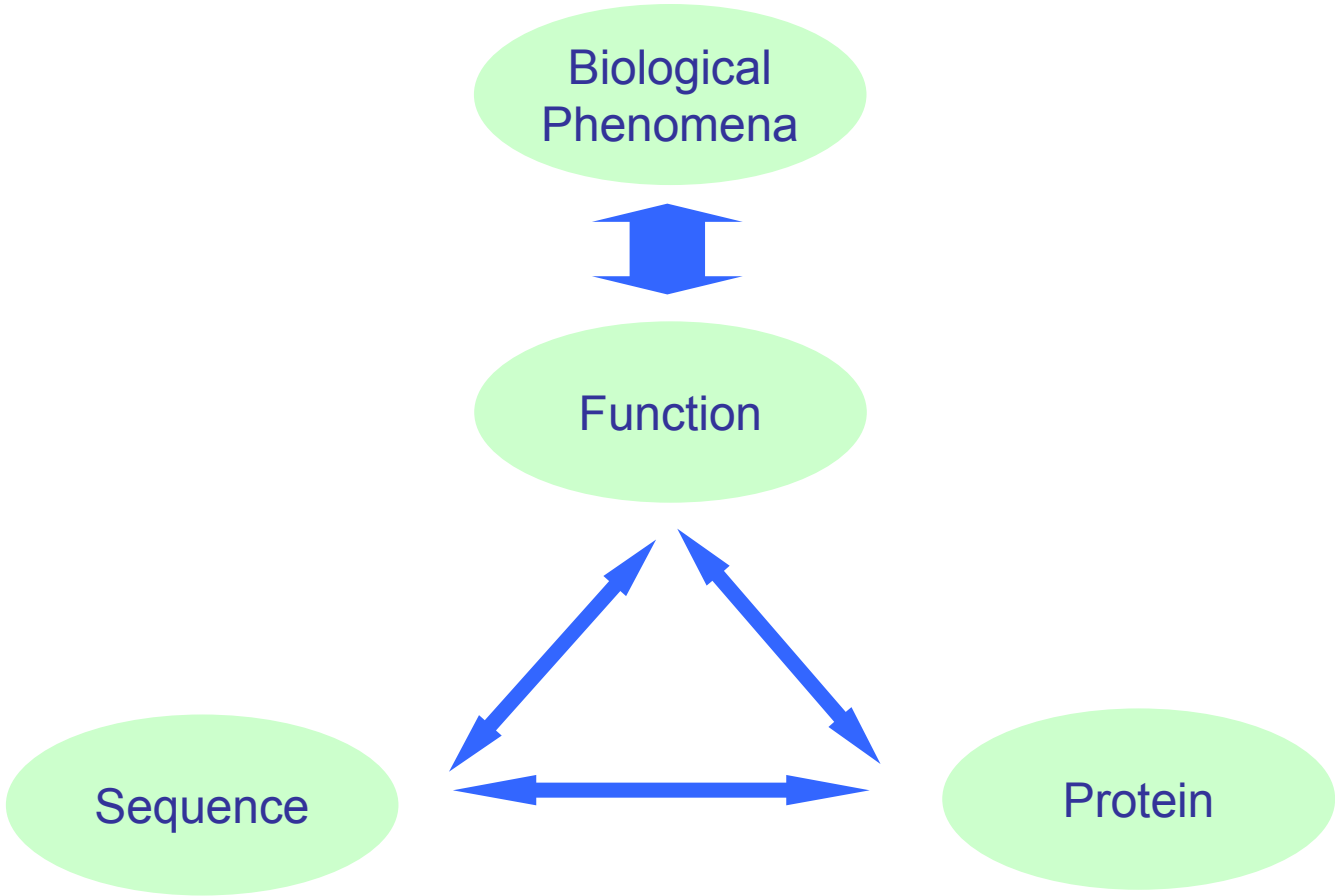
Central dogma

- Central dogma of molecular biology



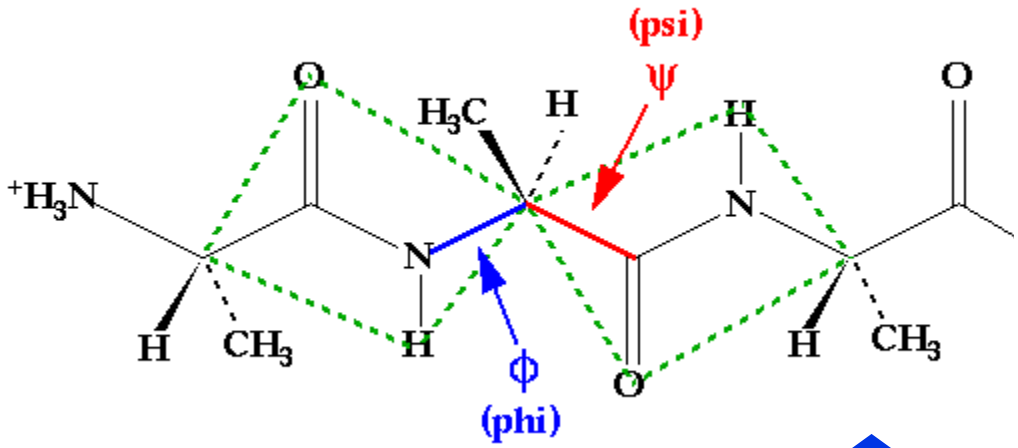
Central dogma

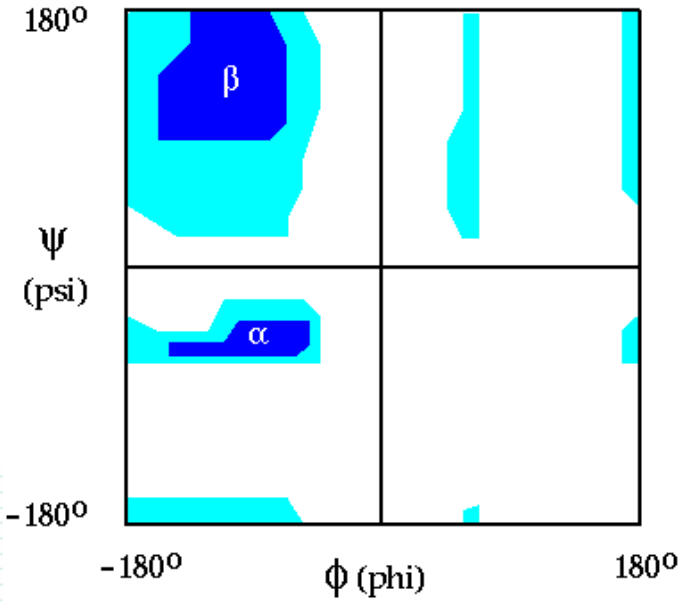
- Central dogma of molecular biology

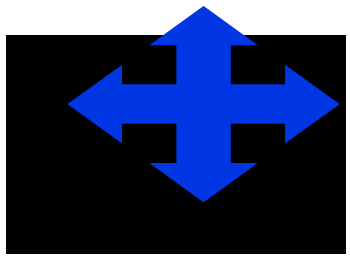


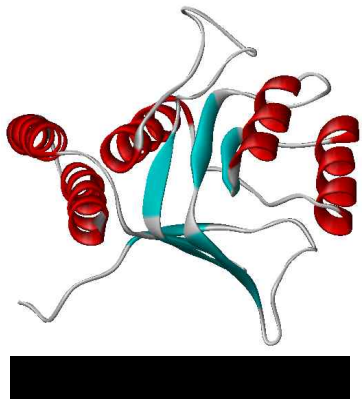
Protein structure

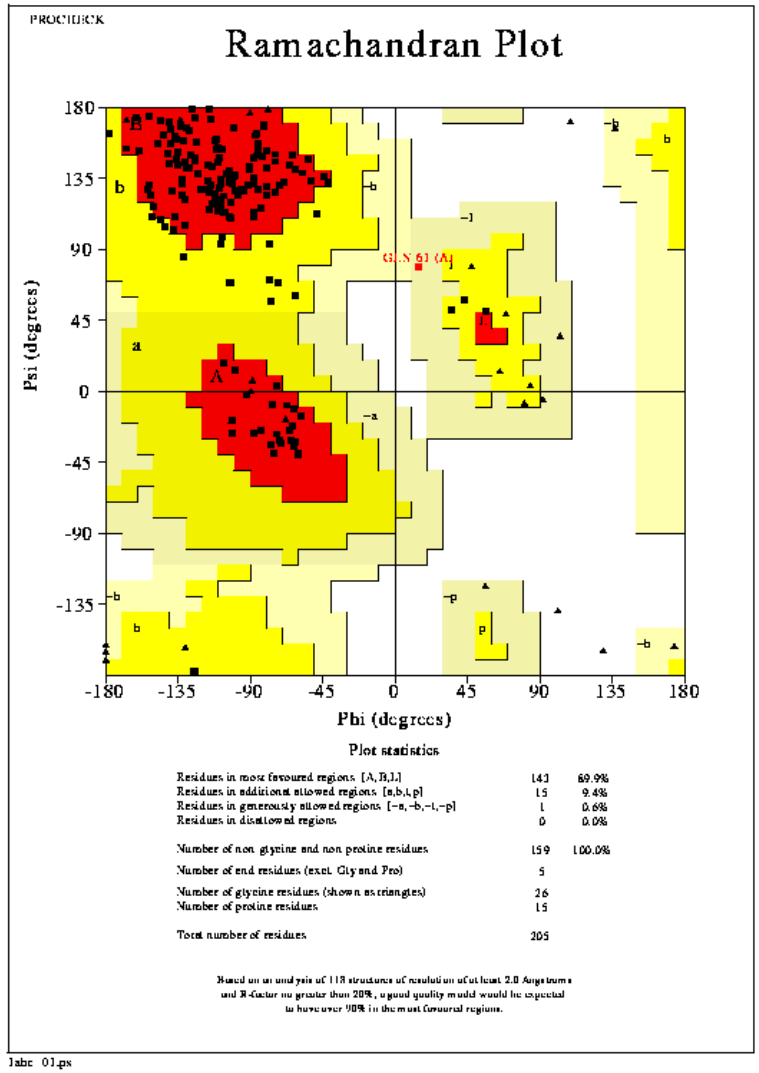
- Protein structure validation: Ramachandran plot









