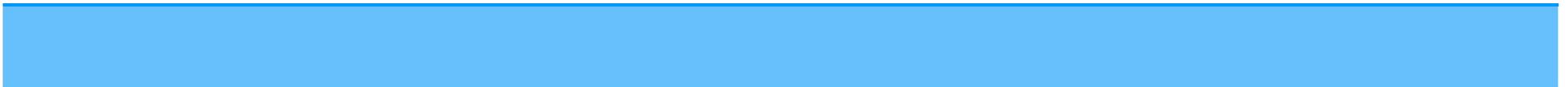


LOSCHMIDT  
LABORATORIES



Protein folding, stability and dynamics



# Outline

- ❑ Revisions
- ❑ Protein folding
- ❑ Protein stability
- ❑ Protein dynamics

# Revisions: molecular interactions



## ❑ Covalent interactions

- sharing of electrons
- under standard condition – very stable
- **primary structure of proteins**

## ❑ Non-covalent (weak) interactions

- electrostatic interactions
- polar interactions
- non-polar interactions
- **secondary, tertiary and quaternary structure of proteins**

# Revisions: electrostatic interactions

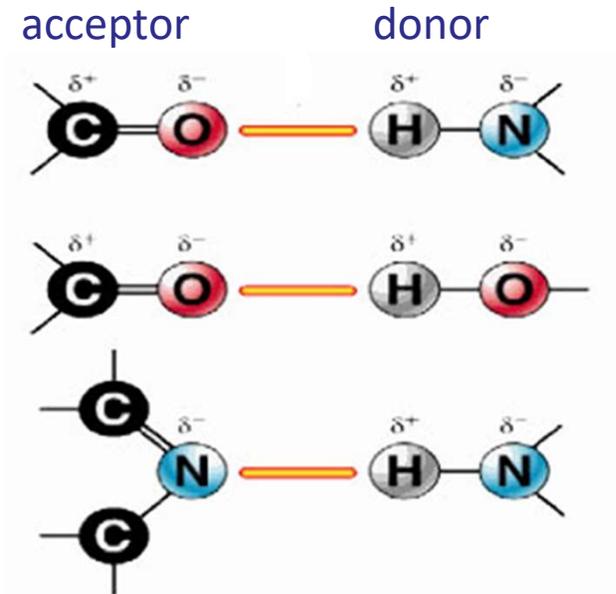
## □ Charge-charge interactions

- **charged residues** – Arg, Lys, Glu, Asp and His (low pH)
- **long-range interaction** – decrease with  $r^2$
- **environment dependent**
  - **permittivity ( $\epsilon$ ):**
    - 1 – vacuum
    - 2-20 – interior of proteins, membranes
    - **80 – bulk water -> water shields the charges from each others**
  - **salt concentration** – **counter ions close to charged residues**
  - **pH** – change in charge of molecule (His)

# Revisions: polar interactions

## □ Hydrogen bonds (H-bonds)

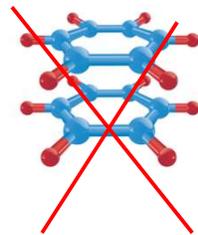
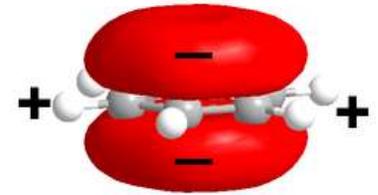
- donor and acceptor atoms sharing hydrogen
- polar residues – Ser, Thr, Asn, Gln, Cys, Trp, Tyr and His (high pH)
- charged residues – Arg, Lys, Glu, Asp and His (low pH)
- governs formation of secondary structure
- H-bond distance: 2.8-3.4 Å



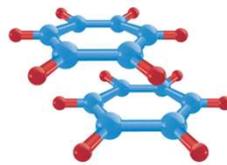
# Revisions: polar interactions

## □ Aromatic ( $\pi$ - $\pi$ ) interactions

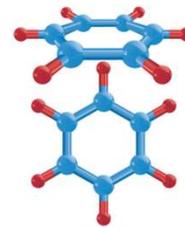
- attractive interaction between aromatic rings
- aromatic residues – Phe, Trp, Tyr and His
- distance of centre of mass – about 5 Å



sandwich



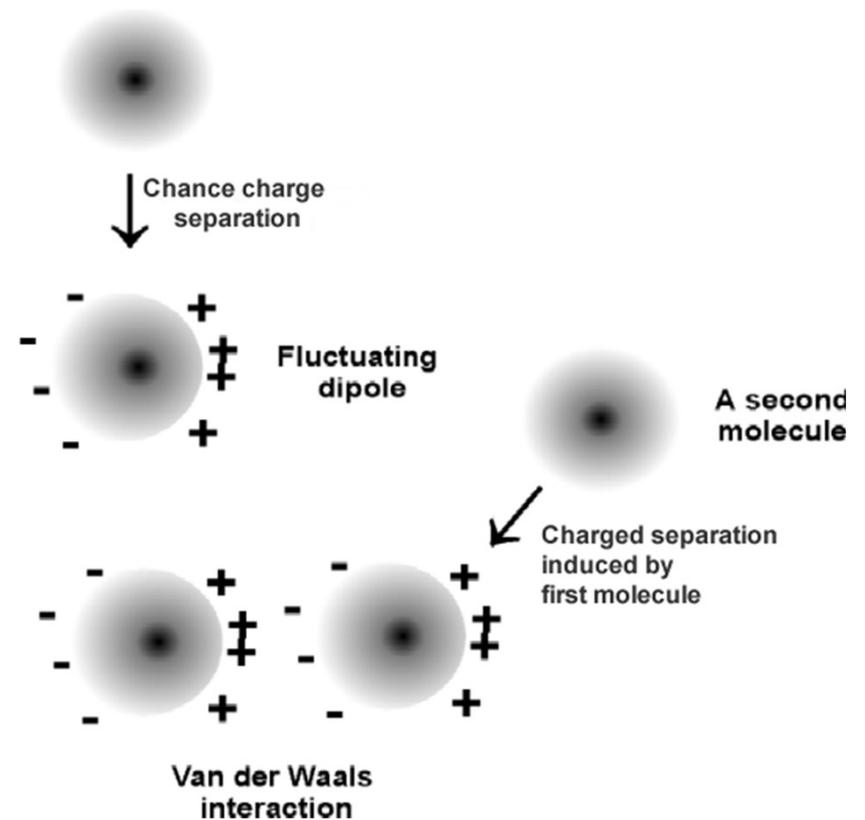
parallel  
displaced



T-shaped

# Revisions: non-polar interactions

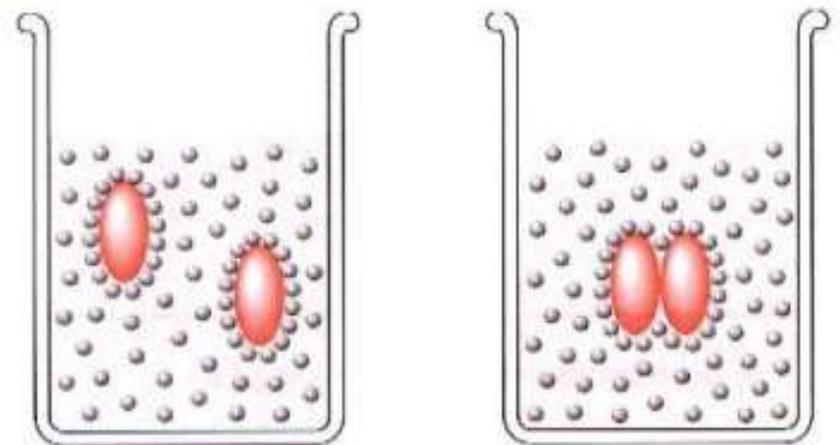
- van der Waals (vdW) interactions
  - between any two atoms -> all residues
  - short-range interactions
  - negligible beyond 5 Å
  - tertiary structure



# Revisions: non-polar interactions

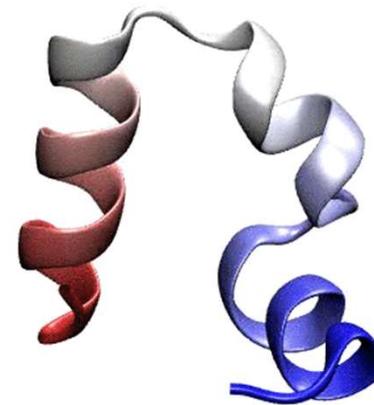
## □ Hydrophobic interactions

- **hydrophobic residues** – Phe, Pro, Met, Leu, Ile, Val, Ala, and possibly also Tyr and Trp
- **entropic origin** – water molecules ordered around hydrophobic residues -> unfavorable
- **hydrophobic packing** -> release of some ordered water -> favorable increase of entropy
- **tertiary structure**



# Protein folding

- ❑ Levinthal's paradox
- ❑ Anfinsen's thermodynamic hypothesis
- ❑ Mechanisms of protein folding
- ❑ Energetics of protein folding
- ❑ Database of protein folding



0.0 ns

# Levinthal's paradox



## □ Cyrus Levinthal

- 1968 – **impossibility of random folding**
- random folding
  - 100 residue protein (average sized)
  - 3 conformation per residue (many more)
  - 0.1 ps sampling time per conformation (much longer)
  - folding time =  $3^{100} * 10^{-13} \text{ s} \approx 5 * 10^{34} \text{ s} \approx$
  - **1 634 251 397 552 039 990 billions of years**

## □ Experimental folding rates

- **1 ms to 10 min**

# Anfinsen's thermodynamic hypothesis



## ❑ Christian Anfinsen

- 1973 – protein folding *in vitro*
- refolding of ribonuclease

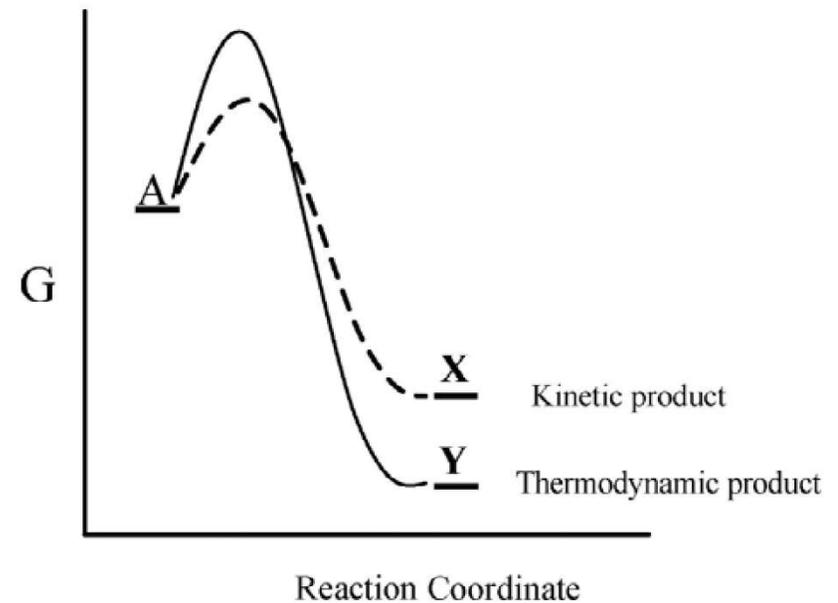
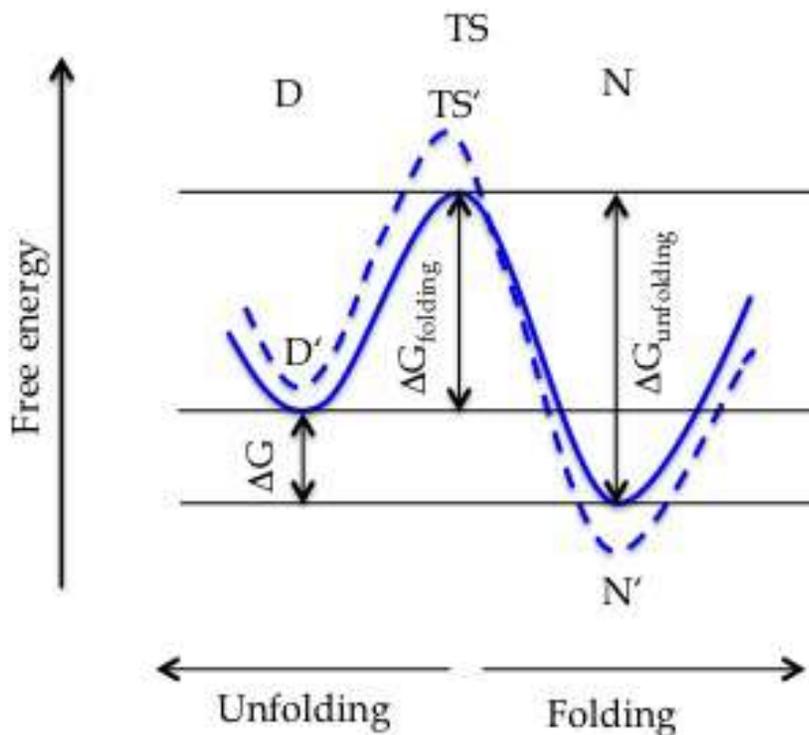
## ❑ Findings

