BIMM 143

Structural Bioinformatics

Lecture 11

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UC San Diego

http://thegrantlab.org/bimm143

http://www.ks.uiuc.edu/Development/Download/download.cgi

“*Bioinformatics is the application of computers to the collection, archiving, organization, and analysis of biological data.*”

… A hybrid of biology and computer science

“Bioinformatics is the application of computers to the collection, archiving, organization, and analysis of biological data.”

Bioinformatics is computer aided biology!

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Bioinformatics is computer aided biology!

Goal: Data to Knowledge

So what is **structural bioinformatics**?

So what is **structural bioinformatics**?

… computer aided structural biology!

Aims to characterize and interpret biomolecules and their assembles at the molecular & atomic level

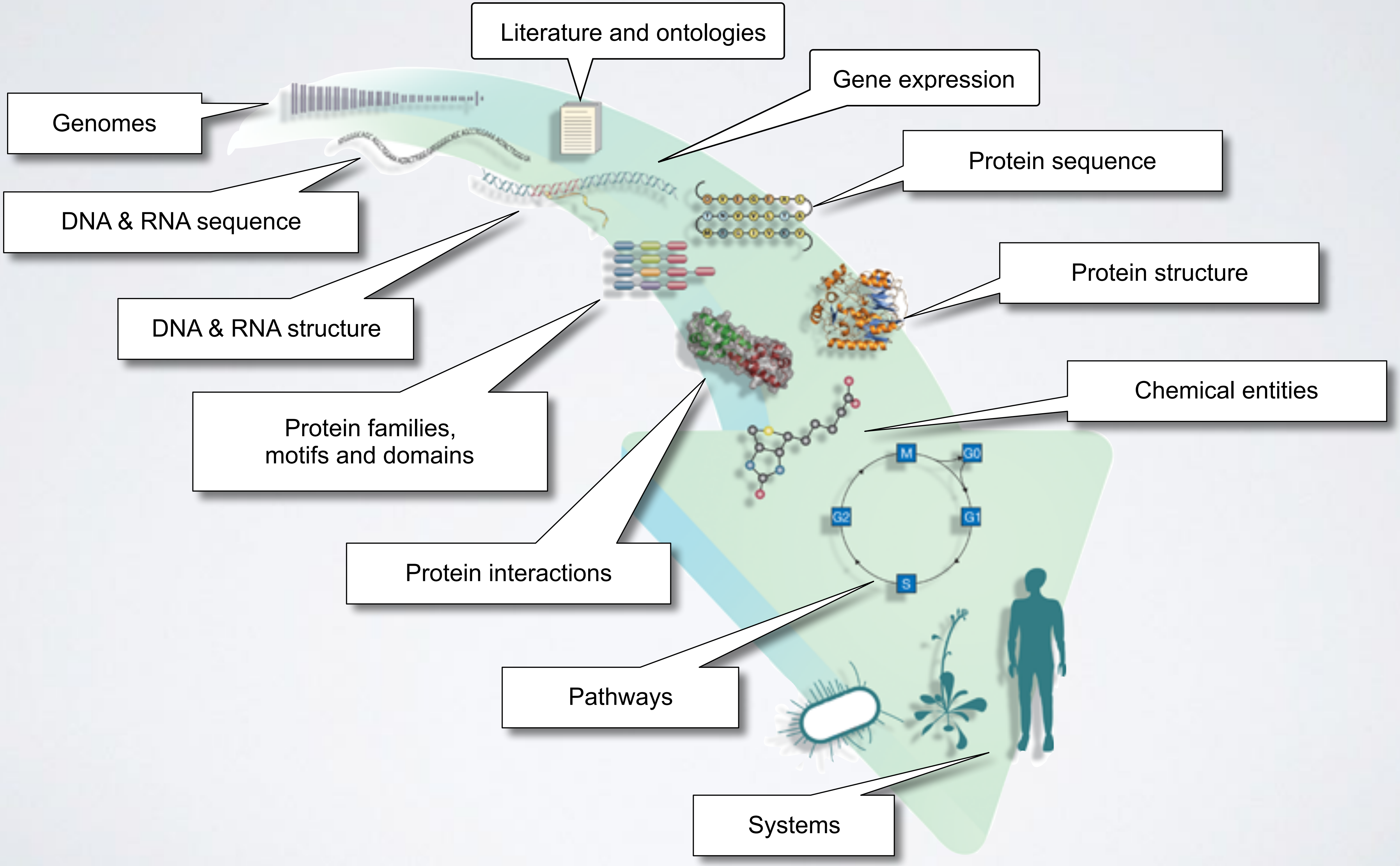
Why should we care?

Why should we care?

Because biomolecules are “nature’s robots”

… and because it is only by coiling into **specific 3D structures** that they are able to perform their functions

BIOINFORMATICS DATA



Literature and ontologies

Genomes

Gene expression

Protein sequence

DNA & RNA sequence

Protein structure

DNA & RNA structure

Chemical entities

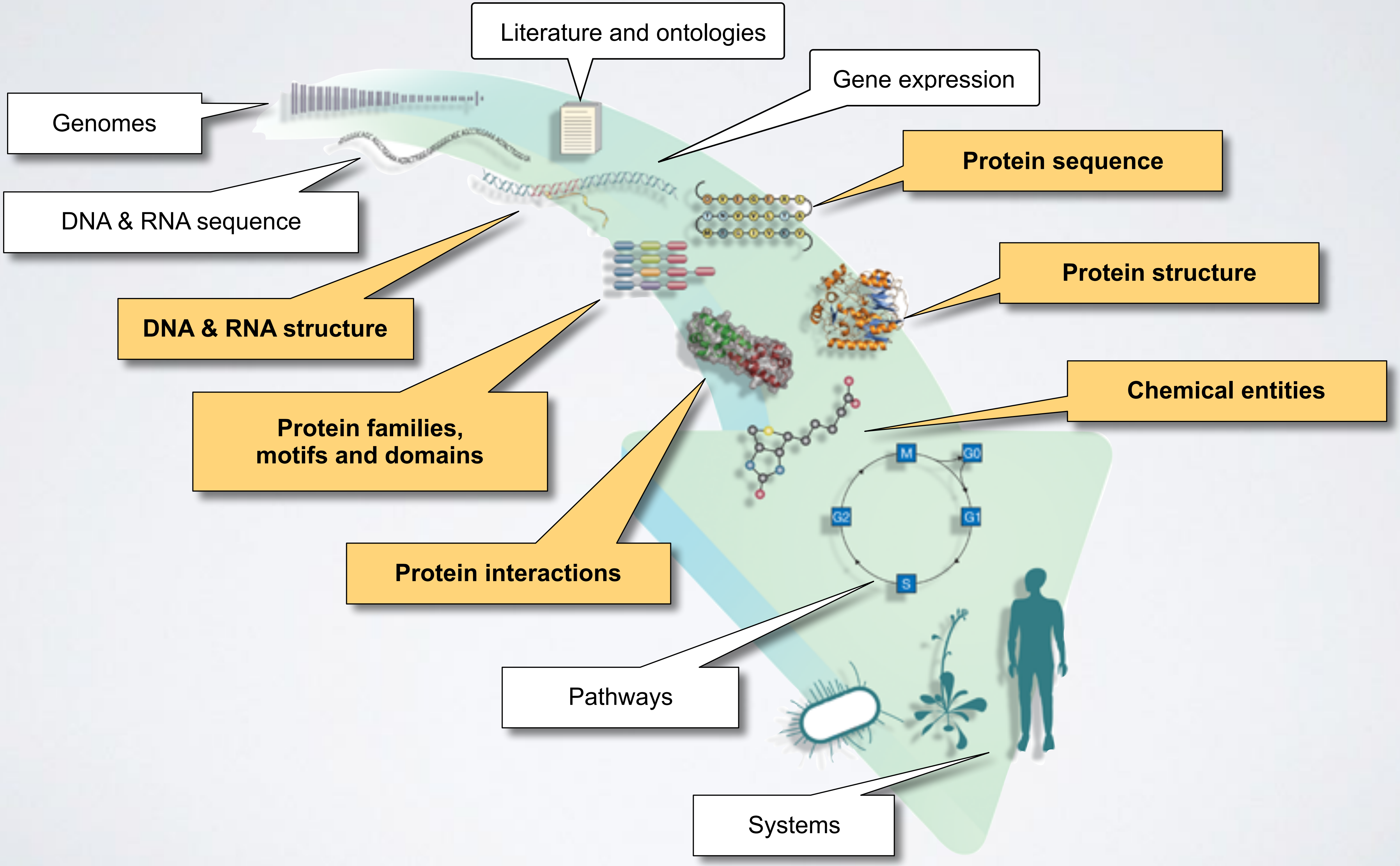
Protein families, motifs and domains

Protein interactions

Pathways

Systems

STRUCTURAL DATA IS CENTRAL



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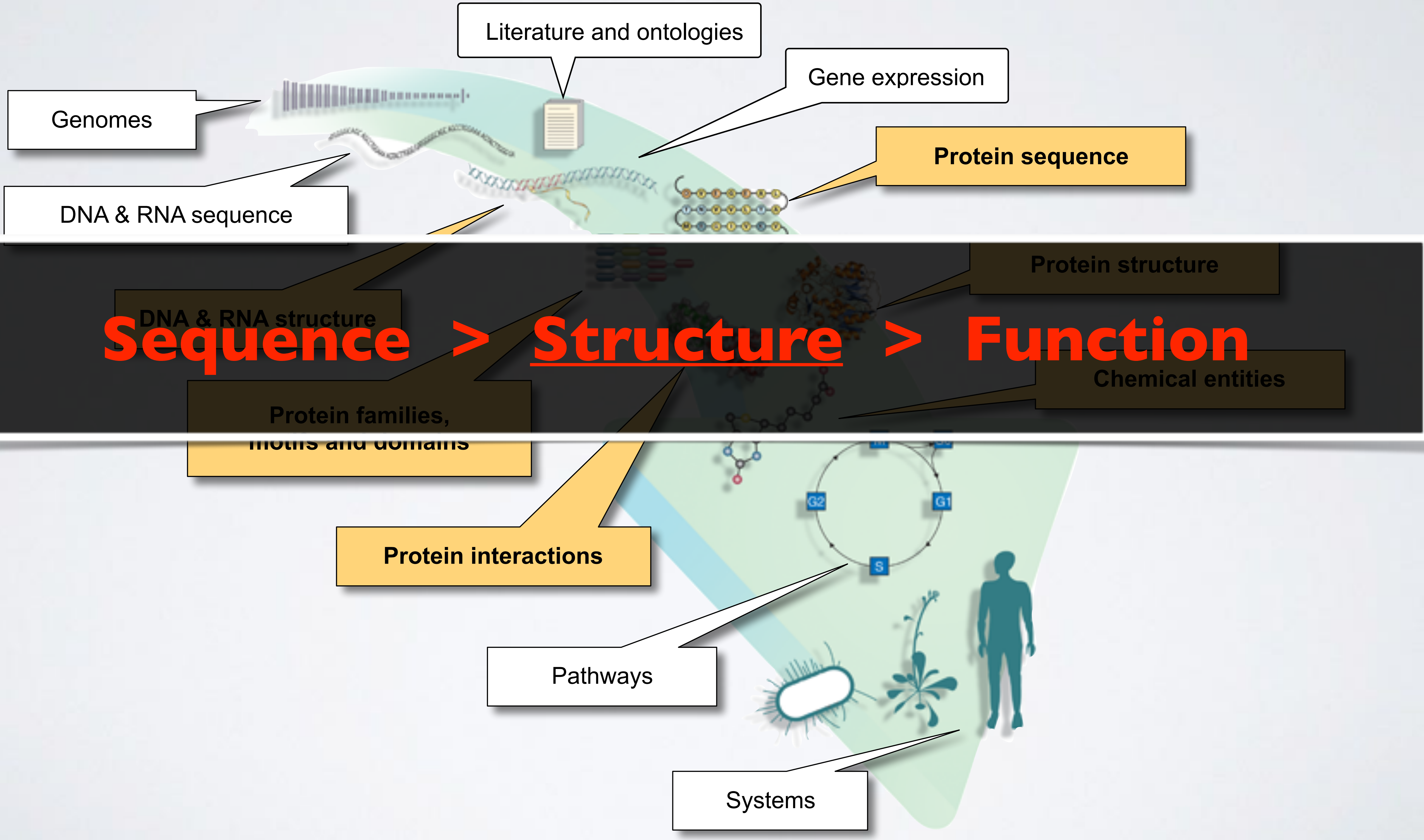

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Sequence > Structure > Function

Protein structure

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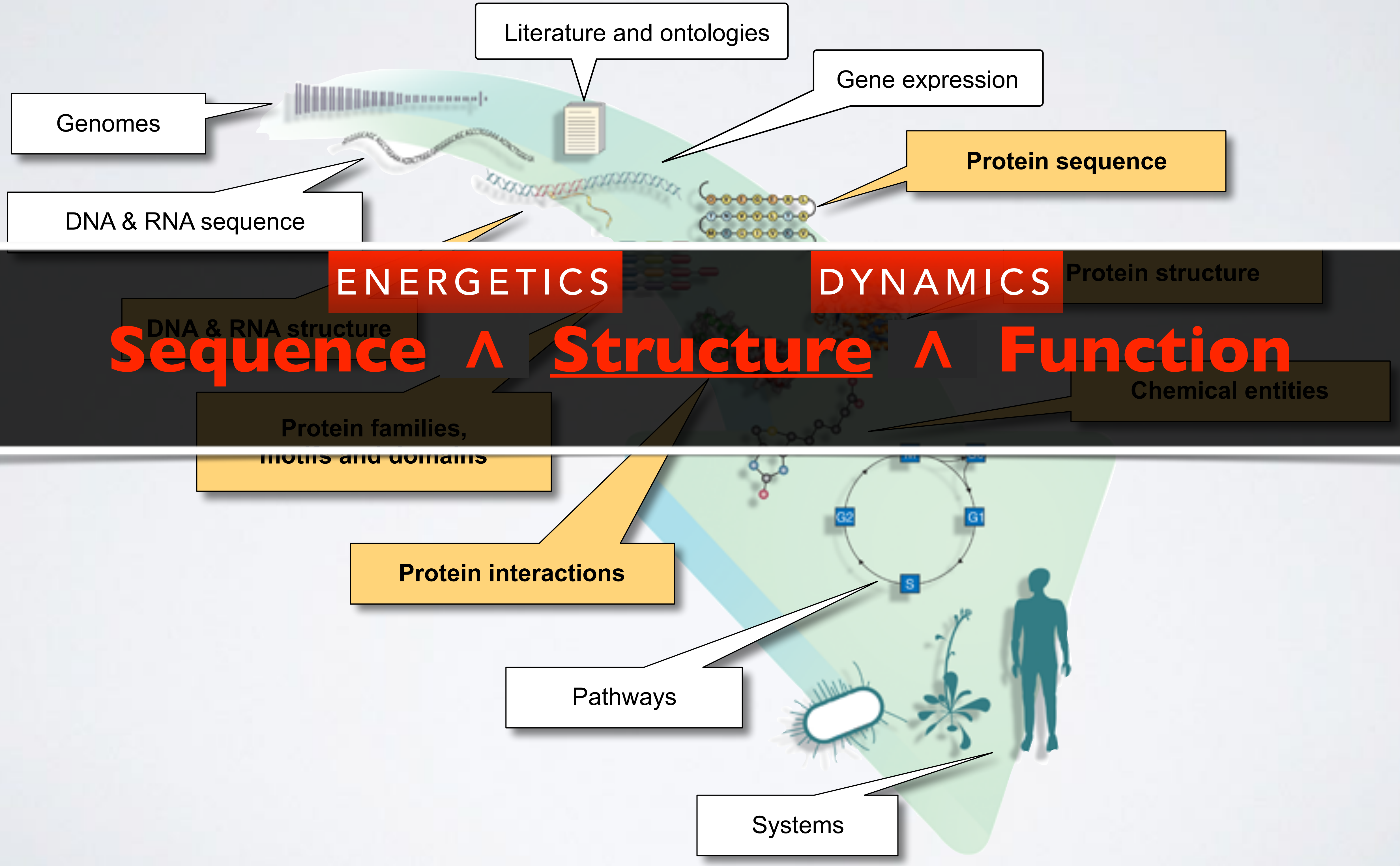


Literature and ontologies

Genomes

Gene expression

Protein sequence

DNA & RNA sequence

ENERGETICS

DYNAMICS

Protein structure

DNA & RNA structure

Sequence ∧ Structure ∧ Function

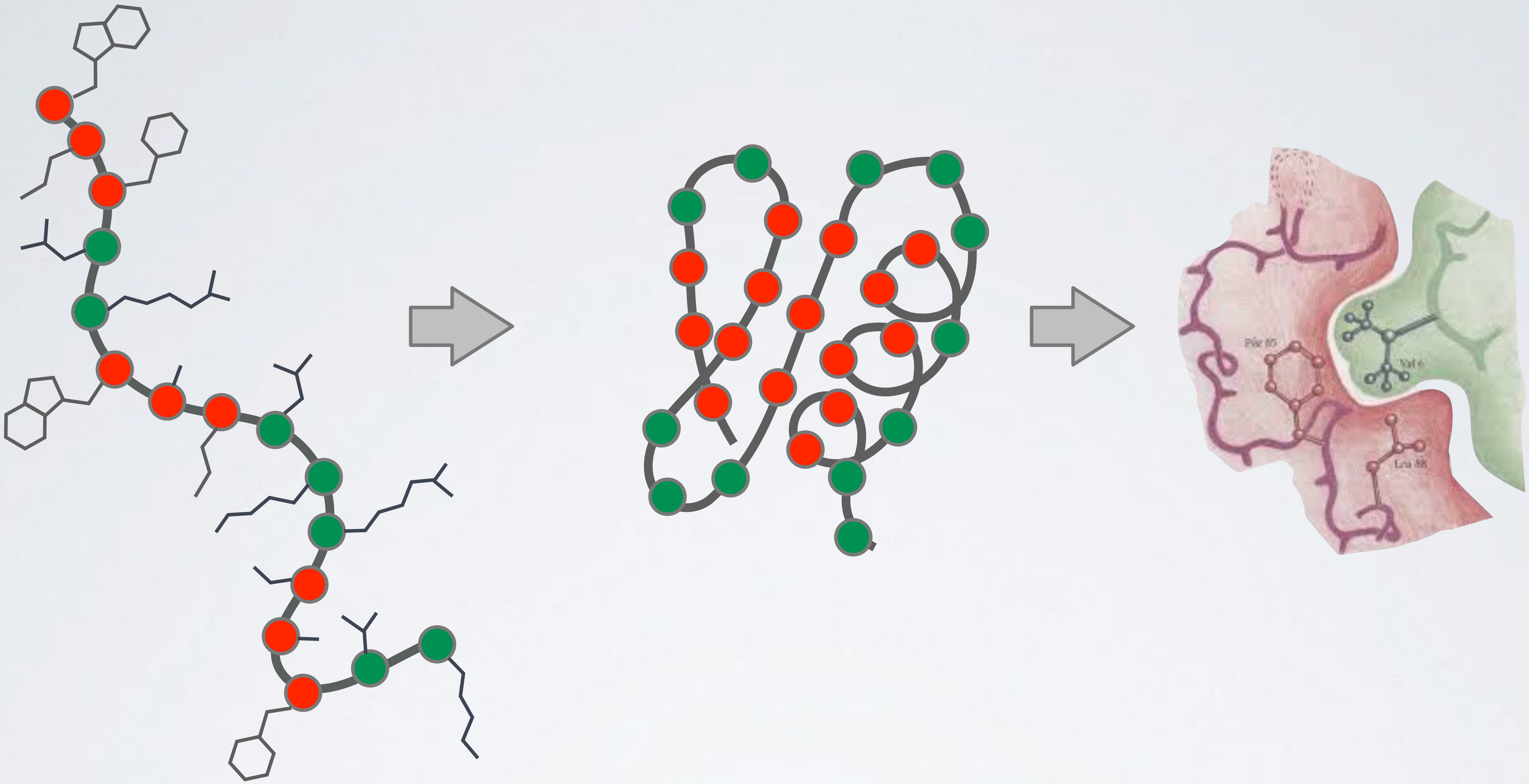
Chemical entities

Protein families, motifs and domains

Protein interactions

Pathways

Systems



Sequence

- Unfolded chain of amino acid chain
- Highly mobile
- Inactive

Structure

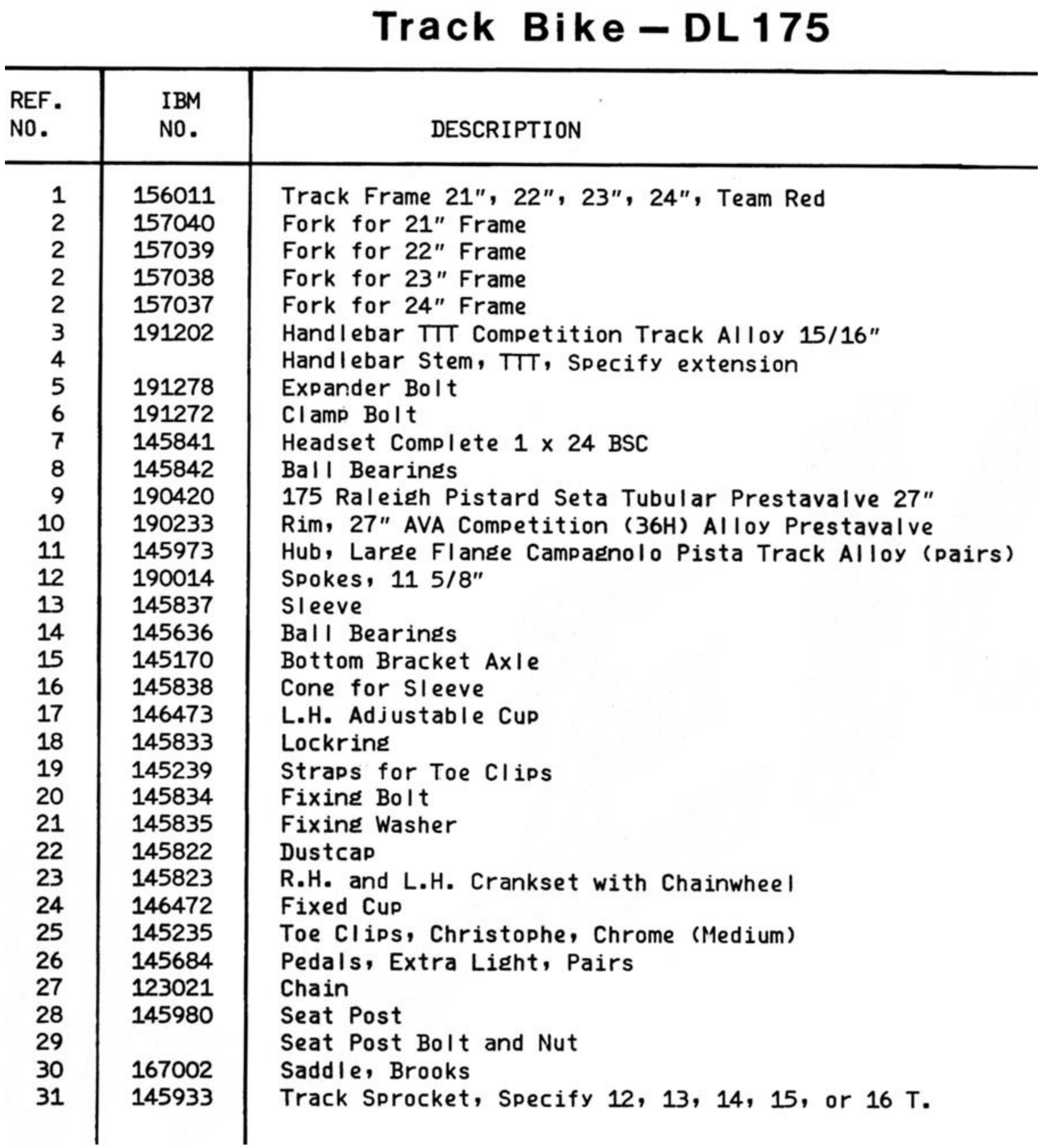
- Ordered in a precise 3D arrangment
- Stable but dynamic

Function

- Active in specific "conformations"
- Specific associations & precise reactions

In daily life, we use machines with functional *structure* and *moving parts*

Genomics is a great start ….

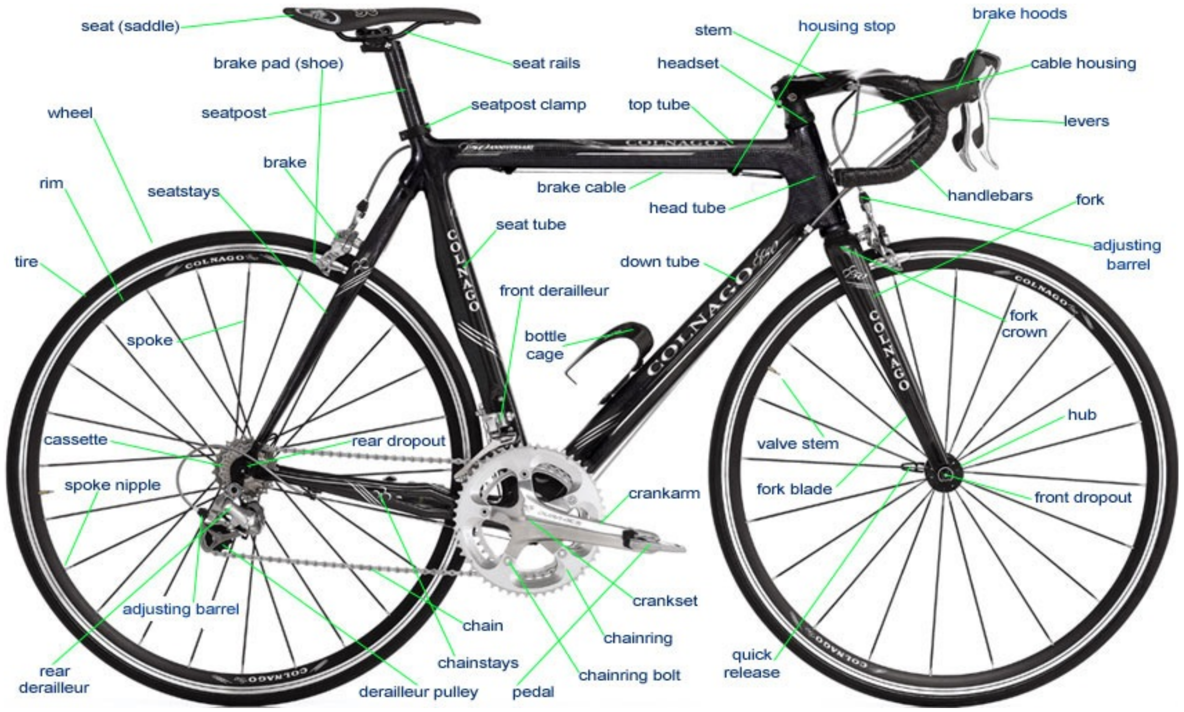


Track Bike — DL 175

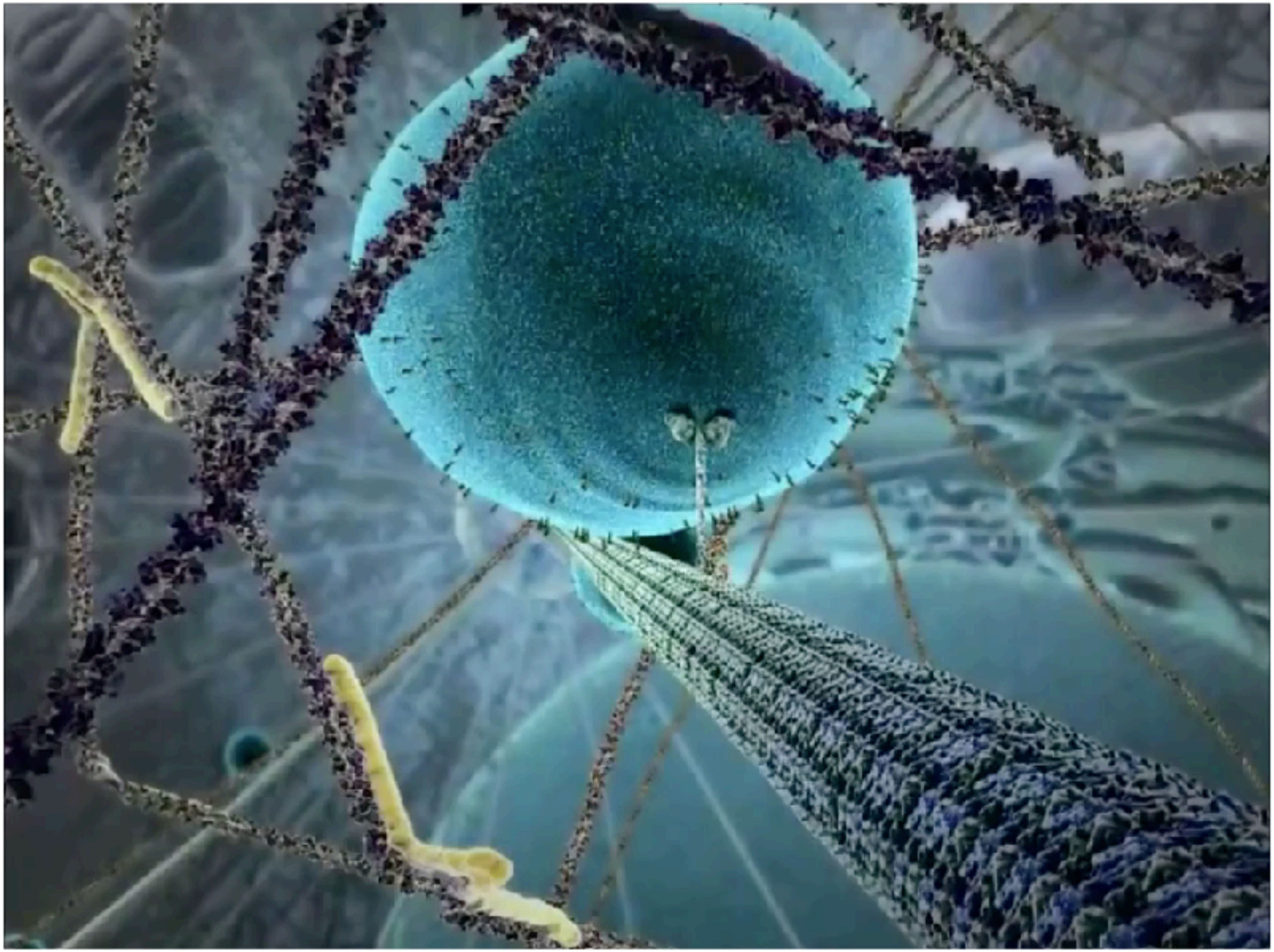
REF. NO.	IBM NO.	DESCRIPTION
1	156011	Track Frame 21″, 22″, 23″, 24″, Team Red
2	157040	Fork for 21″ Frame
2	157039	Fork for 22″ Frame
2	157038	Fork for 23″ Frame
2	157037	Fork for 24″ Frame
3	191202	Handlebar TTT Competition Track Alloy 15/16″
4		Handlebar Stem, TTT, Specify extension
5	191278	Expander Bolt
6	191272	Clamp Bolt
7	145841	Headset Complete 1 x 24 BSC
8	145842	Ball Bearings
9	190420	175 Raleigh Pistard Seta Tubular Prestavalve 27″
10	190233	Rim, 27″ AVA Competition (36H) Alloy Prestavalve
11	145973	Hub, Large Flange Campagnolo Pista Track Alloy (pairs)
12	190014	Spokes, 11 5/8″
13	145837	Sleeve
14	145636	Ball Bearings
15	145170	Bottom Bracket Axle
16	145838	Cone for Sleeve
17	146473	L.H. Adjustable Cup
18	145833	Lockring
19	145239	Straps for Toe Clips
20	145834	Fixing Bolt
21	145835	Fixing Washer
22	145822	Dustcap
23	145823	R.H. and L.H. Crankset with Chainwheel
24	146472	Fixed Cup
25	145235	Toe Clips, Christophe, Chrome (Medium)
26	145684	Pedals, Extra Light, Pairs
27	123021	Chain
28	145980	Seat Post
29		Seat Post Bolt and Nut
30	167002	Saddle, Brooks
31	145933	Track Sprocket, Specify 12, 13, 14, 15, or 16 T.