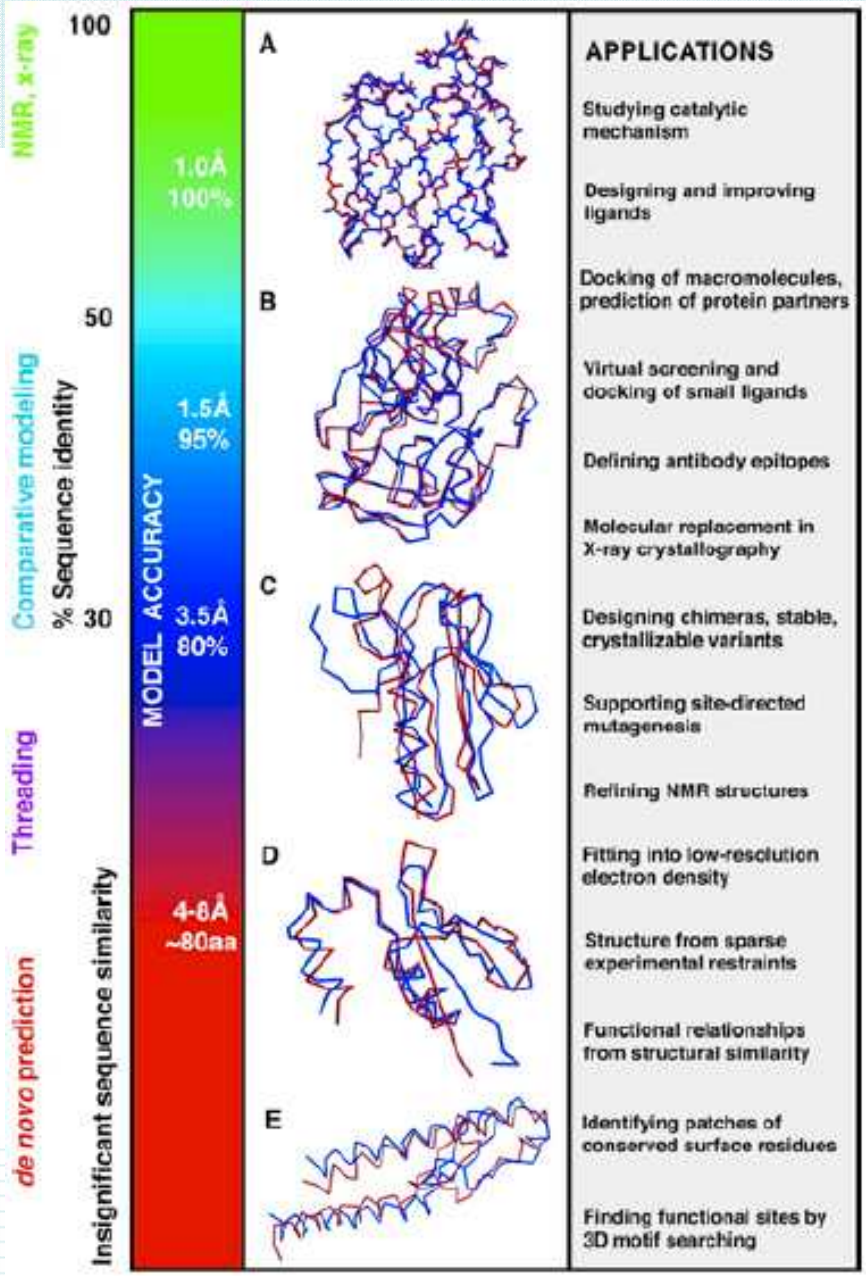


Protein structure

❍ How to predict
protein structure?

✓ Experimental
- X-ray crystallography
- NMR

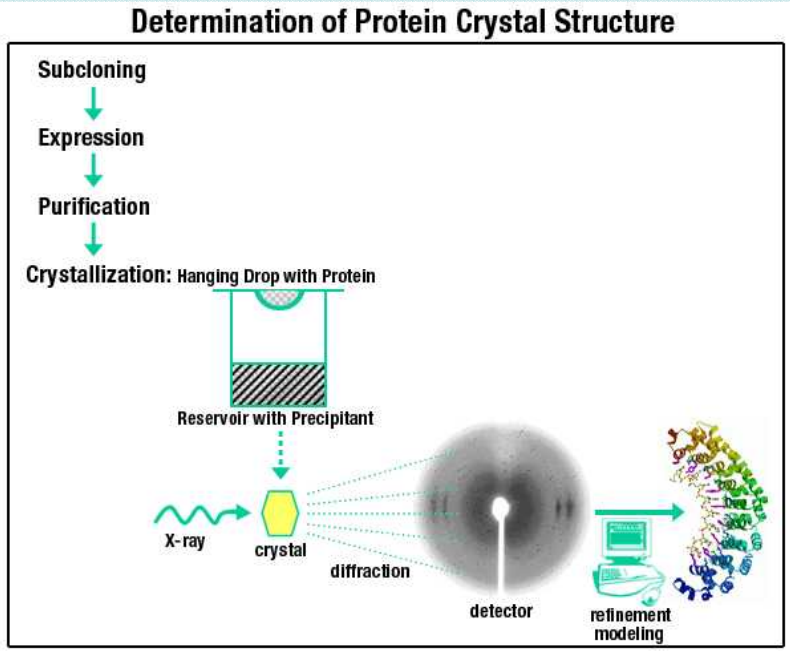
✓ Simulational
- Comparative method
- Threading method
- *Ab initio* method



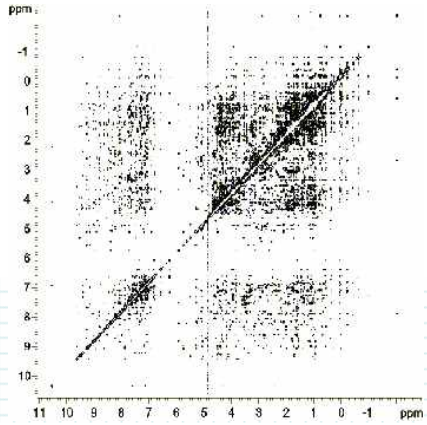
Protein structure

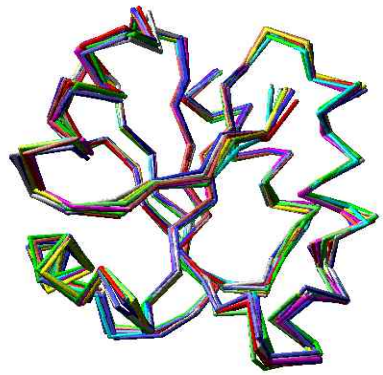
❍ Experimental

✓ X-ray crystallography
- No size limitation
- Single structure



✓ NMR
- Structure determination from chemical shift
- Multiple ensemble structures
- less than 300 a.a





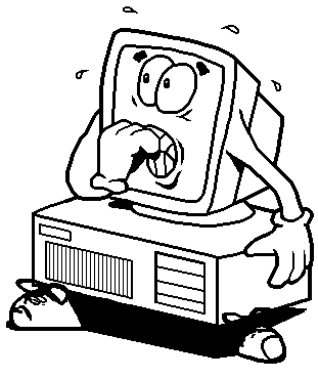
Protein structure

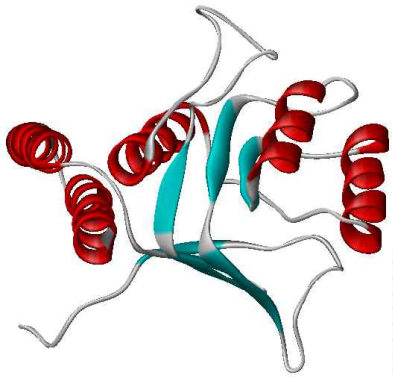
❍ Simulational

✓ *Ab initio* method

- Ab initio = “from the beginning”; in strictest sense uses first principle, not information about other protein structure
- Size limitation : less than 50~60 a.a
- expensive computing time
- Good for finding new fold structure
- Not exact method for already existed fold structure

AKWDSTF
KKGGGLLL





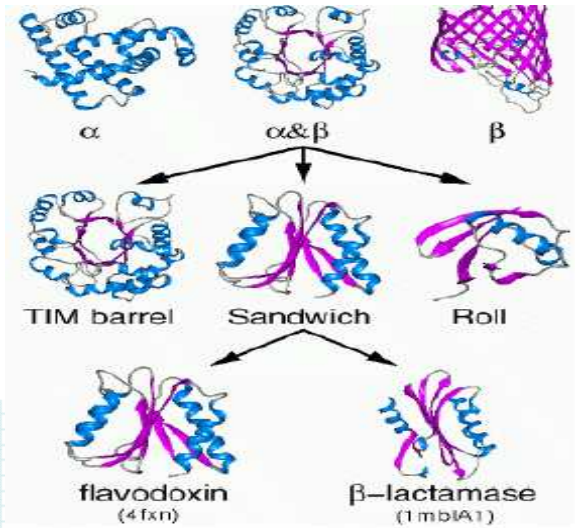
Protein structure

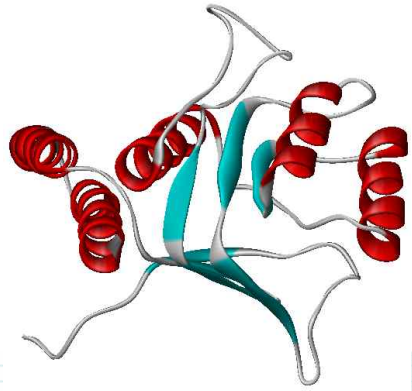
❍ Simulational

✓ Homology modeling

- Comparative protein modeling
- Knowledge – based modeling
- Extrapolation of the structure for a new sequence (target) form the known 3D structure of related family members (template)

AKWDSTF
KKGGGLLL





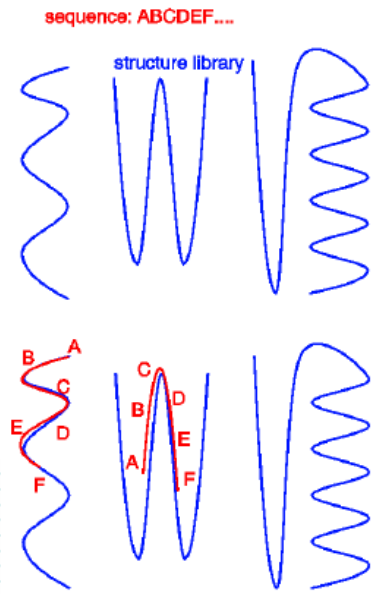
Protein structure

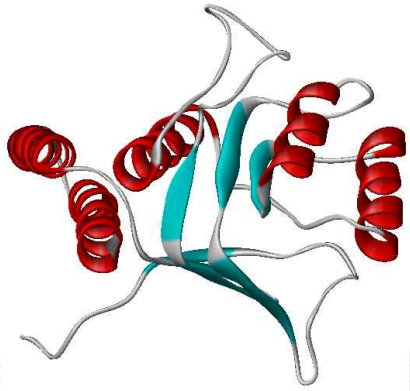
❍ Simulational

✓ Threading method (Folding recognition)

- Find a compatible fold for a given sequence
- Take all possible segments from all PDB structures, “Thread” a target sequence through all conformations and compute some energy value
- Lowest energy conformations are predicted conformations for that segment