- native structure of a protein is the thermodynamically stable structure
- folding depends only on the amino acid sequence and on the conditions of solution, and not on the kinetic folding route

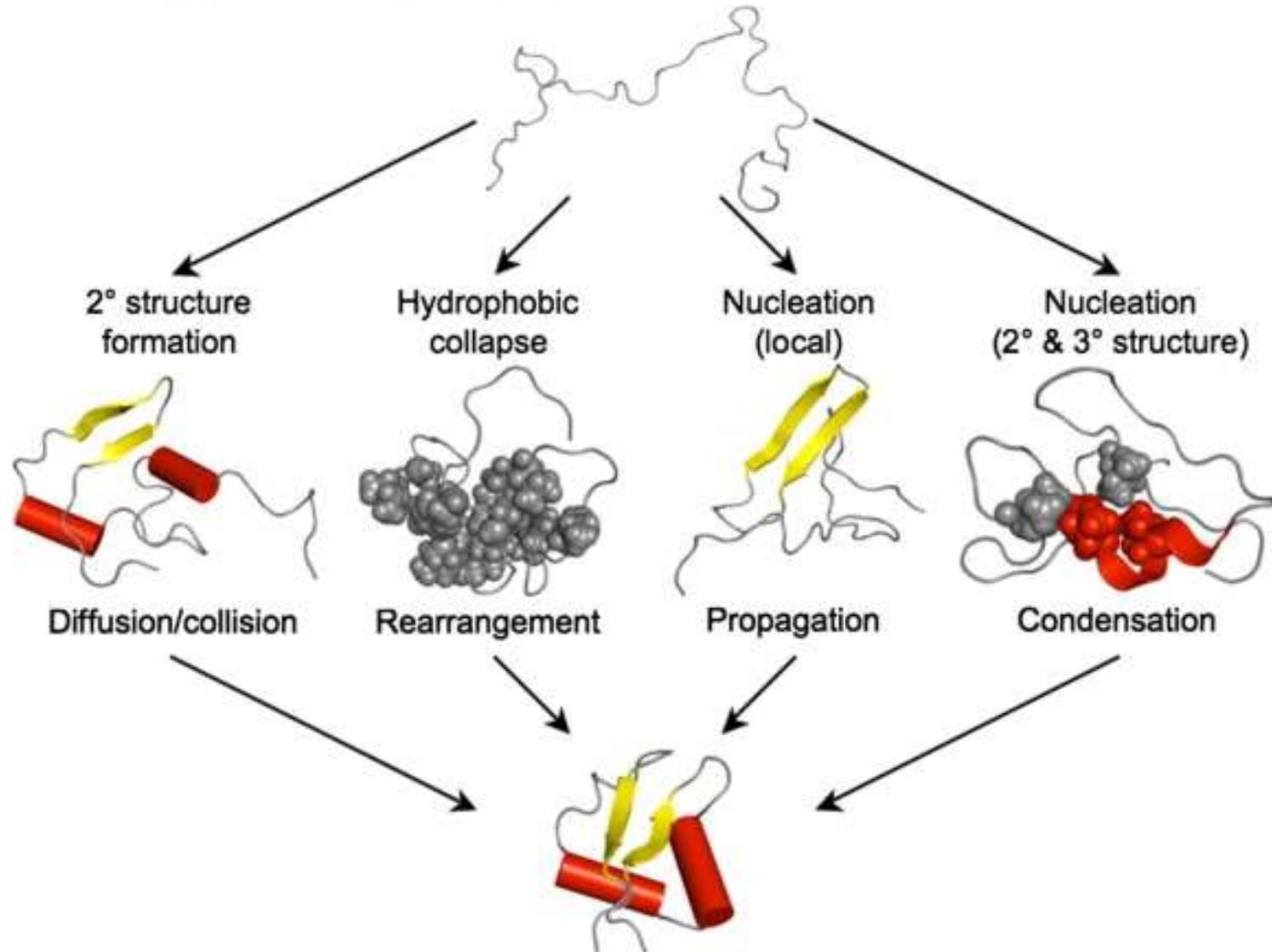
# Thermodynamic and kinetic stability

**Thermodynamic stability**  $Native \xrightleftharpoons{K_{eq}} Denatured$

**Kinetic stability**  $Native \xrightarrow{k} Denatured$



# Mechanisms of protein folding



# Mechanisms of protein folding



## ❑ Nucleation-growth (propagation) model

- continuous growth of tertiary structure from initial nucleus of local secondary structure
- it did not account for folding intermediates -> **model dismissed**

# Mechanisms of protein folding



## ❑ Framework model

- secondary structure folds first -> coalescence of secondary structural units to the native protein

## ❑ Hydrophobic collapse model

- compaction of the protein -> folding in a confined volume -> narrowing the conformational search to the native state

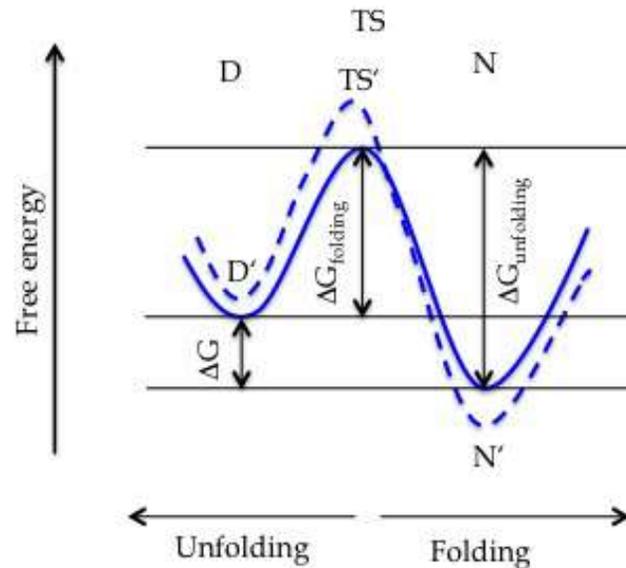
## ❑ Nucleation-condensation model

- concerted & cooperative secondary and tertiary structure formation
- transition state resembles distorted form of the native structure
- the least distorted part called **folding nucleus** or **molten globule**

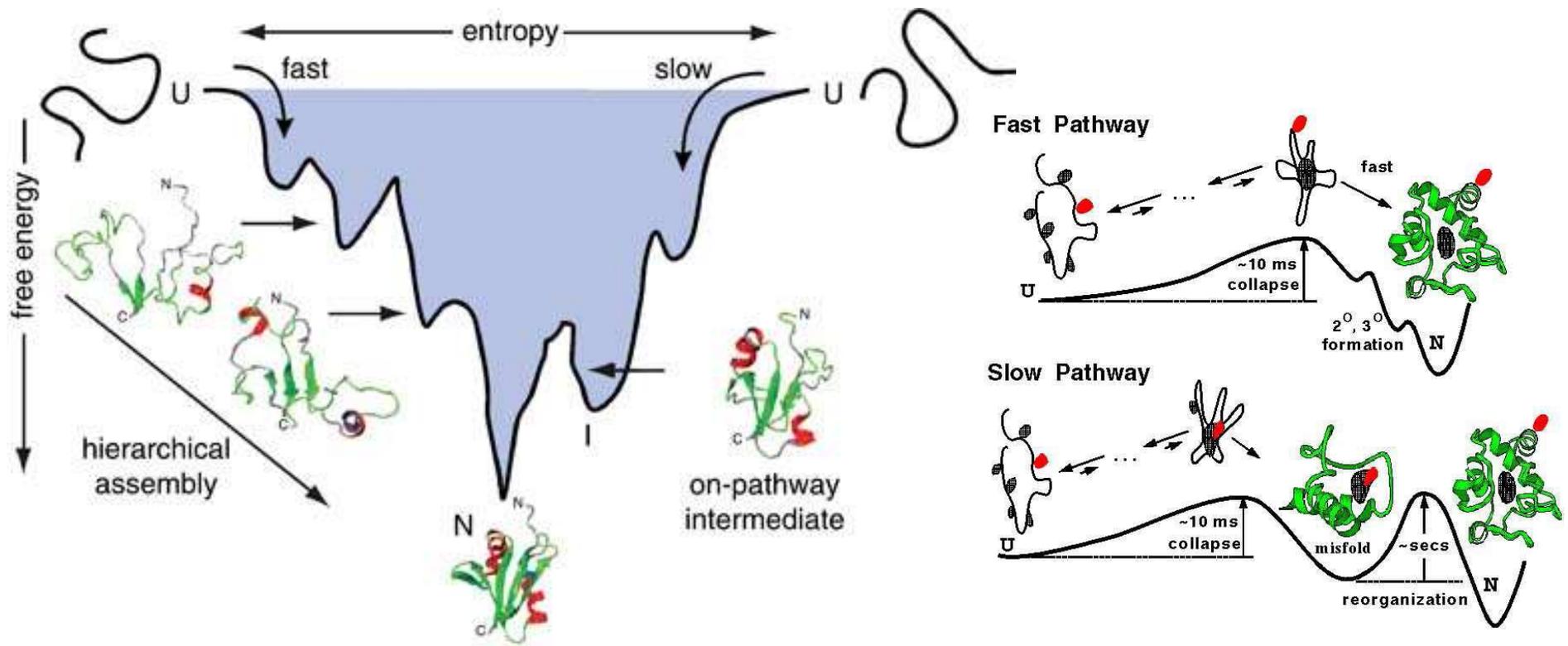
# Energetics of protein folding



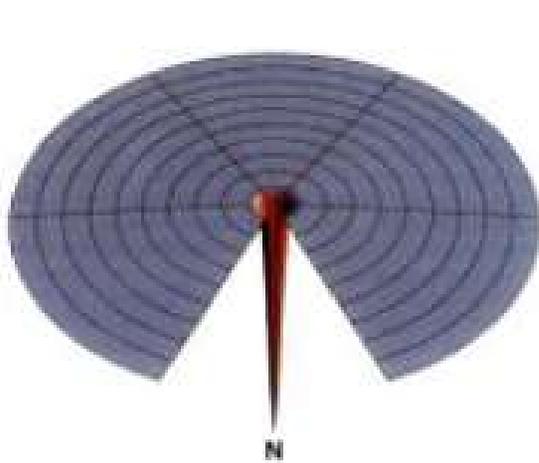
- **Free energy of folding** ( $\Delta G_{\text{fold}} = \Delta H - T.\Delta S$ )
  - protein more structured  $\rightarrow \Delta S \downarrow$  – unfavorable
  - solvent less structured  $\rightarrow \Delta S \uparrow$  – favorable
    - **hydrophobic interactions are driving “force”**
  - more non-covalent interactions  $\rightarrow \Delta H \downarrow$  – favorable