- But a parts list is not enough to understand how a bicycle works

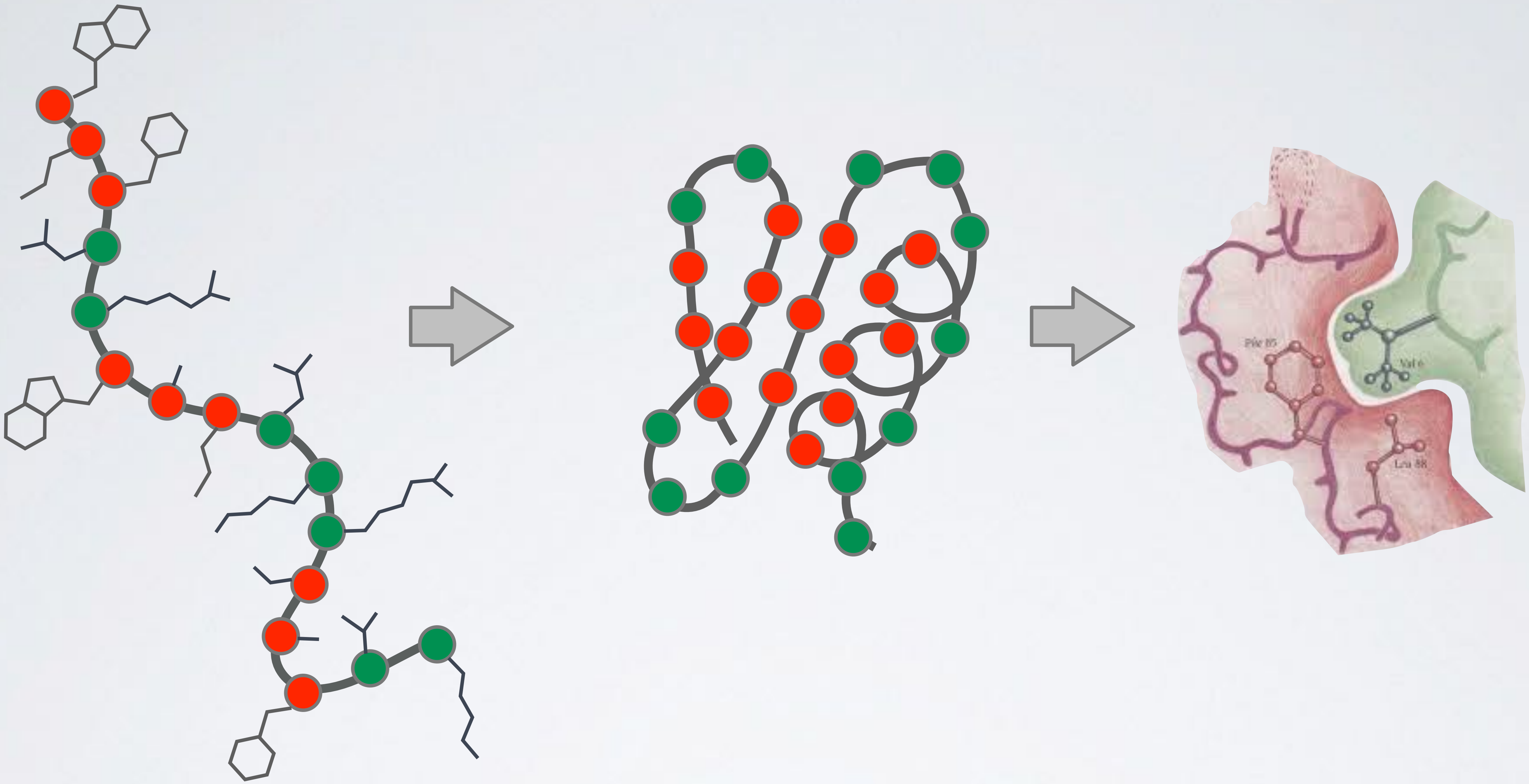
… but not the end



- We want the full spatiotemporal picture, and an ability to control it
- Broad applications, including drug design, medical diagnostics, chemical manufacturing, and energy



Extracted from The Inner Life of a Cell by Cellular Visions and Harvard
[YouTube link: https://www.youtube.com/watch?v=y-uuk4Pr2i8]



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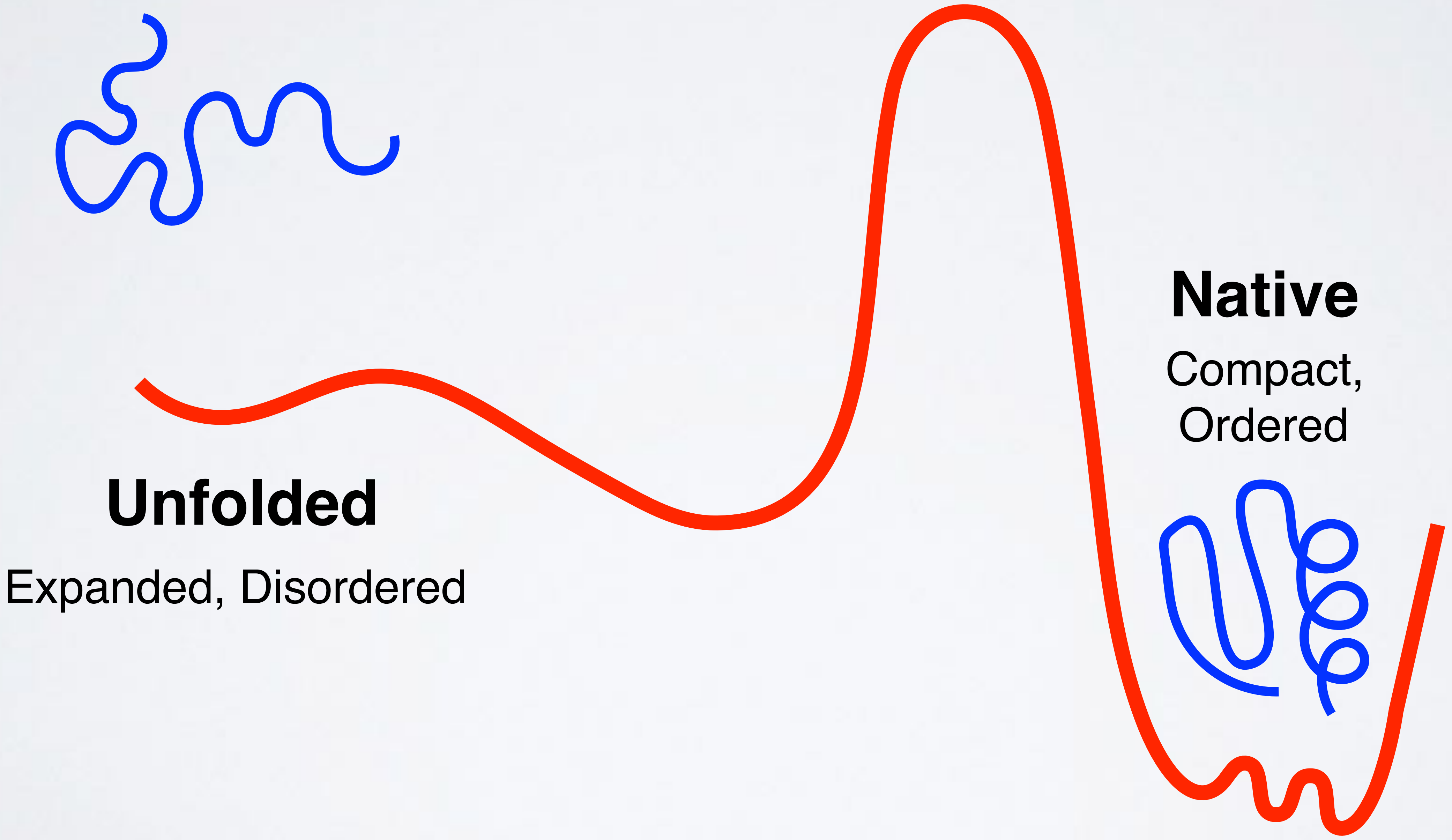
KEY CONCEPT: ENERGY LANDSCAPE



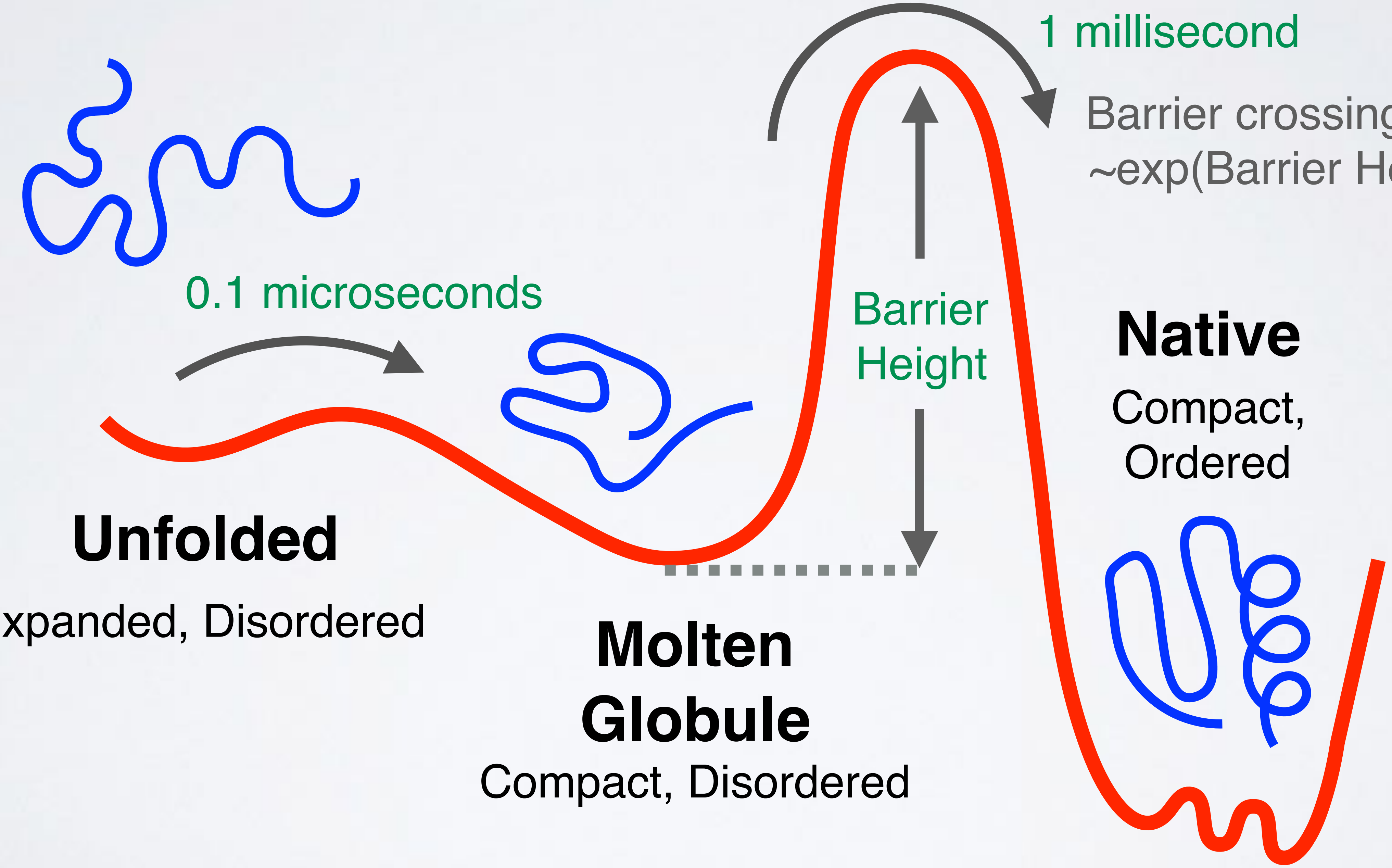
Native

Compact, Ordered

Unfolded

Expanded, Disordered

KEY CONCEPT: ENERGY LANDSCAPE



1 millisecond

Barrier crossing time ~exp(Barrier Height)

0.1 microseconds

Barrier Height

Native

Compact, Ordered

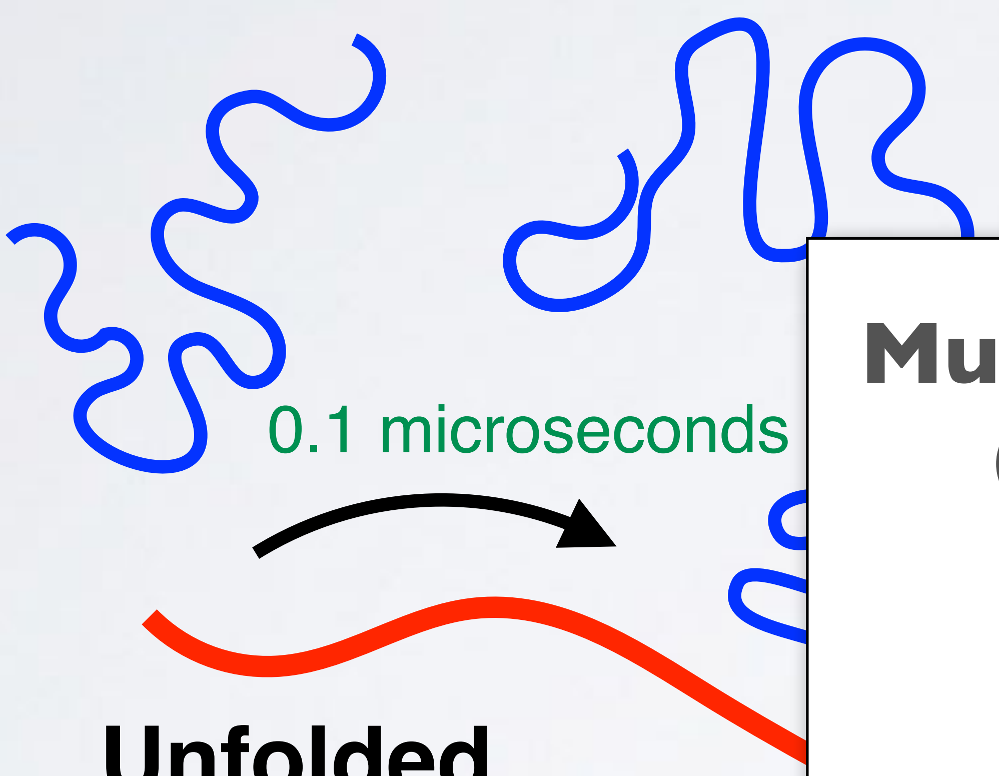
Unfolded

Expanded, Disordered

Molten Globule

Compact, Disordered

KEY CONCEPT: **ENERGY LANDSCAPE**



0.1 microseconds

1 millisecond

Barrier crossing time

exp(Barrier Height)

Unfolded State

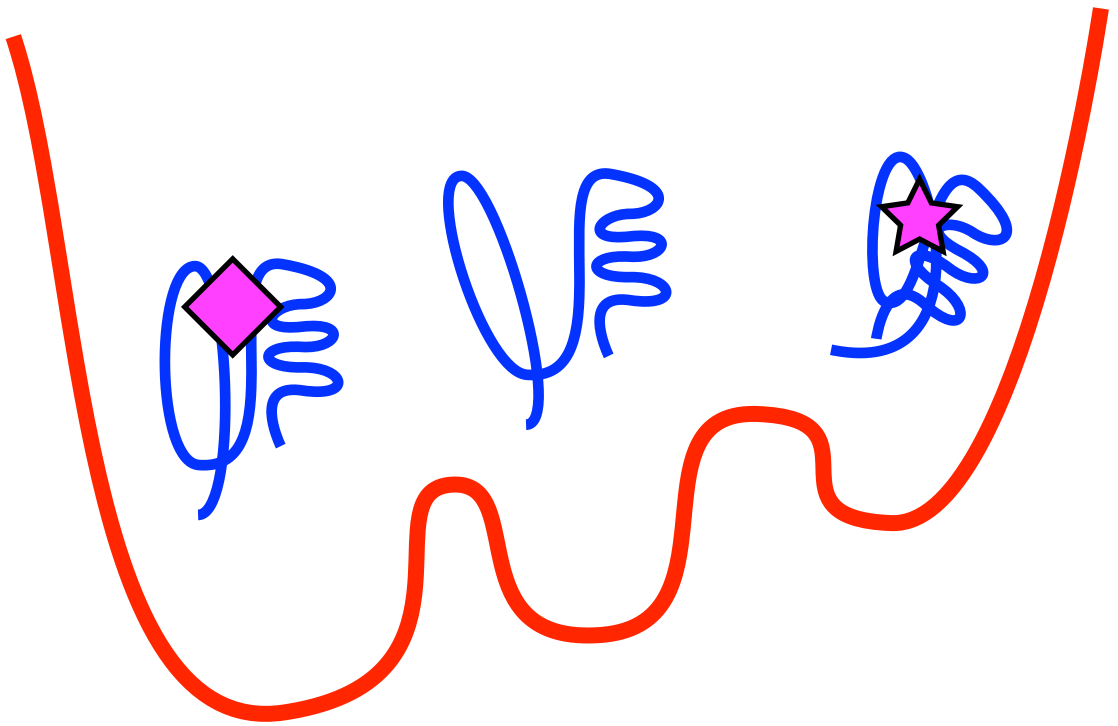
Expanded, Disordered

Mo

Co

Multiple Native Conformations

(e.g. ligand bound and unbound)



OUTLINE:

- **Overview of structural bioinformatics**
  - Major motivations, goals and challenges
- **Fundamentals of protein structure**
  - Composition, form, forces and dynamics
- **Representing and interpreting protein structure**
  - Modeling energy as a function of structure
- **Example application areas**
  - Predicting functional dynamics & drug discovery

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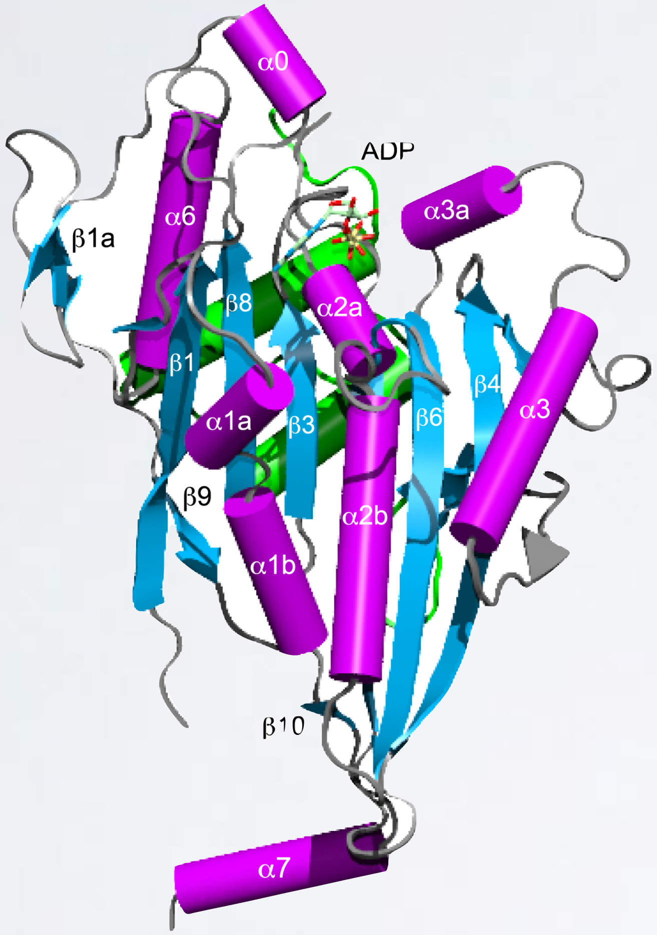
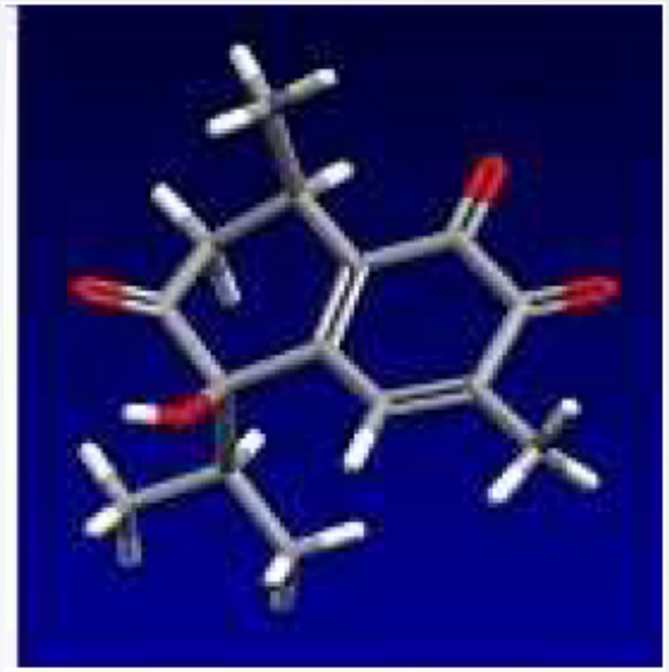
TRADITIONAL FOCUS **PROTEIN**, **DNA** AND **SMALL MOLECULE** DATA SETS WITH **MOLECULAR STRUCTURE**



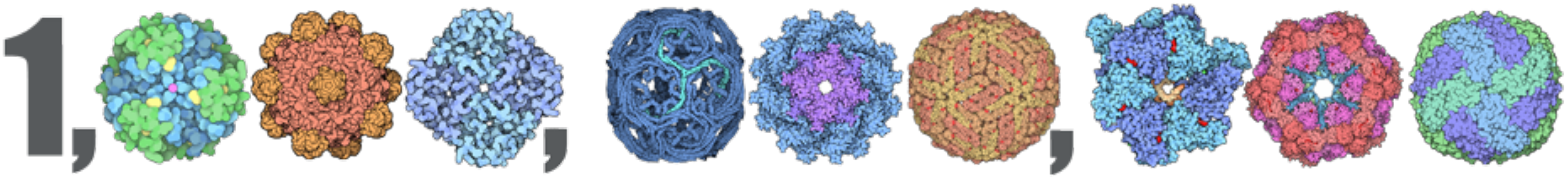
Protein
(PDB)

DNA
(NDB)

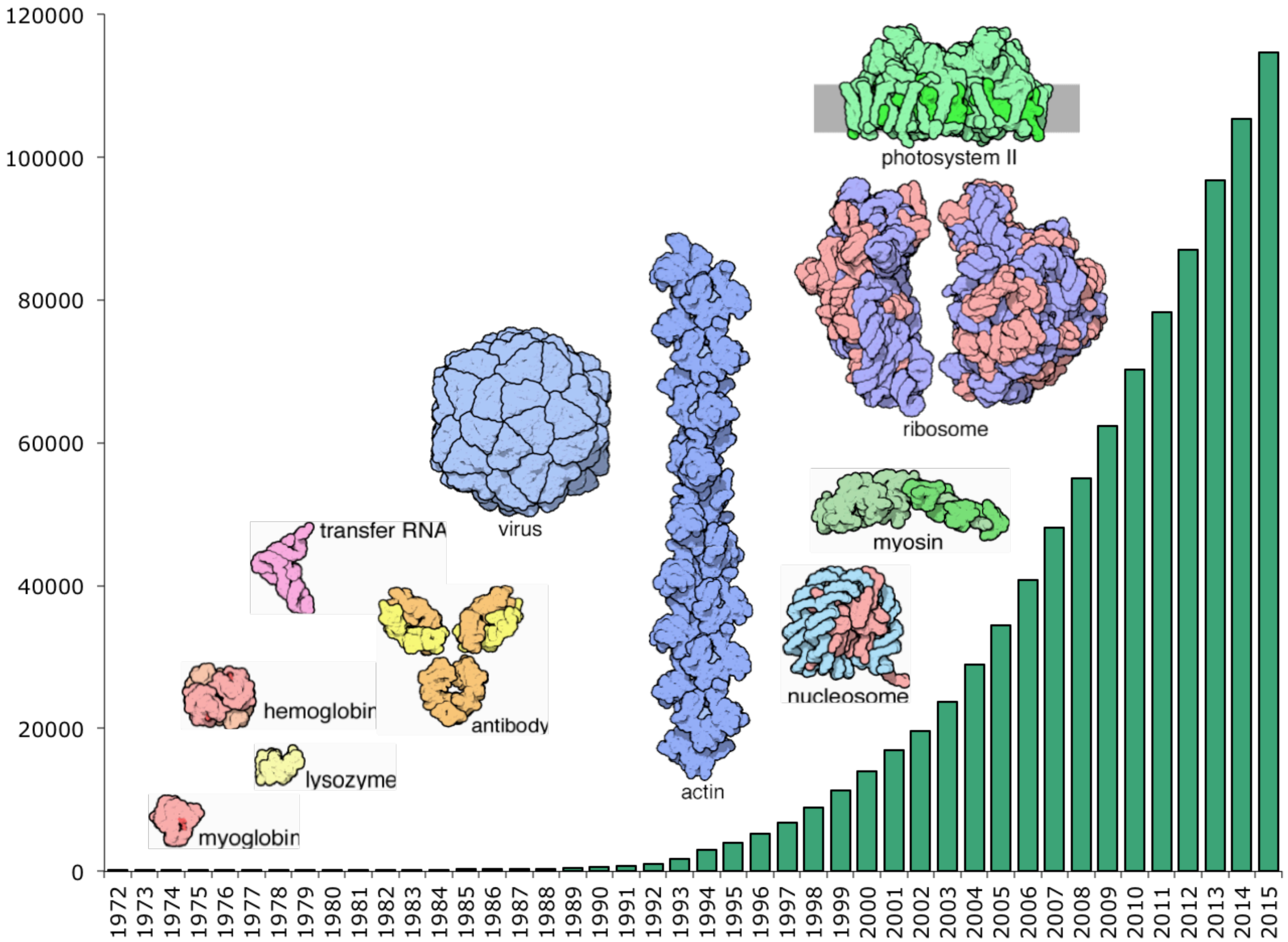


Small Molecules
(CCDB)