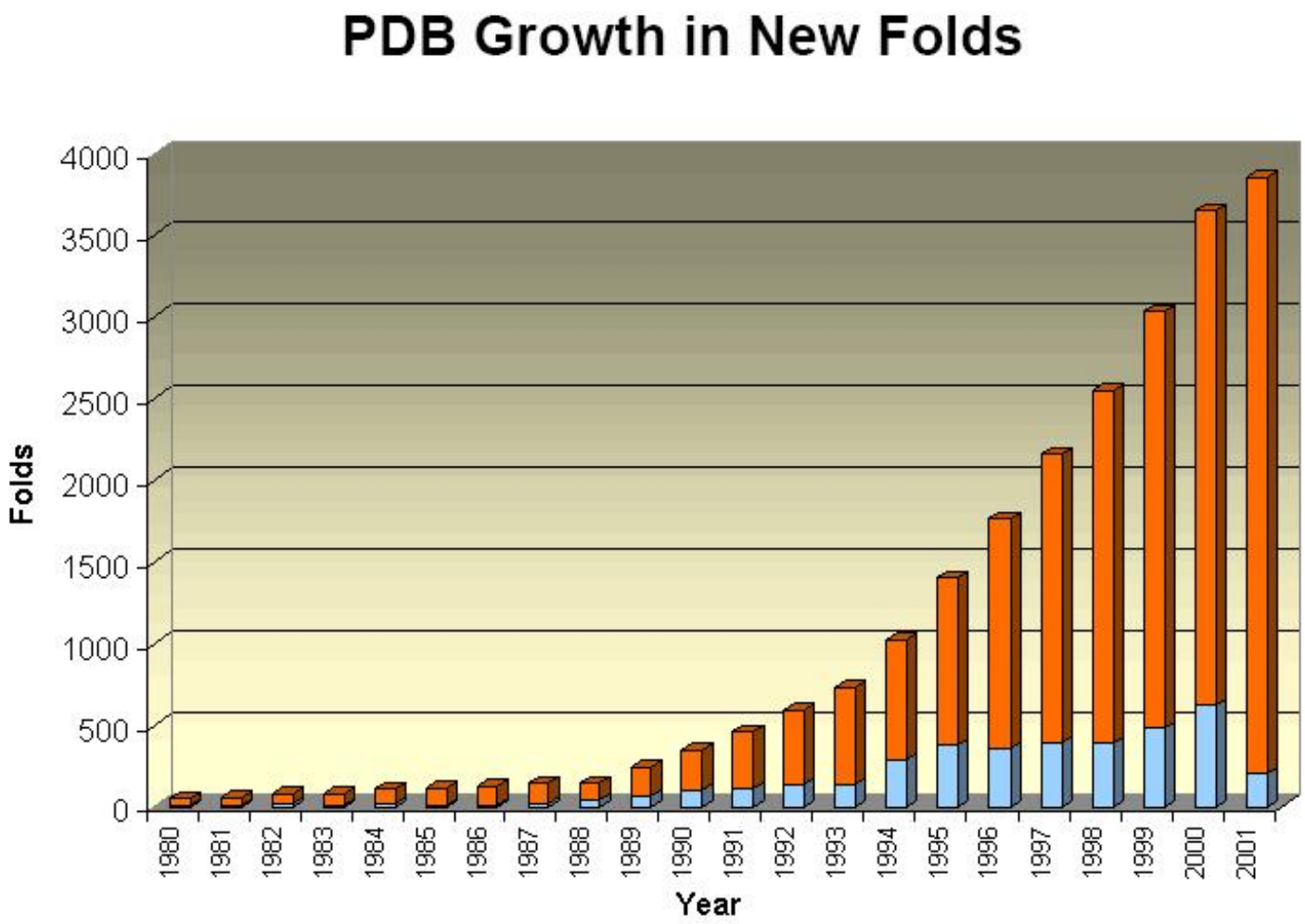
AKWDSTF
KKGGGLLL





Protein structure

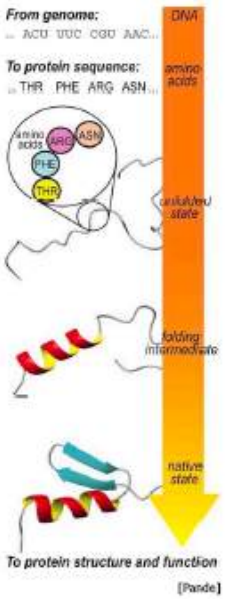
- PDB growth in new fold

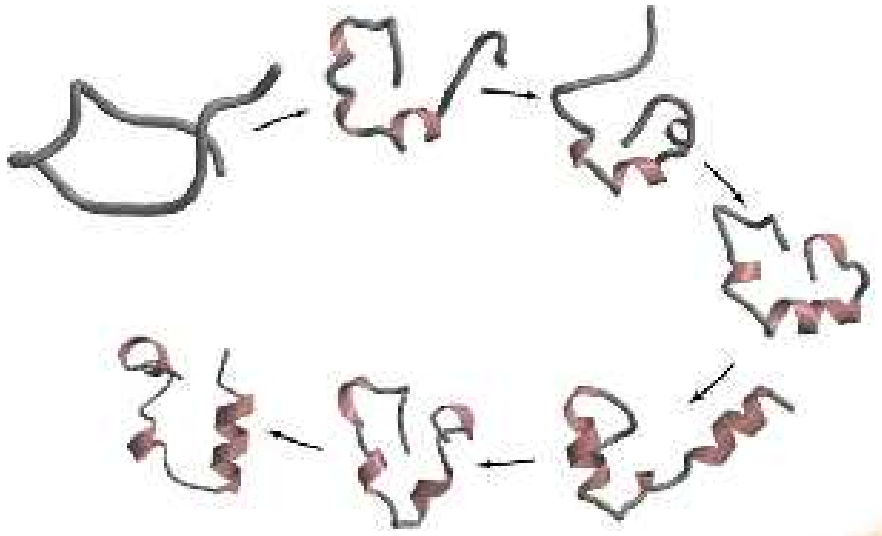


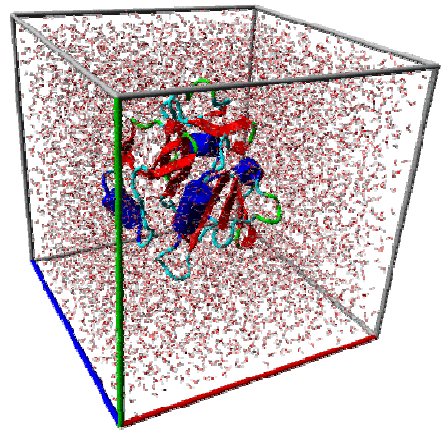
Protein modeling

❍ Protein modeling

- ✓ How can we use computation methods to analyze, design, or predict protein structures and sequences?
- ✓ How can we predict the motion of a given protein structure?