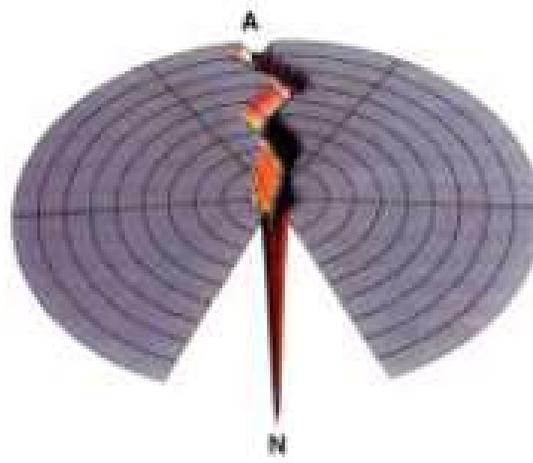
# Energetics of protein folding



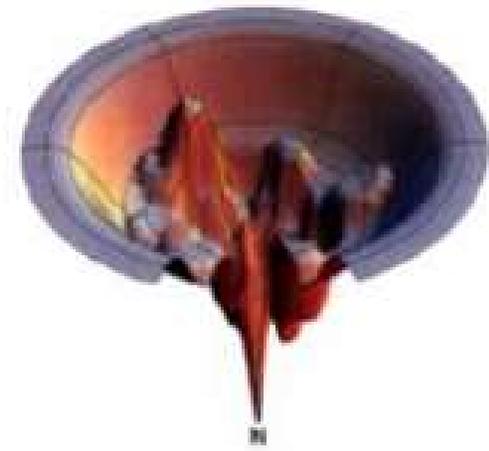
# Energetics of protein folding



**Flat landscape  
(Levinthal paradox)**



**Tunnel landscape  
(discrete pathways)**



**Realistic landscape  
("folding funnel")**

# Protein stability



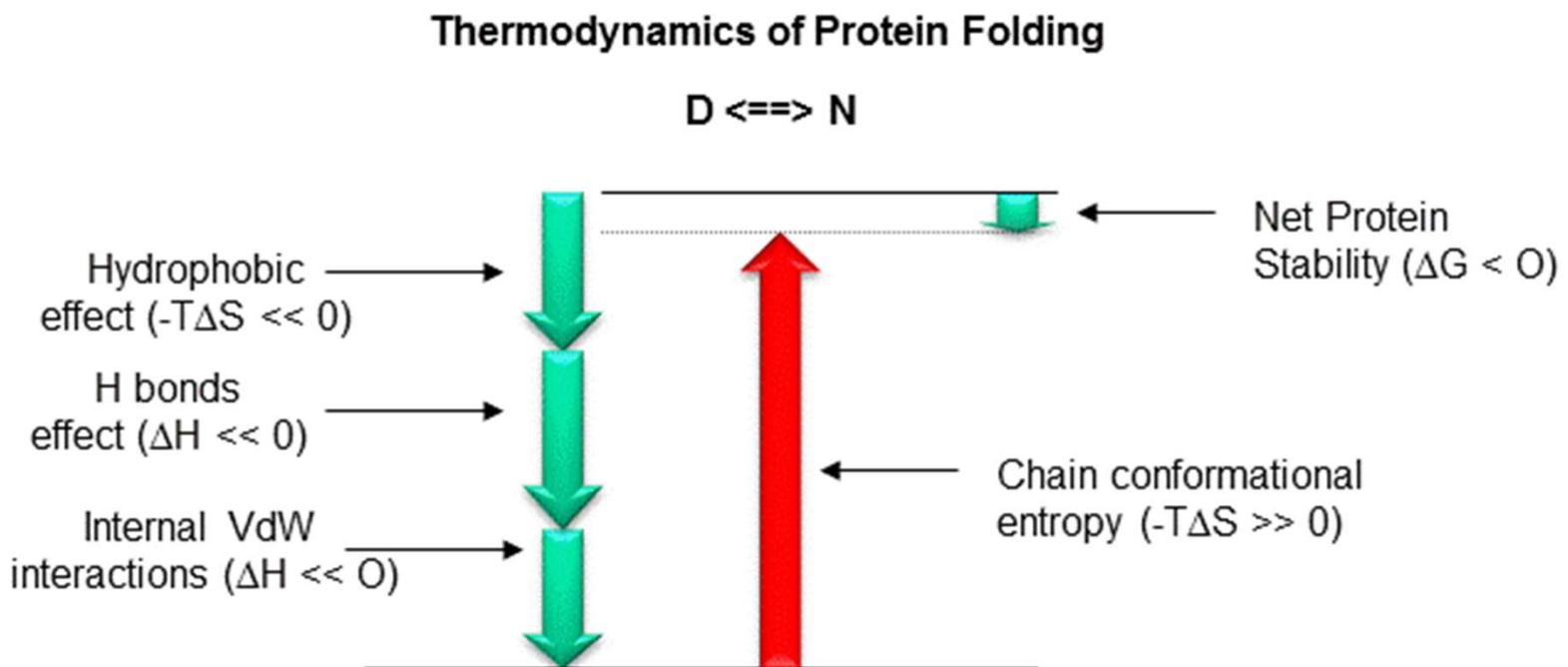
- ❑ Basics of protein stability
- ❑ Database of protein stability

# Basics of protein stability



## □ Tertiary structure of protein

- sum of non-covalent weak interactions vs conformational entropy
- folded protein = thermodynamic compromise
- folded protein **marginally more stable** than unfolded (10-80 kJ/mol)

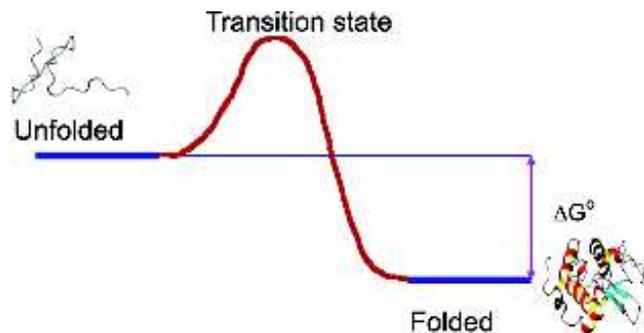


# Basics of protein stability



## □ Tertiary structure of protein

- sum of non-covalent weak interactions vs conformational entropy
- folded protein = thermodynamic compromise
- folded protein **marginally more stable** than unfolded (10-80 kJ/mol)



- Weak interactions are frequently disrupted
  - **denaturation** - disrupted bonds replaced by bonds with solvent
  - **dynamics** - disrupted bonds reformed between protein atoms

# Database of protein stability



## □ ProTherm

- <https://www.iitm.ac.in/bioinfo/ProTherm/index.html>
- set of 746 unique proteins and 311 proteins with mutants
- numerical data of thermodynamic parameters for wild type and mutant proteins

## □ Data

- Gibbs free energy change, enthalpy change, heat capacity change, transition temperature
- secondary structure and accessibility for wild type residues
- experimental conditions, methods and activity information

# Database of protein stability



## ProTherm: Thermodynamic Database for Proteins and Mutants

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### OVERVIEW

Protein Bioinformatics Lab

ProTherm, thermodynamic database Database for Proteins and Mutants (ProTherm) contains more than 300 data of several thermodynamic parameters for wild type and mutant proteins. Each entry includes numerical data for unfolding Gibbs free energy change, enthalpy change, heat capacity change, transition temperature, activity etc., which are important for understanding the mechanism of protein stability. ProTherm also includes structural information such as secondary structure and solvent accessibility of wild type residues, and experimental methods different sorting options for outputs. Further, ProTherm is cross-linked with NCBI PUBMED literature database, Protein Mutant Database, Enzyme Code and Protein Data Bank structural database.

# Database of protein stability

Entry	<input type="text"/>
PDB Code	<input type="text"/>
Protein	<input type="text"/>
Source	<input type="text"/>
Mutation	Mutation type <input type="text"/> <input type="text"/> to <input type="text"/>
Sec. Structure	<input type="checkbox"/> Helix <input type="checkbox"/> Sheet <input type="checkbox"/> Turn <input type="checkbox"/> Coil
Accessibility	<input type="radio"/> Any <input type="radio"/> Burried <input type="radio"/> Partially Burried <input type="radio"/> Exposed <input type="radio"/> ASA (%) <input type="text"/> to <input type="text"/>
Measure	<input type="checkbox"/> Absorbance <input type="checkbox"/> CD <input type="checkbox"/> DSC <input type="checkbox"/> Fluorescence <input type="checkbox"/> Others
Method	<input type="checkbox"/> Thermal <input type="checkbox"/> GdnHCl <input type="checkbox"/> Others
pH (0-13)	<input type="text"/> to <input type="text"/>
dTm/Tm/T	<input type="text"/> <input type="text"/> to <input type="text"/>
ddG/ddG_H2O	<input type="text"/> <input type="text"/> to <input type="text"/>
dH/dCp/dG_H2O	<input type="text"/> <input type="text"/> to <input type="text"/>
State	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> >3
Keyword	<input type="text"/>
Reversibility	<input type="text"/>
Author	<input type="text"/> OR <input type="text"/>
Year	Since <input type="text"/> Until <input type="text"/>

# Database of protein stability

Entry	Protein	Source	Mutation	Tm	Measure	Reversibility
<a href="#">5</a>	Ribonuclease HI	Escherichia coli	WILD	49.80	CD	YES
<a href="#">6</a>	Ribonuclease HI	Escherichia coli	WILD	52.00	CD	YES
<a href="#">7</a>	Ribonuclease HI	Escherichia coli	K 91 R	49.80	CD	YES
<a href="#">8</a>	Ribonuclease HI	Escherichia coli	K 91 R	52.00	CD	YES
<a href="#">9</a>	Ribonuclease HI	Escherichia coli	D 94 E	49.80	CD	YES
<a href="#">10</a>	Ribonuclease HI	Escherichia coli	D 94 E	52.00	CD	YES
<a href="#">11</a>	Ribonuclease HI	Escherichia coli	K 95 G	49.80	CD	YES
<a href="#">12</a>	Ribonuclease HI	Escherichia coli	K 95 G	52.00	CD	YES
<a href="#">13</a>	Ribonuclease HI	Escherichia coli	K 95 A	49.80	CD	YES
<a href="#">14</a>	Ribonuclease HI	Escherichia coli	K 95 A	52.00	CD	YES
<a href="#">15</a>	Ribonuclease HI	Escherichia coli	K 95 N	49.80	CD	YES
<a href="#">16</a>	Ribonuclease HI	Escherichia coli	K 95 N	52.00	CD	YES
<a href="#">124</a>	Ribonuclease HI	Escherichia coli	WILD	53.00	CD	YES
<a href="#">125</a>	Ribonuclease HI	Escherichia coli	A 52 I	59.20	CD	YES
<a href="#">126</a>	Ribonuclease HI	Escherichia coli	A 52 V	58.50	CD	YES
<a href="#">127</a>	Ribonuclease HI	Escherichia coli	A 52 L	57.30	CD	YES
<a href="#">128</a>	Ribonuclease HI	Escherichia coli	A 52 C	55.50	CD	YES
<a href="#">129</a>	Ribonuclease HI	Escherichia coli	A 52 M	54.60	CD	YES
<a href="#">130</a>	Ribonuclease HI	Escherichia coli	A 52 F	51.50	CD	YES
<a href="#">131</a>	Ribonuclease HI	Escherichia coli	A 52 T	50.30	CD	YES
<a href="#">132</a>	Ribonuclease HI	Escherichia coli	A 52 Q	49.10	CD	YES
<a href="#">133</a>	Ribonuclease HI	Escherichia coli	A 52 E	48.00	CD	YES
<a href="#">134</a>	Ribonuclease HI	Escherichia coli	A 52 P	47.60	CD	YES
<a href="#">135</a>	Ribonuclease HI	Escherichia coli	A 52 S	47.20	CD	YES
<a href="#">136</a>	Ribonuclease HI	Escherichia coli	A 52 N	47.10	CD	YES
<a href="#">137</a>	Ribonuclease HI	Escherichia coli	A 52 D	46.90	CD	YES
<a href="#">138</a>	Ribonuclease HI	Escherichia coli	A 52 Y	45.40	CD	YES
<a href="#">139</a>	Ribonuclease HI	Escherichia coli	A 52 G	44.10	CD	YES
<a href="#">140</a>	Ribonuclease HI	Escherichia coli	A 52 H	41.20	CD	YES
<a href="#">141</a>	Ribonuclease HI	Escherichia coli	A 52 K	33.50	CD	YES

# Database of protein stability



## ❑ FireProtDB

- <https://loschmidt.chemi.muni.cz/fireprotdb/>
- numerical data of thermodynamic parameters for wild type and mutant proteins
- More than 14,000 experimental stability data on ~ 300 proteins
- **Manual curation**

## ❑ Data

- Gibbs free energy change, enthalpy change, heat capacity change, transition temperature
- experimental conditions and methods

# Database of protein stability



v1.1

Mutational data for protein stability

Search

Enter search phrase...