PDB – A Billion Atom Archive



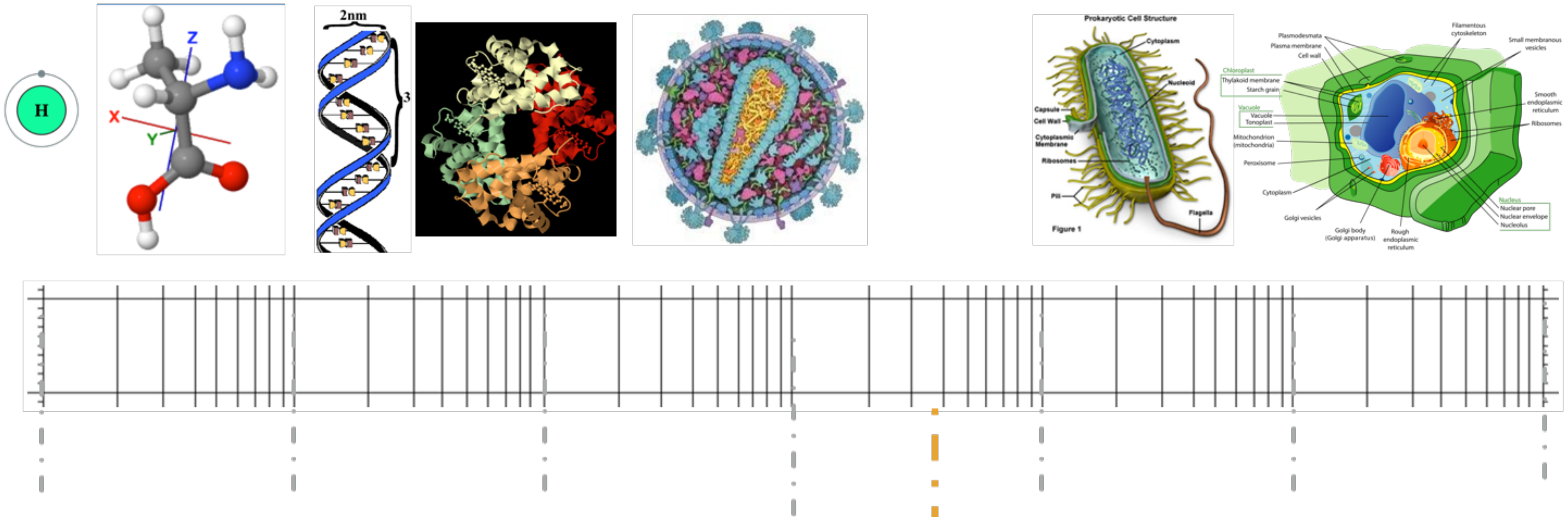
> 1 billion atoms in the asymmetric units



~140,000 Structures in May 2018

Slide Credit: Peter Rose

Growing Structure Size and Complexity



1Å 1nm 10nm 100nm 1µm 10µm 0.1mm

Optical resolution limit

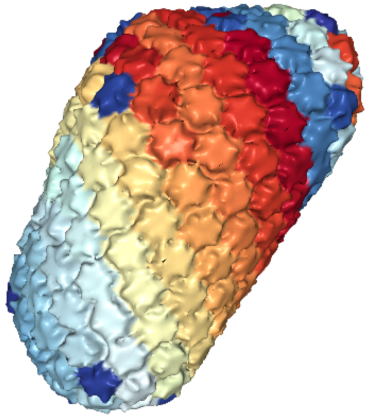
In situ Structural Biology

PDB

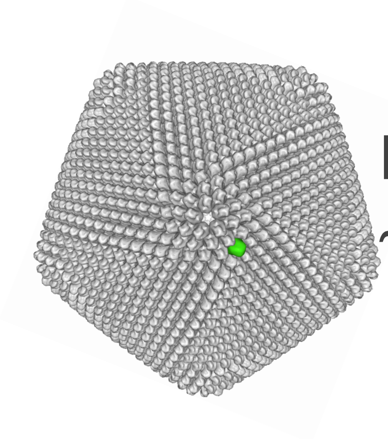
chr22 unpacked: 10mm

Largest asymmetric structure in PDB

Largest symmetric structure in PDB



HIV-1 capsid: PDB ID 3J3Q
~2.4M unique atoms

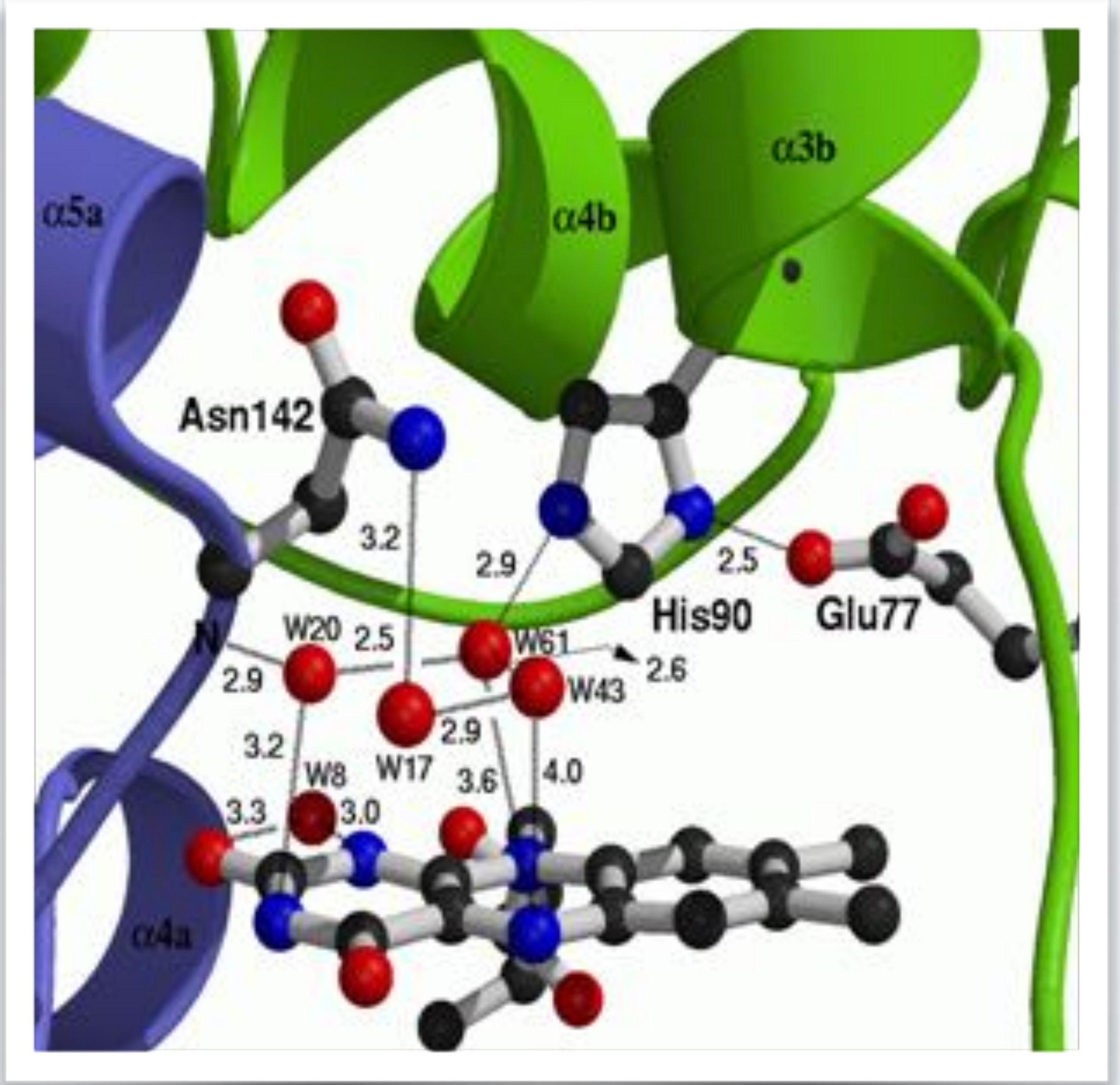


Faustovirus major capsid: PDB ID 5J7V
~40M overall atoms

Slide Credit: Peter Rose

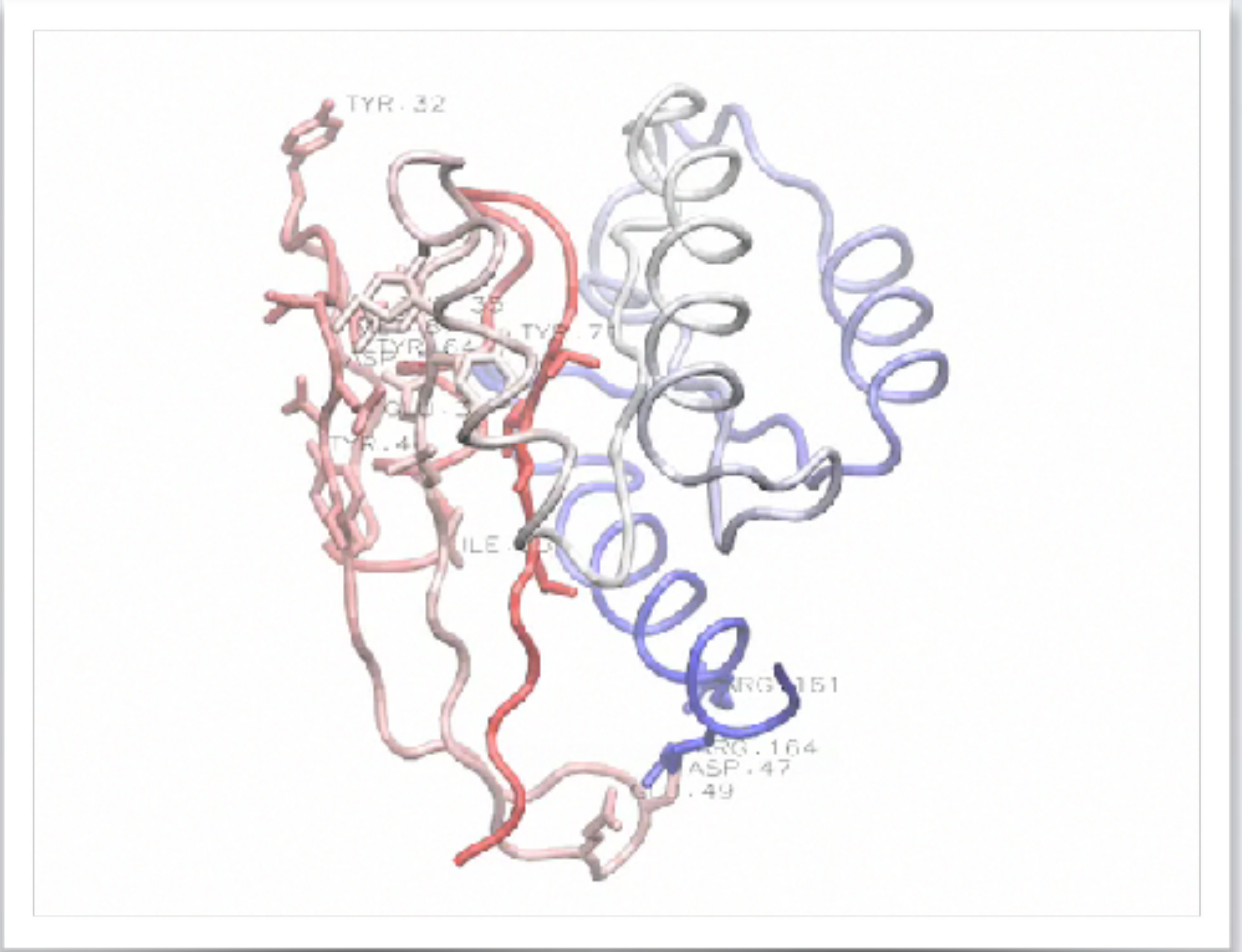
Motivation 1:
Detailed understanding of molecular interactions

Provides an invaluable structural context for conservation and mechanistic analysis leading to functional insight.



Motivation 1:
Detailed understanding of
molecular interactions

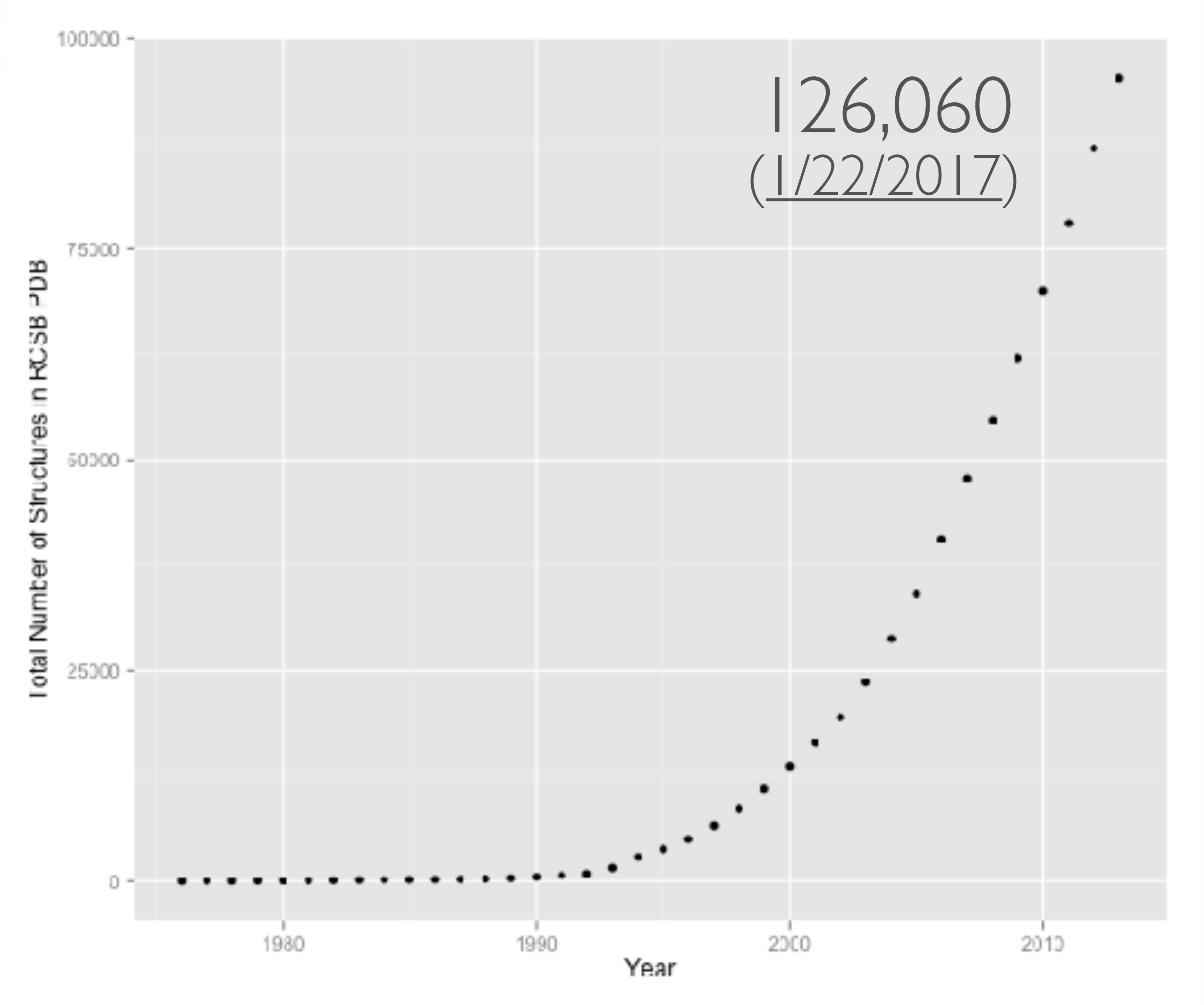
Computational modeling can provide detailed insight into functional interactions, their regulation and potential consequences of perturbation.



Grant *et al.* PLoS. Comp. Biol. (2010)

Motivation 2:
Lots of structural data is becoming available

Structural Genomics has contributed to driving down the cost and time required for structural determination



126,060
(1/22/2017)

Data from: http://www.rcsb.org/pdb/statistics/

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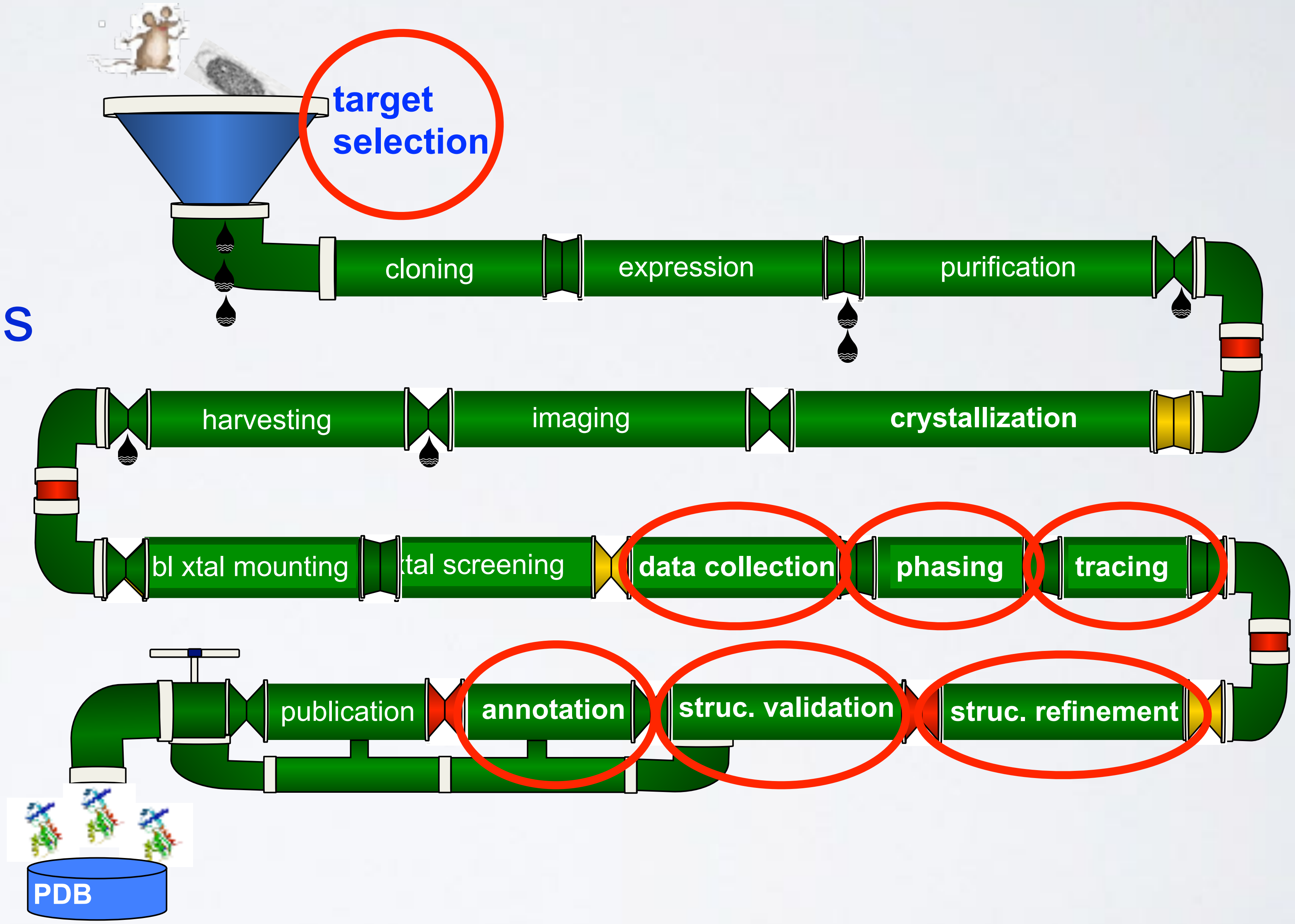
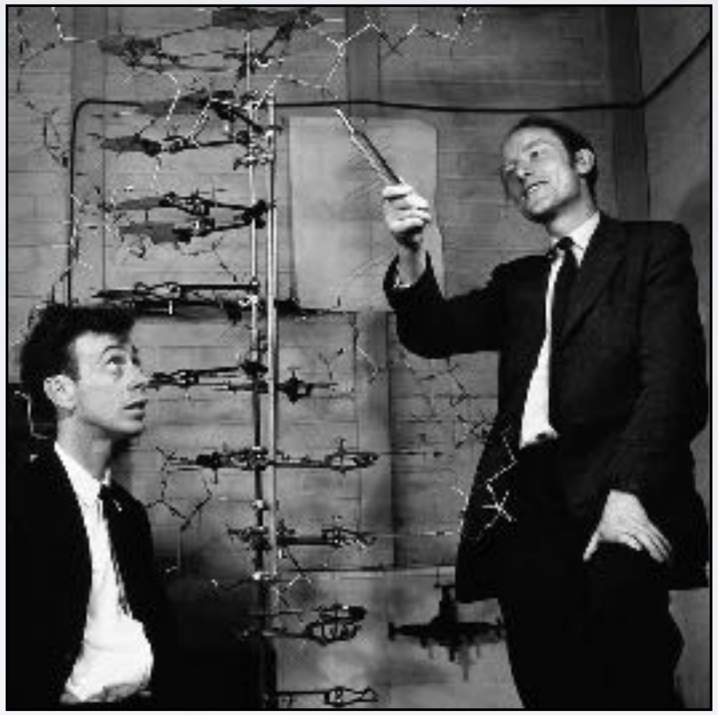
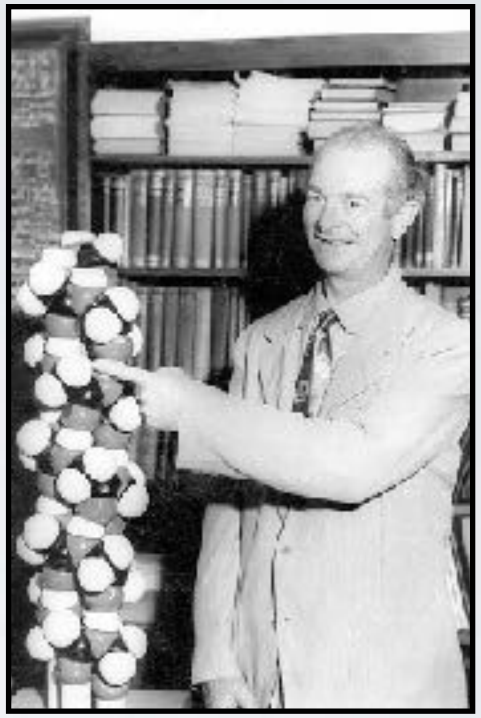


Image Credit: "Structure determination assembly line" Adam Godzik





Motivation 3:

Theoretical and computational predictions have been, and continue to be, enormously valuable and influential!