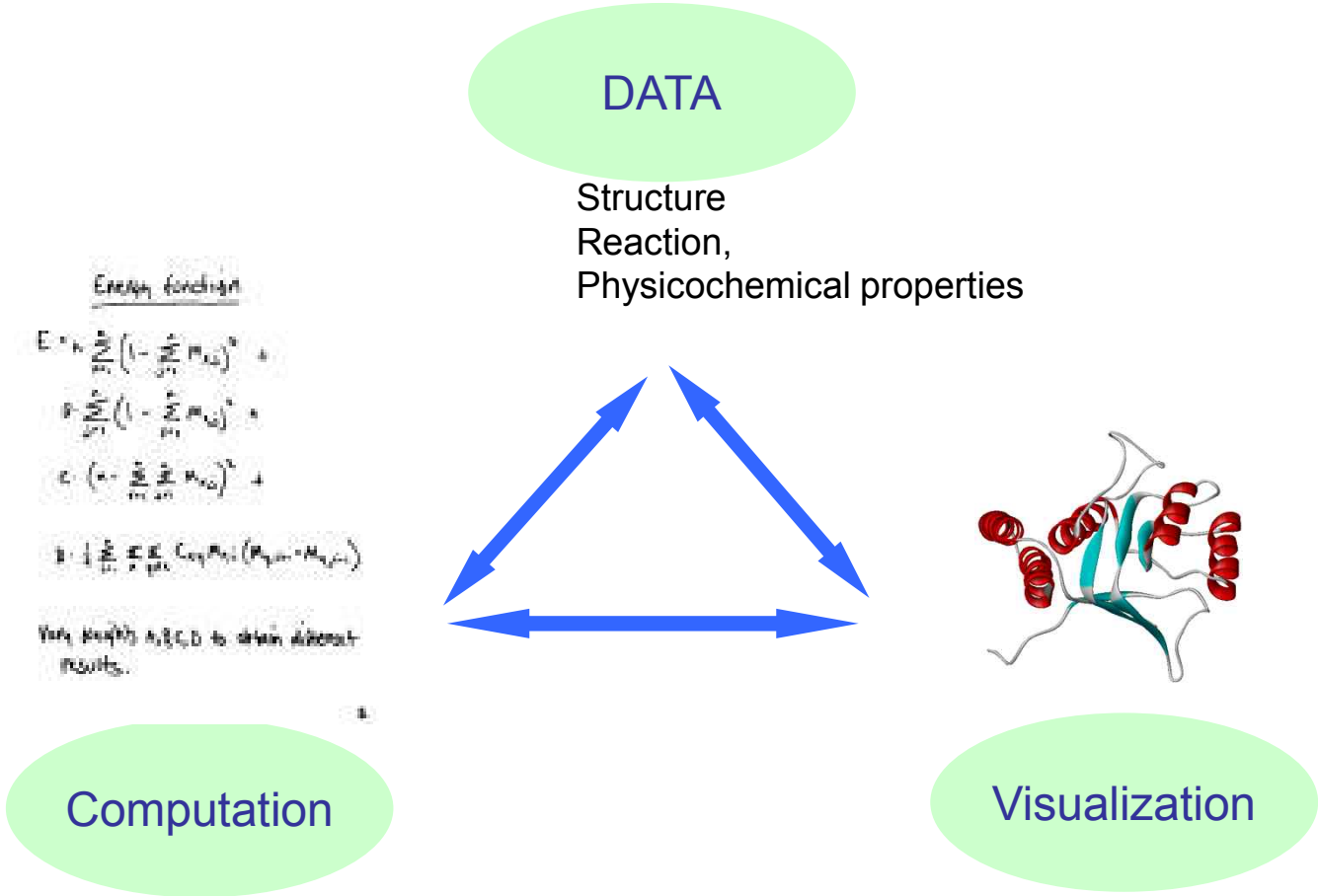
Native structure

Folding pathway

Protein dynamics

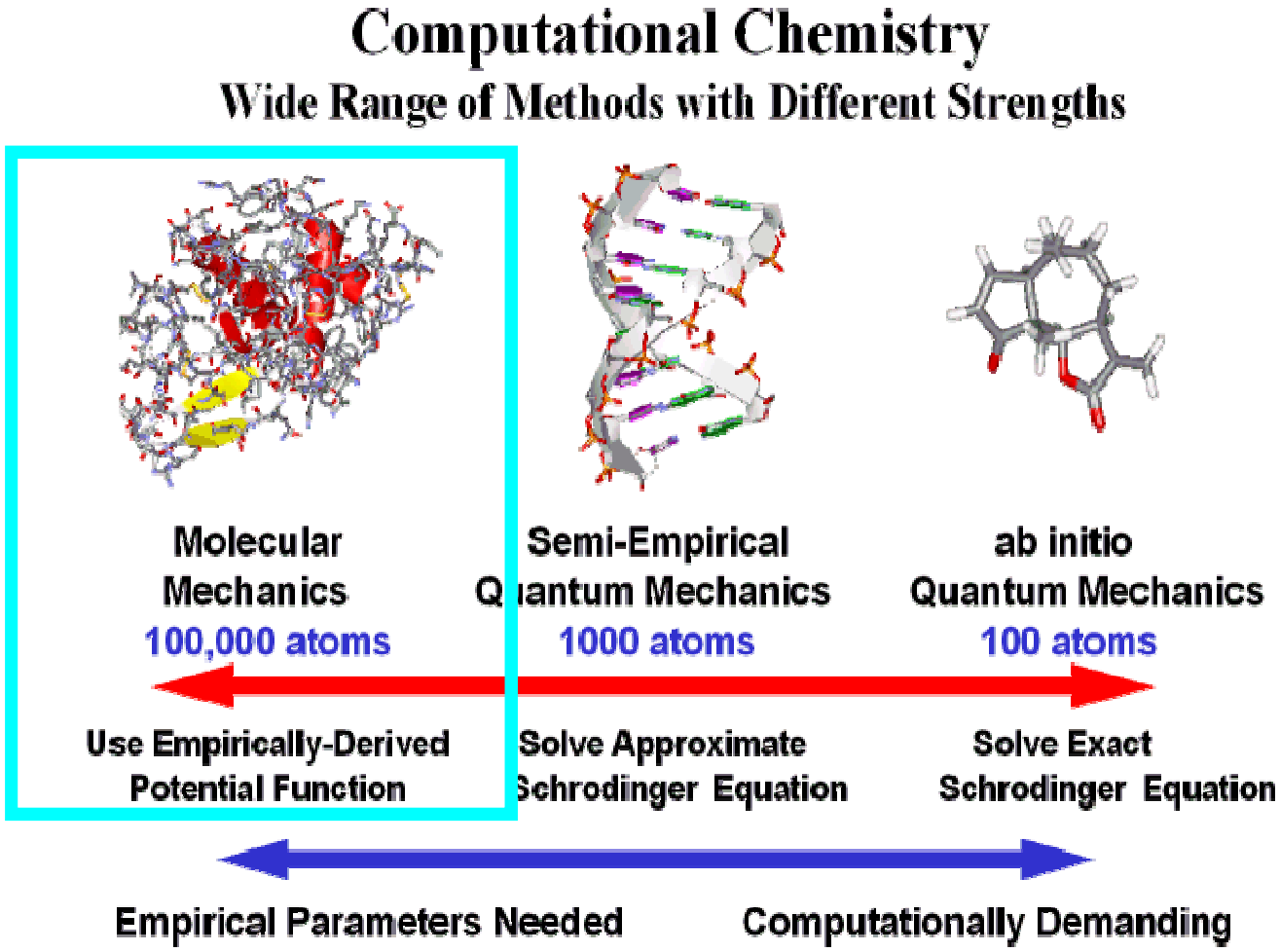
Protein modeling

- Major components of protein modeling



Protein modeling

- Power of computation methods



Protein modeling

❍ Software for protein modeling

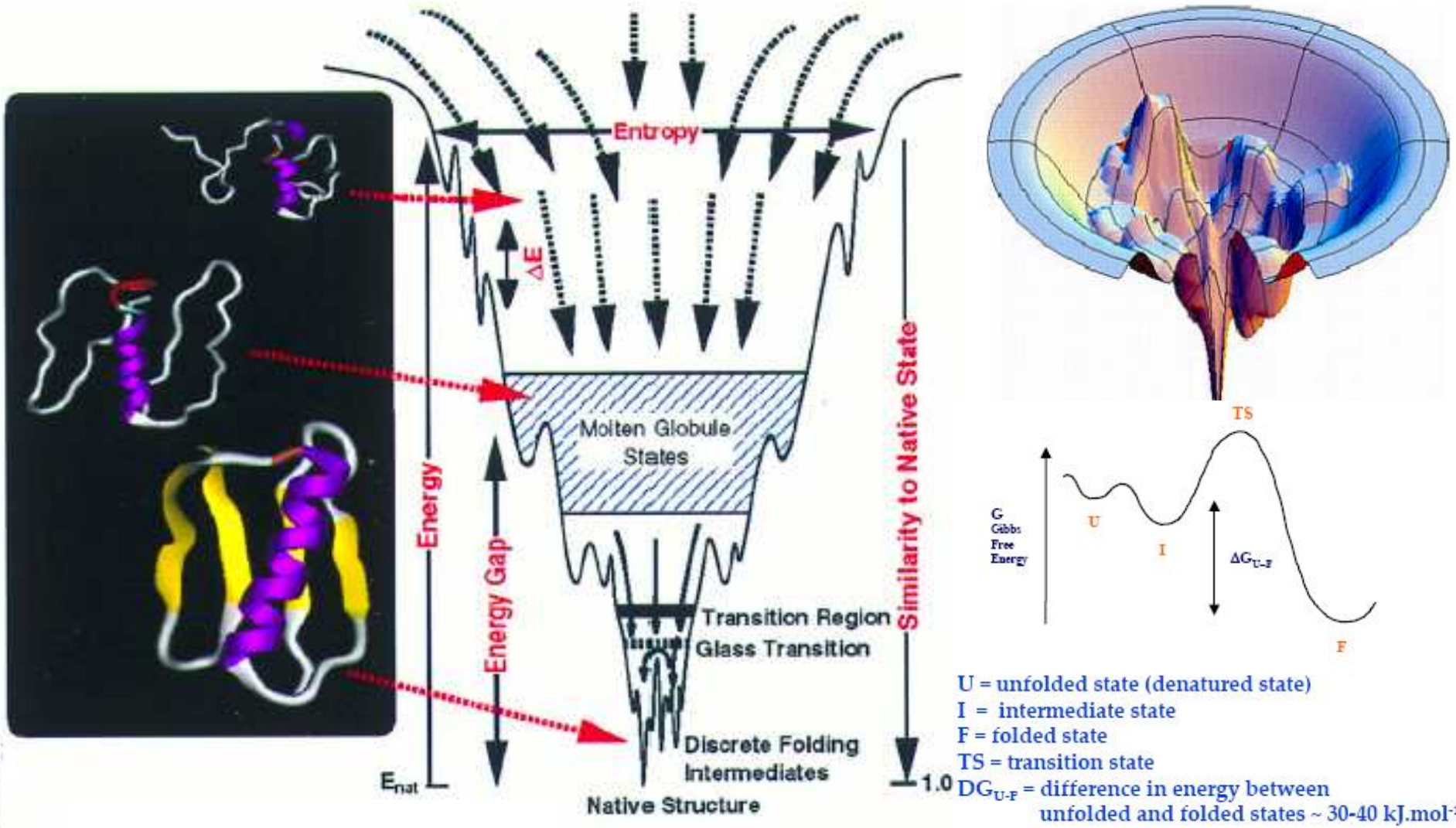
✓ *Ab initio* method : ACES, CADPAC, Gaussian, MOLPRO…

✓ Semi-empirical method : CNDO, MNDO, NNDO…

✓ Empirical method : AMBER, CAChe, CHARMM, GROMOS, X-PLOR

Protein modeling

- Protein folding landscape

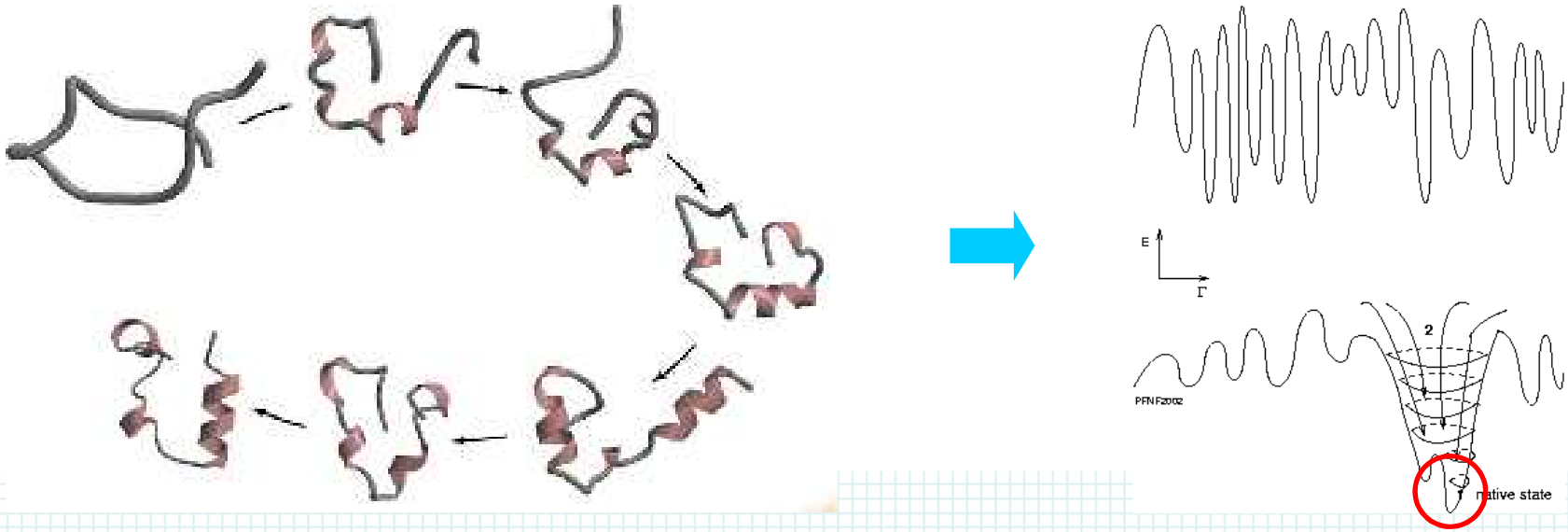


Protein modeling

❍ Protein folding : global minimal

✓ Energy minimization is frequently used to find out global minimal state of protein, especially mutant protein.

✓ But there are many local minima, so energy function should be accurate to find out global minima among them.



Protein modeling

❍ Protein folding : Energy function

✓ To predict exact protein structures, more exact energy function is needed.

$$
\begin{aligned}
U\left(\vec{R}\right) = & \sum_{\text{bonds}} K_b \left(b - b_0\right)^2 + \sum_{\text{UB}} K_{UB} \left(S - S_0\right)^2 + \sum_{\text{angle}} K_\theta \left(\theta - \theta_0\right)^2 \\
& + \sum_{\text{dihedrals}} K_\chi \left(1 + \cos\left(n\chi - \delta\right)\right) + \sum_{\text{impropers}} K_{\text{imp}} \left(\phi - \phi_0\right)^2 \\
& + \sum_{\text{nonbond}} \epsilon \left[\left(\frac{R_{min_{ij}}}{r} \right)^{12} - \left(\frac{R_{min_{ij}}}{r} \right)^{6} \right] + \frac{q_i q_j}{\epsilon_1 r_{ij}}
\end{aligned}
$$

K_b, K_{UB}, K_θ, K_χ, K_{imp} are constants, b is the bond length, b_0 is the equilibrium bond length, S is the UB 1,3-distance, S_0 is the ideal UB 1,3-distnace, θ is the angle value, θ_0 is the equilibrium angle value, χ is the dihedral angle value, n is the periodicity, ϕ is the improper angle value, ϕ_0 is the ideal improper angle value, ϵ is the Lennard-Jones well depth, $R_{min_{ij}}$ is the distance at the Lennard Jones minimum, q_i and q_j are the atoms' charge ϵ_1 is the effective dielectric constant, r_{ij} is the distance between the atoms

Protein modeling

❍ Molecular dynamics

- ✓ Cvff : peptide, protein
- ✓ AMBER : protein, DNA
- ✓ CHARMM : large macromolecules
- ✓ ECEPP : peptide, protein
- ✓ Merck : organic molecules
- ✓…

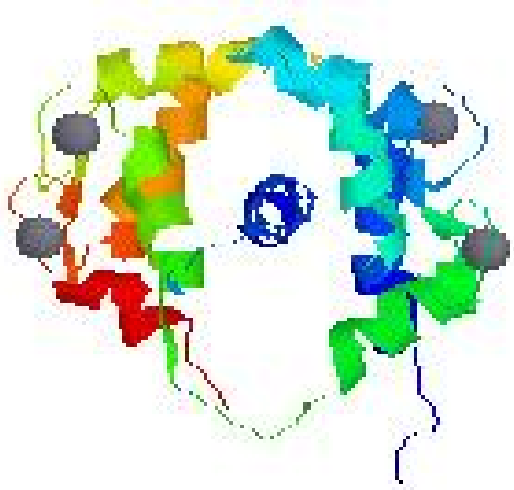
➔ FF is dependant upon the kind of target molecules.

Protein modeling

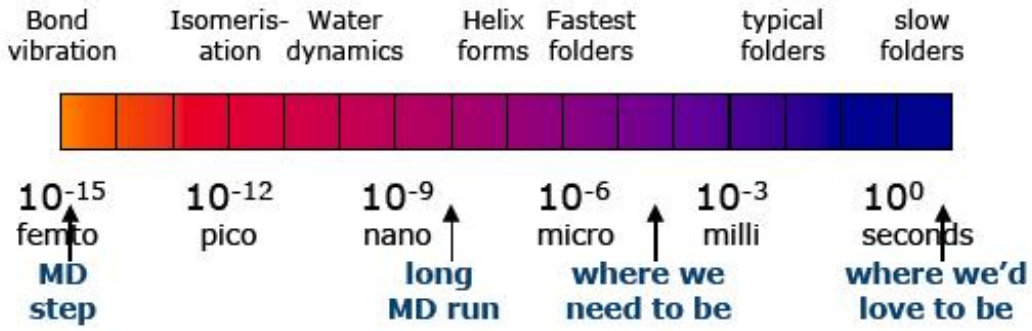
❍ Protein motion : Molecular dynamics

✓ Molecular dynamics can show how the protein will move.