ADVANCED ▾

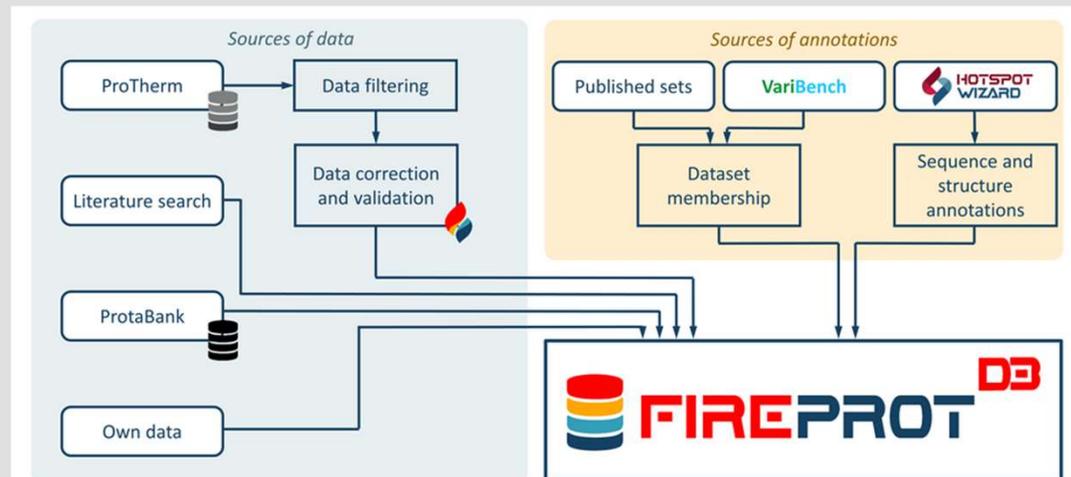


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**FireProtDB** is a comprehensive, manually curated database of the protein stability data for single-point mutants.

Proteins find their use in numerous biomedical and biotechnological applications. Naturally occurring proteins usually cannot withstand harsh industrial environments since they have evolved to function under mild conditions. Increasing protein stability is one of the key determinants of protein applicability. The predictive power of the current computational tools is compromised by the limited experimental data that would allow a rigorous training and testing.

This database combines the published datasets from [ProTherm](#) and [ProtaBank](#), the data extracted from the recent literature, and the measurements collected in our laboratory. The annotations were obtained from [VariBench](#) and [HotSpot Wizard](#). The graphical user interface is designed to facilitate both types of the expected use: (i) the interactive explorations of individual entries on the level of a protein or a mutation and (ii) the construction of highly customized, machine learning-friendly datasets using advanced searching and filtering.



# Database of protein stability



## FireprotDB search results

Export CSV

■ Stabilizing ■ Destabilizing ■ Neutral

Protein ↑	Curated ↑	Mutation ↑	$\Delta\Delta G$ (kcal/mol) ↑	$\Delta T_m$ (°C) ↑
Halohydrin dehalogenase	★	E64A	-	1
Halohydrin dehalogenase	★	S22A	-	-0.5
Halohydrin dehalogenase	★	N113H	-	-3.5
Halohydrin dehalogenase	★	N113H	-	-2
Halohydrin dehalogenase	★	D96H	-	-9
Halohydrin dehalogenase	★	A29L	-	3
Halohydrin dehalogenase	★	P253G	-	-0.5
Halohydrin dehalogenase	★	P253G	-	-2.5
Halohydrin dehalogenase	★	T134I	-	-1
Halohydrin dehalogenase	★	T134I	-	0.5

# Protein dynamics



- ❑ Basics of protein dynamics
- ❑ Characteristics of protein motions
- ❑ Dynamics and protein function
- ❑ Approaches to study dynamics
- ❑ Databases of dynamics
- ❑ Protein dynamics in biology

# Introduction to protein dynamics



- ❑ **Origin of dynamics** – disruption of weak interactions by
  - thermal kinetic energy ( $k_b.T$ )
  - binding interactions (ligands or other proteins) – induced fit
  
- ❑ **Protein atoms fluctuates around their average positions**
  - in tightly packed interior – movement restricted
  - near surface – movement promoted by solvent movements
  - -> proteins considered as “**semi-liquids**”

# Characteristics of protein motions

## □ Divisions of protein motions

Type of motion	Moving moiety	Functionality
Local	atoms; side-chains	bond vibration; ligand flexibility; temporal diffusion pathways
Medium-scale	secondary structures	active site conformational changes; motion of hinge; peptide bond rotation;
Large-scale	domains	hinge facilitated domain movements; allosteric transition
Global	subunits	helix-loop transition; folding/unfolding

# Amplitudes of protein motions



## ❑ **Fluctuations**

- less than 1 Å
- local motions

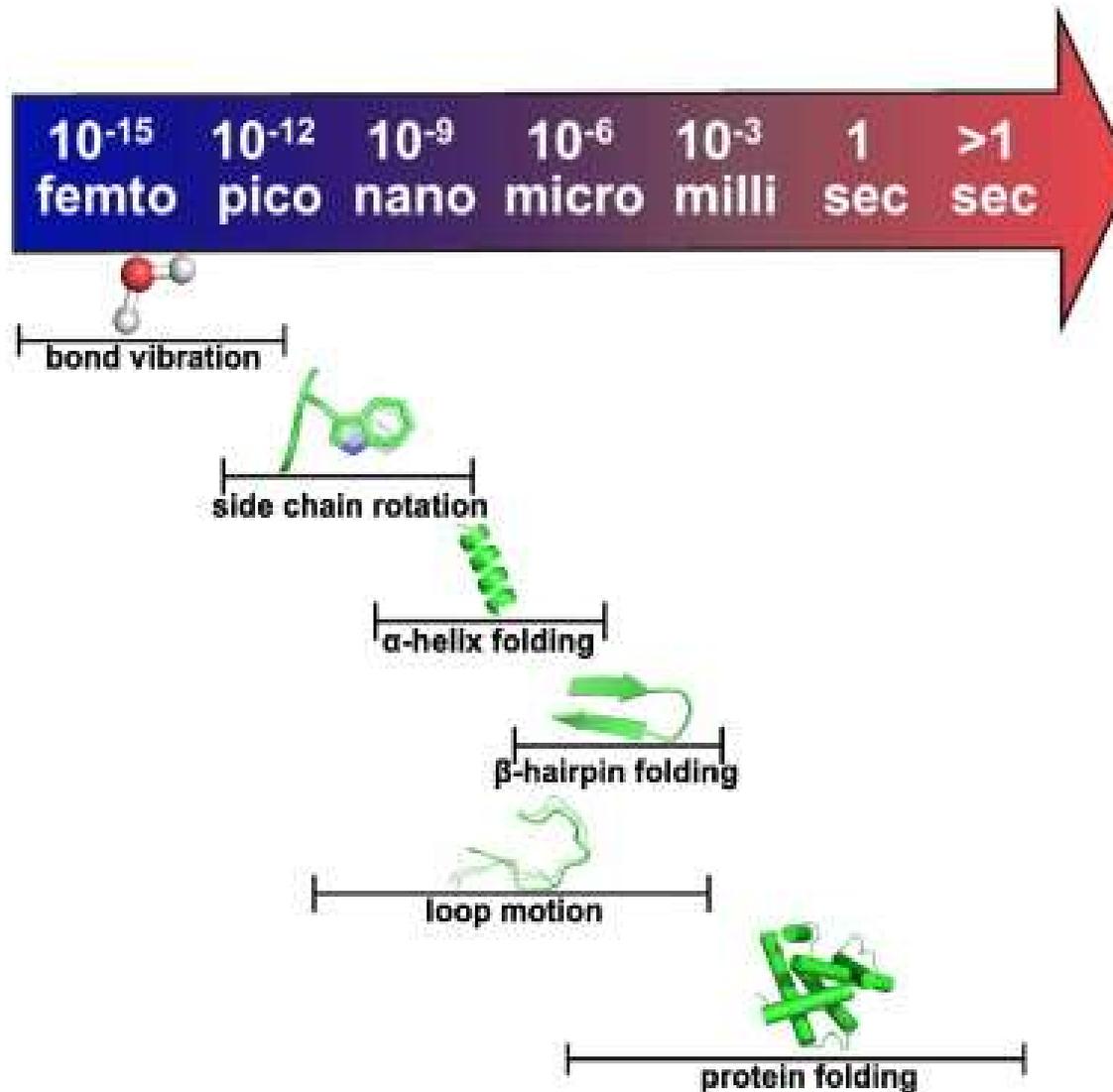
## ❑ **Collective motions**

- 1-10 Å
- medium and large-scale motions

## ❑ **Triggered conformational changes**

- more than 10 Å
- global motions

# Time scales of protein motions



# Time scales of protein motions



## □ Time scales governed by local environment

- interior – motions coupled due to packing restraints
- surface – no coupling of motions

## □ Example: aromatic ring flipping

- can occur on ps time scale, but often observed on ms time scale
- aromatic residues -> hydrophobic -> inside protein -> tightly packed
- -> low probability of synchronized movement of surrounding atoms
- -> prolonged time scale

# Approaches to study dynamics

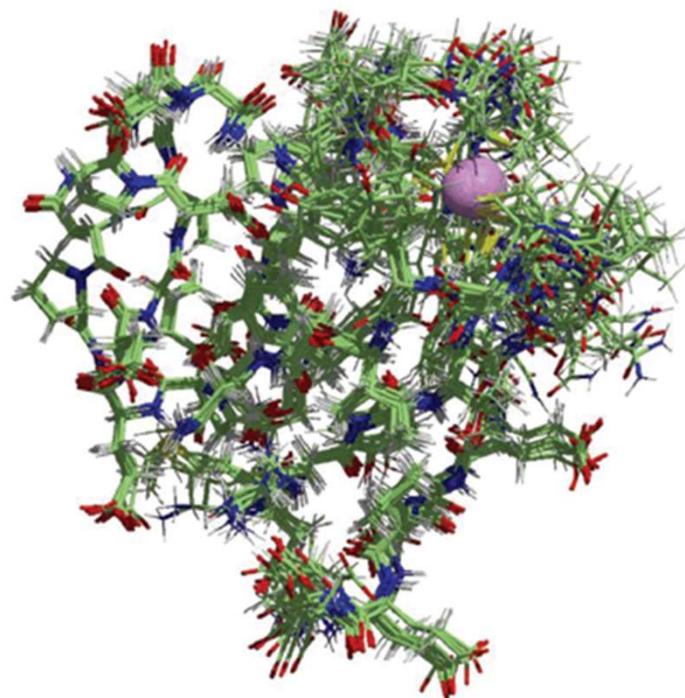


- ❑ NMR spectroscopy
- ❑ High resolution X-ray crystallography
- ❑ Computational
  - Normal mode analysis (NMA)
  - Molecular dynamics (MD)

# NMR spectroscopy



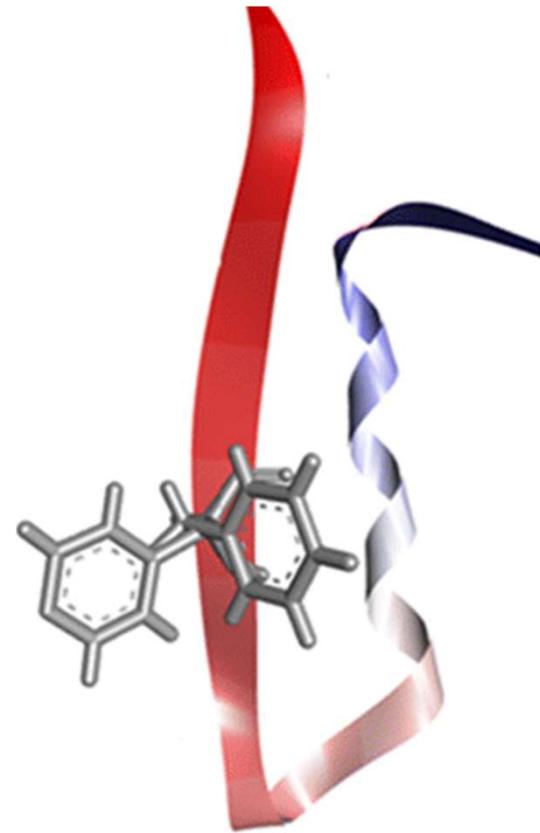
- ❑ **Ensemble of possible low energy conformations**
- ❑ Directly shows possible amplitudes of motion
- ❑ Limited applicability to larger proteins
- ❑ **Does not describe**
  - very fast motions & transition states
  - time scales & energetics of motions