SUMMARY OF KEY **MOTIVATIONS**

Sequence > Structure > Function

- Structure determines function, so understanding structure helps our understanding of function

Structure is more conserved than sequence

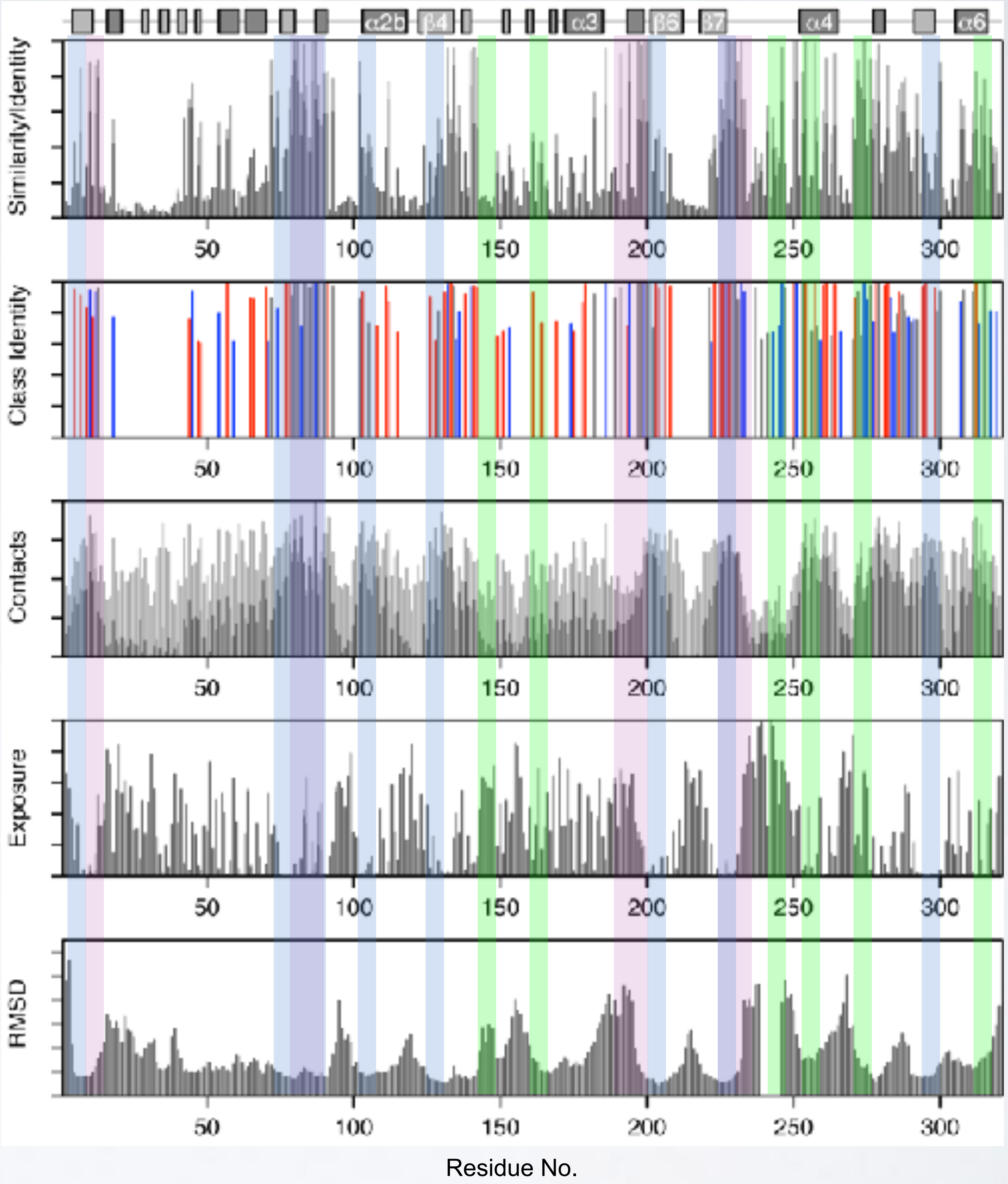
- Structure allows identification of more distant evolutionary relationships

Structure is encoded in sequence

- Understanding the determinants of structure allows design and manipulation of proteins for industrial and medical advantage

Goals:

- Analysis
- Visualization
- Comparison
- Prediction
- Design



Grant *et al.* JMB. (2007)

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Scarabelli and Grant. PLoS. Comp. Biol. (2013)

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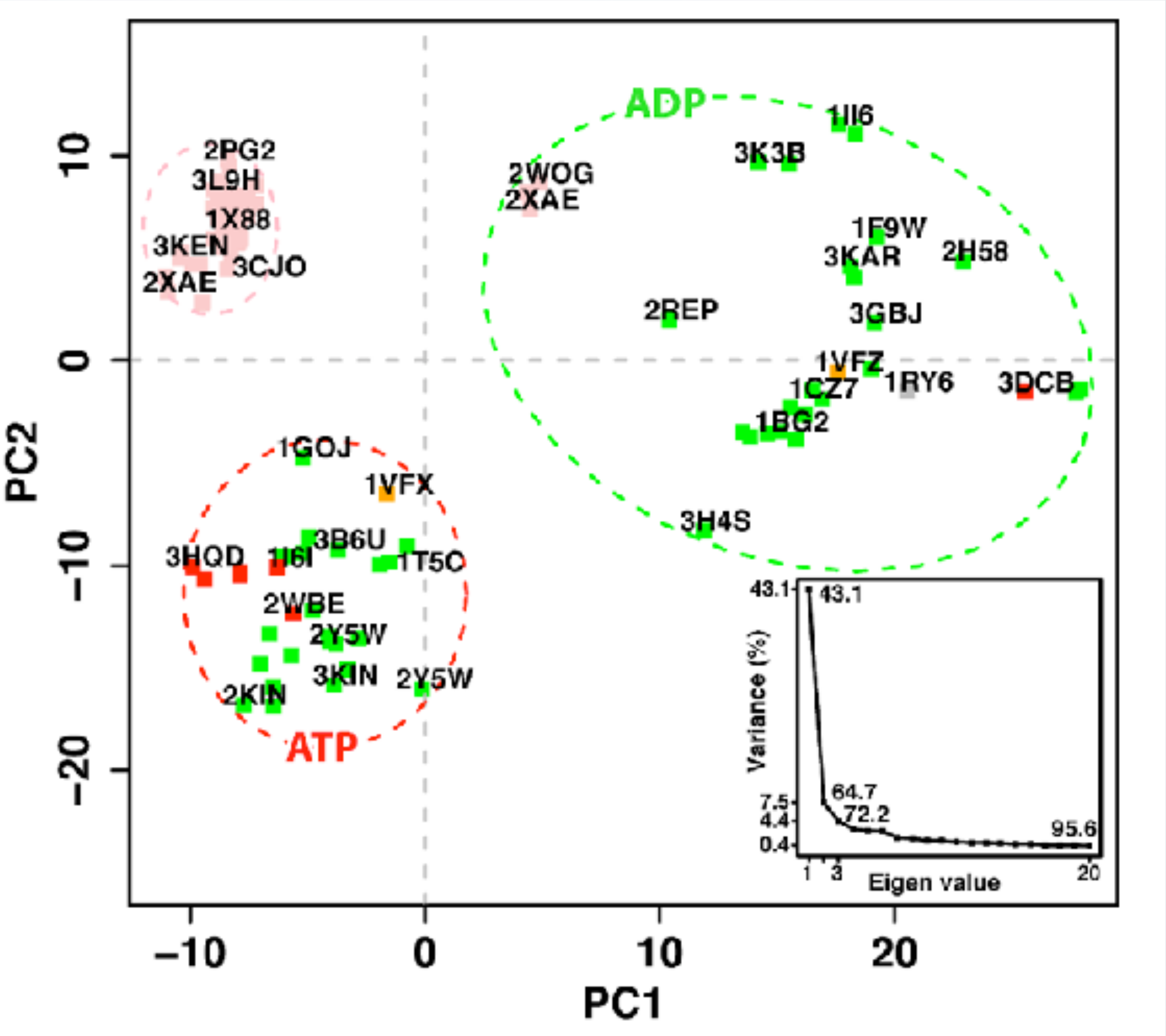

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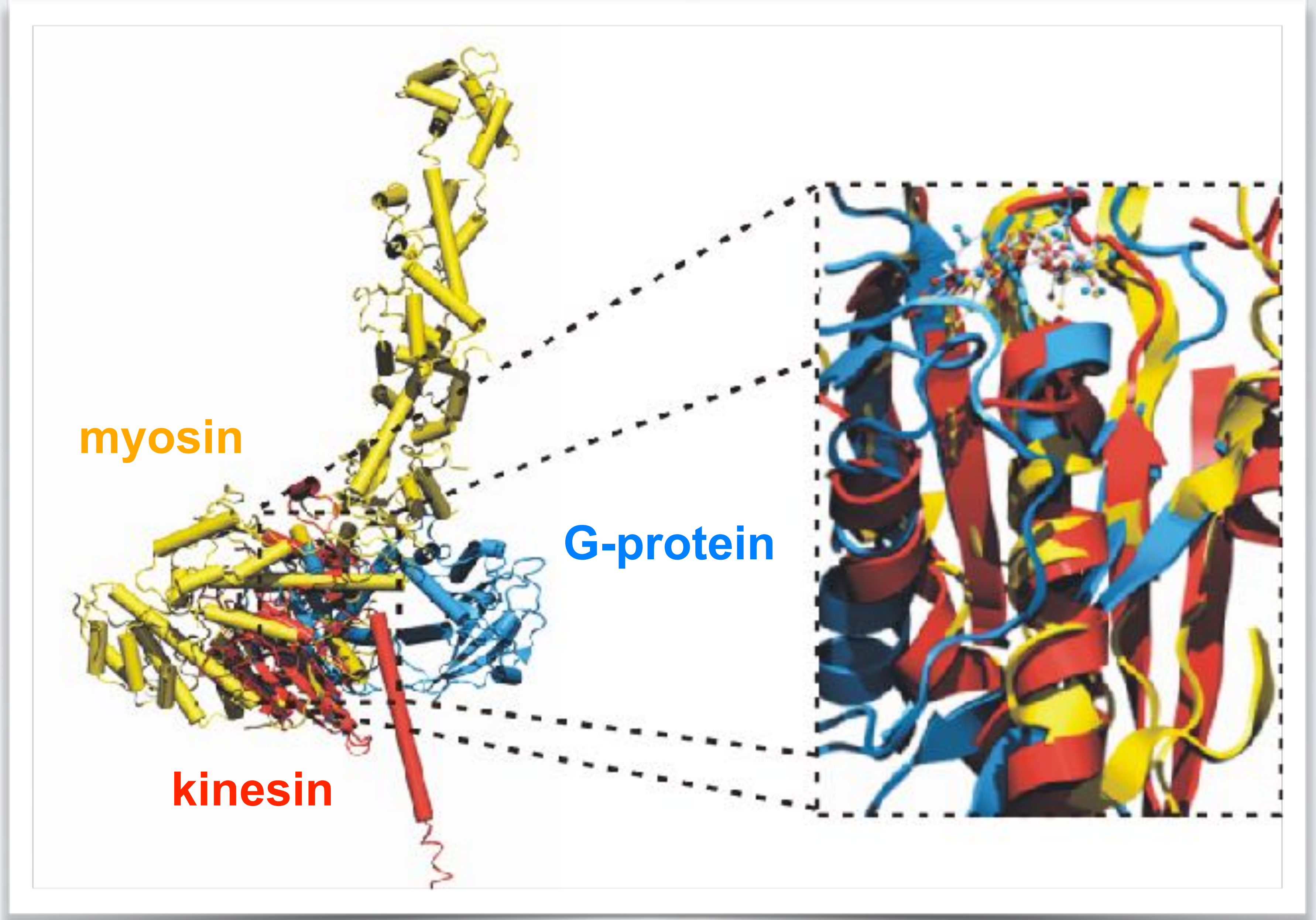

Grant *et al.* unpublished

Goals:

- Analysis
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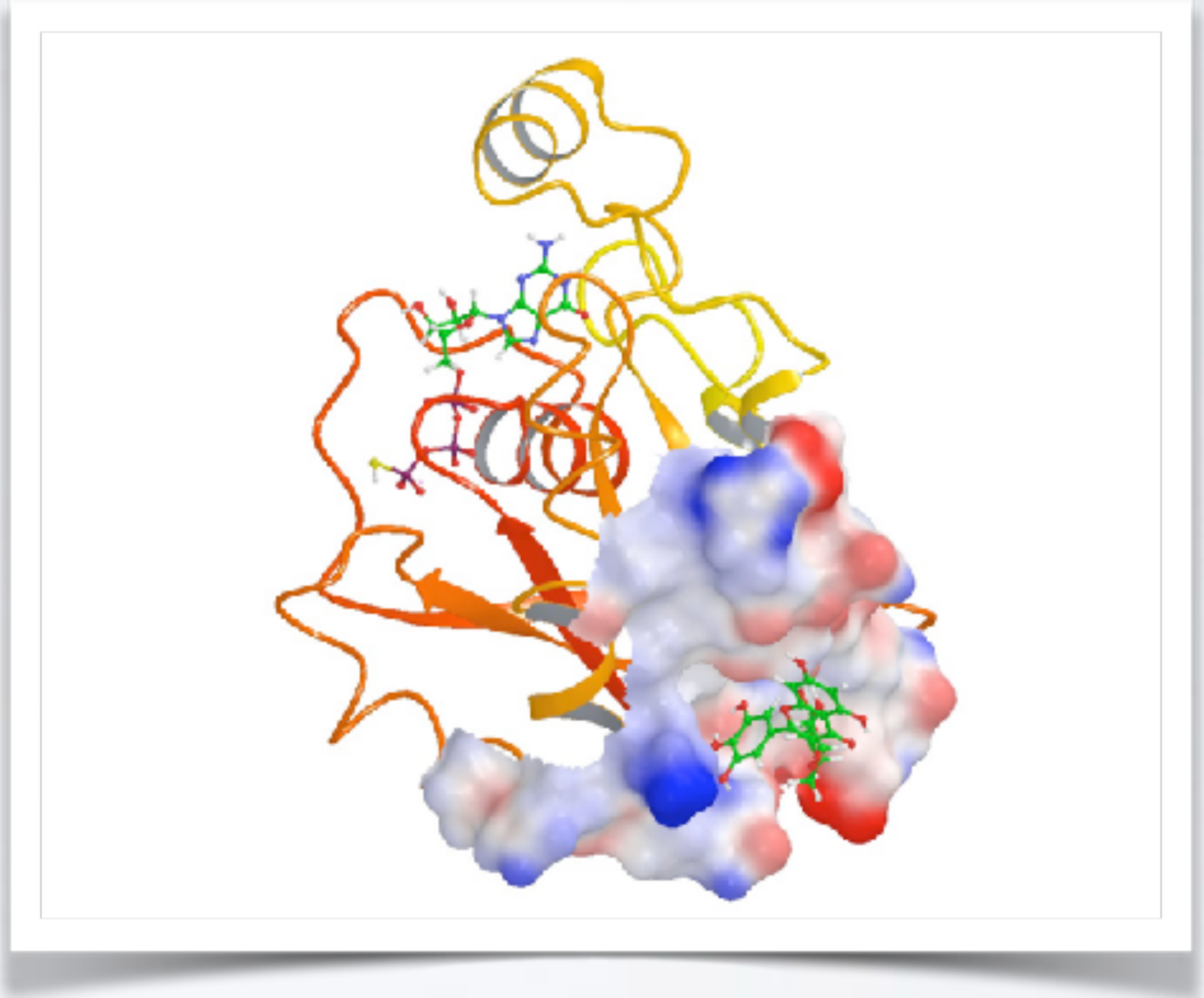
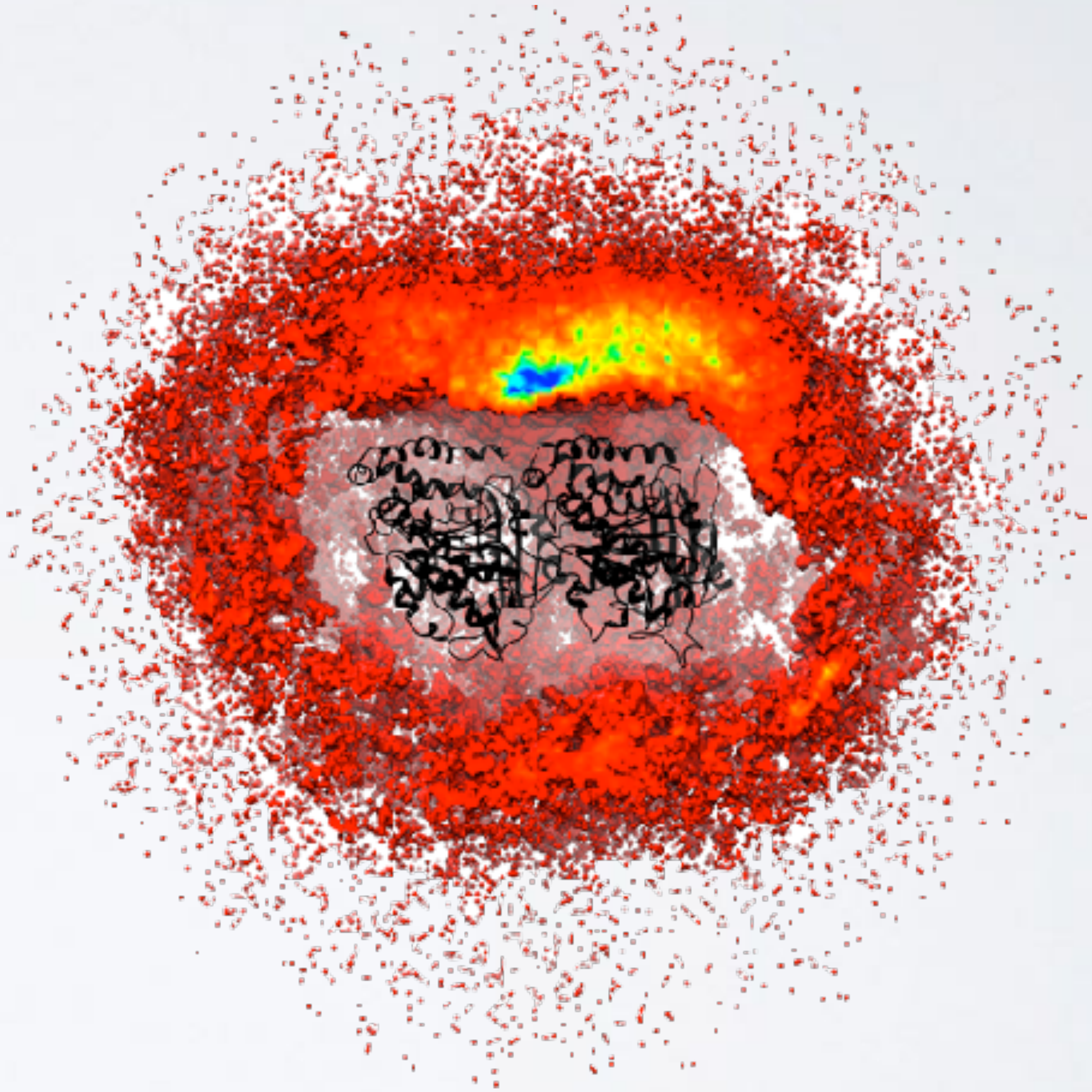


Grant *et al.* PLoS One (2011, 2012)

Goals:

- Analysis
- Visualization
- Comparison
- Prediction
- Design



Grant *et al.* PLoS Biology (2011)

MAJOR RESEARCH AREAS AND CHALLENGES

Include but are not limited to:

- Protein classification
- Structure prediction from sequence
- Binding site detection
- Binding prediction and drug design
- Modeling molecular motions
- Predicting physical properties (stability, binding affinities)
- Design of structure and function
- etc...

With applications to Biology, Medicine, Agriculture and Industry

NEXT UP:

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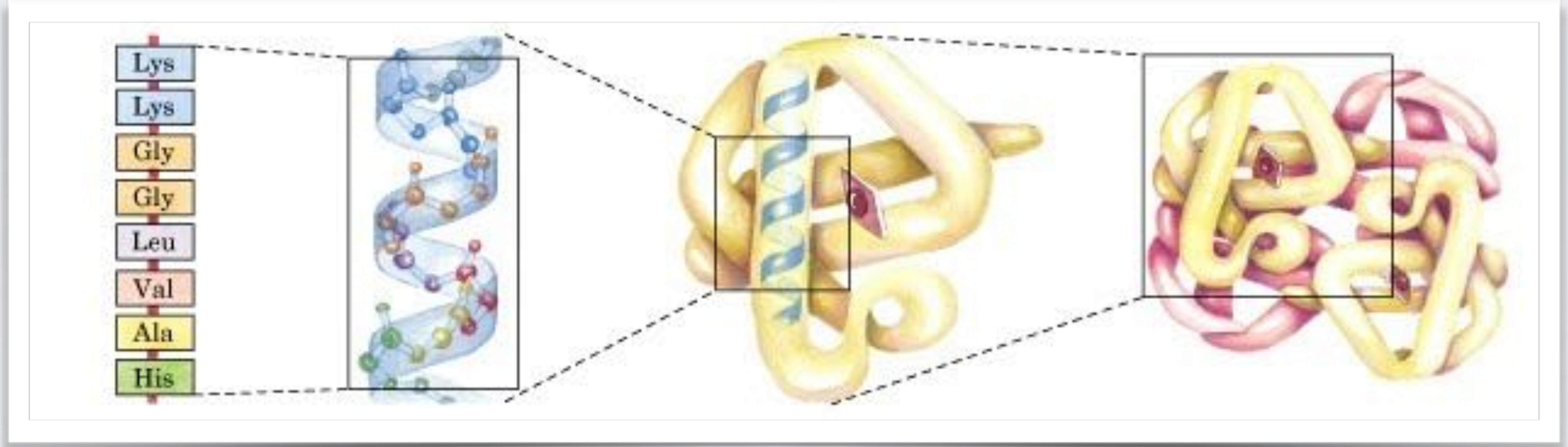
HIERARCHICAL STRUCTURE OF PROTEINS

Primary > Secondary > Tertiary > Quaternary



amino acid residues

Alpha helix

Polypeptide chain

Assembled subunits

Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

RECAP: AMINO ACID NOMENCLATURE

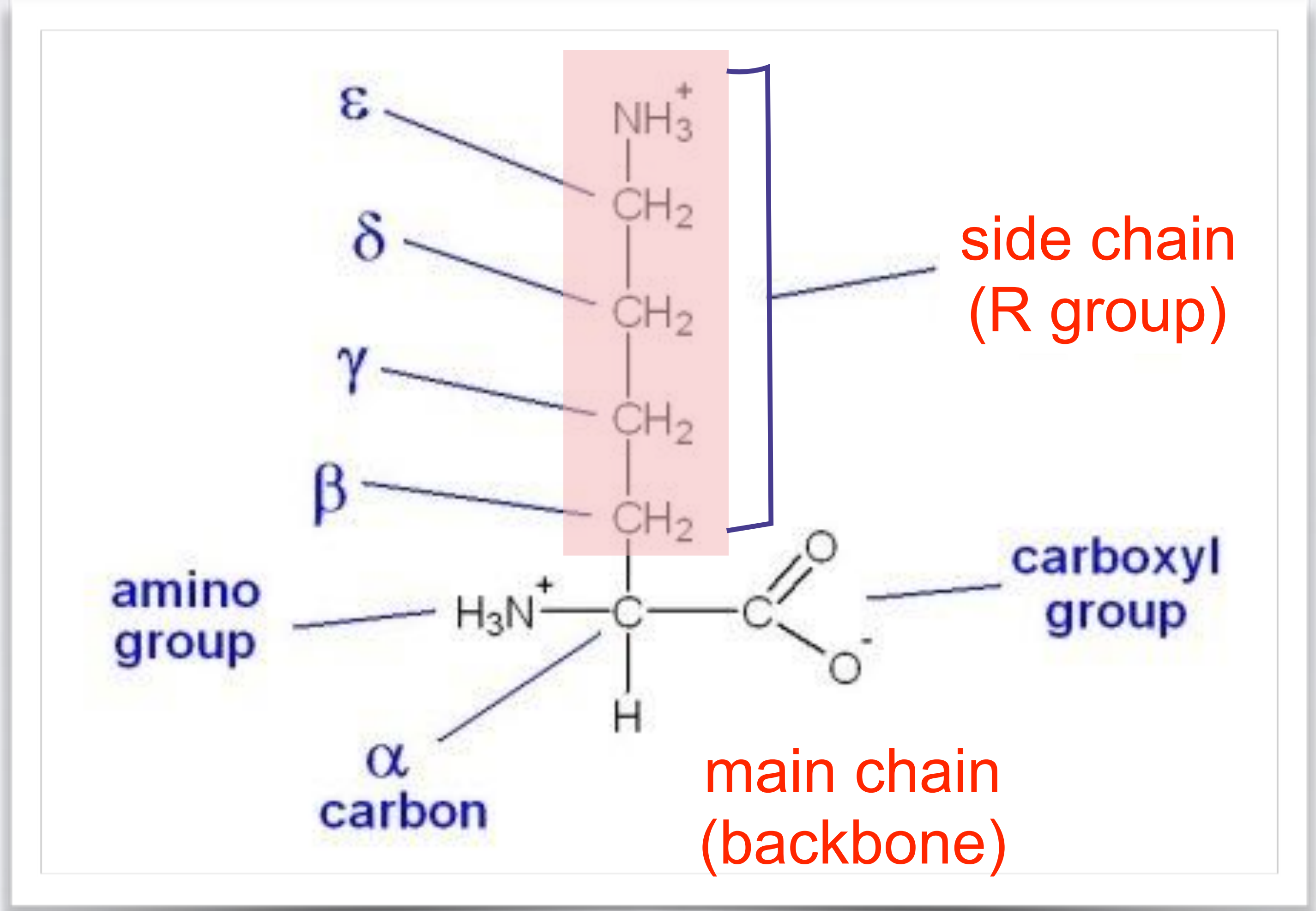
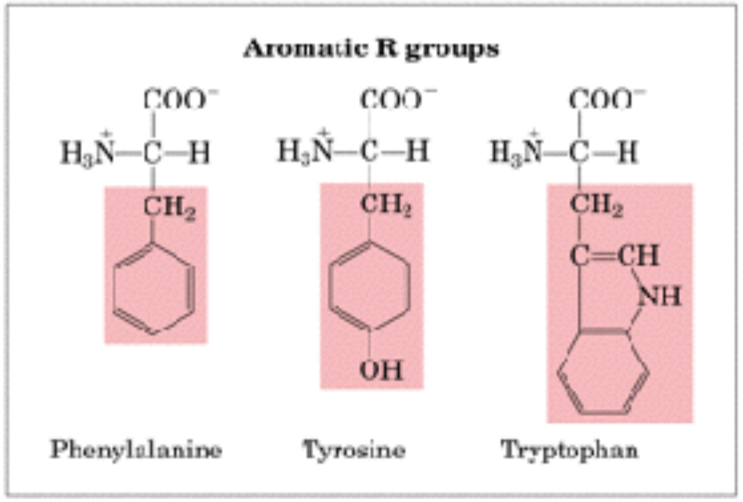
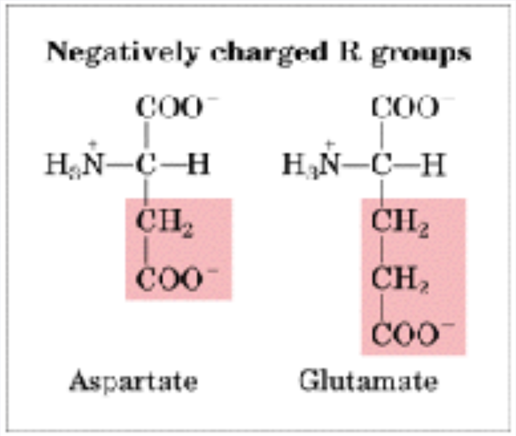
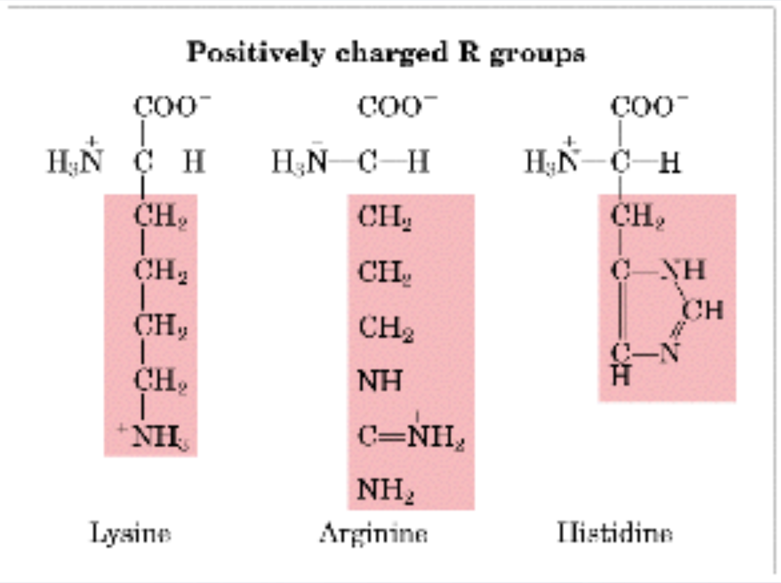


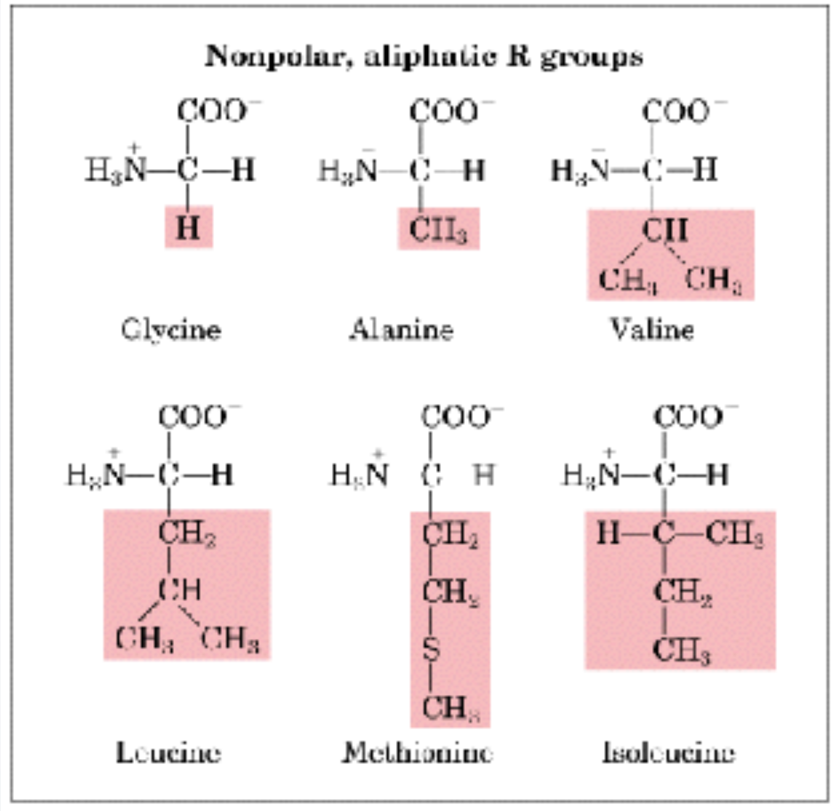
Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