✓ Protein motion can give much more information on protein function rather than static 3D structure.



Relevant time scales



✓ Femtosecond timesteps

✓ Need to simulate micro to milliesceonds

Protein modeling

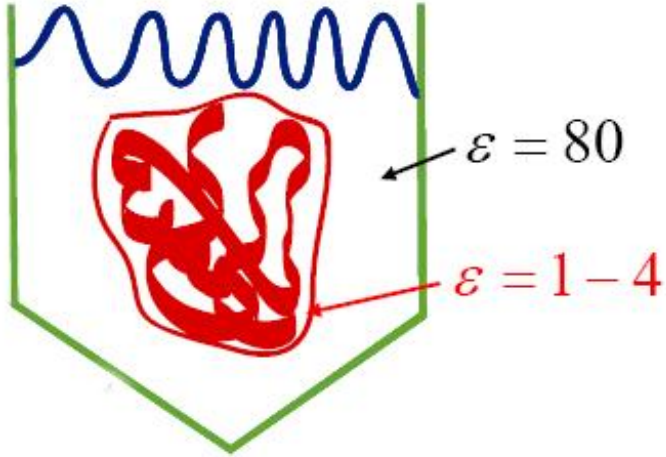
❍ Protein motion : Water dynamics

- ✓ Water is important for the biological phenomena.
- ✓ But it is difficult to reflect exact water dynamics.

Microscopic treatment

Explicit model

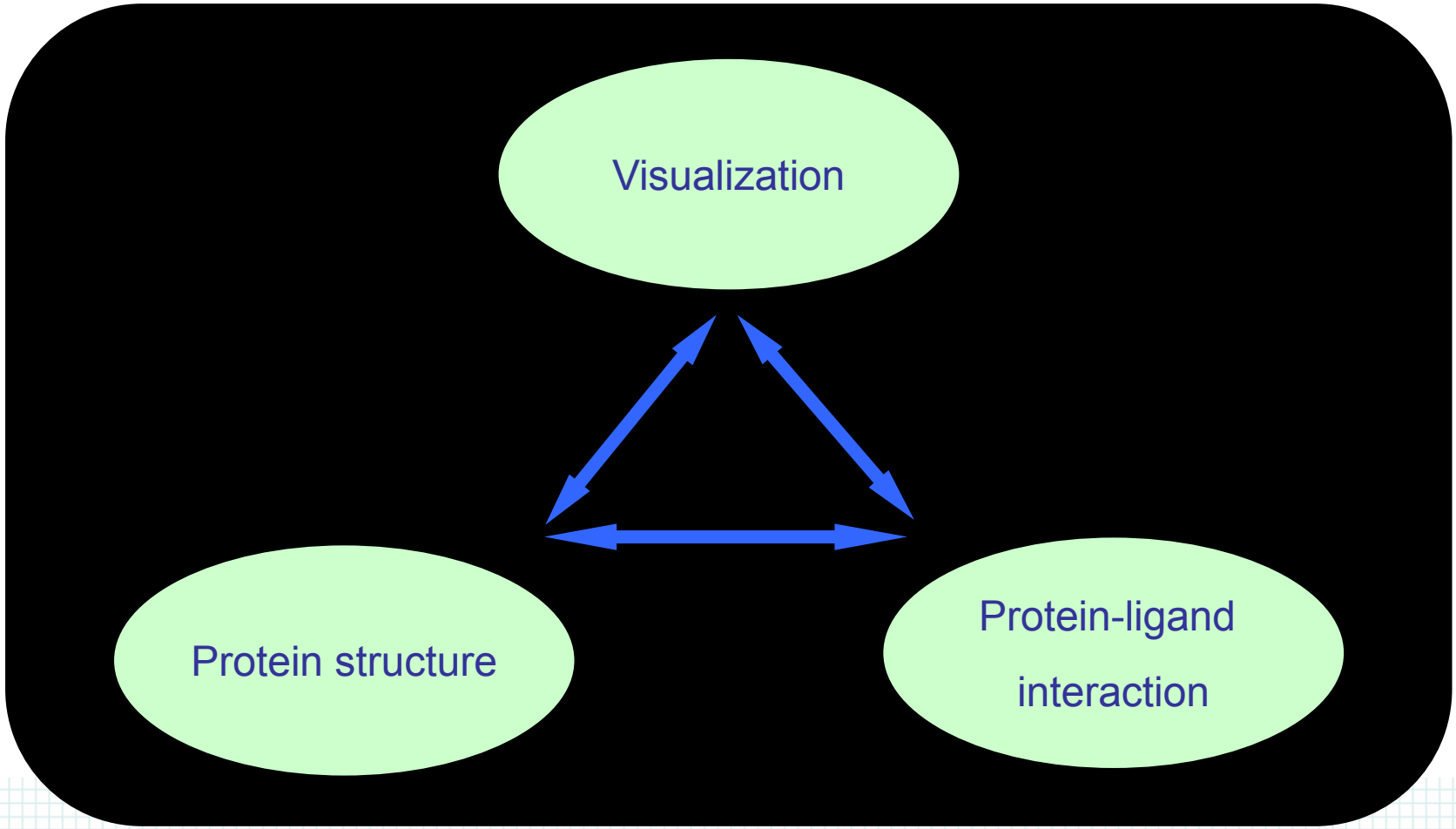
Macroscopic treatment



Implicit model

Protein modeling

- Softwares for protein modeling

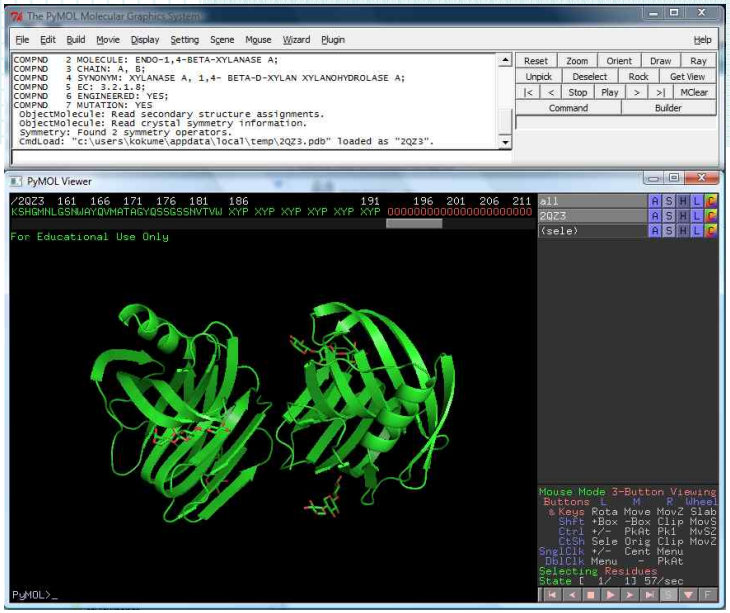


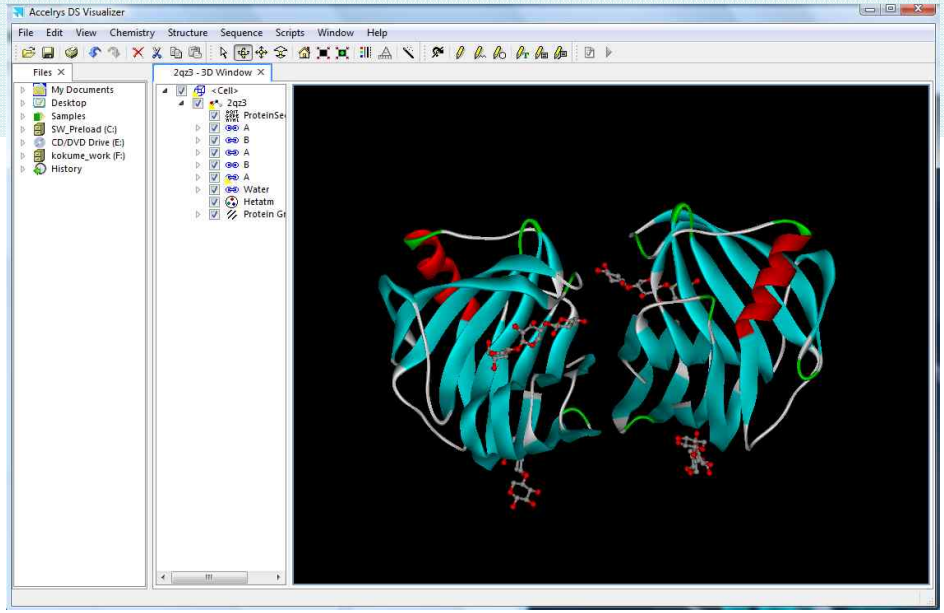
Protein modeling

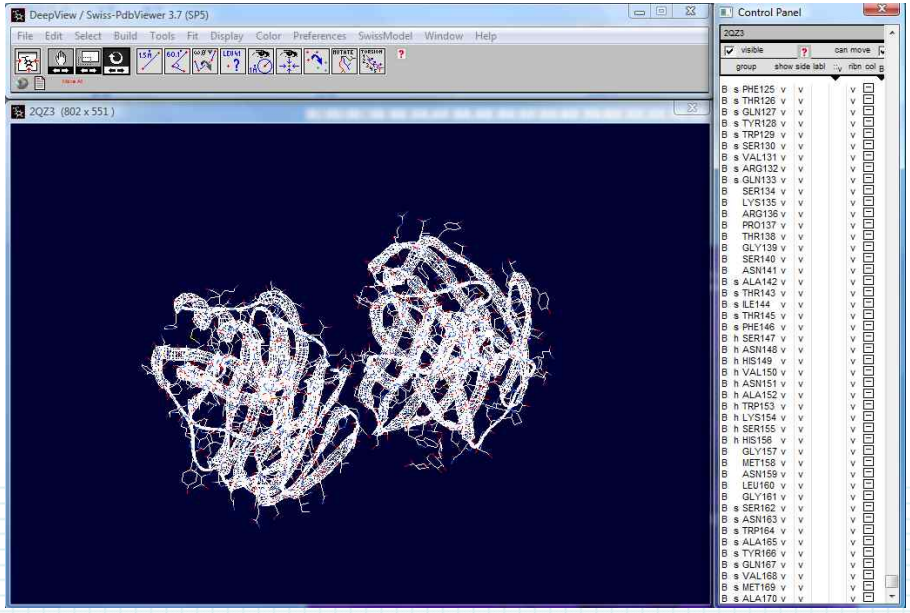
- Softwares for visualization

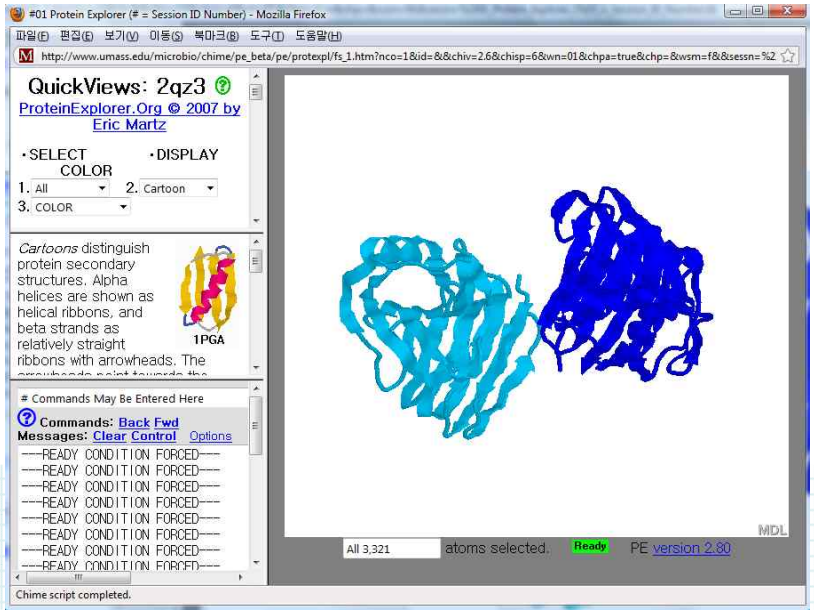
  - ✓ Pymol: http://pymol.sourceforge.net
  - ✓ Swiss-PdbViwer: http://spdbv.vital-it.ch
  - ✓ Ds visualizer: http://accelrys.com
  - ✓ Protein explorer: http:// proteinexplorer.org
  - ✓…