# High resolution X-ray crystallography



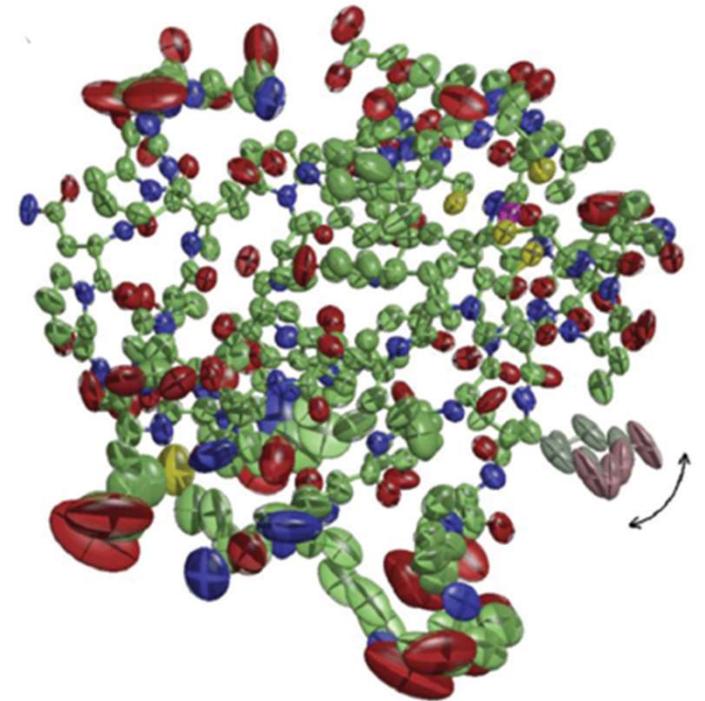
- **Average low energy structure** - more conformations:
  - in one structure only if both are separated by barrier
  - in multiple structures



# High resolution X-ray crystallography



- ❑ **Average low energy structure** - more conformations:
  - in one structure only if both are separated by barrier
  - in multiple structures
- ❑ **Crystalline state**
  - non-native contacts
  - artificially lower amplitudes of motions
- ❑ **Range of fluctuations – B-factors**
- ❑ **Does not describe**
  - very flexible regions
  - collectiveness of motions
  - time scales & energetics of motions



# Normal mode analysis



## □ Principle

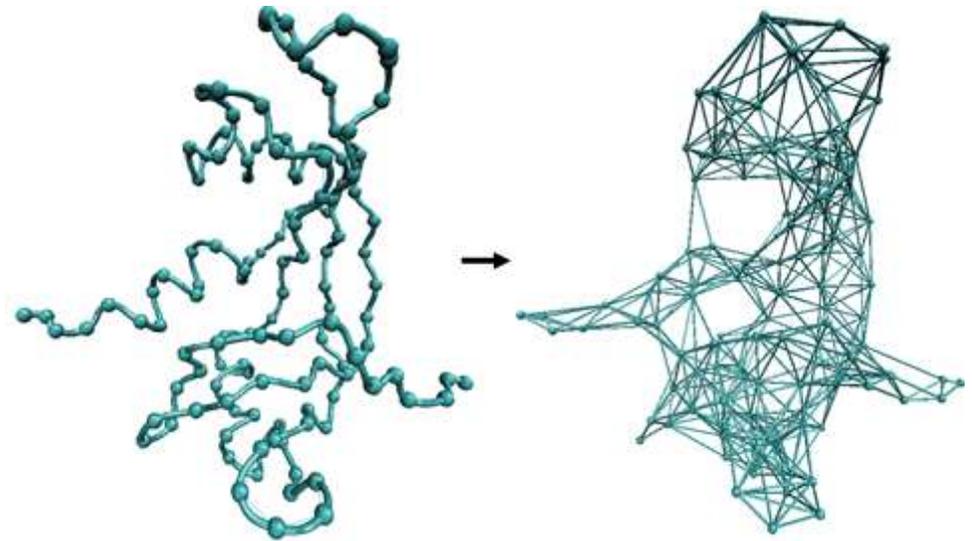
- motion of system as harmonic vibration around a local minimum
- Coarse-grained model, residues connected with springs

## □ Small number of low-frequency normal modes

- shows directionality, collectiveness and sequence of global motions

## □ Does not describe

- local movements
- amplitudes & time scales
- energetics of motions



# Molecular dynamics

## □ Principle

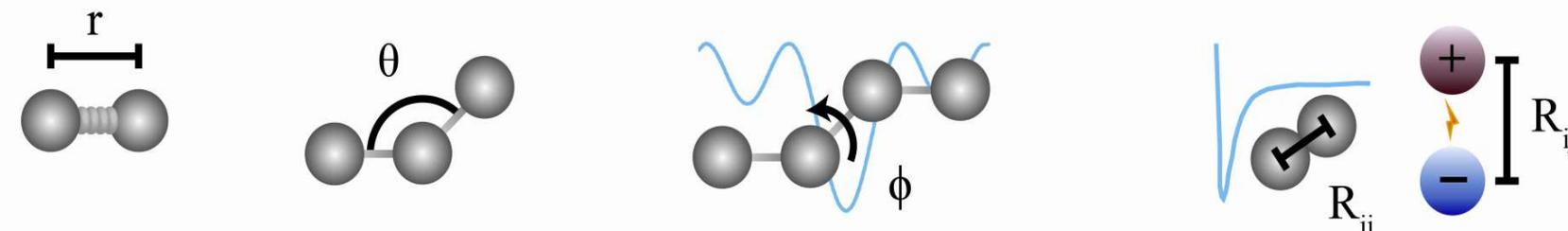
- physical description of interactions within system (force field)
- Newton's laws of motions
- forces acting on all atoms due to all atoms
- small time-step  $\sim 2$  fs

$$E_{total} = \sum_{bonds} K_r (r - r_{eq})^2 + \sum_{angles} K_\theta (\theta - \theta_{eq})^2 + \sum_{dihedrals} \frac{V_n}{2} [1 + \cos(n\phi - \gamma)] + \sum_{i < j} \left[ \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon R_{ij}} \right]$$

# Molecular dynamics

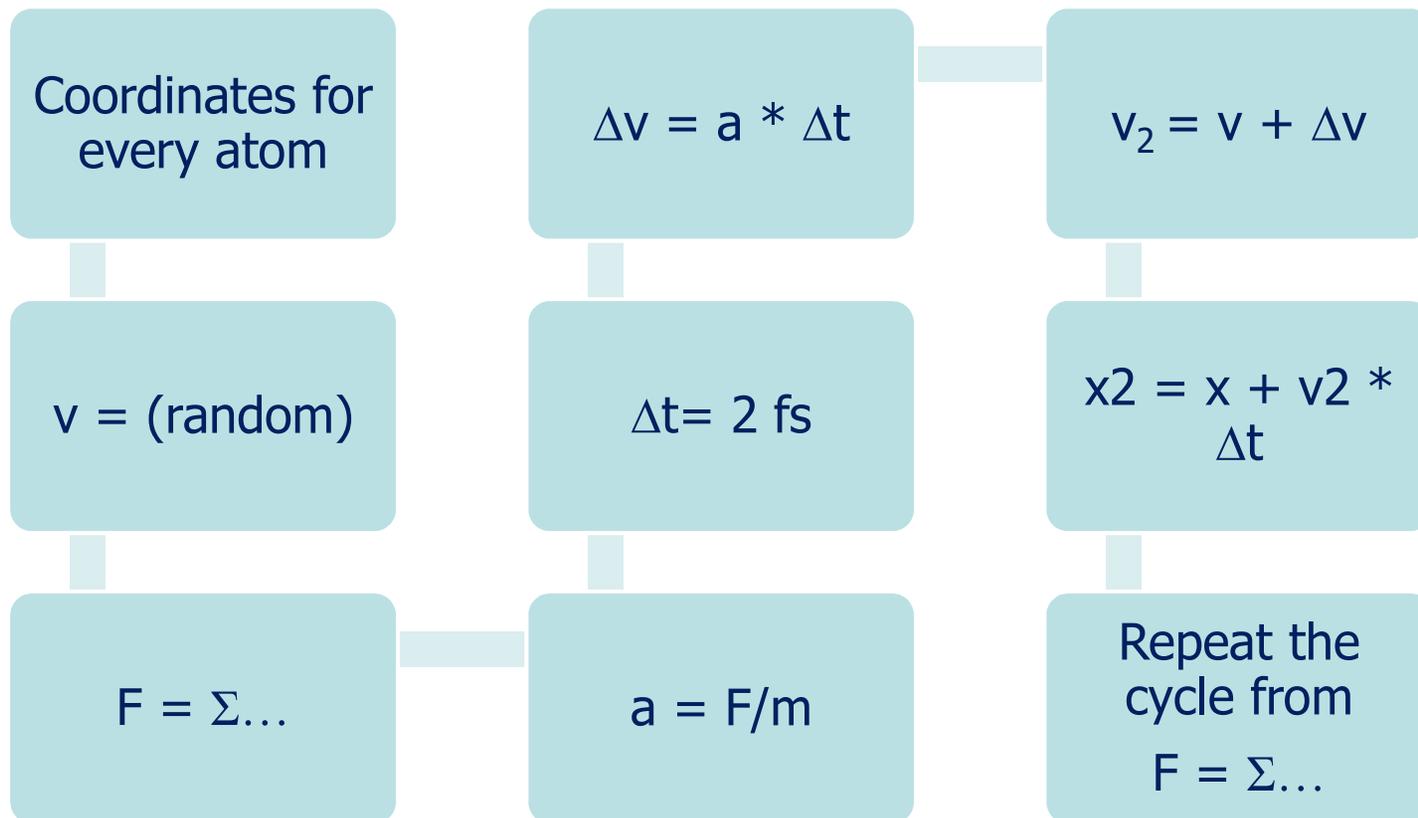
## □ Principle

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# Molecular dynamics

## Calculation of atom coordinates in time



# Molecular dynamics



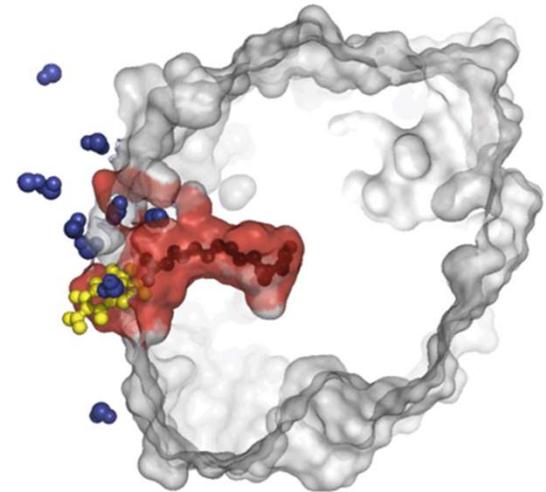
## □ Principle

- physical description of interactions within system (force field)
- Newton's laws of motions