AMINO ACIDS CAN BE GROUPED BY THE **PHYSIOCHEMICAL PROPERTIES**









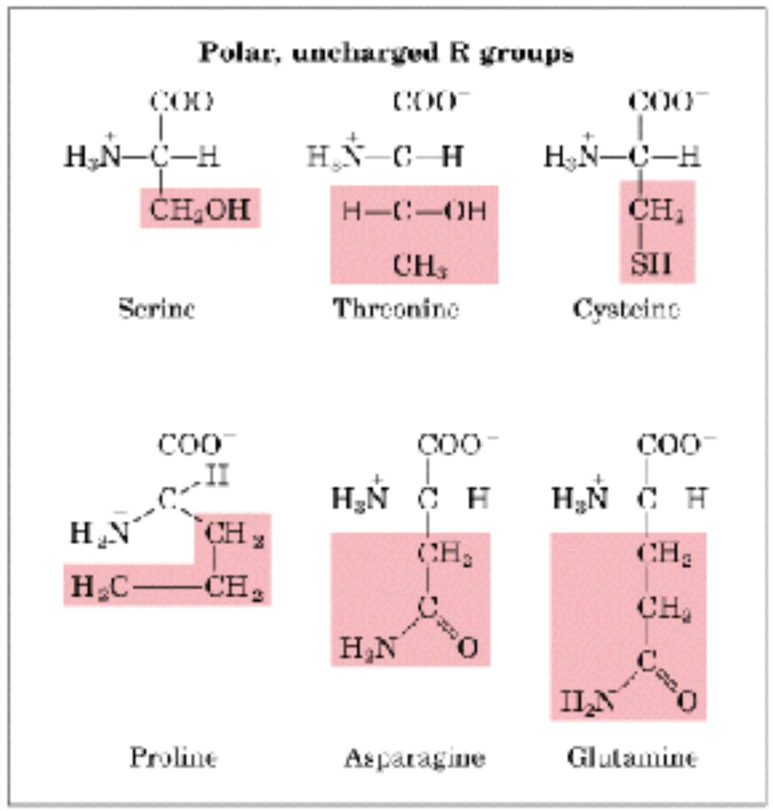
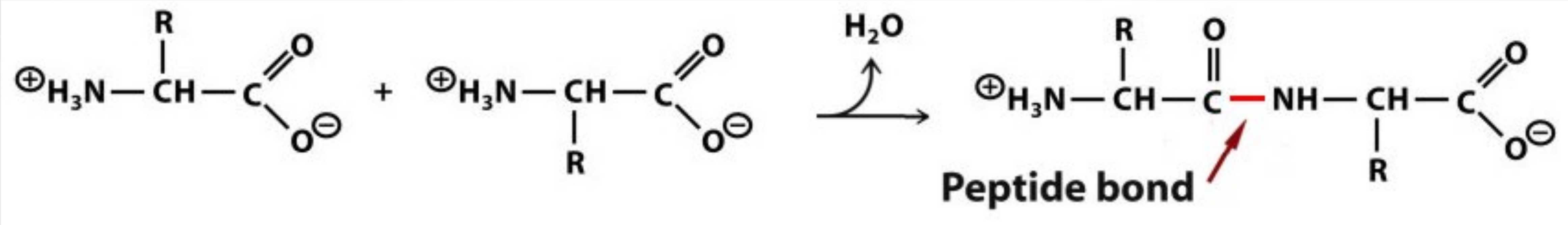


Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

AMINO ACIDS POLYMERIZE THROUGH **PEPTIDE BOND** FORMATION


$^{\oplus}H_3N-CH(R)-COO^{\ominus}$ + $^{\oplus}H_3N-CH(R)-COO^{\ominus}$
H_2O
$^{\oplus}H_3N-CH(R)-C(=O)-NH-CH(R)-COO^{\ominus}$
Peptide bond

side chains

backbone

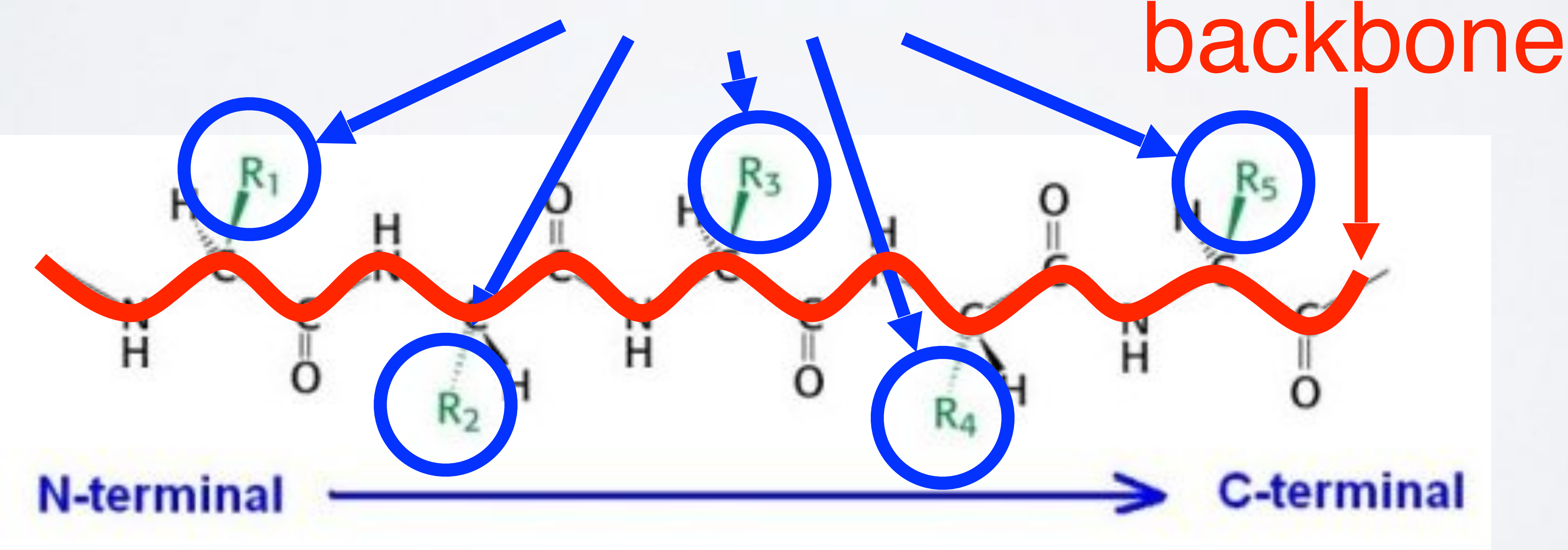
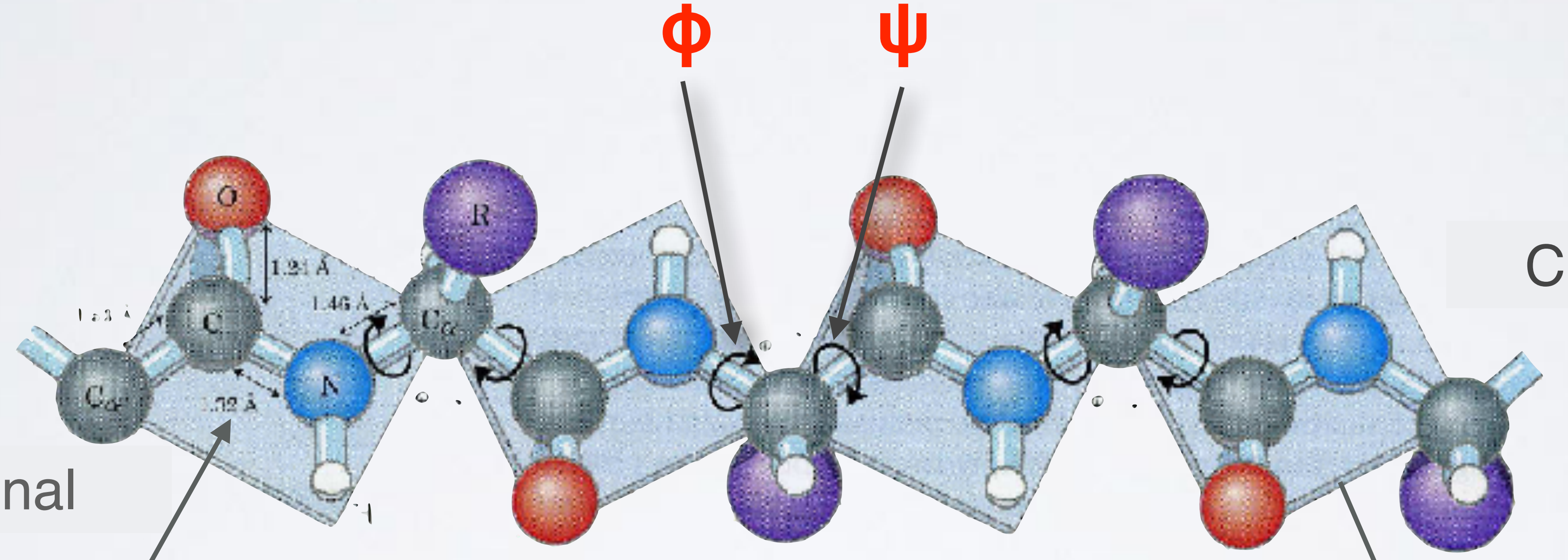


Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

PEPTIDES CAN ADOPT DIFFERENT CONFORMATIONS BY VARYING THEIR **PHI & PSI BACKBONE TORSIONS**



C-terminal

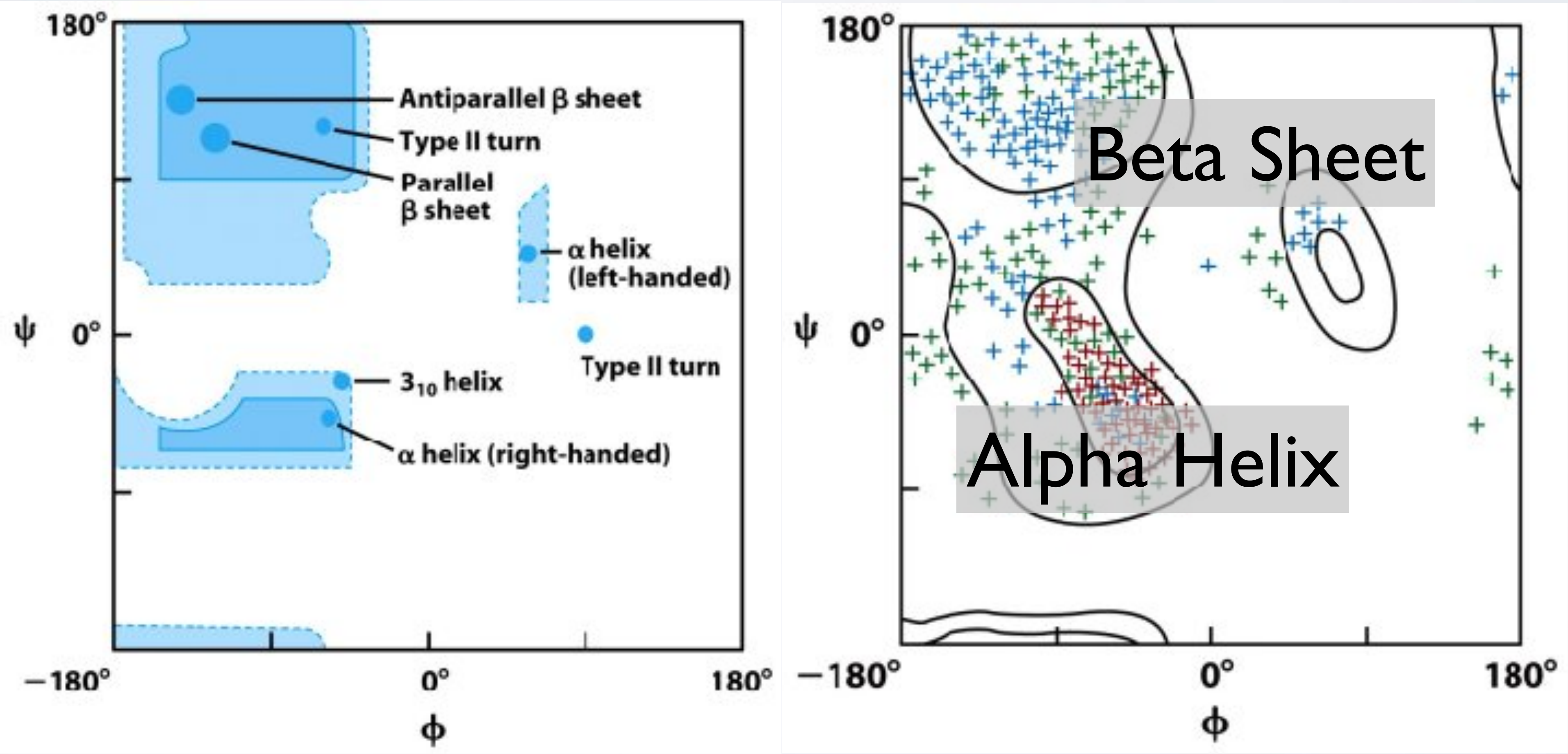
N-terminal

Bond angles and lengths are largely invariant

Peptide bond is planer (Cα, C, O, N, H, Cα all lie in the same plane)

Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

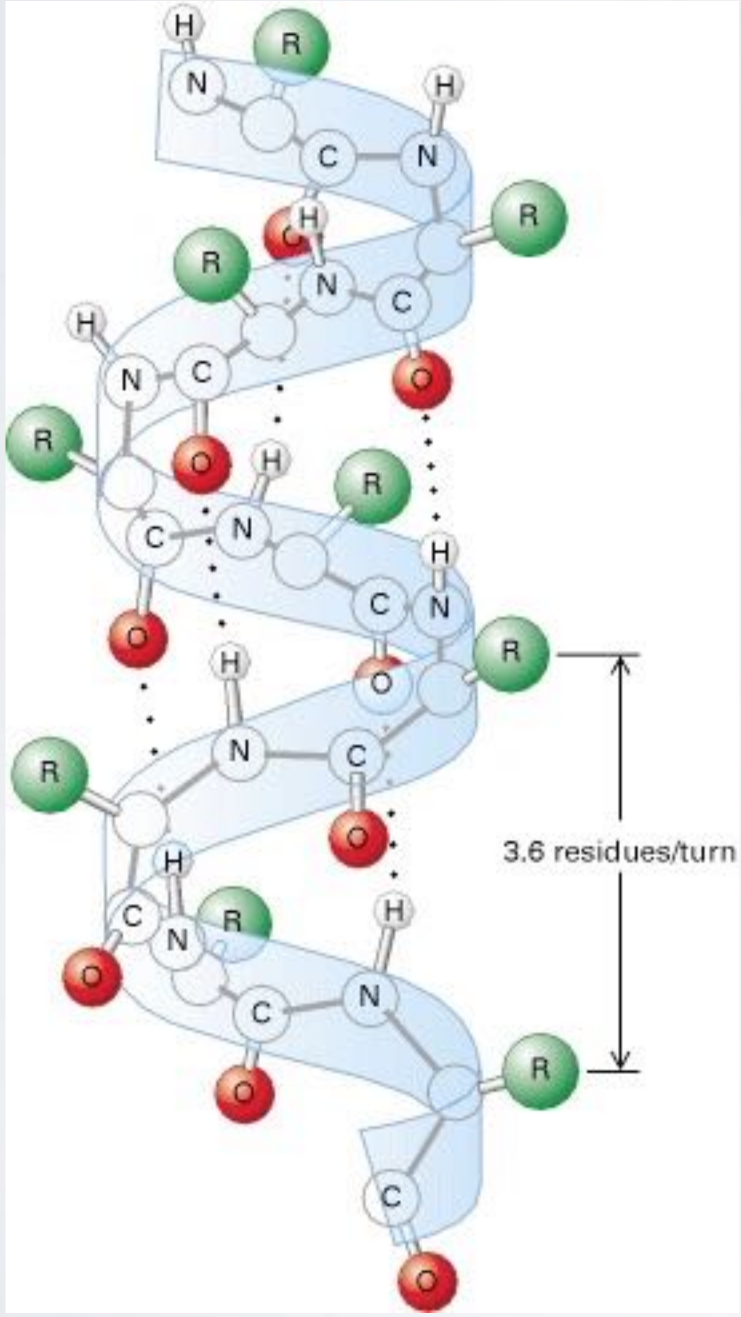
PHI vs PSI PLOTS ARE KNOWN AS **RAMACHANDRAN DIAGRAMS**



- Steric hindrance dictates torsion angle preference
- Ramachandran plot show preferred regions of φ and ψ dihedral angles which correspond to major forms of **secondary structure**

Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

MAJOR SECONDARY STRUCTURE TYPES **ALPHA HELIX** & BETA SHEET

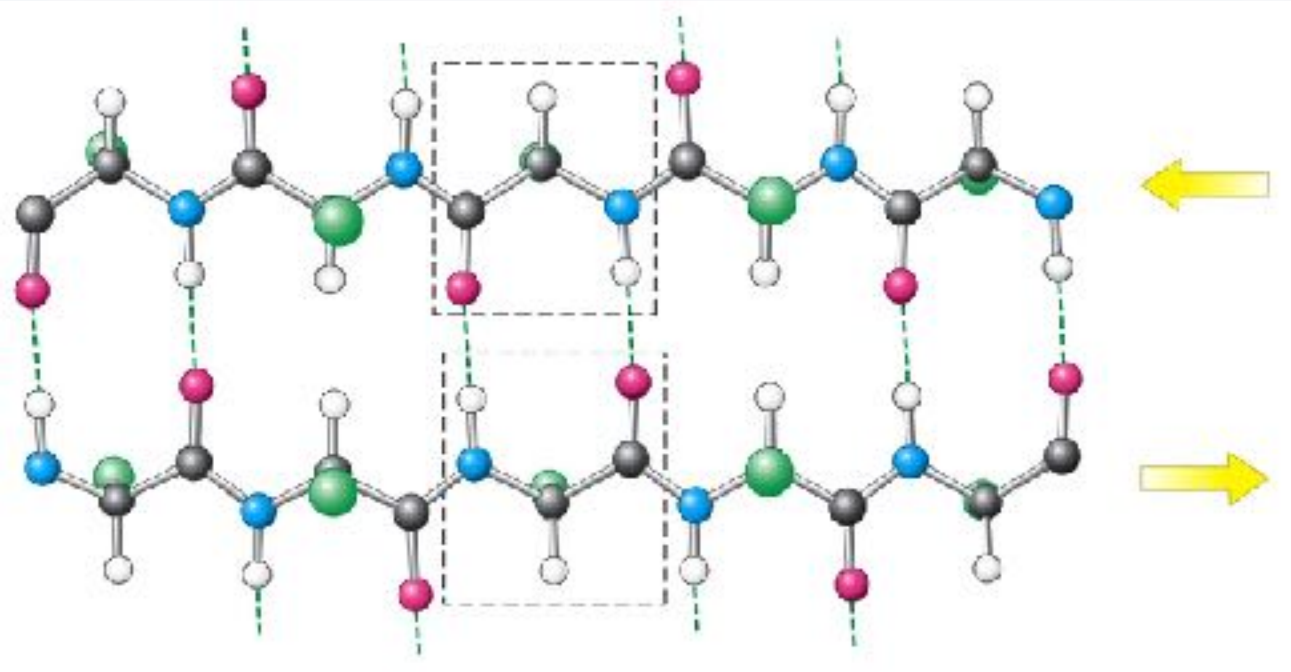


α-helix

- Most common from has 3.6 residues per turn (number of residues in one full rotation)
- Hydrogen bonds (dashed lines) between residue *i* and *i+4* stabilize the structure
- The side chains (in green) protrude outward
- 3_{10}-helix and π-helix forms are less common

Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

MAJOR SECONDARY STRUCTURE TYPES ALPHA HELIX & **BETA SHEET**

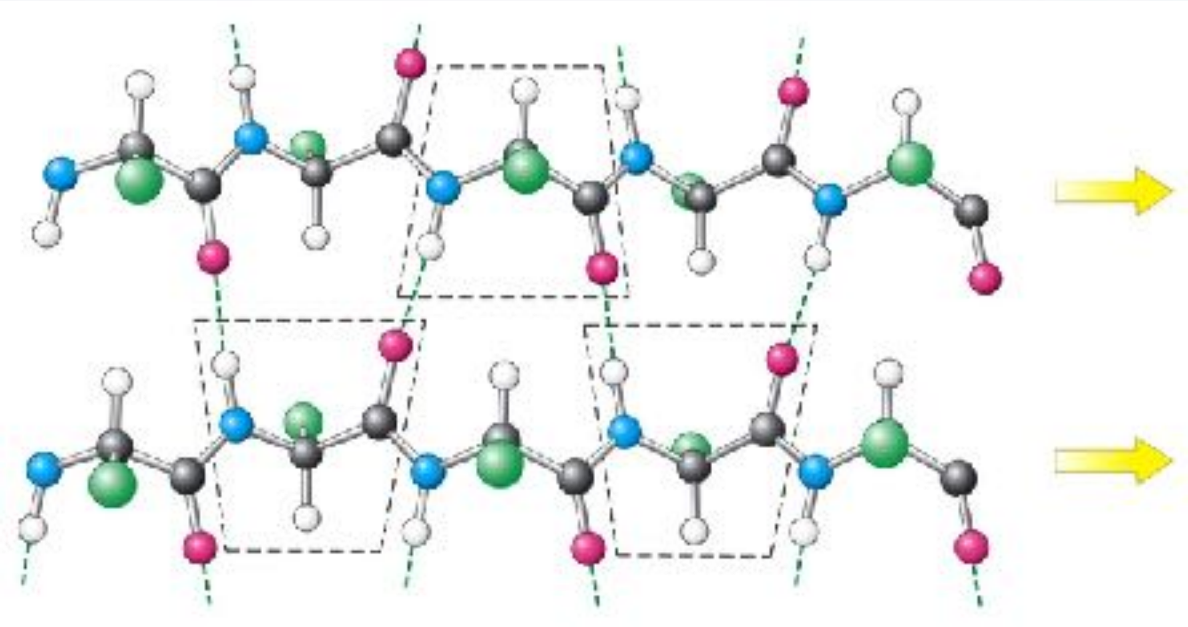


In **<u>antiparallel</u> β-sheets**

- Adjacent β-strands run in opposite directions
- Hydrogen bonds (dashed lines) between NH and CO stabilize the structure
- The side chains (in green) are above and below the sheet

Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

MAJOR SECONDARY STRUCTURE TYPES ALPHA HELIX & **BETA SHEET**

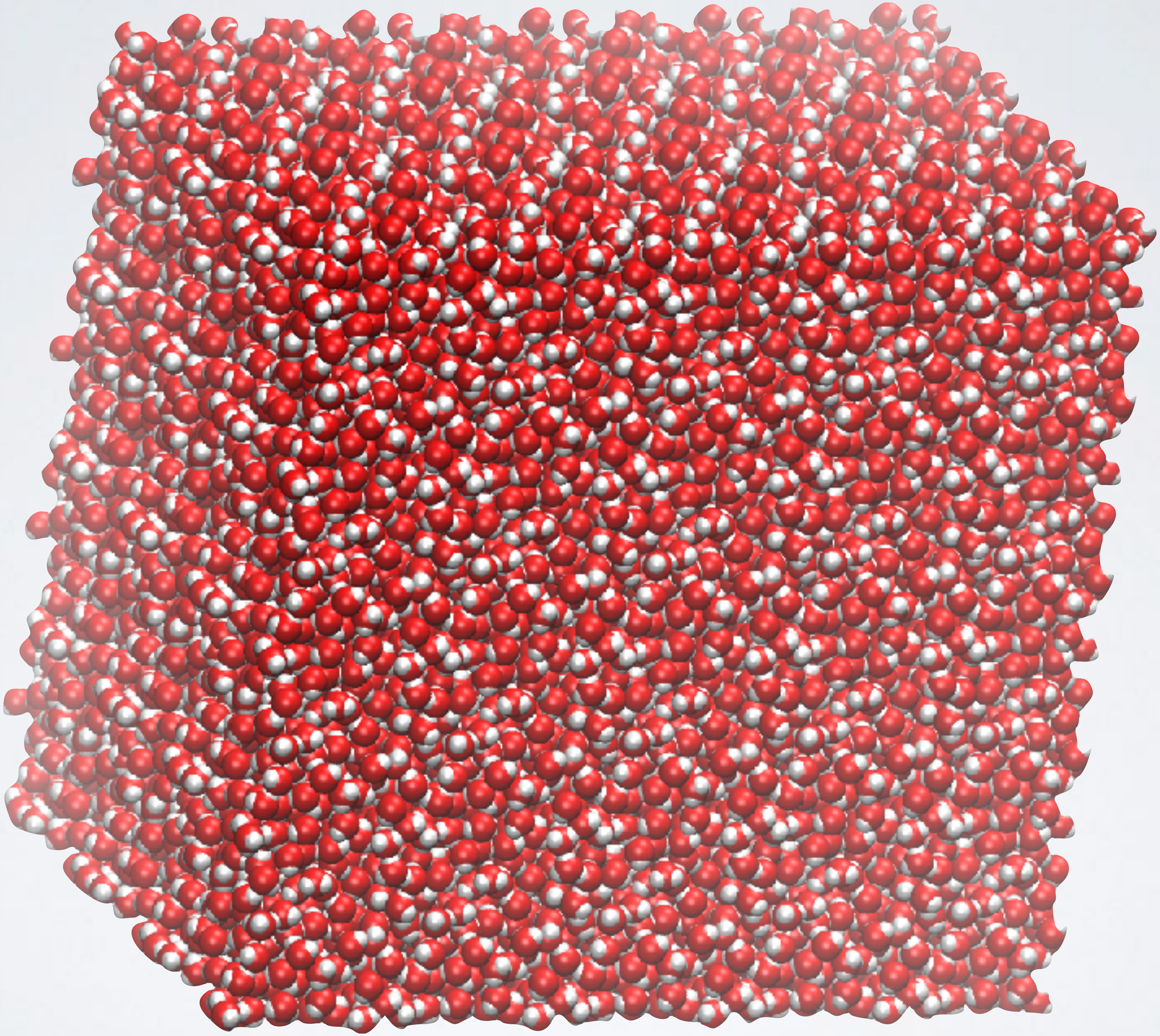


In **<u>parallel</u> β-sheets**

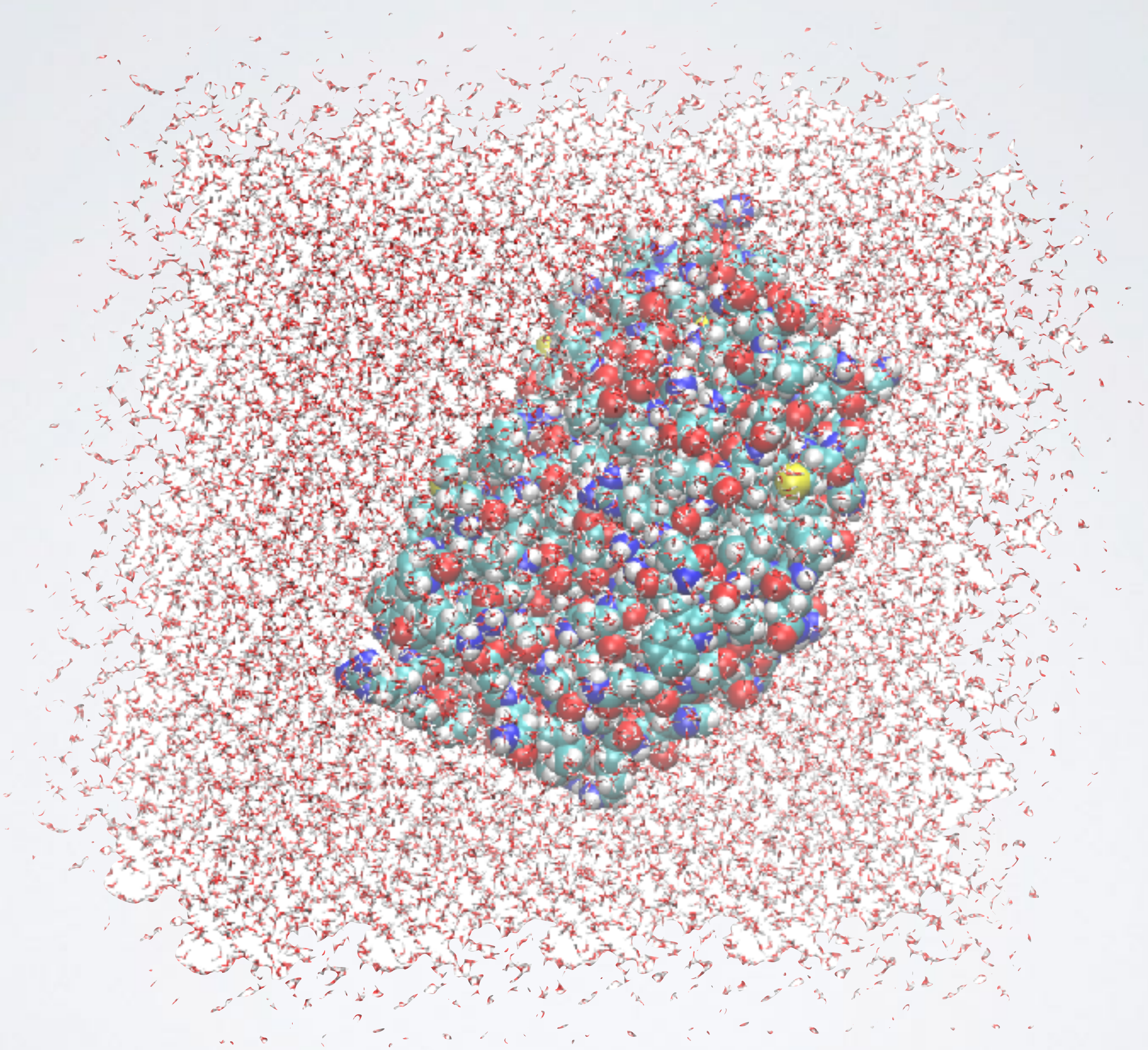
- Adjacent β-strands run in <u>same</u> direction
- Hydrogen bonds (dashed lines) between NH and CO stabilize the structure
- The side chains (in green) are above and below the sheet

Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

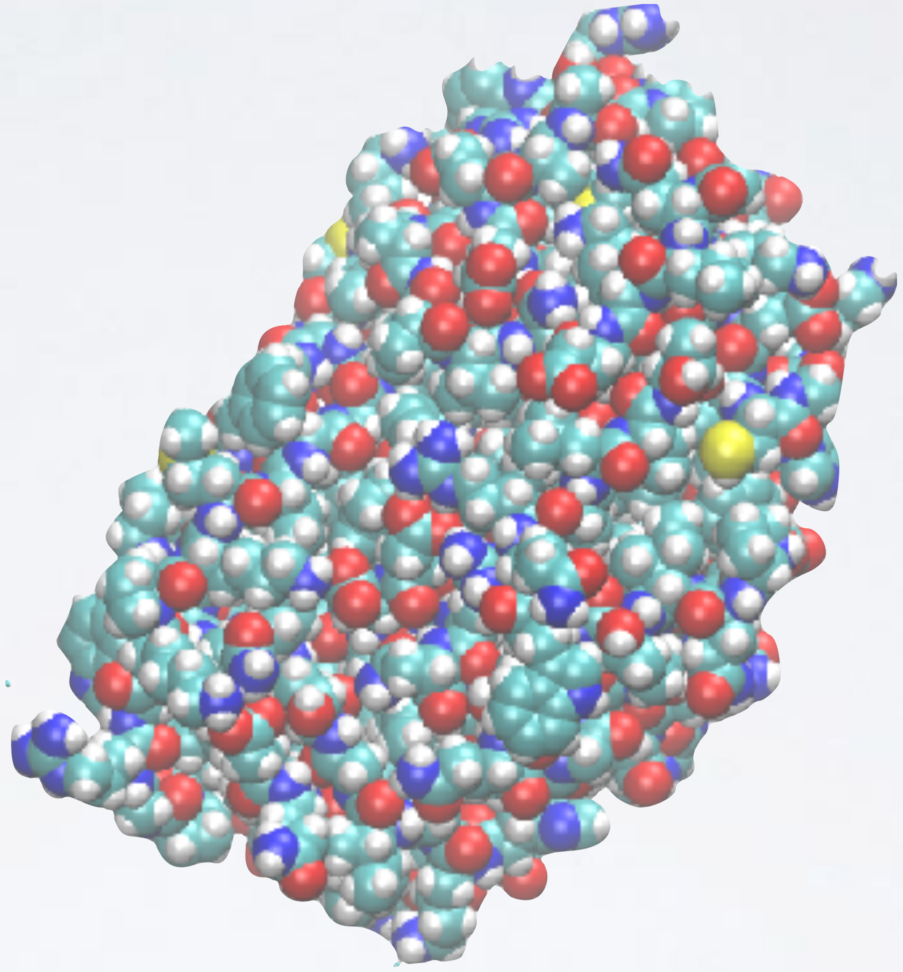
What Does a Protein Look like?