Protein modeling







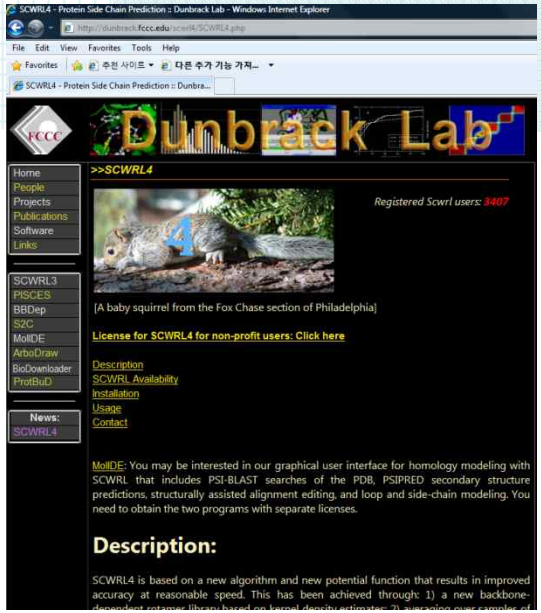


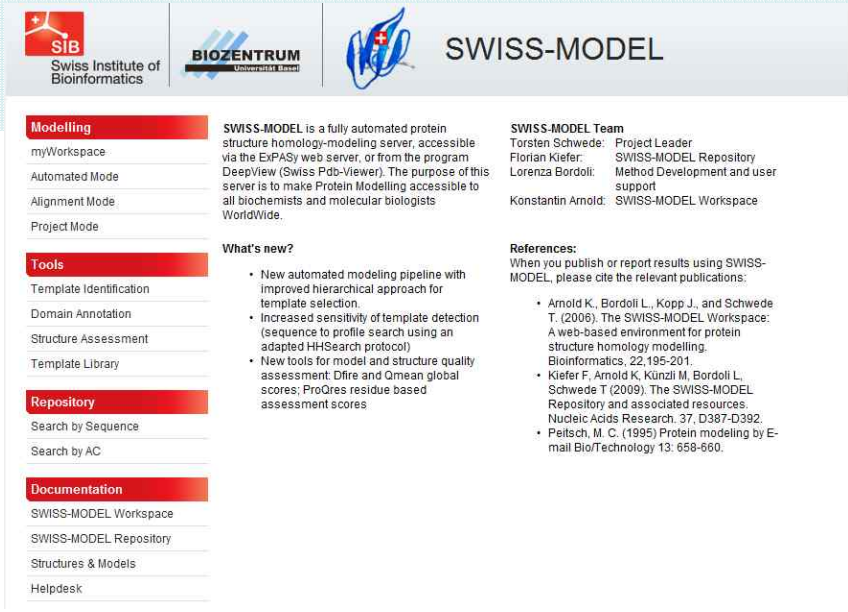
Protein modeling

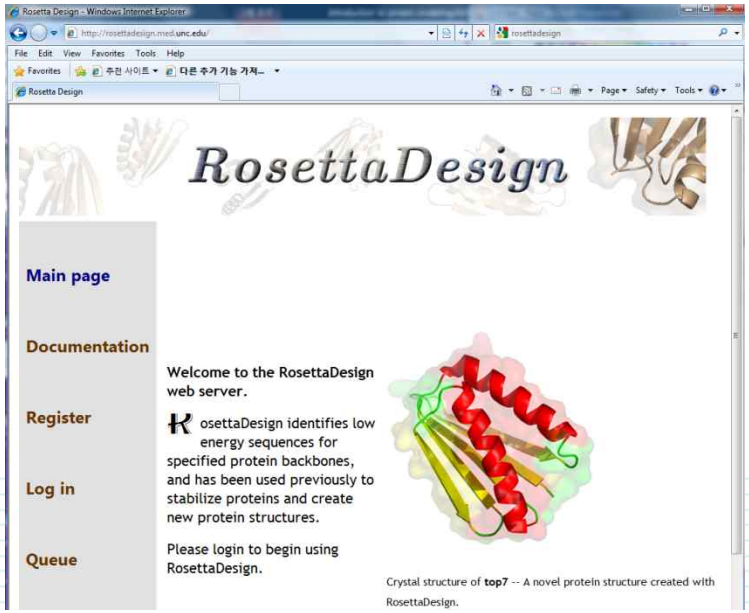
- Softwares for structure prediction

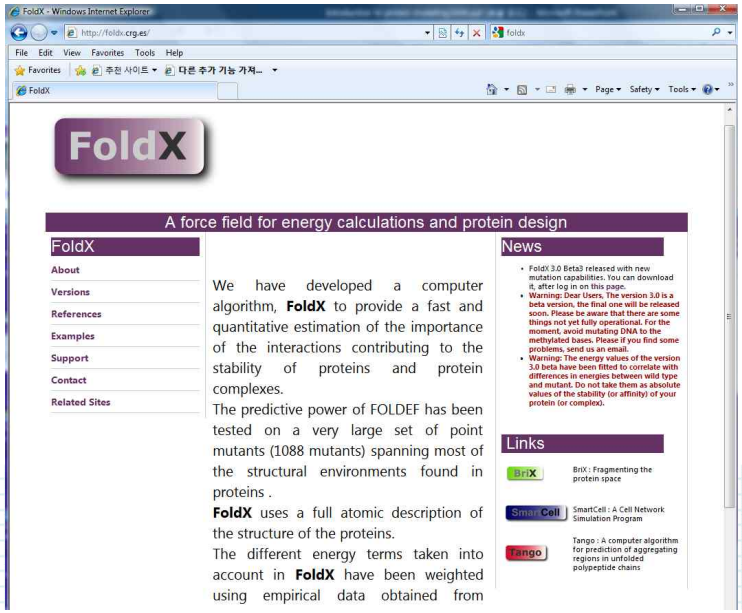
  - ✓ Scwrl 4.0: http://dunbrack.fccc.edu/scwrl4/SCWRL4.php
  - ✓ Swiss Model: http://swissmodel.expasy.org
  - ✓ RosettaDesign: http://rosettadesign.med.unc.edu
  - ✓ FoldX: http://foldx.crg.es
  - ✓…

Protein modeling









Protein modeling

❍ Softwares for protein-ligand interaction

✓ GRAMM-X : http://vakser.bioinformatics.ku.edu/resources/gramm/grammx

✓ ZDOCK: http://zdock.bu.edu

✓ Autodock: http://autodock.scripps.edu/

✓…

Protein modeling

Vakser Lab

>로그인

GRAMM-X Protein Docking Web Server v.1.2.0

This is the Web interface to our current protein docking software made available to the public. This software is different from the original GRAMM, except that both packages use FFT for the global search of the best rigid body conformations.

You can submit input files and parameters to this web server and the docking simulation will be run on our computer cluster.

When the results are ready, they will be saved in a temporary directory on the web server and the link to that directory will be sent to you.

Please, read the Conditions of Use before proceeding.

Questions

Send questions or comments to Andrey Tovchigrechko.

Start new GRAMM-X simulation

Main Input

Receptor PDB file *

Select the PDB file on your computer to use as the receptor. This file will be uploaded to our server.

Browse...

Chain Ids of the Receptor

Specify chain id's for the receptor as one or several letters. Examples: LH - chains L and H; C - chain C; leaving this field empty will mean to use all chains from the receptor file.

ZDOCK SERVER

Zdock Zlab Help Contact

Upload file 1: Browse...

Upload file 2: Browse...

Enter your email:

Submit

First time using this server? Try the tutorial.

Note: Please refrain from submitting more than approximately 10 jobs per day as this can back up the server and prevent other users' jobs from running.

AVERAGE WAIT TIME IS: 01:26:35 (HH:MM:SS)

AutoDock

site map accessibility

검색

home downloads resources faqs & help forum wiki contact

로그인

현재 위치: 홈

The Scripps Research Institute

이정표

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- Downloads
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- FAQs & Help
- Forum
- Wiki
- Contact

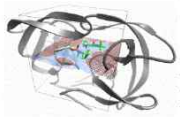
AutoDock

by morris — 최종 수정일: 2009-10-08 09:35

Contributors: Sargis Dallakyan

Welcome!

- What is AutoDock?
- What's new?
- What is AutoDockTools?
- Where is AutoDock used?
- Why use AutoDock?
- Run AutoDock on World Community Grid!



Garrett M. Morris
David S. Goodsell
Ruth Huey
William Lindstrom
William E. Hart
Scott Kurowski
Scott Halliday
Rik Belew
Arthur J. Olson

What is AutoDock?