## □ Provides information on energetics, amplitudes and time scales of local motions on atomic level

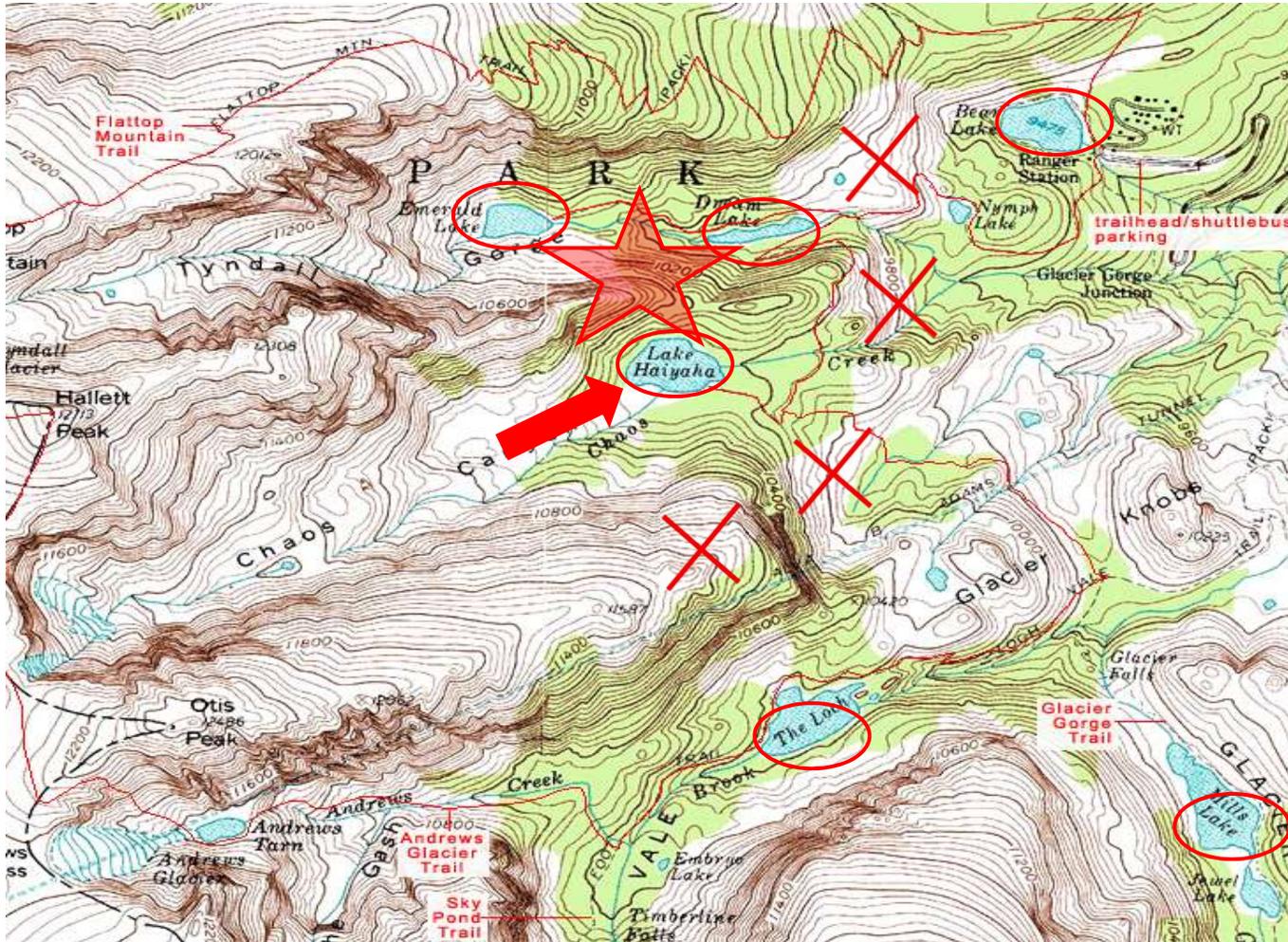
## □ Does not describe

- slower large scale motions ( $> \text{ms}$ )



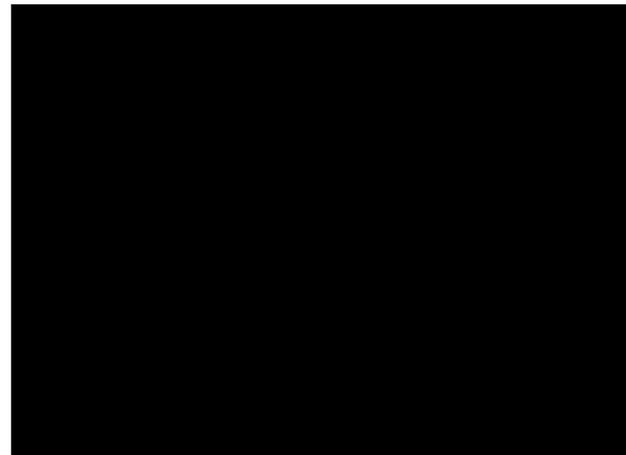
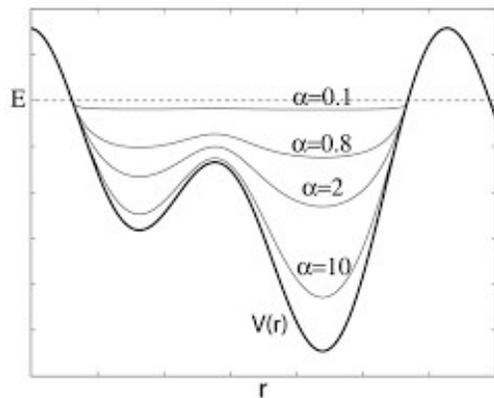
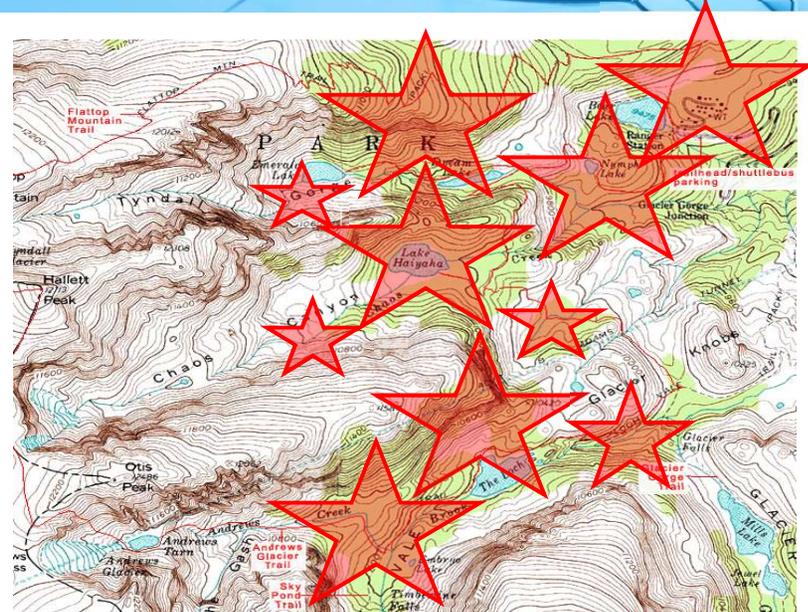
# Molecular dynamics

## □ Classical MD



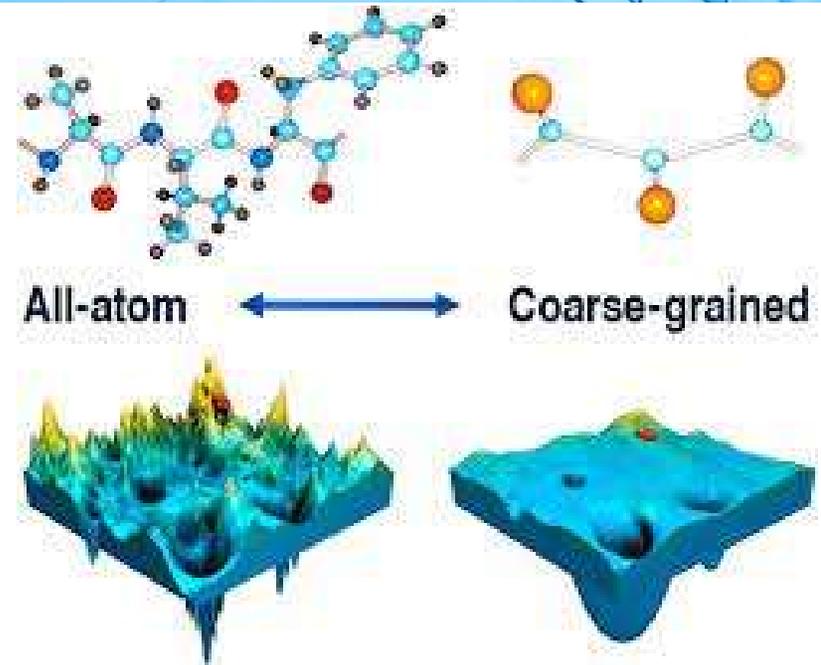
# Molecular dynamics

- **Classical MD**
- **Enhanced sampling**
  - Adaptive sampling
  - Metadynamics
  - Accelerated MD
  - Umbrella sampling

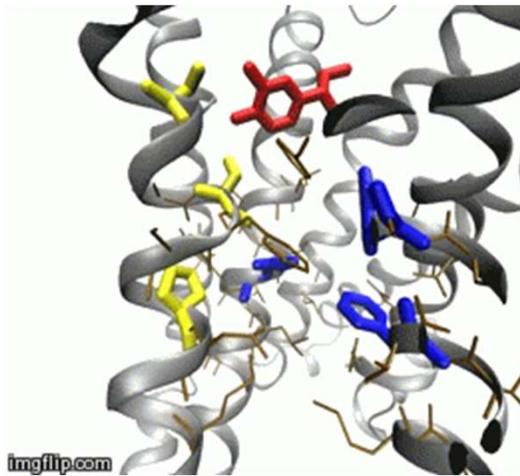


# Molecular dynamics

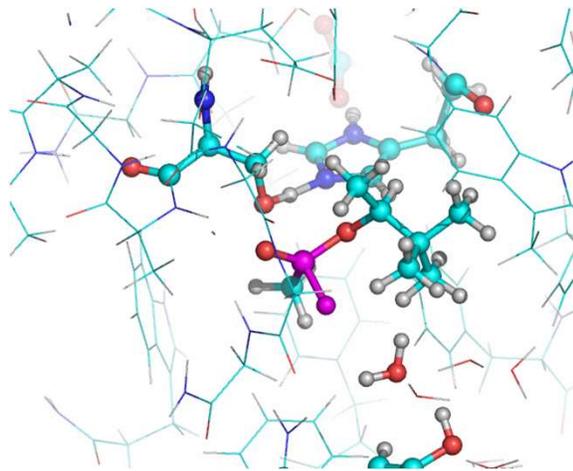
- **Classical MD**
- **Enhanced sampling**
  - Adaptive sampling
  - Metadynamics
  - Accelerated MD
  - Umbrella sampling
- **Coarse-grained molecular dynamics**



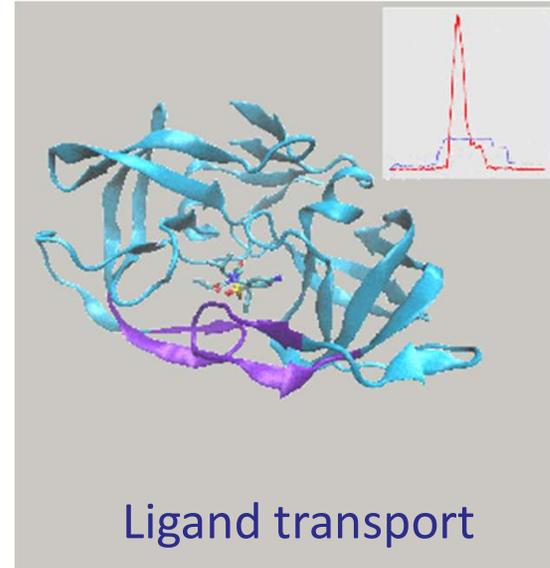
# Molecular dynamics



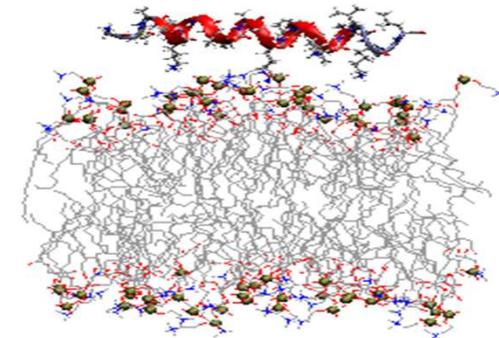
Analysis of interactions



Ligand conversion



Ligand transport



Interactions of molecules

# Databases of dynamics



- ❑ Molecular Dynamics Extended Library (MoDEL)
- ❑ Dynameomics
- ❑ Molecular Movements Database (MolMovDB)
- ❑ ProMode-Elastic

# MoDEL

- ❑ <http://mmb.pcb.ub.es/MoDEL/>
- ❑ >1,700 MD simulations of proteins representatives of all monomeric soluble structures in PDB
- ❑ 10 ns trajectories from MD simulations
- ❑ Data
  - pre-computed analysis of geometry, secondary structure, flexibility and inter-residue contacts
  - trajectory video
  - downloadable trajectories

# MoDEL

**MoDEL**  
Molecular dynamics extended library

Professional Platform INB

Quick Search: by pdb code... user: password: HELP

**BROWSE BY ID**

**1ASS. APICAL DOMAIN OF THE CHAPERONIN FROM THERMOPLASMA ACIDOPHILUM**

Simulation: AMBER 8.0.P99 (T3P).10000 Program Version AMBER8.0  
 Time Slice: 1 - 10000 Simulation time 10000 ps  
 Structure Fragment: (MET A1 - LYS A152) Total atoms 46547  
 Force field parm99 tip3P

[more details:](#)

**RMSd**

Reference	Average	Experimental
<b>CA</b>	1.364 ± 0.379 (0.881 - 3.024) Å	2.916 ± 2.895 (1.022 - 4.128) Å
<b>Backbone</b>	1.369 ± 0.372 (0.902 - 2.988) Å	2.895 ± 0.677 (1.025 - 4.109) Å
<b>Heavy</b>	1.946 ± 0.354 (1.511 - 3.629) Å	3.783 ± 0.639 (1.736 - 4.916) Å
<b>All</b>	1.914 ± 0.353 (1.479 - 3.592) Å	3.732 ± 0.638 (1.702 - 4.866) Å

**GEOMETRY**

- RMSd
- SASA
- TM Score
- Other

**SECONDARY STRUCTURE**

- Secondary structure

**FLEXIBILITY & DYNAMICS**

- B Factors
- Entropy
- Principal Components
- Lindemann Coefficient

**INTERACTIONS & CONTACTS**

- Contacts

[Switch to 3D \(Jmol\)](#)

[Jmol animation](#)  
[trajectory video](#)  
[FlexServ](#)  
[Download trajectories](#)

Do you need a custom-made analysis?