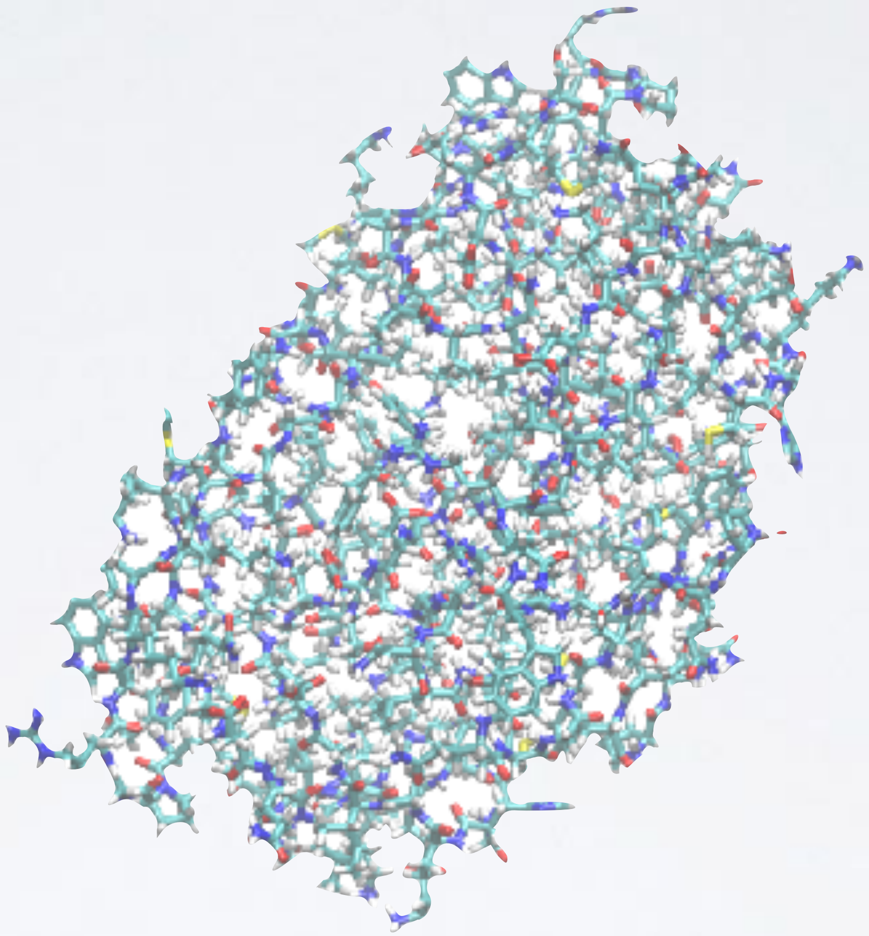
- Proteins are stable (and hidden) in water



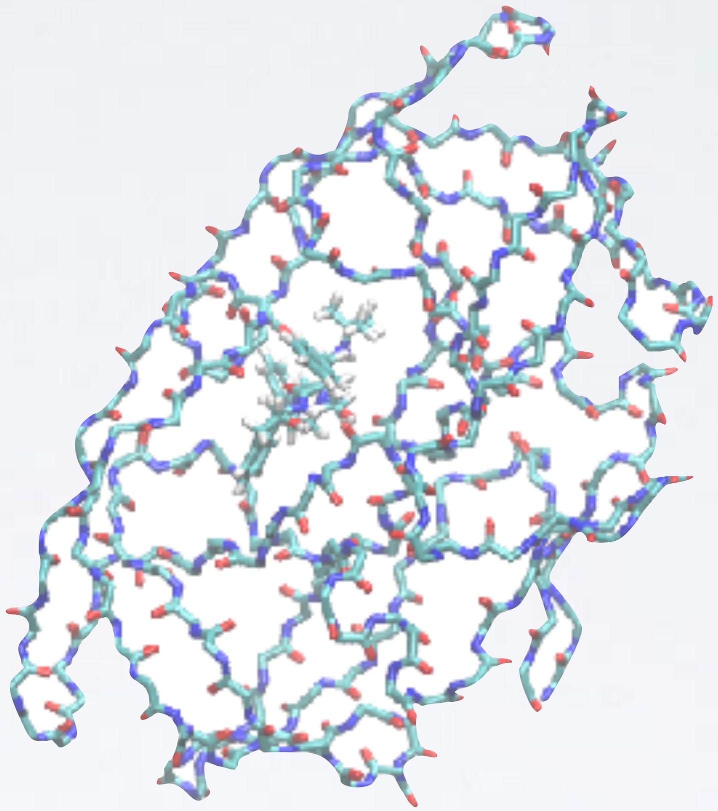
- Proteins closely interact with water



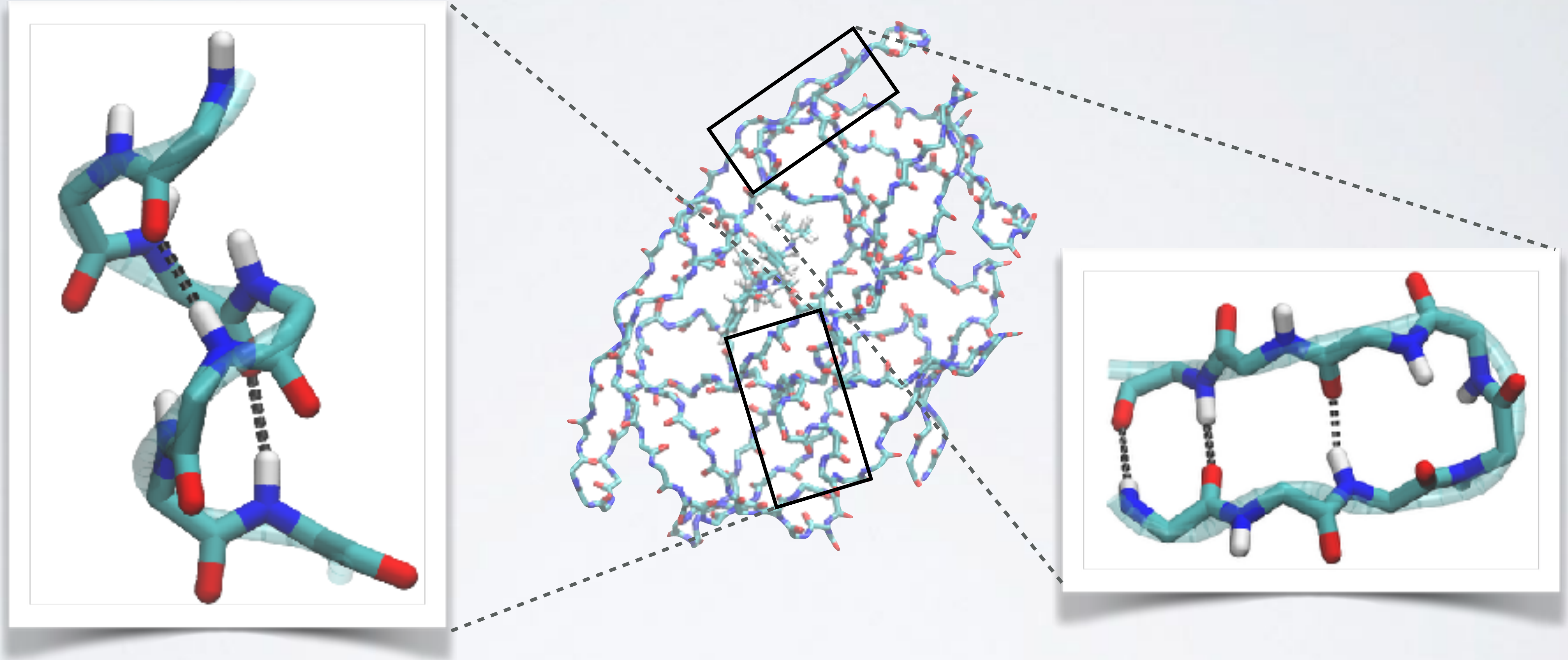
- Proteins are close packed solid but flexible objects (globular)



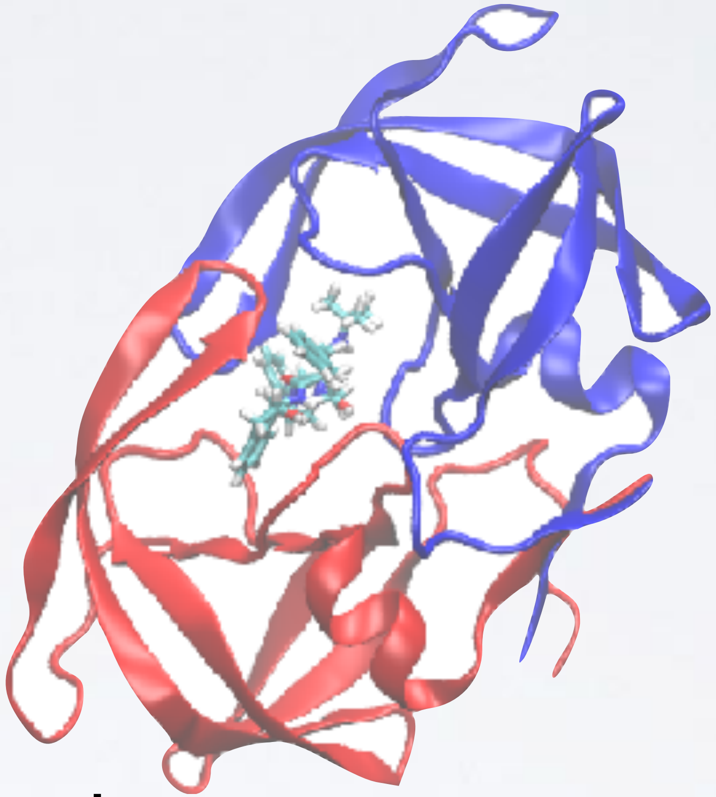
- Due to their large size and complexity it is often hard to see whats important in the structure



- Backbone or main-chain representation can help trace chain topology

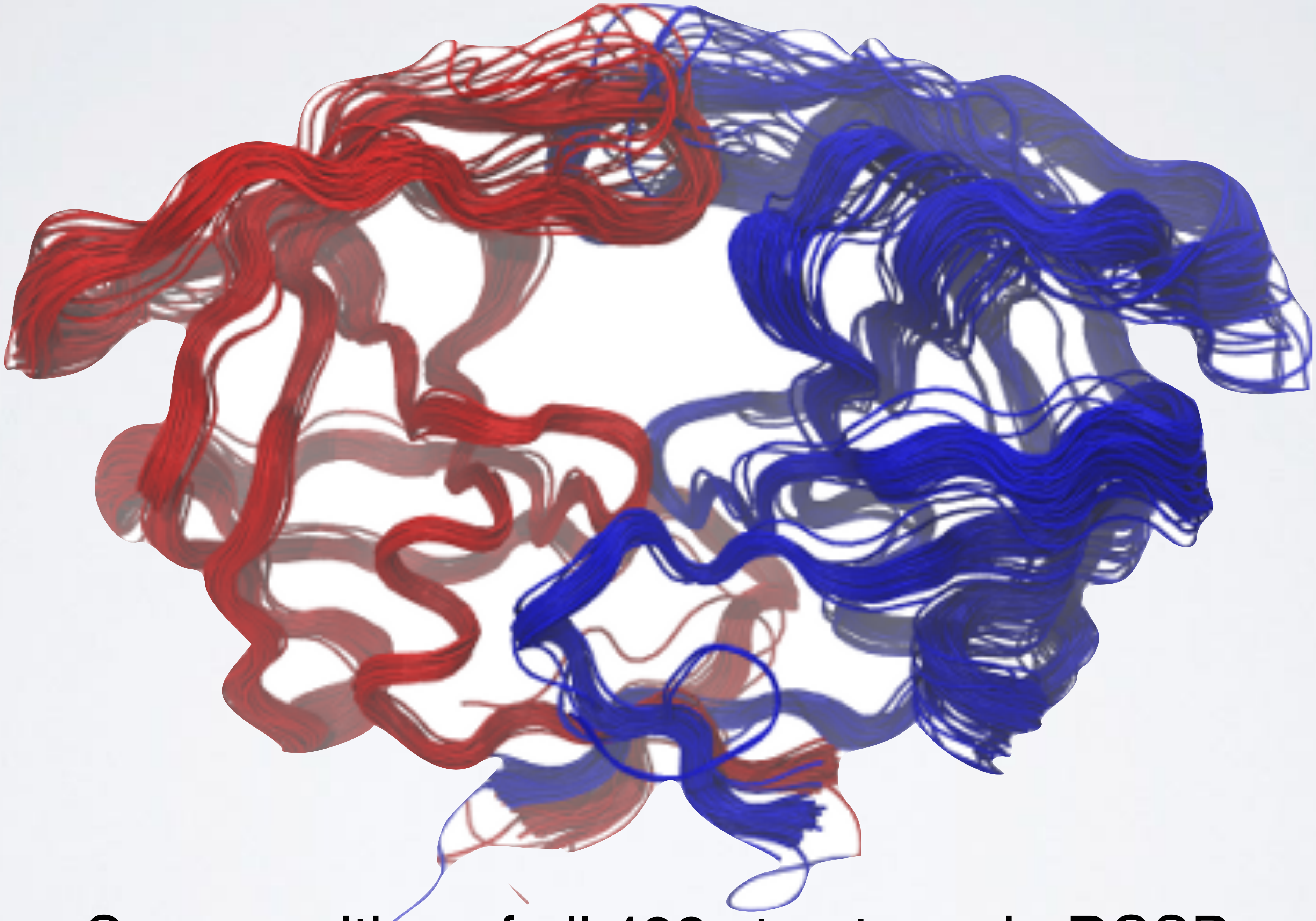


- Backbone or main-chain representation can help trace chain topology & reveal secondary structure



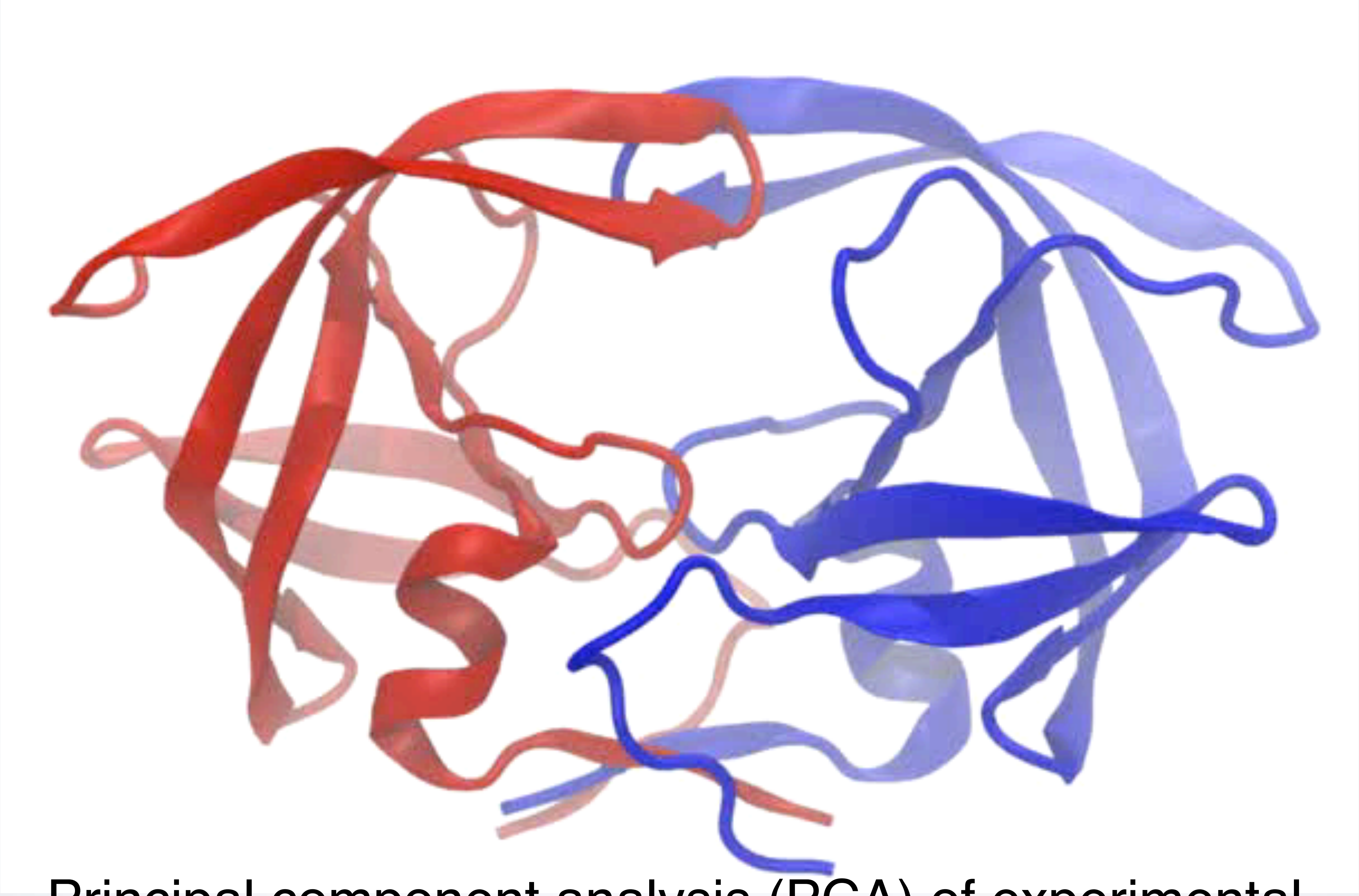
- Simplified secondary structure representations are commonly used to communicate structural details
- Now we can clearly see 2^o, 3^o and 4^o structure
- Coiled chain of connected secondary structures

DISPLACEMENTS REFLECT INTRINSIC FLEXIBILITY



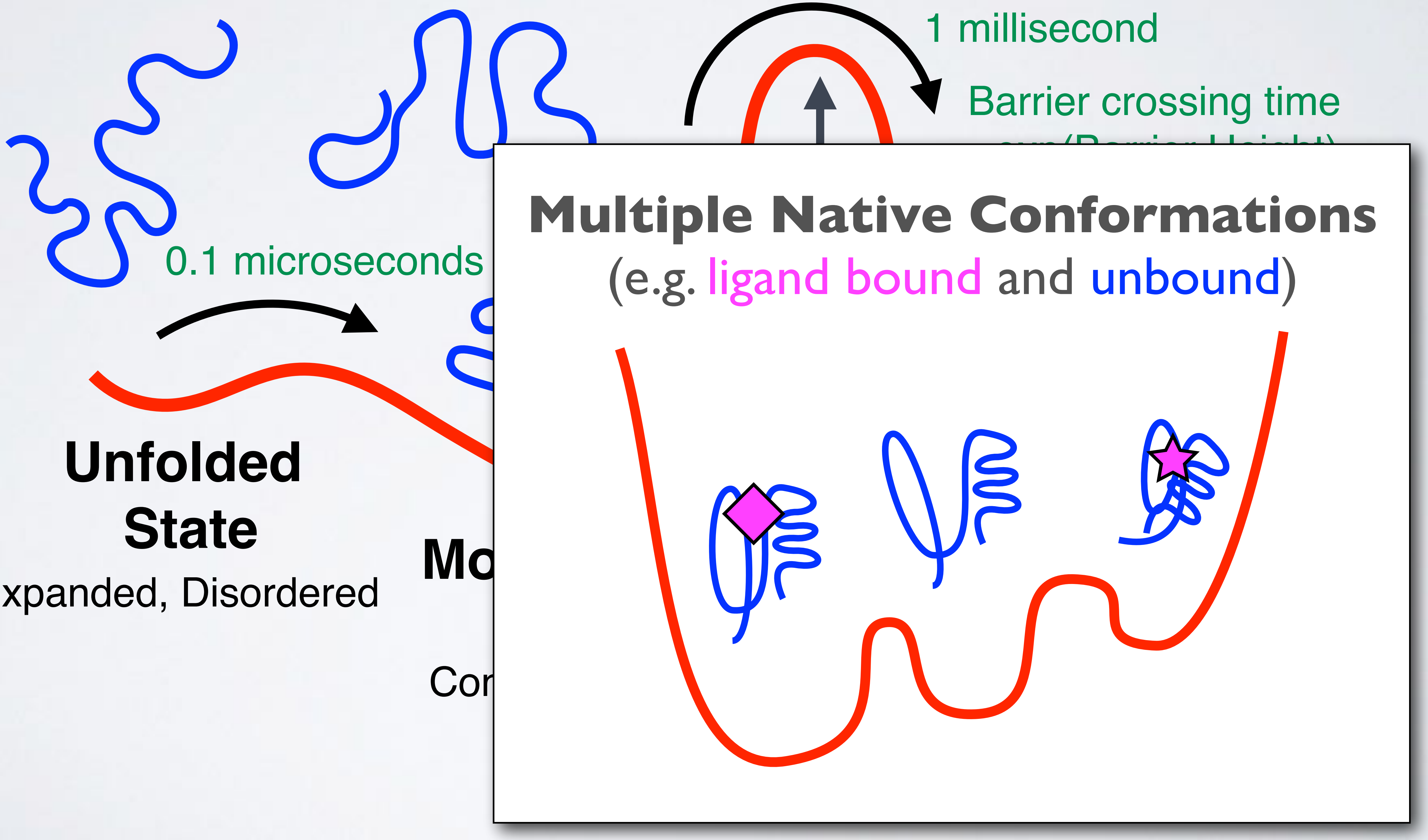
Superposition of all 482 structures in RCSB PDB (23/09/2015)

DISPLACEMENTS REFLECT INTRINSIC FLEXIBILITY



Principal component analysis (PCA) of experimental structures

KEY CONCEPT: **ENERGY LANDSCAPE**

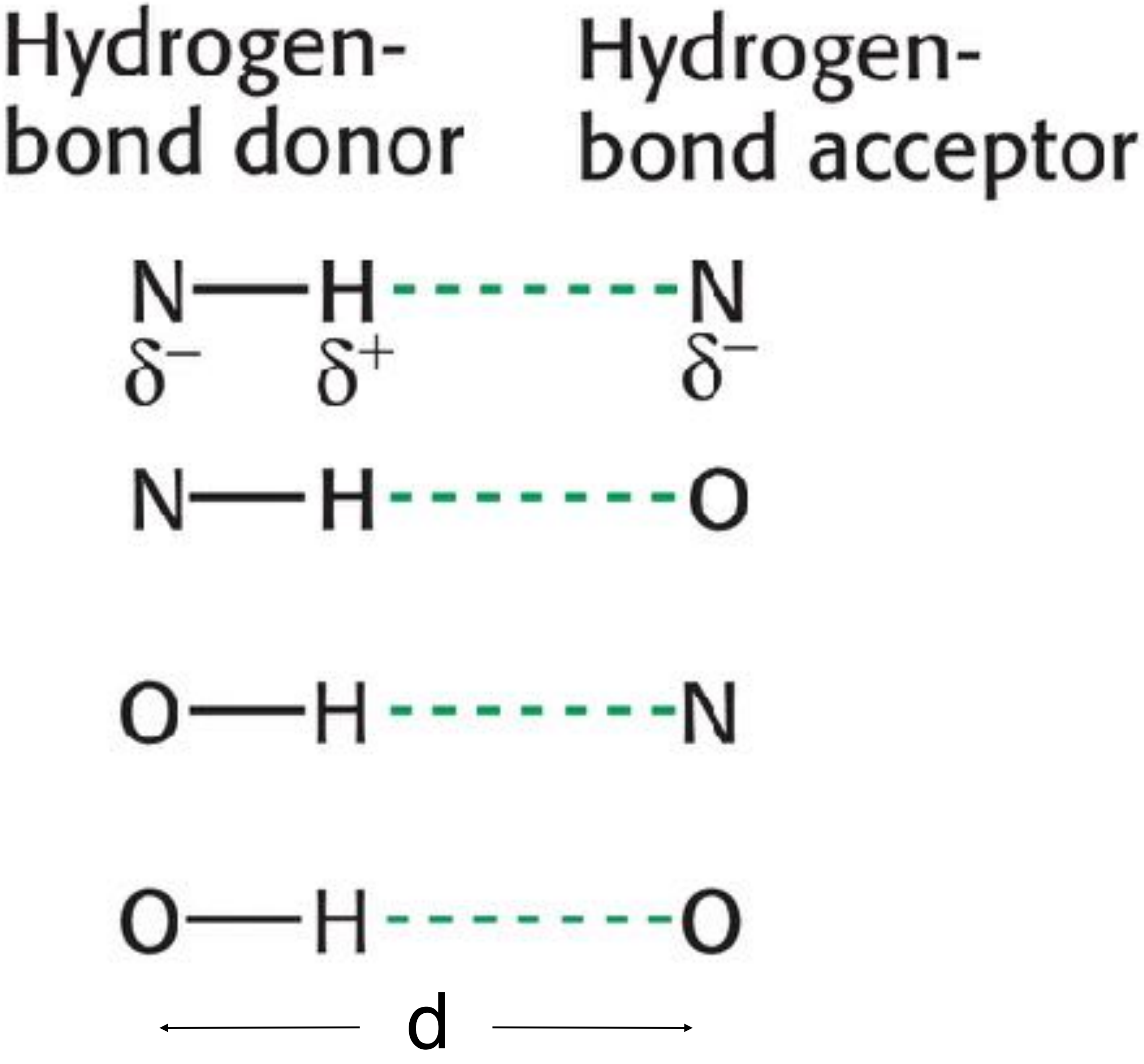


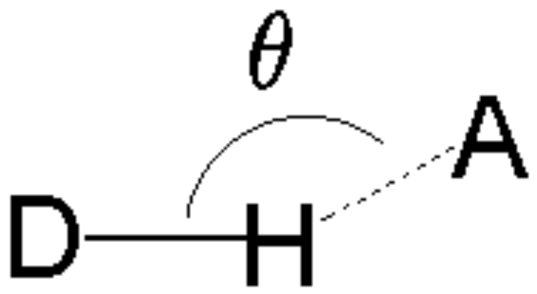
Multiple Native Conformations

(e.g. ligand bound and unbound)