AutoDock is a suite of automated docking tools. It is

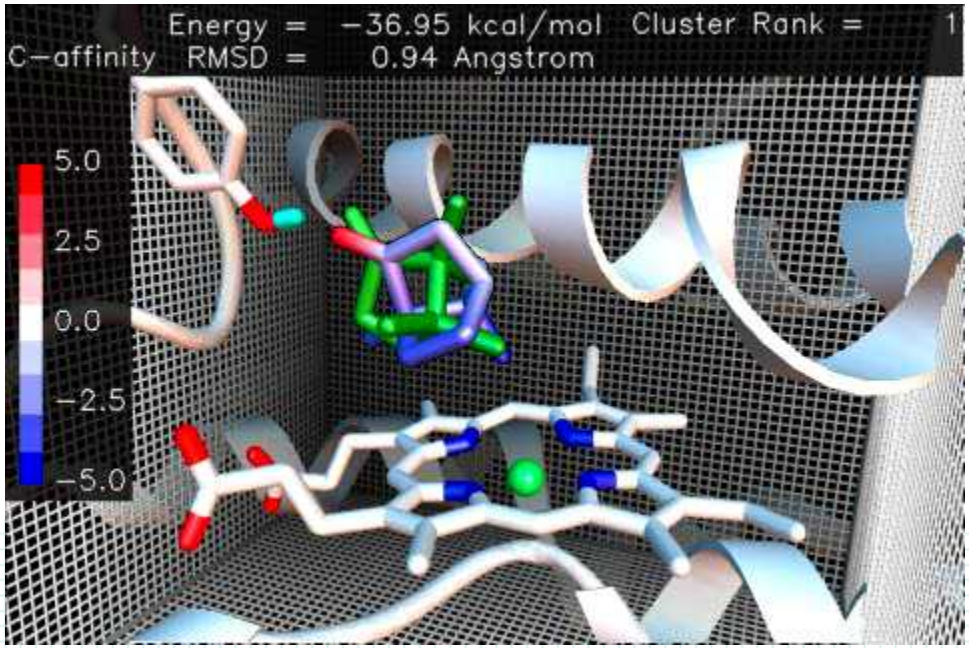
새소식

AutoDock Vina 1.0 released!
2009-06-10

AutoDock Vina new beta release
2009-02-19

Run your AutoDock Research project on World Community Grid!
2009-02-10

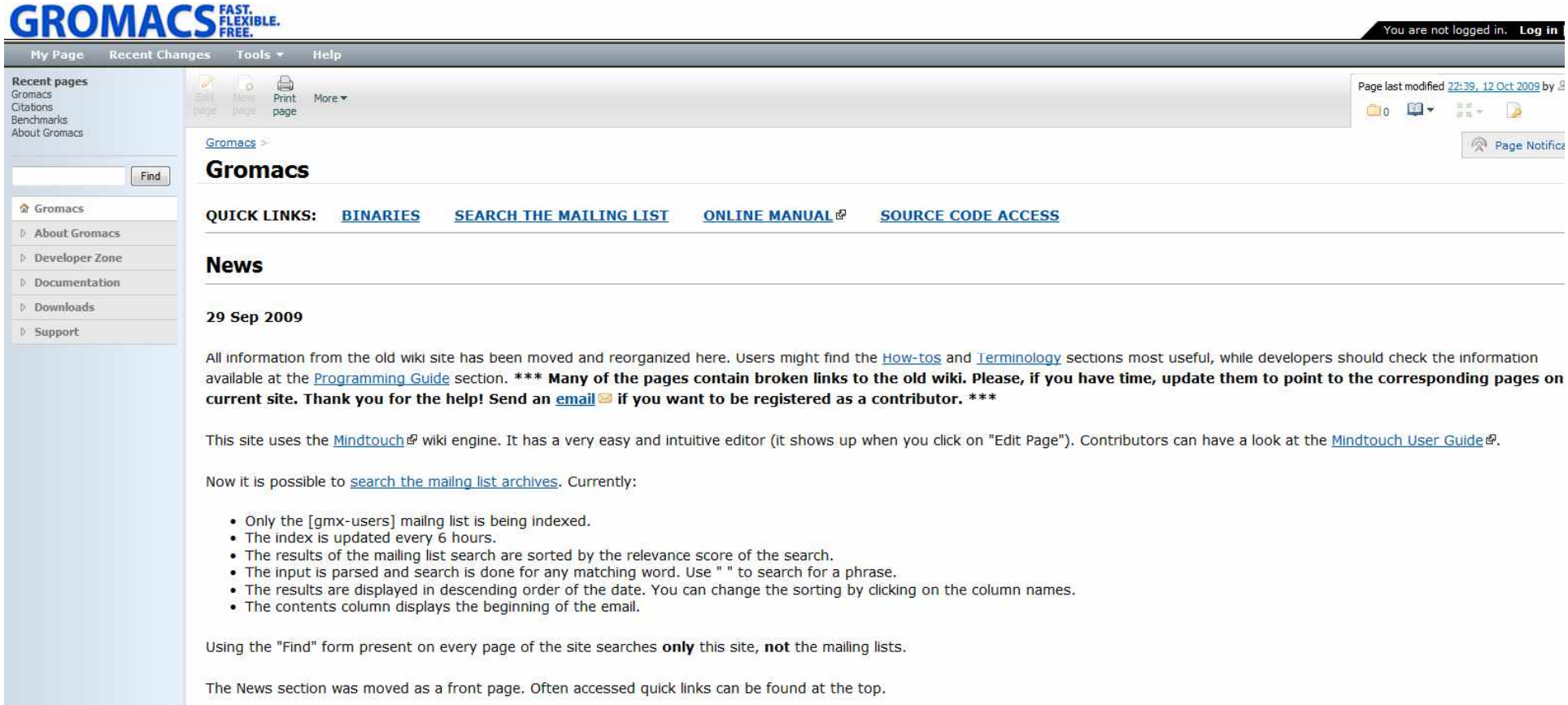
AutoDock's role in Developing the First Clinically-Approved HIV Integrase Inhibitor
2007-12-07



Protein modeling

- Software for molecular dynamics

✓ Gromacs : http://www.gromacs.org



Protein modeling

❍ How do we use this computation method?
: Case studies

✓ Design of protein for increasing stability

✓ Redesign of protein-ligand interactions

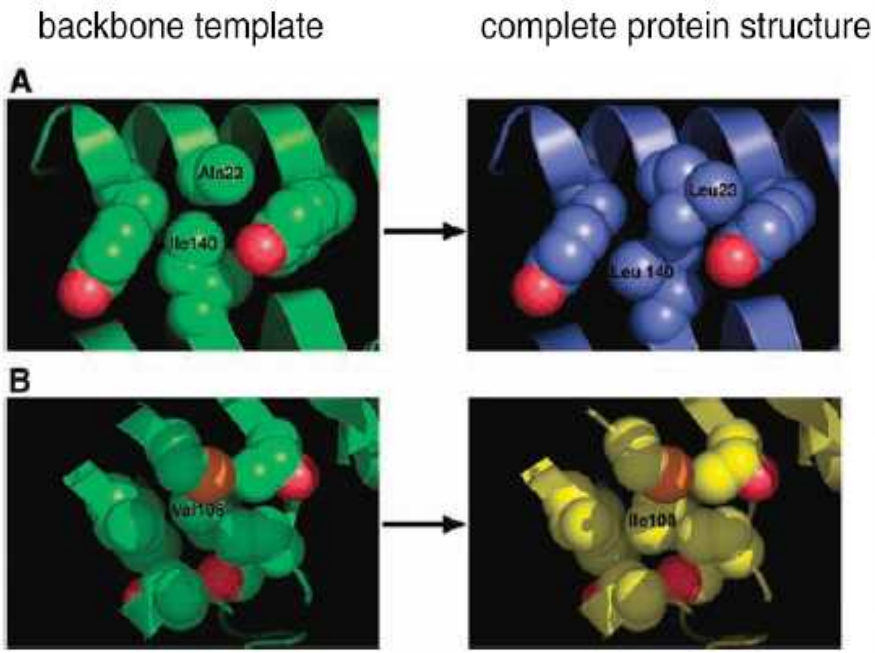
✓ Investigation on protein dynamics in organic solvents