IRB, INB, and other logos at the bottom.

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# Dynameomics



- ❑ [www.dynameomics.org](http://www.dynameomics.org)
- ❑ MD simulations of over 800 proteins
- ❑ Longer trajectories (> 31 ns)
- ❑ Data
  - pre-computed analysis of RMSD, SASA, Phi-Psi, and contacts
  - trajectory video
  - visualization of individual snapshots
  - downloadable trajectories **on request**

# Dynameomics

**DYNAMEOMICS** | the daggett group at the university of washington

PDB ID or Keyword

[Target Stats](#) [Target List](#) [SNPs](#) [SLIRP](#) [Methods](#) [Database](#) [Data Mining](#) [Publications](#) [Help](#)

### Analysis Tools

A recent Java software security vulnerability has caused Dynamical's sort function on some clients. If you are unable to load the Dynamical application, please update your Java software at JAVA.

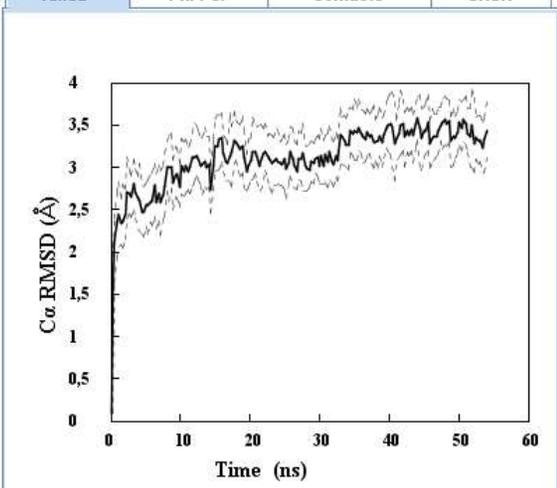
#### Twitchin 18th igsf module (Iwit)

**Dynamical Documentation**

Current Viewtime = 0 ns      time\_range = 54,157 ns      run = 1      temp = 298K

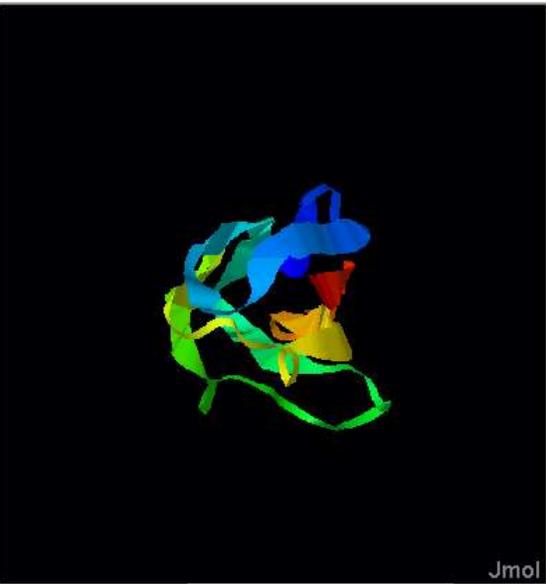
**DSSP** **Congeneal** **Radius of Gyration**

**RMSD** **Phi-Psi** **Contacts** **SASA**



**Iwit**

rmsd     display min/max     Advanced



50 ps

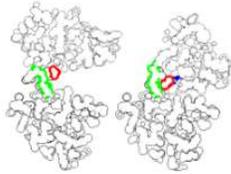
Note: Select a time point in the graph on the left and the appropriate structure will be displayed on the right. Right click on either panel for additional options. It can take several minutes for a structure to load, depending on your network connection speed.

Daggett Group | University of Washington | College of Engineering | Department of Bioengineering | Sponsors | Citing Dynameomics.org

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# MolMovDB

- ❑ <http://www.molmovdb.org/>
- ❑ Collection of over 178 molecular motions
- ❑ Based on **morphing** – interpolation of motion between two experimental crystal structures
- ❑ Data
  - **classification scheme for molecular motions**
  - movements animations
  - hinge identification, structural analysis tools, references to experimental crystal structures
  - downloadable morphs as multi-model PDB



## Molecular Movements Database

This outline presents the current database classified by any classification scheme for which data has been compiled. The original schema which separates motions by type of movement is defined on the [help page](#). Thumbnail images appear for motions which have available movies, and link to the best morph for that particular protein.

Many more movies can be seen [here](#), including structures not represented on this page. The movies page also allows searches for protein names or specific PDB IDs.

[Switch to CATH survey](#)

### I. Motions of Fragments Smaller than Domains

#### A. Motion is predominantly shear

##### F-s-2. Proteins for which two or more conformations are known



Adenosylcobinamide Kinase [\[motion\]](#) [\[morph\]](#)



Small G-protein Arf6 [\[motion\]](#) [\[morph\]](#)



Bacteriorhodopsin (bR) [\[motion\]](#) [\[morph\]](#)



Calbindin [\[motion\]](#) [\[morph\]](#)



Dihydrofolate Reductase (DHFR) [\[motion\]](#) [\[morph\]](#)



Histidine-Containing Phosphocarrier Protein [\[motion\]](#) [\[morph\]](#)

# ProMode-Elastic

- ❑ <https://pdj.org/promode-elastic>
- ❑ Normal mode analysis of PDB data – **on PDB database**
- ❑ Data
  - fluctuation of atoms and dihedral angles
  - correlation between fluctuating atoms
  - distance map between residues
  - animation of fluctuating molecules
  - displacement vectors

# ProMode-Elastic



Database of normal mode analysis of PDB data using elastic network model in torsional angle space

[Home](#) | [What is ProMode-Elastic](#) | [Help](#)

[Japanese](#)

No. of entries  
103529

FDB code (4 chars)   Example 1a00  
Select from a list of entries

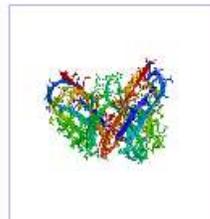
Submission of your data to be analyzed.

[Download of software.](#)

ProMode-Elastic is a database of normal mode analysis of PDB data. The normal mode analysis is performed by the program PDBETA we have developed. PDBETA is a program of Elastic-network-model based normal mode analysis in Torsional Angle space for PDB data. PDBETA can describe molecular structures with relatively smaller number of degrees of freedom, and take into computation not only proteins but also DNA, RNA, and ligand molecules (hydrogen atoms and water molecules are excluded currently to suppress the number of variables).

In each protein page its characteristic dynamic features can be observed through animation and displacement vectors on a viewer such as jV and Jmol. We hope that a user learns more about dynamics from these pages than a static three-dimensional structure image of PDB data.

Reference: Hiroshi Wako and Shigeru Endo, "Ligand-induced conformational change of a protein reproduced by a linear combination of displacement vectors obtained from normal mode analysis." *Biophys. Chem.* vol. 159, pp.257-266, 2011 [DOI:10.1016/j.bpc.2011.07.004]



PDB ID: 1a7r. Fv fragment of mouse monoclonal antibody IgG1-kappa d1.3 (light and heavy chains). The third lowest-frequency

Click on image for an enlarged image and more information.

## TOPICS

- 14/5/2012 ProMode-Elastic server has been moved to PDBj. IPR, Osaka University. URL was also changed.
- 9/10/2010 ProMode-Elastic first version is released.
- 12/12/2009 ProMode-Elastic test version is released.

[PageTop](#) | [Back](#)

(latest update: 2012.07.20)

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Database of normal mode analysis of PDB data using elastic network model in torsional angle space

[Home](#) | [What is ProMode-Elastic](#) | [Help](#)

[Japanese](#)

Go to PDB code    
Select from a list of entries

**1cqw**

HEADER	HYDROLASE	11-AUG-99	1CGW
TITLE	NAI COCRYSTALLISED WITH HALOALKANE DEHALOGENASE FROM A		
TITLE	2 RHODOCOCOCCUS SPECIES		
COMPND	MOL ID: 1:		
COMPND	2 MOLECULE: HALOALKANE DEHALOGENASE: 1-CHLOROHXANE		
COMPND	3 HALOXYDROLASE:		
COMPND	4 CHAIN: A:		
COMPND	5 EC: 3.8.1.5:		
COMPND	6 ENGINEERED: YES:		
COMPND	7 OTHER_DETAILS: COCRYSTALLIZED WITH NAI		
SOURCE	MOL ID: 1:		

[1cqw in other DBs >>>](#) [PDB](#) [PDBj](#) [PDBsum](#) [SCOP](#) [CATH](#) [FSSP](#)

## 3D molecular view of vibration

[Help](#)

Choose a mode and then click on a 'Viewer' button to launch a viewer. It may take a while to load data files.

Displacement vectors (Choose up to three modes.)

<input checked="" type="checkbox"/> Mode 1	<input type="checkbox"/> Mode 2	<input type="checkbox"/> Mode 3	<input type="checkbox"/> Mode 4	<input type="checkbox"/> Mode 5	<a href="#">PDBj</a>	<a href="#">Jmol</a>
<input type="checkbox"/> Mode 6	<input type="checkbox"/> Mode 7	<input type="checkbox"/> Mode 8	<input type="checkbox"/> Mode 9	<input type="checkbox"/> Mode 10	<input type="button" value="Viewer"/>	<input type="button" value="Viewer"/>
Animation (Choose one mode.)						
<input checked="" type="radio"/> Mode 1	<input type="radio"/> Mode 2	<input type="radio"/> Mode 3	<input type="radio"/> Mode 4	<input type="radio"/> Mode 5	<a href="#">PDBj</a>	<a href="#">Jmol</a>
<input type="radio"/> Mode 6	<input type="radio"/> Mode 7	<input type="radio"/> Mode 8	<input type="radio"/> Mode 9	<input type="radio"/> Mode 10	<input type="button" value="Viewer"/>	<input type="button" value="Viewer"/>

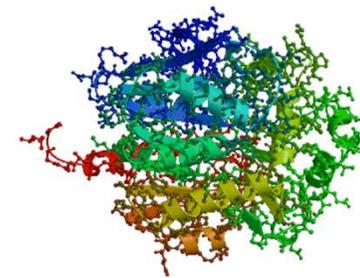
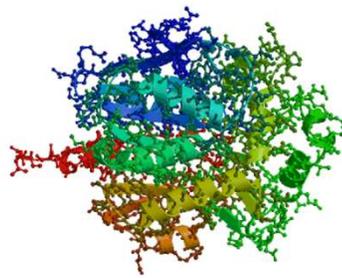
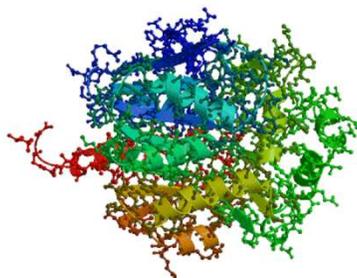
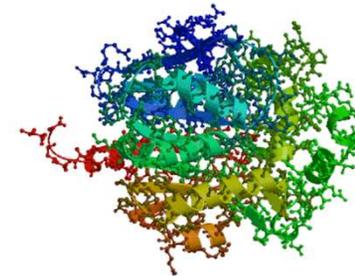
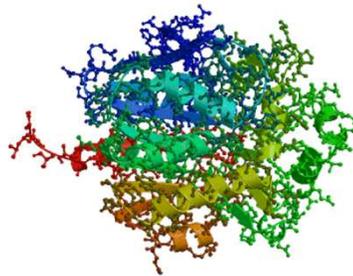
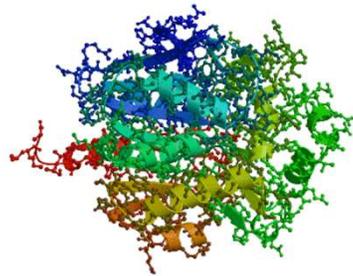
## Still image of displacement vectors and GIF animation