Key forces affecting structure:

- H-bonding
- Van der Waals
- Electrostatics
- Hydrophobicity



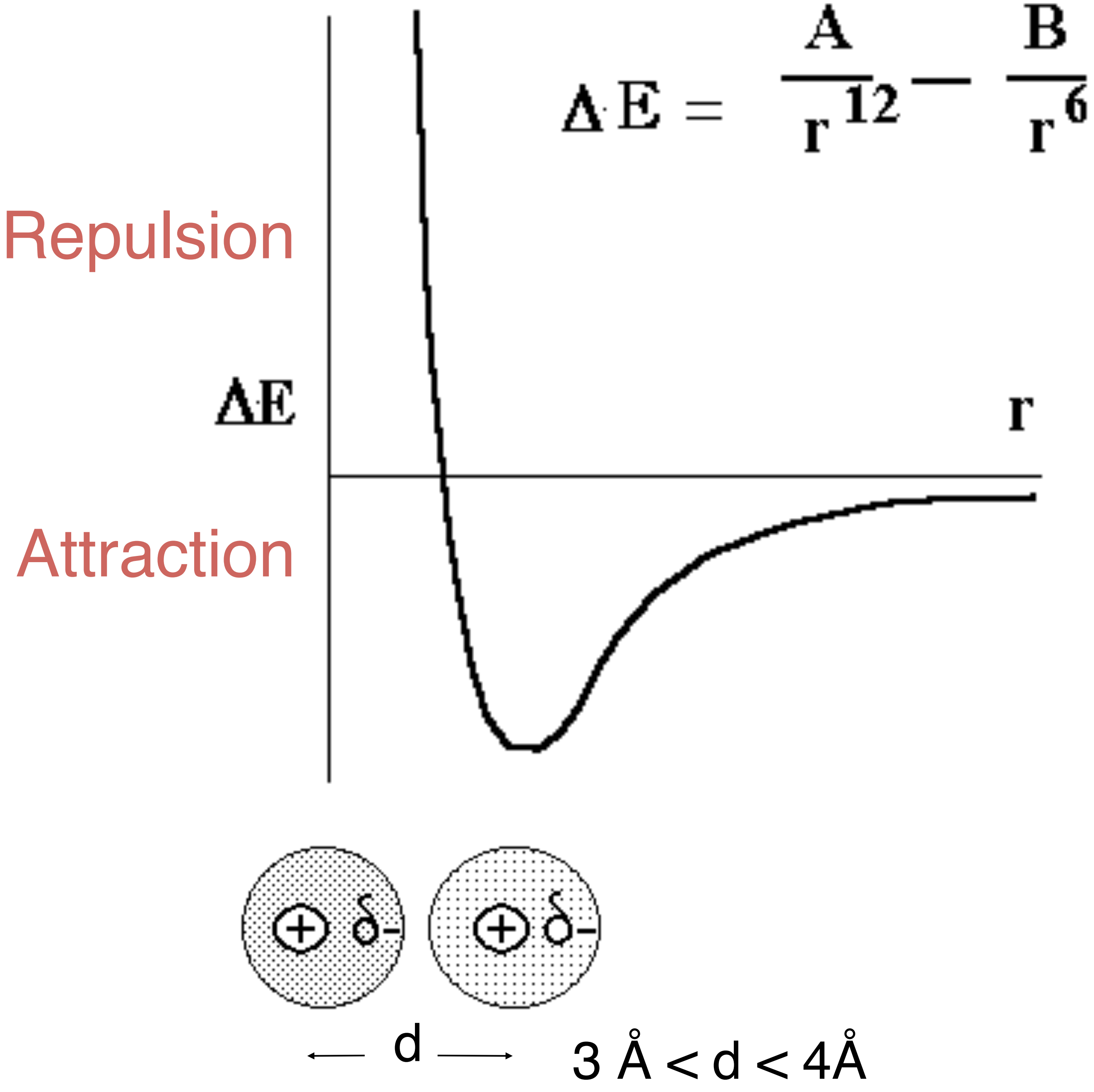


$2.6\ \text{Å} < d < 3.1\text{Å}$

$150° < \theta < 180°$

Key forces affecting structure:

- H-bonding
- Van der Waals
- Electrostatics
- Hydrophobicity



$$\Delta E = \frac{A}{r^{12}} - \frac{B}{r^{6}}$$

3 Å < d < 4Å

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- Electrostatics
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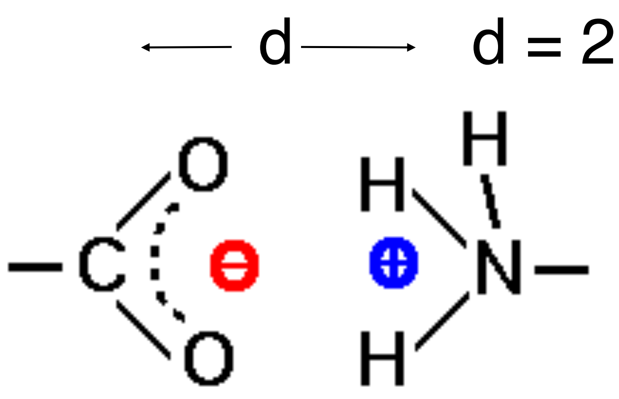
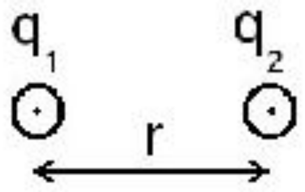


d = 2.8 Å

carboxyl group and amino group

(some time called IONIC BONDs or SALT BRIDGEs)



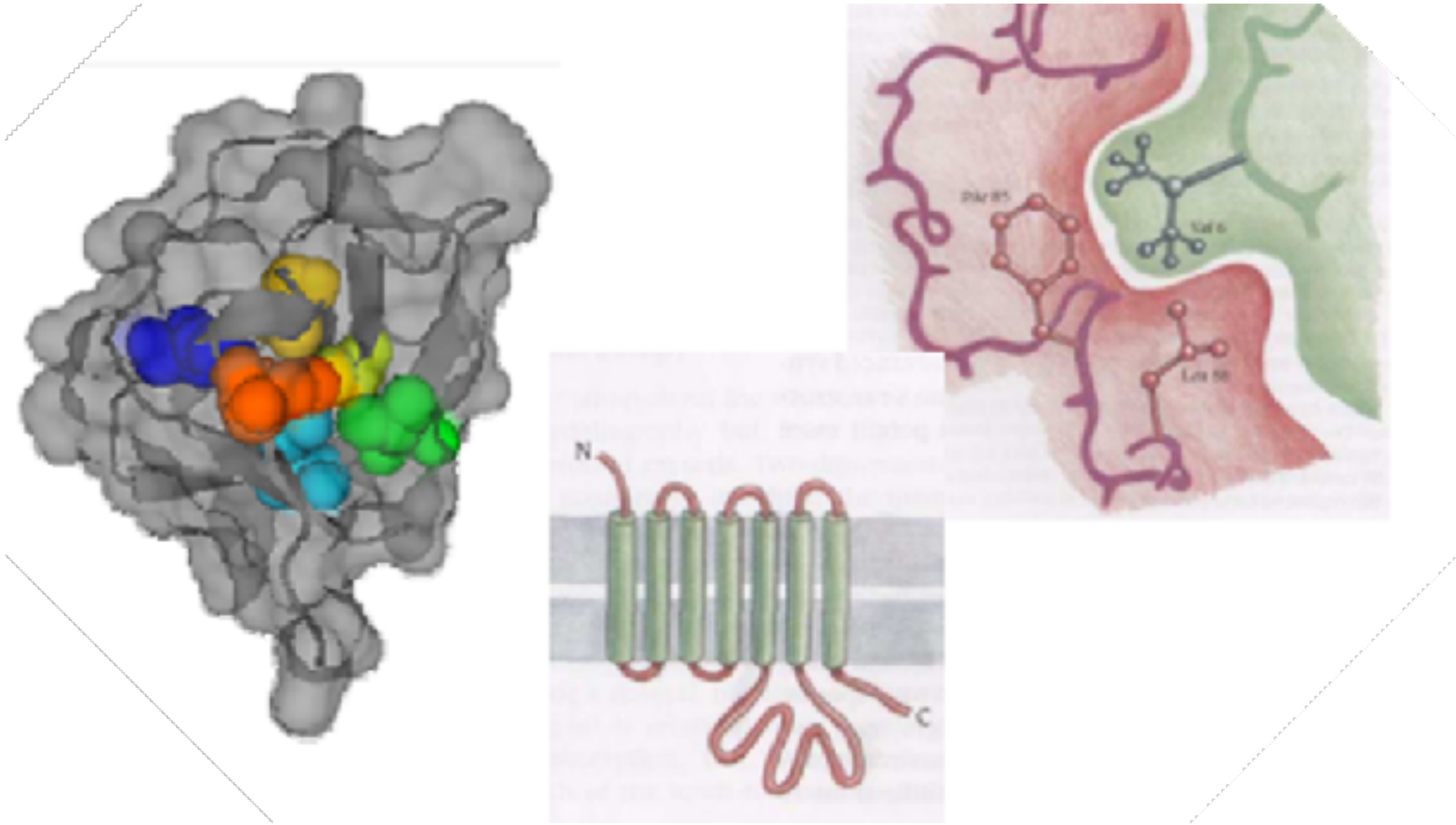
Coulomb's law

$$E = \frac{K q_1 q_2}{D r}$$

E = Energy
k = constant
D = Dielectric constant (vacuum = 1; H_2O = 80)
q_1 & q_2 = electronic charges (Coulombs)
r = distance (Å)

Key forces affecting structure:

- H-bonding
- Van der Waals
- Electrostatics
- Hydrophobicity



The force that causes hydrophobic molecules or nonpolar portions of molecules to aggregate together rather than to dissolve in water is called Hydrophobicity (*Greek, "water fearing"*). This is not a separate bonding force; rather, it is the result of the energy required to insert a nonpolar molecule into water.

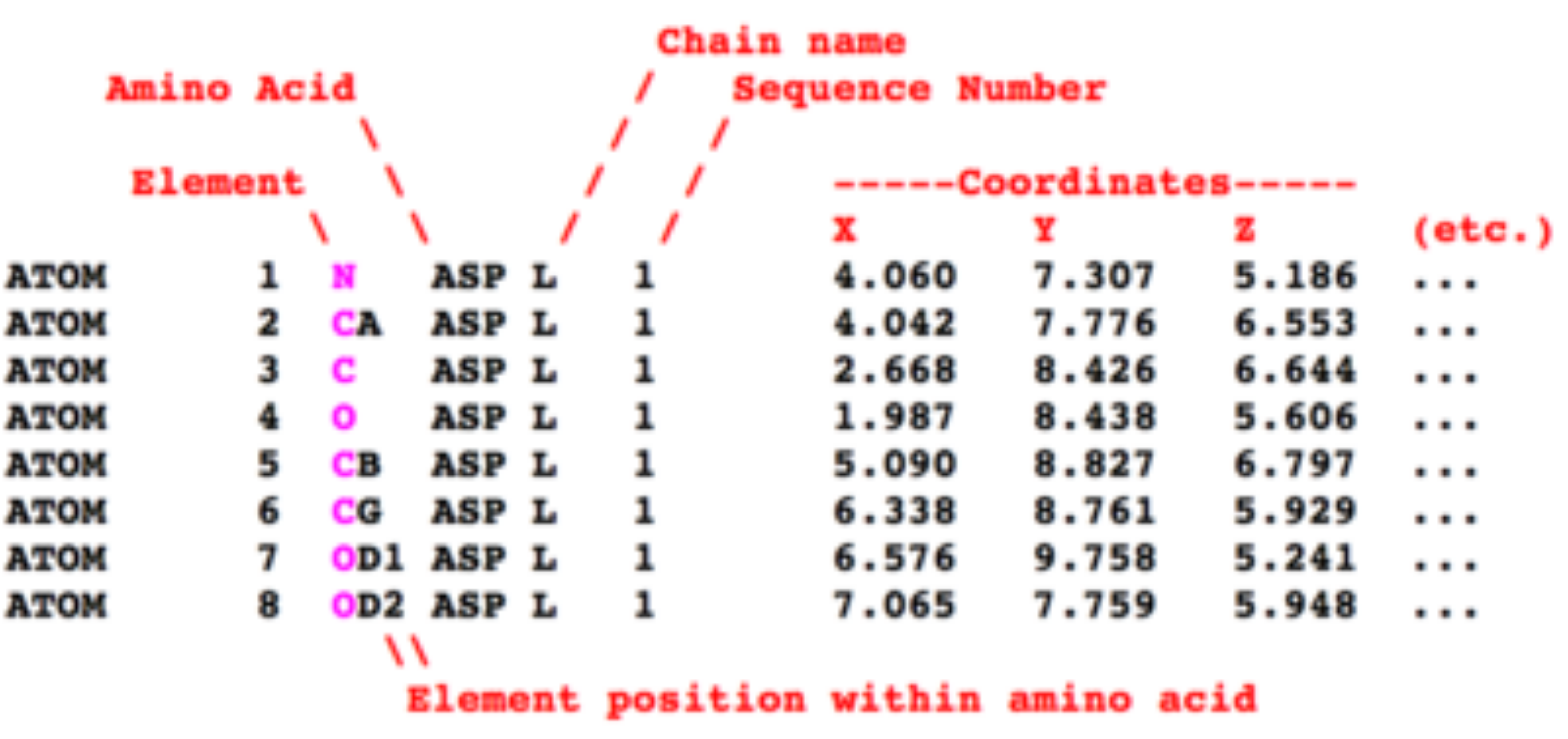
Do it Yourself!

Hand-on time!

https://bioboot.github.io/bimm143_S18/lectures/#11

Focus on **section 1** to **3** only please!

SIDE-NOTE: **PDB FILE FORMAT**



```
                                 Chain name
    Amino Acid                /   Sequence Number
             \               /   /
     Element  \             /   /        ------Coordinates------
           \   \           /   /         X         Y         Z        (etc.)
ATOM       1  N    ASP L   1             4.060     7.307     5.186    ...
ATOM       2  CA   ASP L   1             4.042     7.776     6.553    ...
ATOM       3  C    ASP L   1             2.668     8.426     6.644    ...
ATOM       4  O    ASP L   1             1.987     8.438     5.606    ...
ATOM       5  CB   ASP L   1             5.090     8.827     6.797    ...
ATOM       6  CG   ASP L   1             6.338     8.761     5.929    ...
ATOM       7  OD1  ASP L   1             6.576     9.758     5.241    ...
ATOM       8  OD2  ASP L   1             7.065     7.759     5.948    ...
                \\
                 Element position within amino acid
```

- **PDB files** contains atomic coordinates and associated information.

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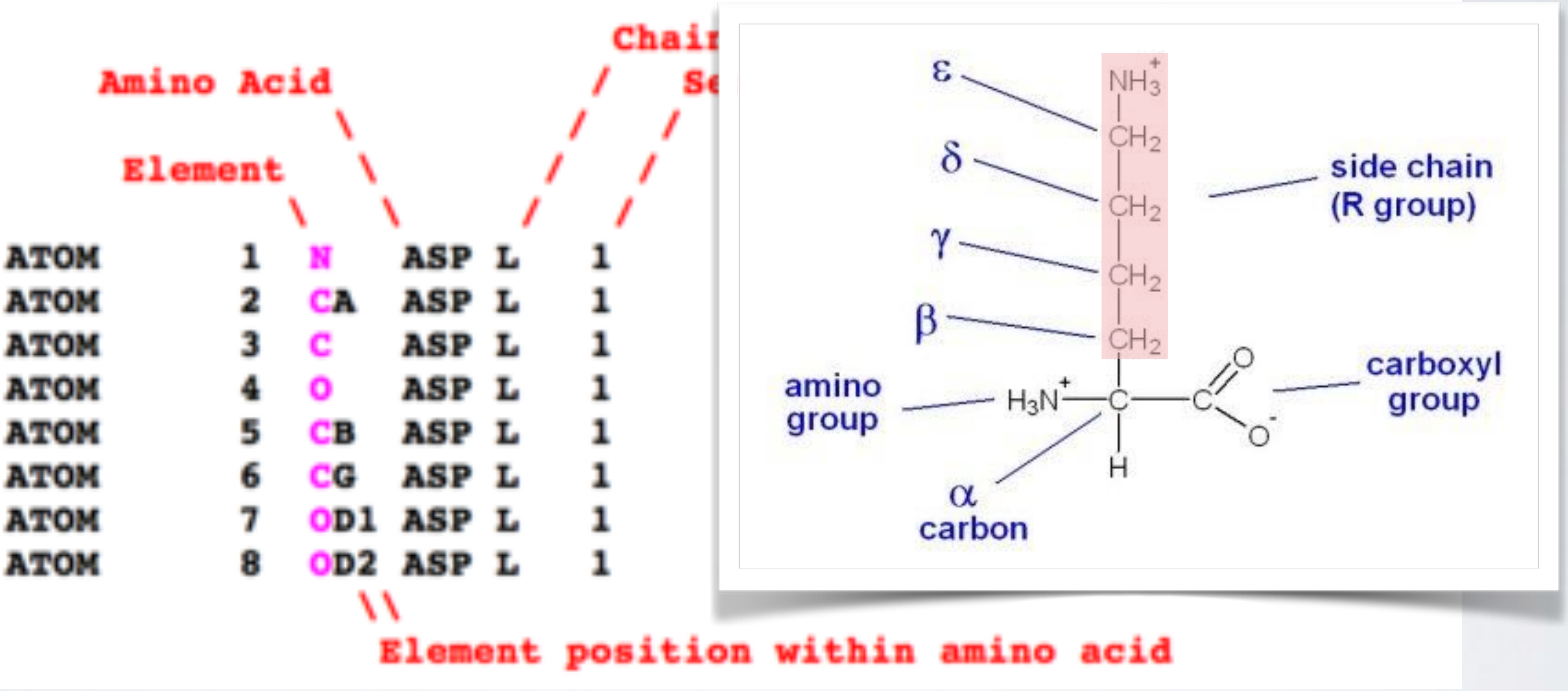

```
                                          Chai
       Amino Acid                       /    Se
                  \                    /    /
        Element    \                  /    /
               \    \                /    /
ATOM         1  N    ASP L   1
ATOM         2  CA   ASP L   1
ATOM         3  C    ASP L   1
ATOM         4  O    ASP L   1
ATOM         5  CB   ASP L   1
ATOM         6  CG   ASP L   1
ATOM         7  OD1  ASP L   1
ATOM         8  OD2  ASP L   1
                  \\
                   Element position within amino acid
```

- **PDB files** contains atomic coordinates and associated information.

NEXT UP:

- **Overview of structural bioinformatics**
  - Major motivations, goals and challenges
- **Fundamentals of protein structure**
  - Compositio nd dynamics
- **Representing eting protein structure**
  - Modeling energy as a function of structure
- **Example application areas**
  - Predicting functional dynamics & drug discovery

Change from here on!!!

Just do docking???

KEY CONCEPT: POTENTIAL FUNCTIONS DESCRIBE A SYSTEMS **ENERGY** AS A FUNCTION OF ITS **STRUCTURE**

Two main approaches:

(1). **Physics-Based**

(2). **Knowledge-Based**

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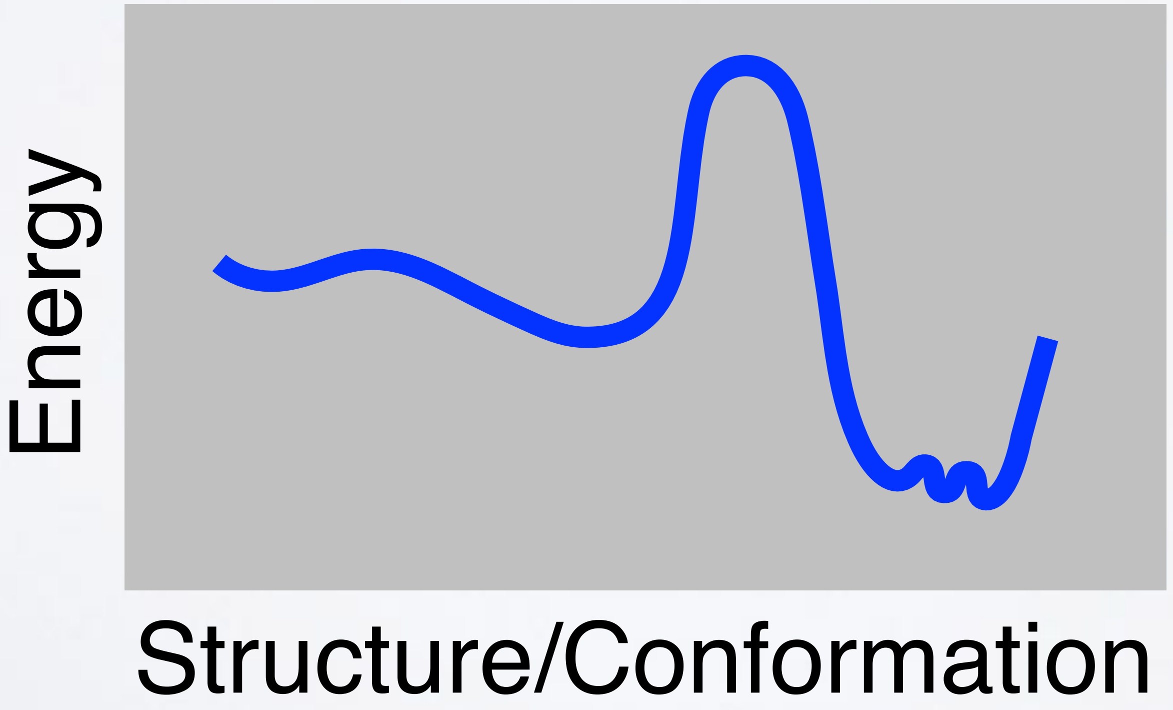

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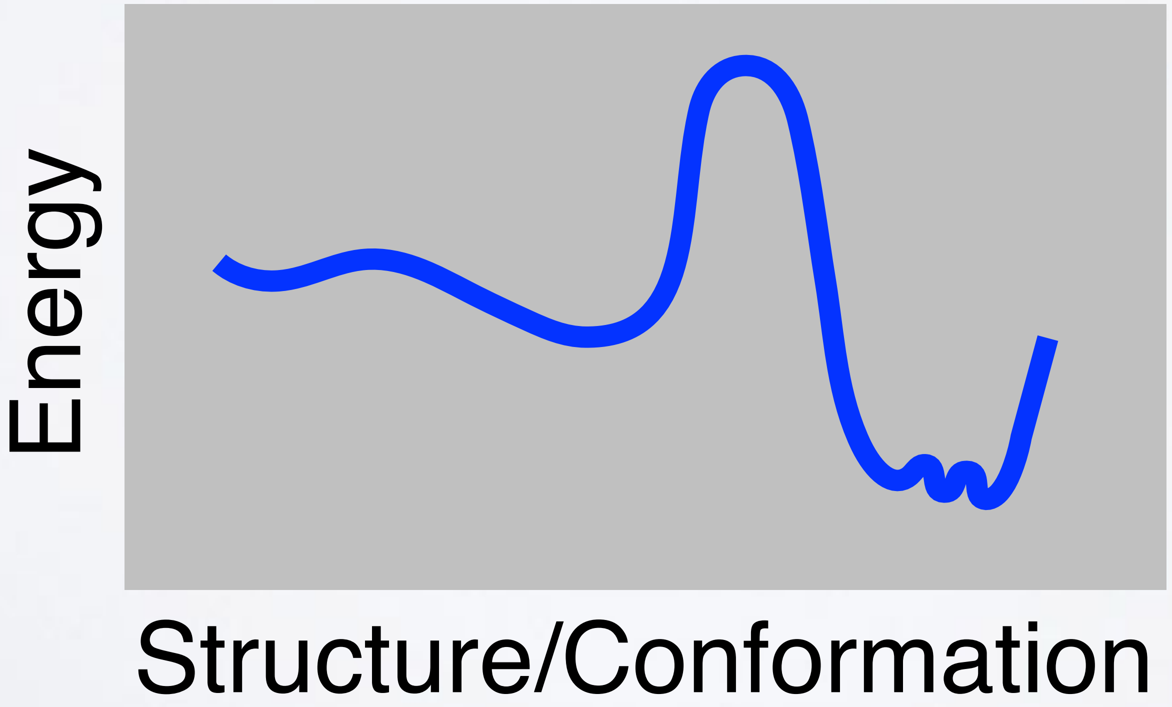