✓ …

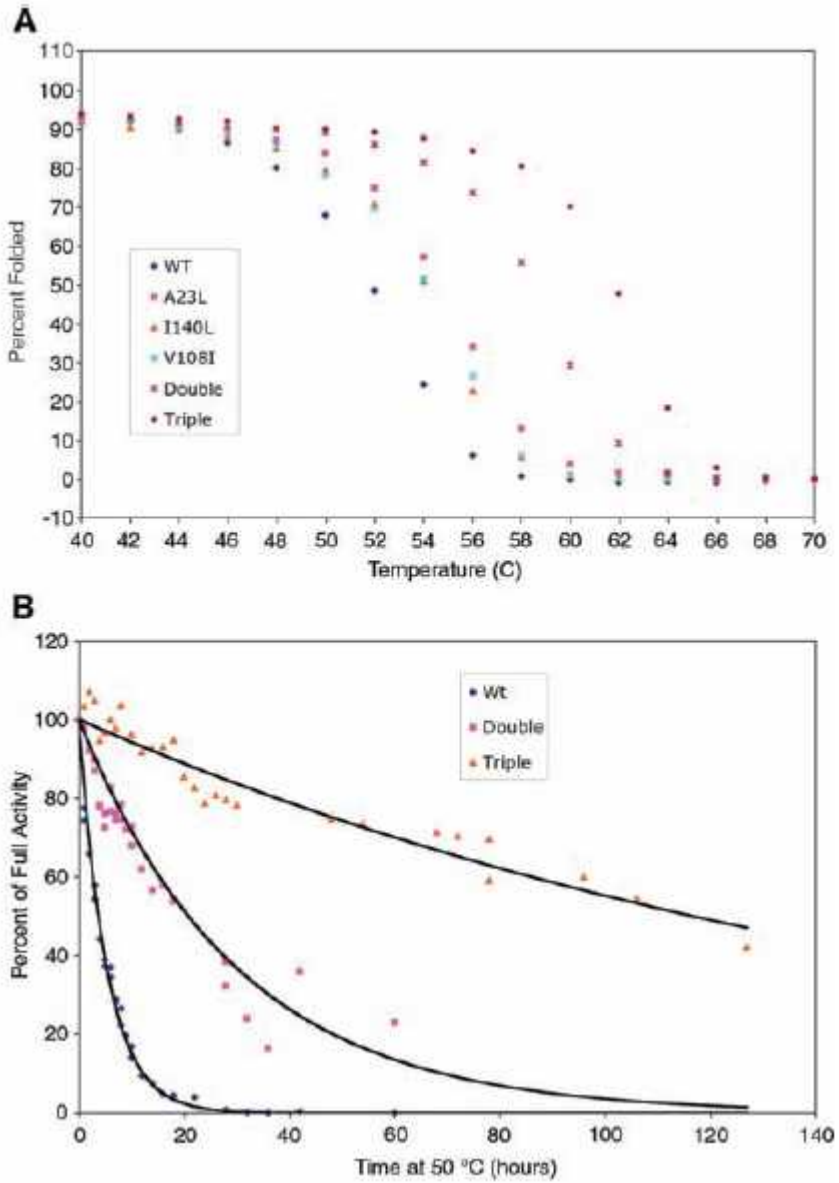
Protein modeling

- Redesign of protein for increasing stability

  - ✓ Computational thermostabilization of an



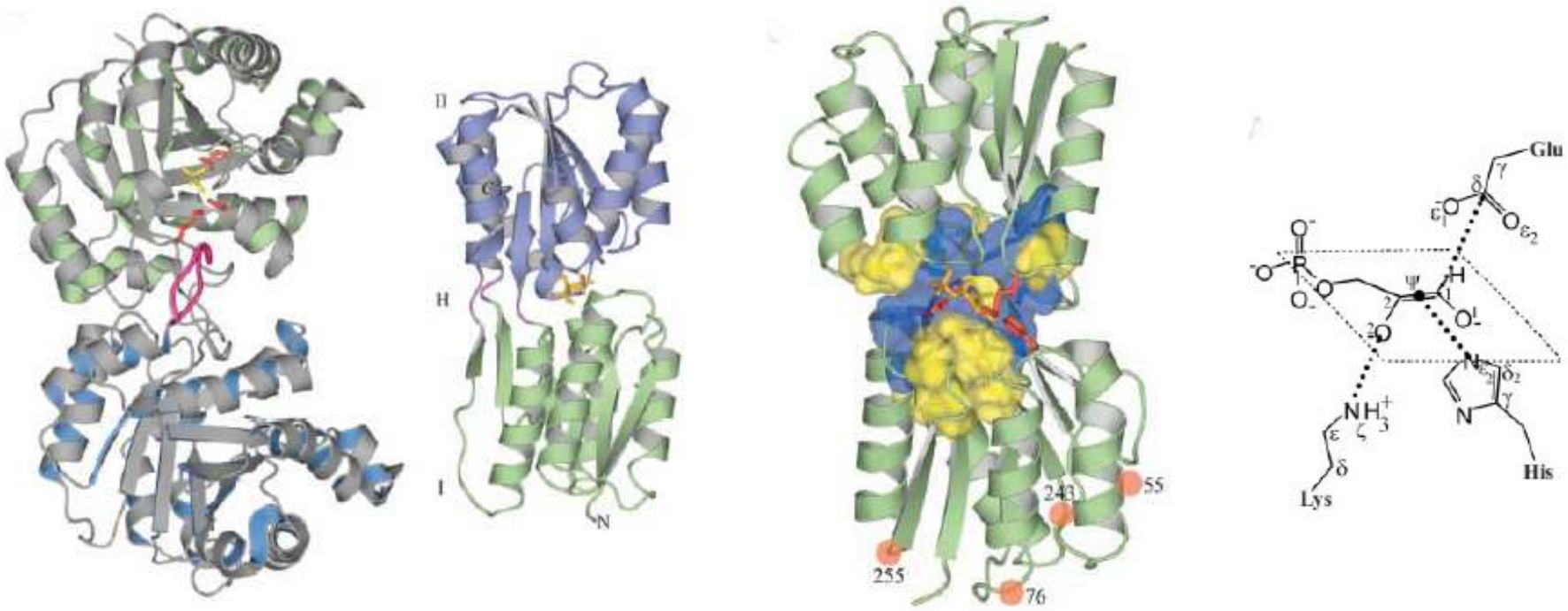
Redesign of yeast cytosine deaminase



Protein modeling

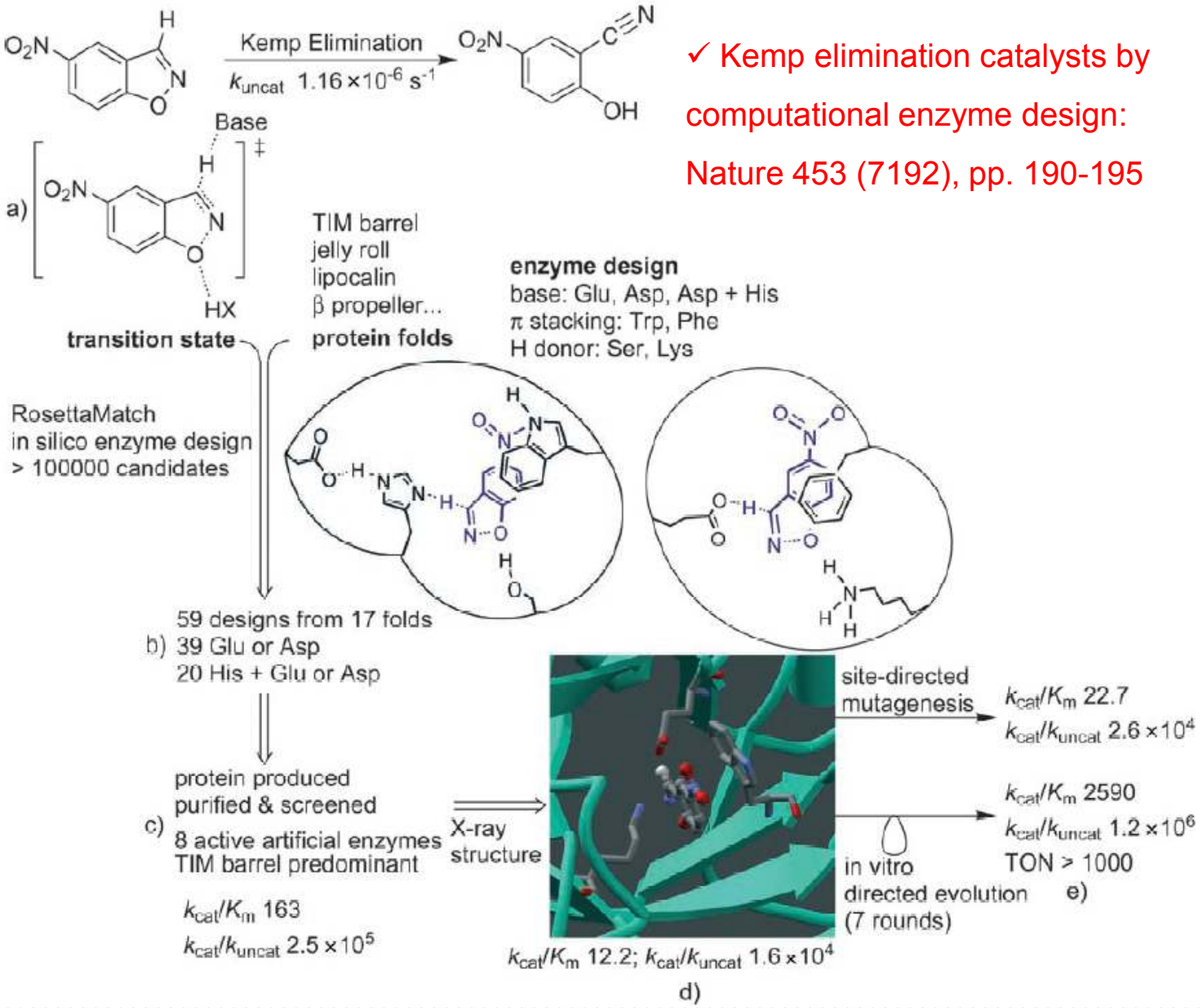
❍ Redesign of protein to enzyme

✓ Computational design of a biologically active enzyme : Science , 304, 1967-1971



Comparison TIM (Triose phosphate isomerase) with RBP

Protein modeling

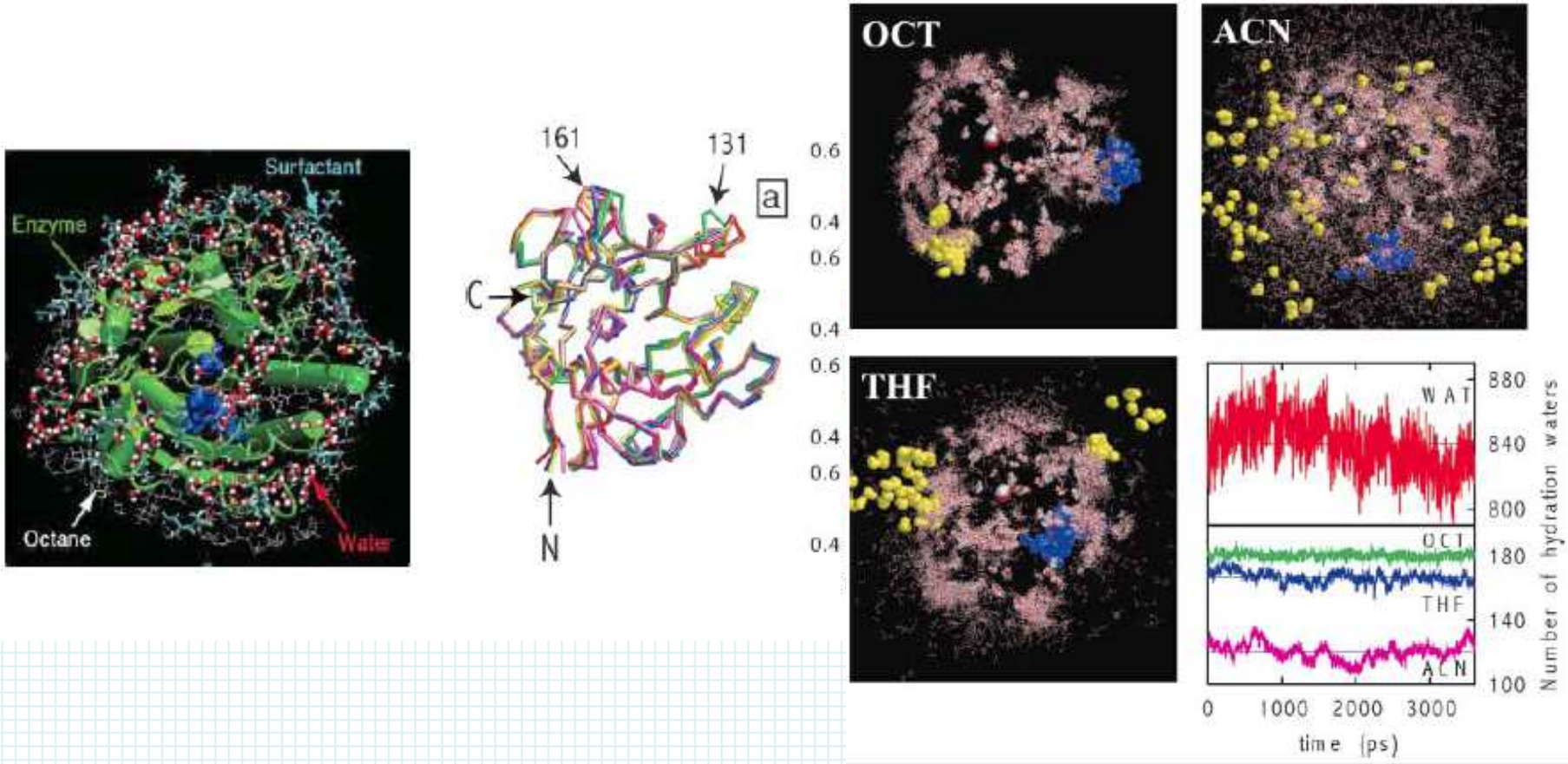


✓ Kemp elimination catalysts by computational enzyme design: Nature 453 (7192), pp. 190-195

Protein modeling

❍ Investigation on protein dynamics in organic solvents

✓ Hydration of enzyme in nonaqueous media is consistent with solvent dependence of its activity : Biophysical Journal 87, 812-821

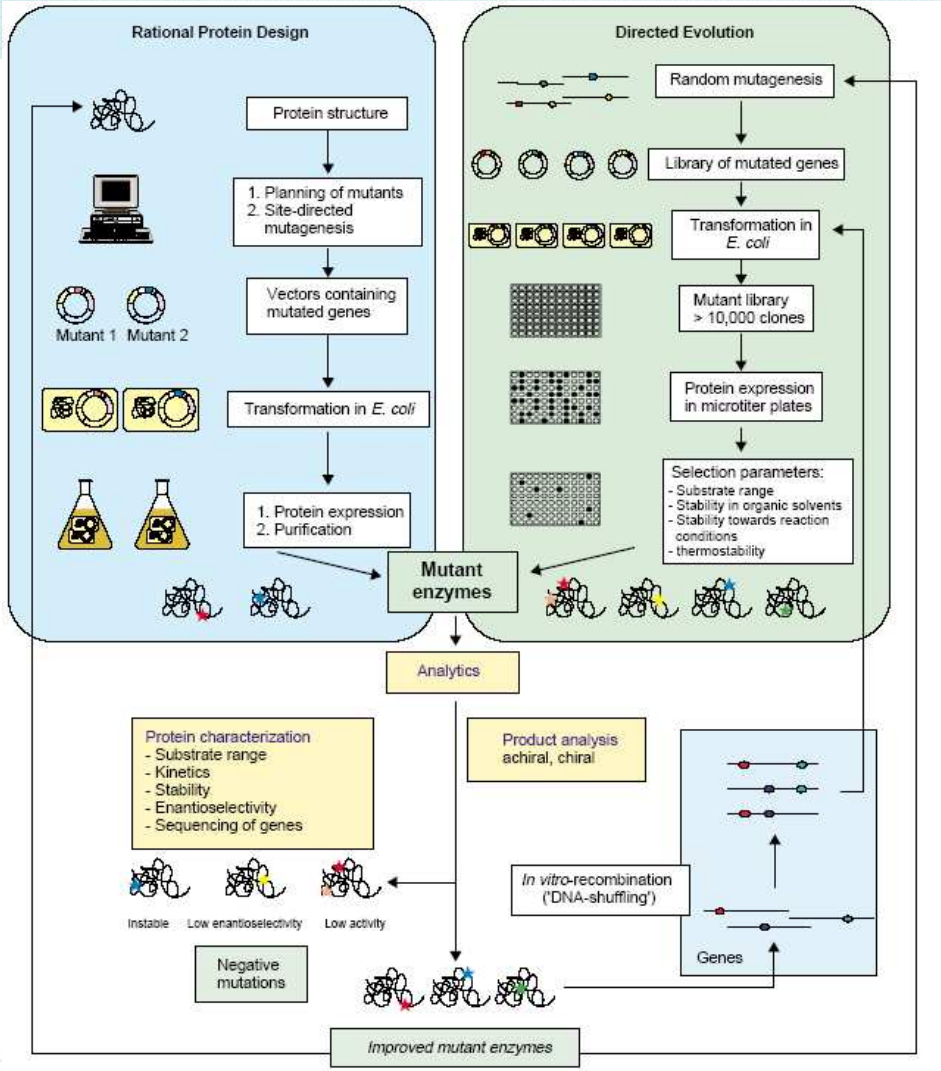


Protein Function

Rational/

Computational

design



Directed

evolution

Protein stability

❍ Rational/computational design vs Directed evolution