Click on All, MainC or GIF for large image or GIF animation

Displacement vectors: All=All atoms and MainC=Main chain atoms. GIF=GIF animation

Mode 1	Mode 2	Mode 3
<a href="#">All</a> <a href="#">MainC</a> <a href="#">GIF</a>	<a href="#">All</a> <a href="#">MainC</a> <a href="#">GIF</a>	<a href="#">All</a> <a href="#">MainC</a> <a href="#">GIF</a>

# ProMode-Elastic



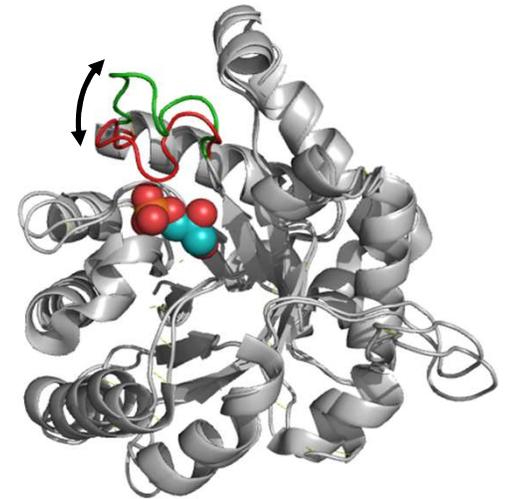
# Protein dynamics in biology



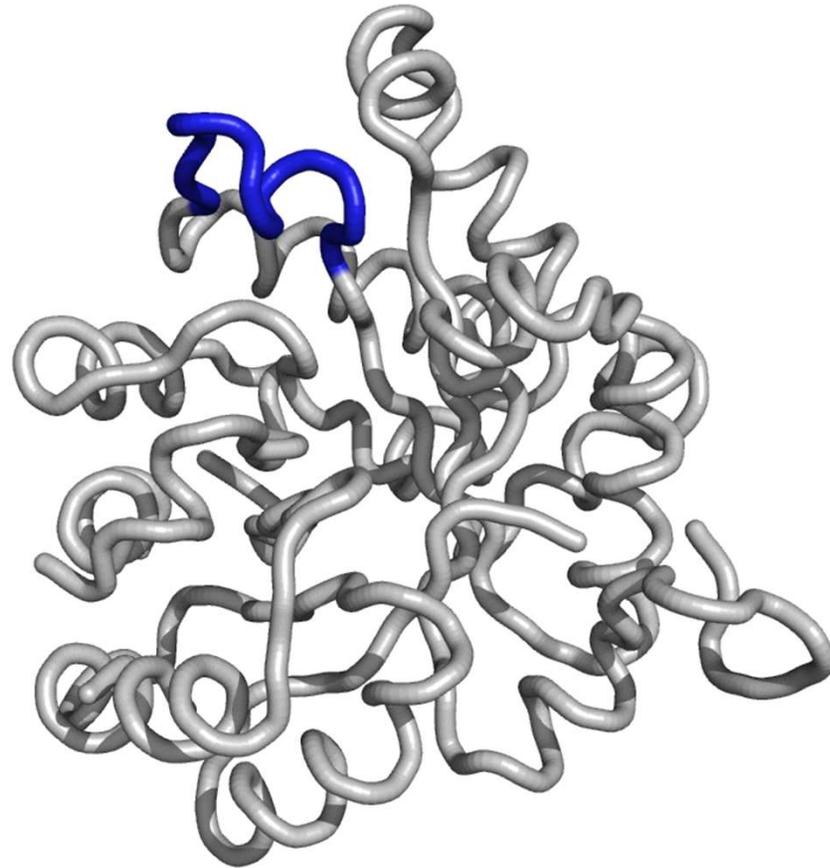
- ❑ Triose phosphate isomerase
- ❑ Adenylate kinase
- ❑ Motor proteins

# Triose phosphate isomerase

- Biological processes
  - catalyzes the reversible interconversion of the triose phosphate isomers in the glycolytic pathway
- Typical lid-like movement
  - flexible eleven-residue loop (residues 168-178)
  - ligand-induced movement of about 7 Å
  - shielding of bound substrate from solvent – decomposition of the enediolate intermediate (about 100x faster than isomerization)

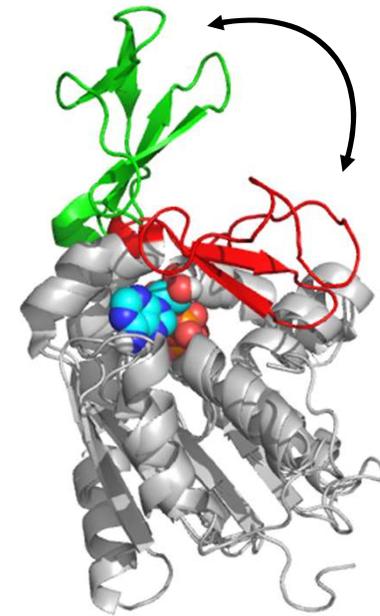


# Triose phosphate isomerase

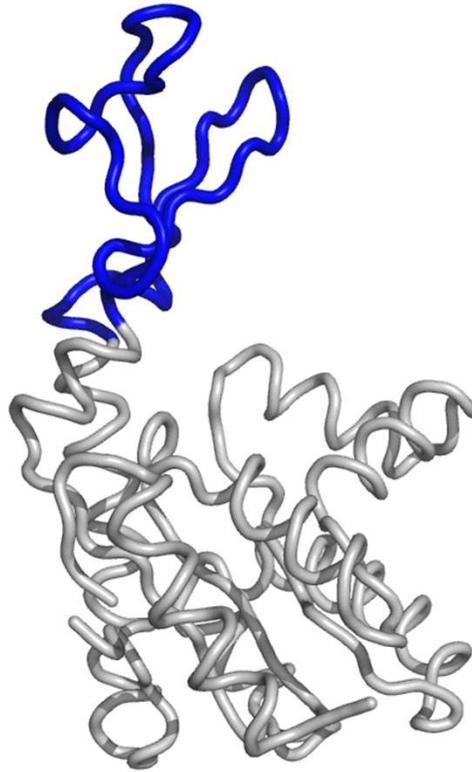


# Adenylate kinase

- ❑ Biological processes
  - catalyzes interconversion of  $\text{ATP} + \text{AMP} \rightleftharpoons 2 \text{ADP}$
- ❑ Large conformational change
  - 90 degrees rotation of whole domain, up to 30 Å amplitude
  - induced by binding of ATP
  - shielding of bound substrate from solvent



# Adenylate kinase

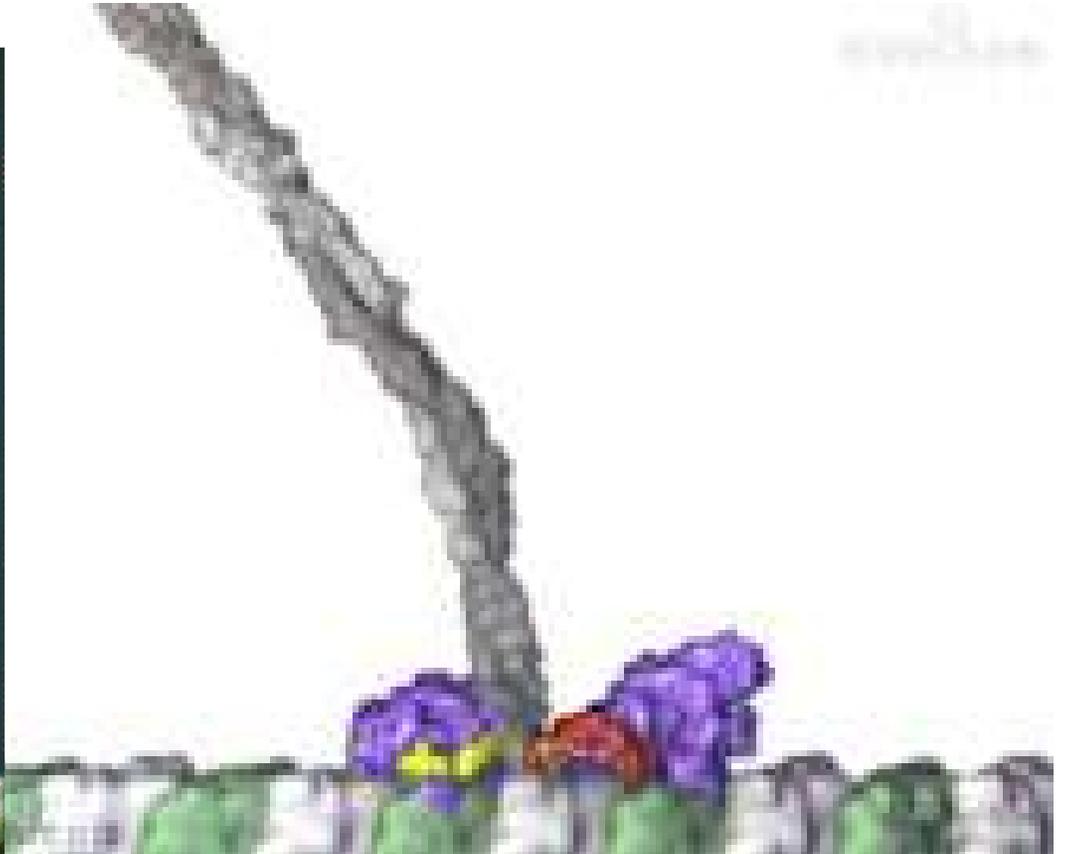
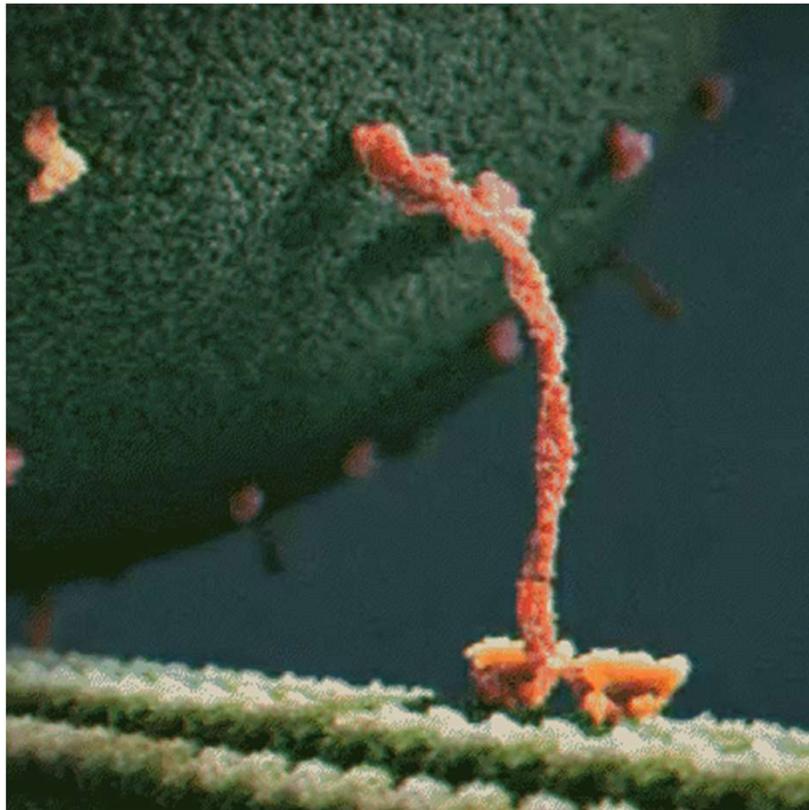


# Motor proteins



- ❑ Biological processes
  - myosin movement along actin filament
  - kinesin movement along microtubule
- ❑ Motor head
  - ATPase domain – binding of ATP
  - linker domain – changes conformation upon ATP binding
- ❑ One step
  - moves a motor head for about 160 Å
  - moves an attached cargo for about 80 Å

# Motor proteins



# References



- ❑ Gu, J. & Bourne, P. E. (2009). **Structural Bioinformatics, 2<sup>nd</sup> Edition**, Wiley-Blackwell, Hoboken.
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- ❑ Dill, K. A. *et al.* (2008). The protein folding problem. *Annual Review of Biophysics* **37**: 289-316.