PHYSICS-BASED POTENTIALS

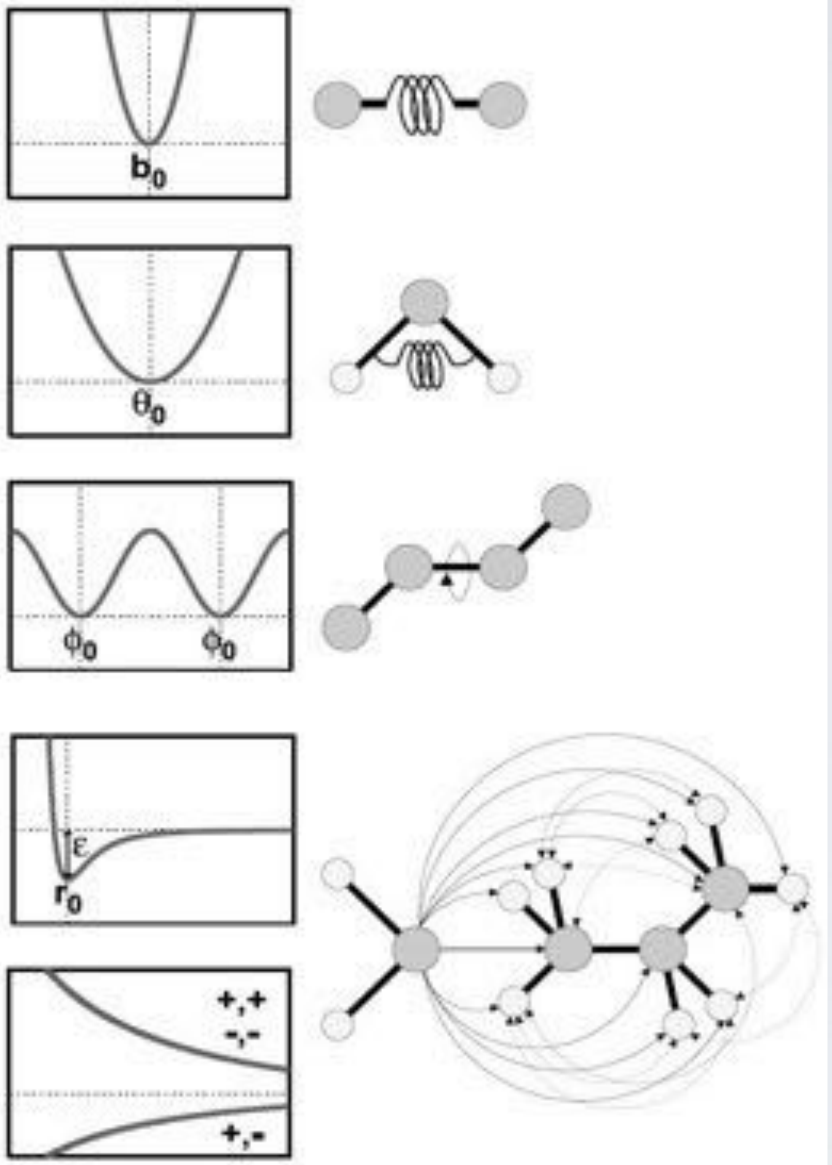
ENERGY TERMS FROM PHYSICAL THEORY

$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} +$$

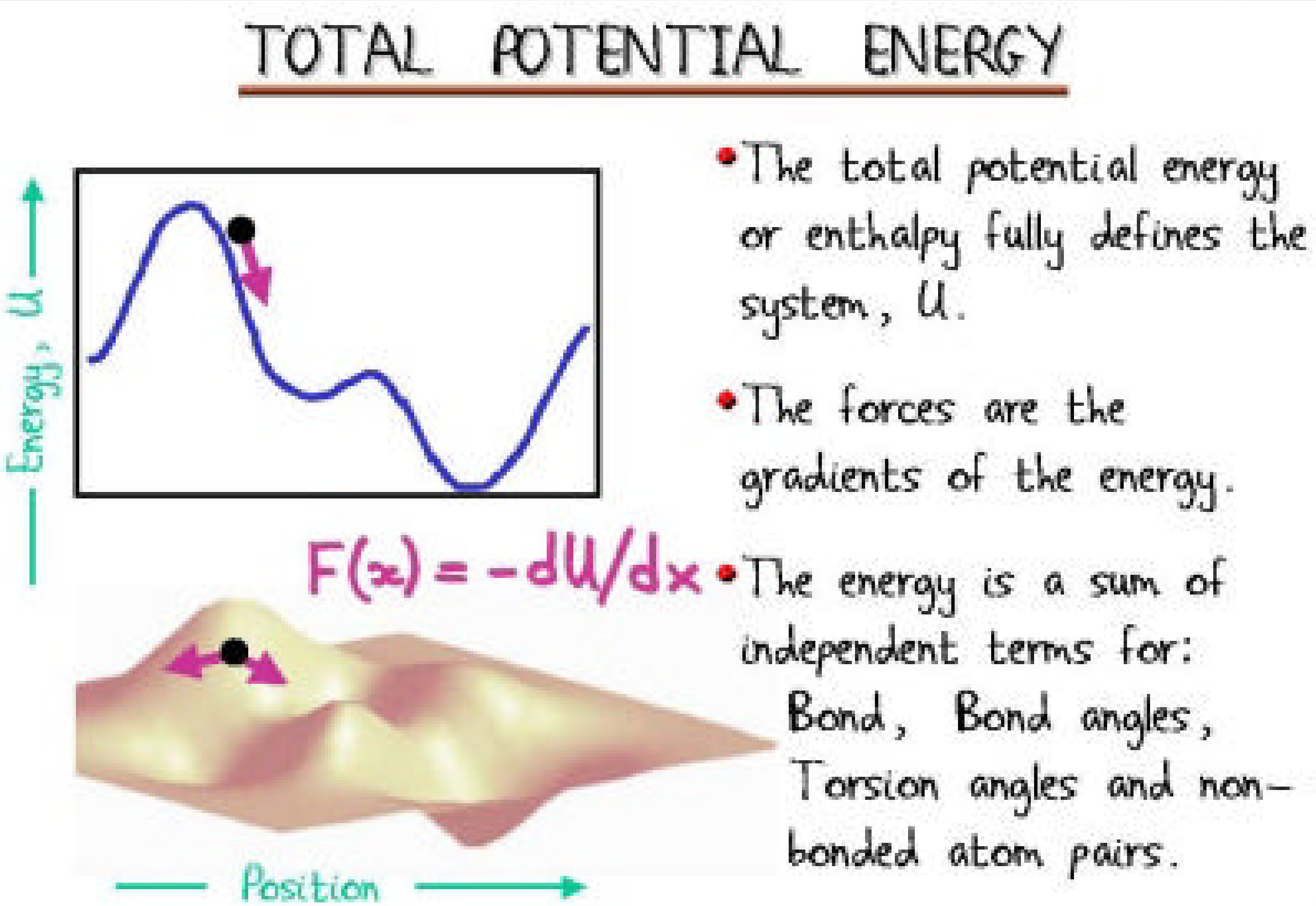
$$\underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} +$$

$$\underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$

U_{bond} = oscillations about the equilibrium bond length
U_{angle} = oscillations of 3 atoms about an equilibrium bond angle
$U_{dihedral}$ = torsional rotation of 4 atoms about a central bond
$U_{nonbond}$ = non-bonded energy terms (electrostatics and Lenard-Jones)



CHARMM P.E. function, see: http://www.charmm.org/

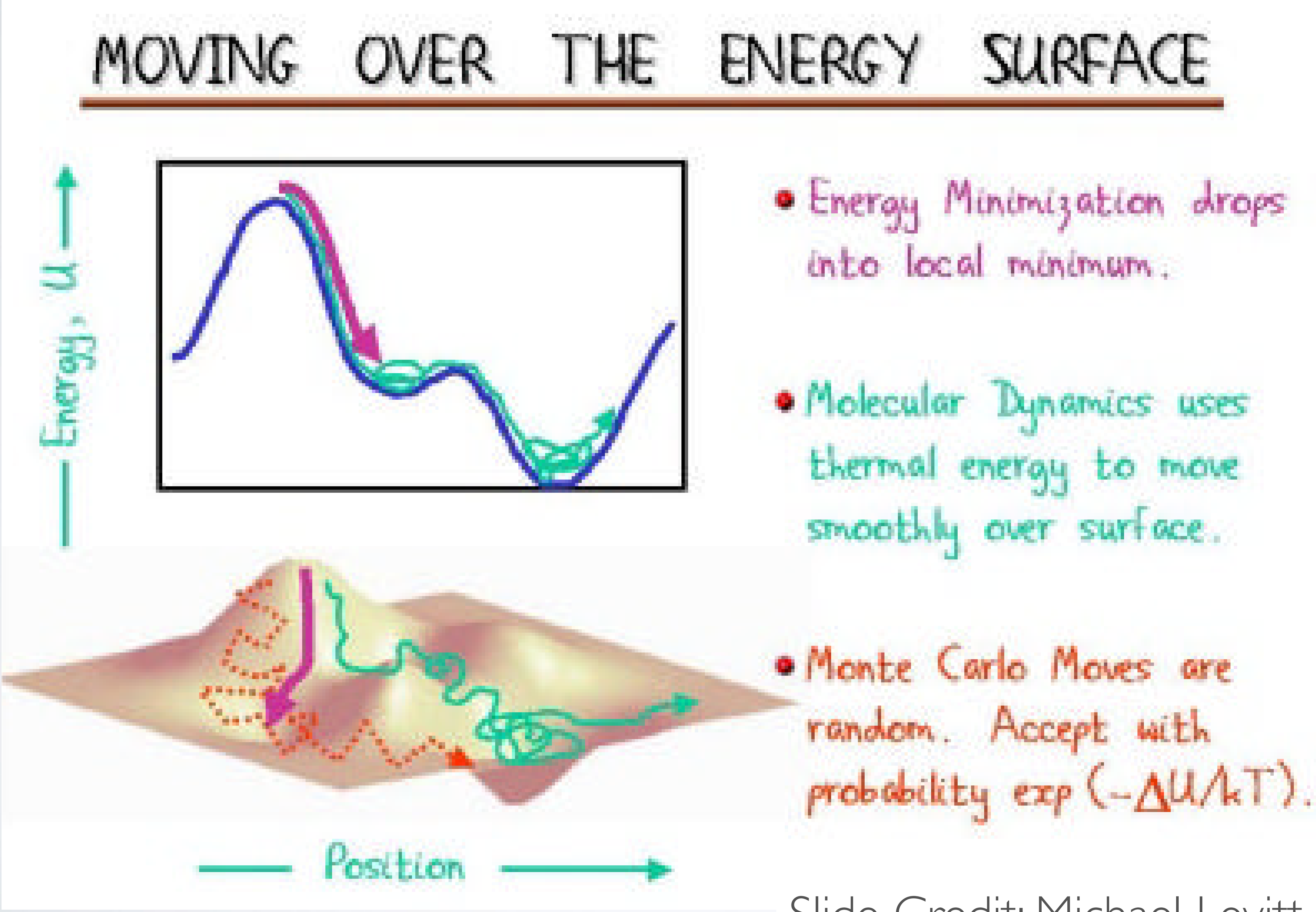


TOTAL POTENTIAL ENERGY

$F(x) = -dU/dx$

- The total potential energy or enthalpy fully defines the system, U.
- The forces are the gradients of the energy.
- The energy is a sum of independent terms for: Bond, Bond angles, Torsion angles and non-bonded atom pairs.

Slide Credit: Michael Levitt



MOVING OVER THE ENERGY SURFACE

- Energy Minimization drops into local minimum.
- Molecular Dynamics uses thermal energy to move smoothly over surface.
- Monte Carlo Moves are random. Accept with probability exp(−ΔU/kT).

Slide Credit: Michael Levitt

PHYSICS-ORIENTED APPROACHES

Weaknesses

Fully physical detail becomes computationally intractable

Approximations are unavoidable

(Quantum effects approximated classically, water may be treated crudely)

Parameterization still required

Strengths

Interpretable, provides guides to design

Broadly applicable, in principle at least

Clear pathways to improving accuracy

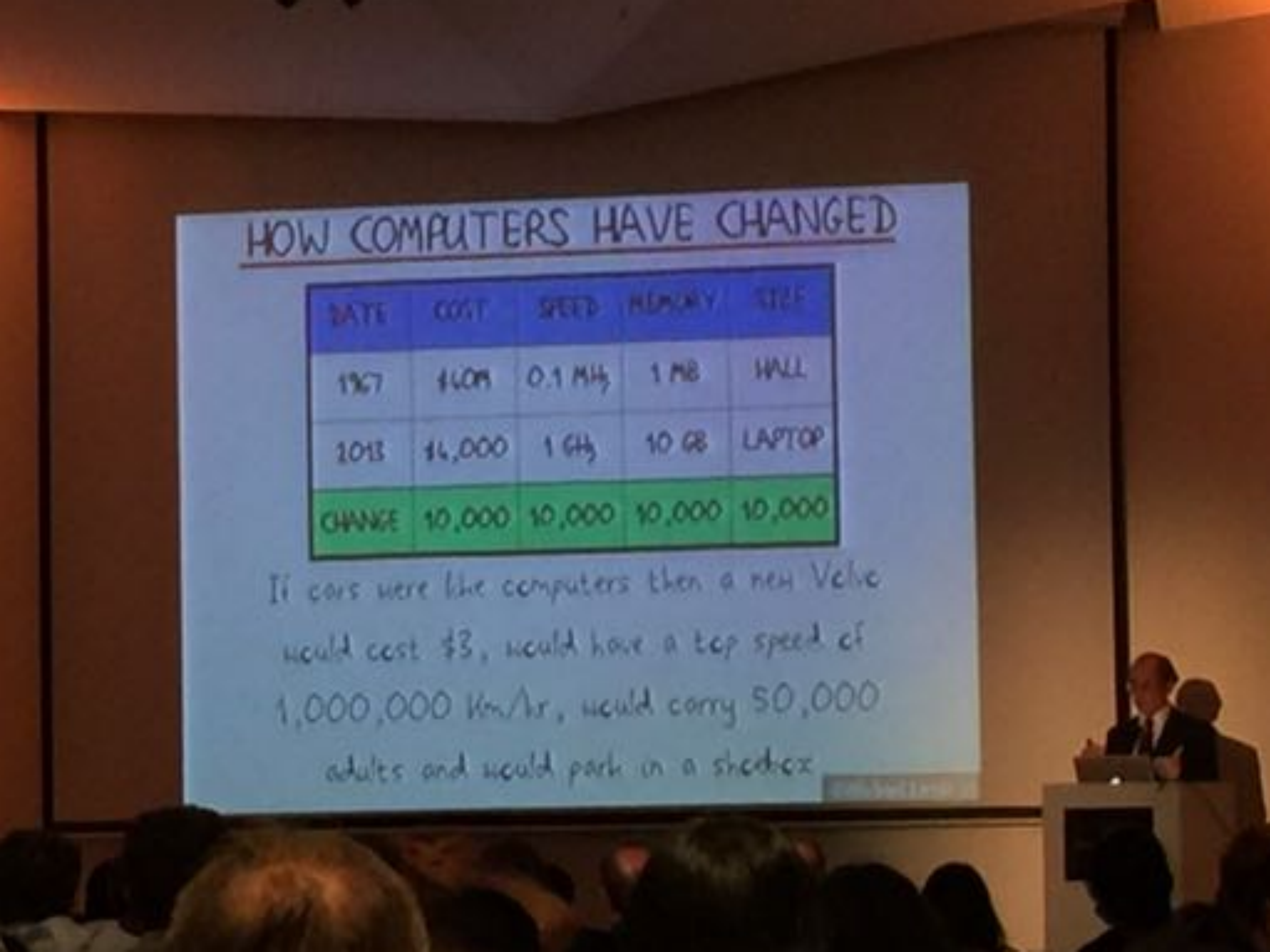
Status

Useful, widely adopted but far from perfect

Multiple groups working on fewer, better approxs

Force fields, quantum
entropy, water effects

Moore's law: hardware improving

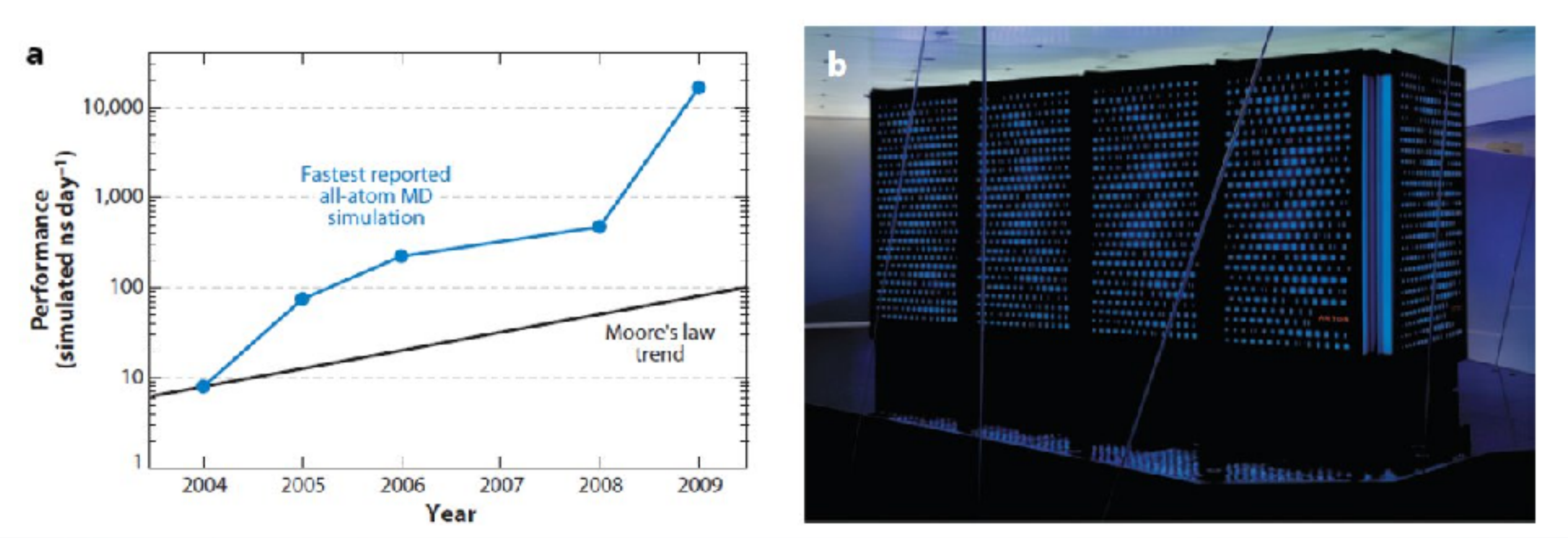


HOW COMPUTERS HAVE CHANGED

DATE	COST	SPEED	MEMORY	SIZE
1967	$60M	0.1 MHz	1 MB	HALL
2013	$6,000	1 GHz	10 GB	LAPTOP
CHANGE	10,000	10,000	10,000	10,000

If cars were like computers then a new Volvo would cost $3, would have a top speed of 1,000,000 Km/hr, would carry 50,000 adults and would park in a shoebox

SIDE-NOTE: GPUS AND ANTON SUPERCOMPUTER



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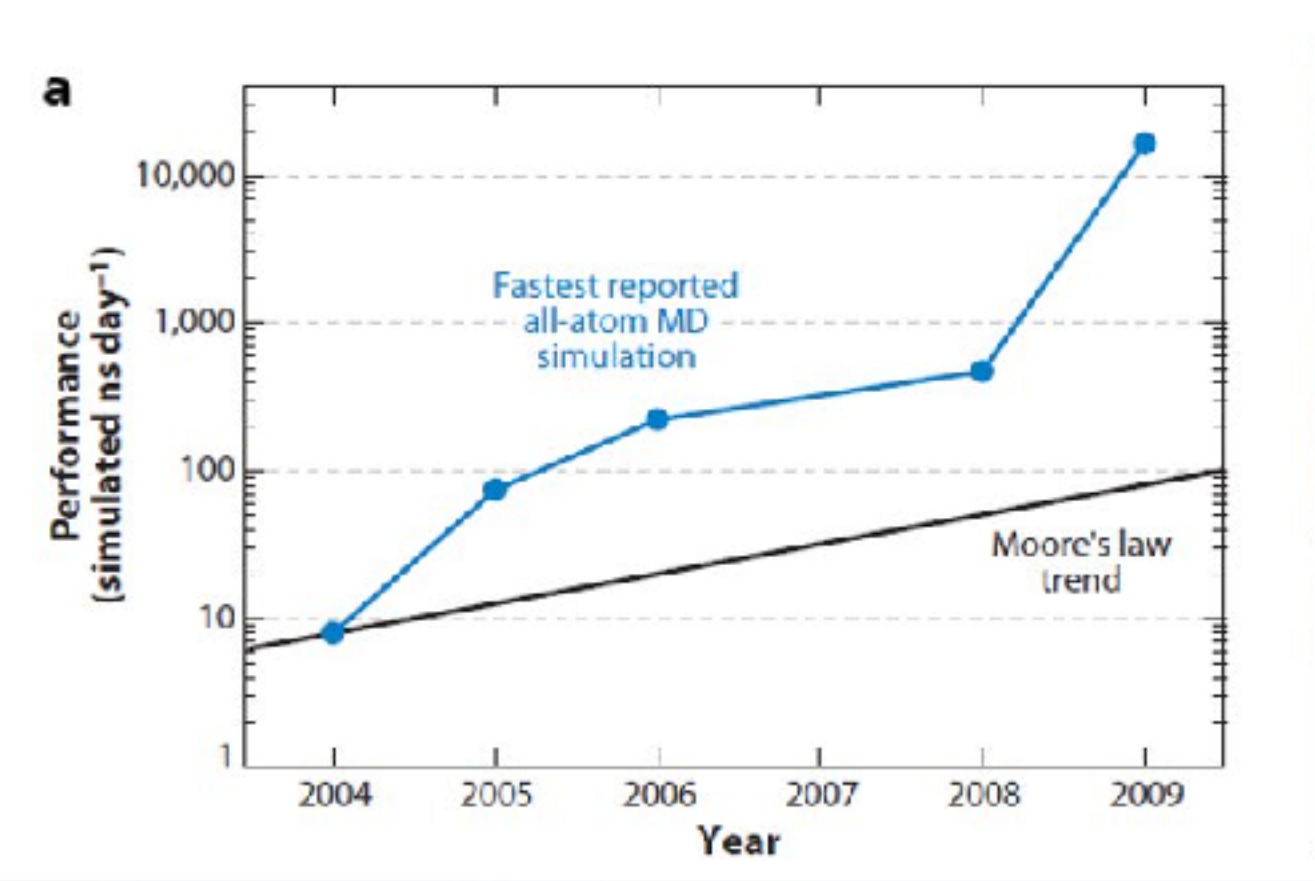

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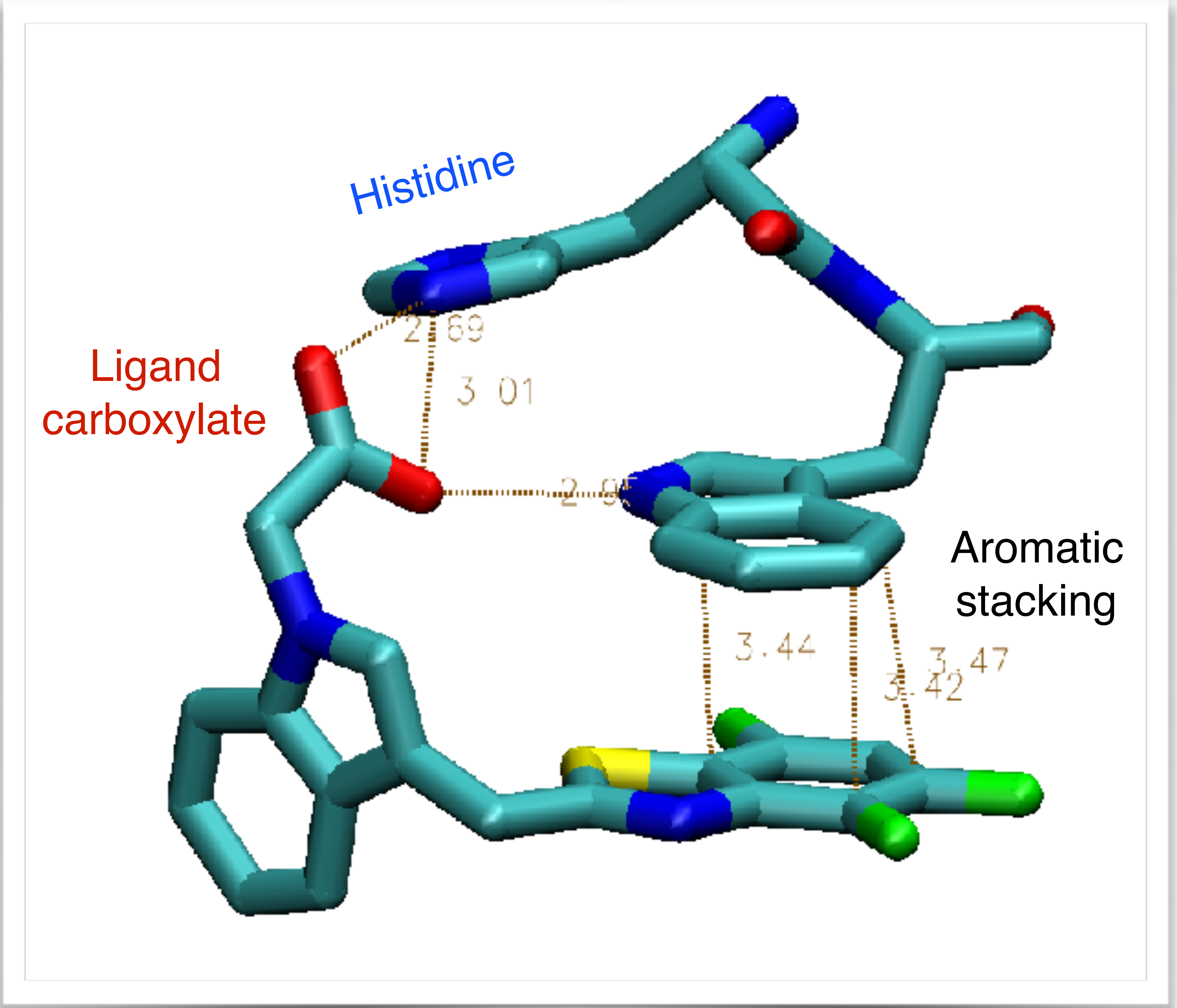
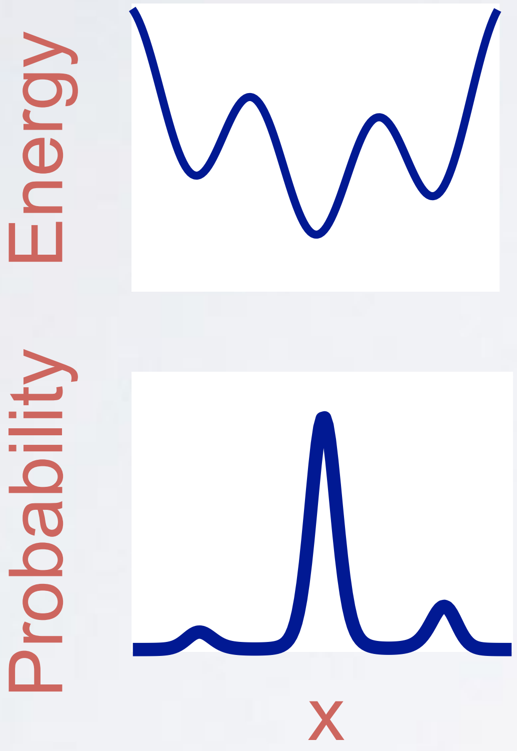
KNOWLEDGE-BASED DOCKING POTENTIALS



ENERGY DETERMINES **PROBABILITY** (STABILITY)

Basic idea: Use probability as a proxy for energy



Boltzmann:

$$p(r) \propto e^{-E(r)/RT}$$

Inverse Boltzmann:

$$E(r) = -RT\ln\left[p(r)\right]$$

Example: ligand carboxylate O to protein histidine N

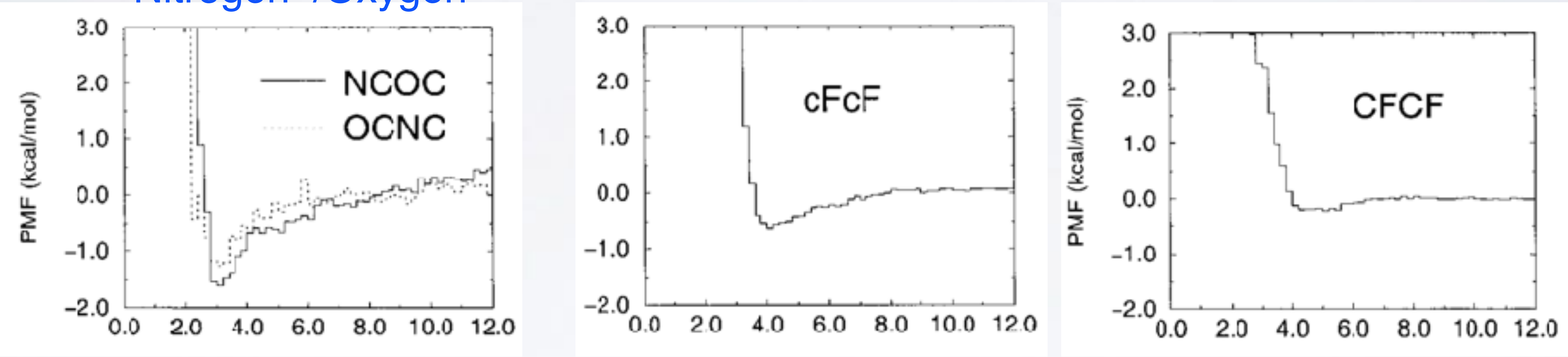
Find all protein-ligand structures in the PDB with a ligand carboxylate O

1. For each structure, histogram the distances from O to every histidine N
2. Sum the histograms over all structures to obtain $p(r_{O\text{-}N})$
3. Compute $E(r_{O\text{-}N})$ from $p(r_{O\text{-}N})$

KNOWLEDGE-BASED DOCKING POTENTIALS

"PMF", Muegge & Martin, J. Med. Chem. (1999) 42:791

A few types of atom pairs, out of several hundred total



Nitrogen$^+$/Oxygen$^-$

Aromatic carbons

Aliphatic carbons

Atom-atom distance (Angstroms)

$$E_{prot-lig} = E_{vdw} + \sum_{pairs\ (ij)} E_{type(ij)}(r_{ij})$$

KNOWLEDGE-BASED POTENTIALS

Weaknesses

Accuracy limited by availability of data

Strengths

Relatively easy to implement

Computationally fast

Status

Useful, far from perfect

May be at point of diminishing returns

(not always clear how to make improvements)

Do it Yourself!

Hand-on time!

https://bioboot.github.io/bimm143_S18/lectures/#11

Focus on **section 4** & **5**

NEXT UP:

- **Overview of structural bioinformatics**
  - Major motivations, goals and challenges
- **Fundamentals of protein structure**
  - Composition, form, forces and dynamics
- **Representing and interpreting protein structure**
  - Modeling energy as a function of structure
- **Example application areas**
  - Predicting functional dynamics & drug discovery

NMA models the protein as a network of elastic strings

Proteinase K

Do it Yourself!

Hand-on time!

https://bioboot.github.io/bimm143_S18/lectures/#11

Focus on **section 6** to **7**

Optional:
Stop here for Today!

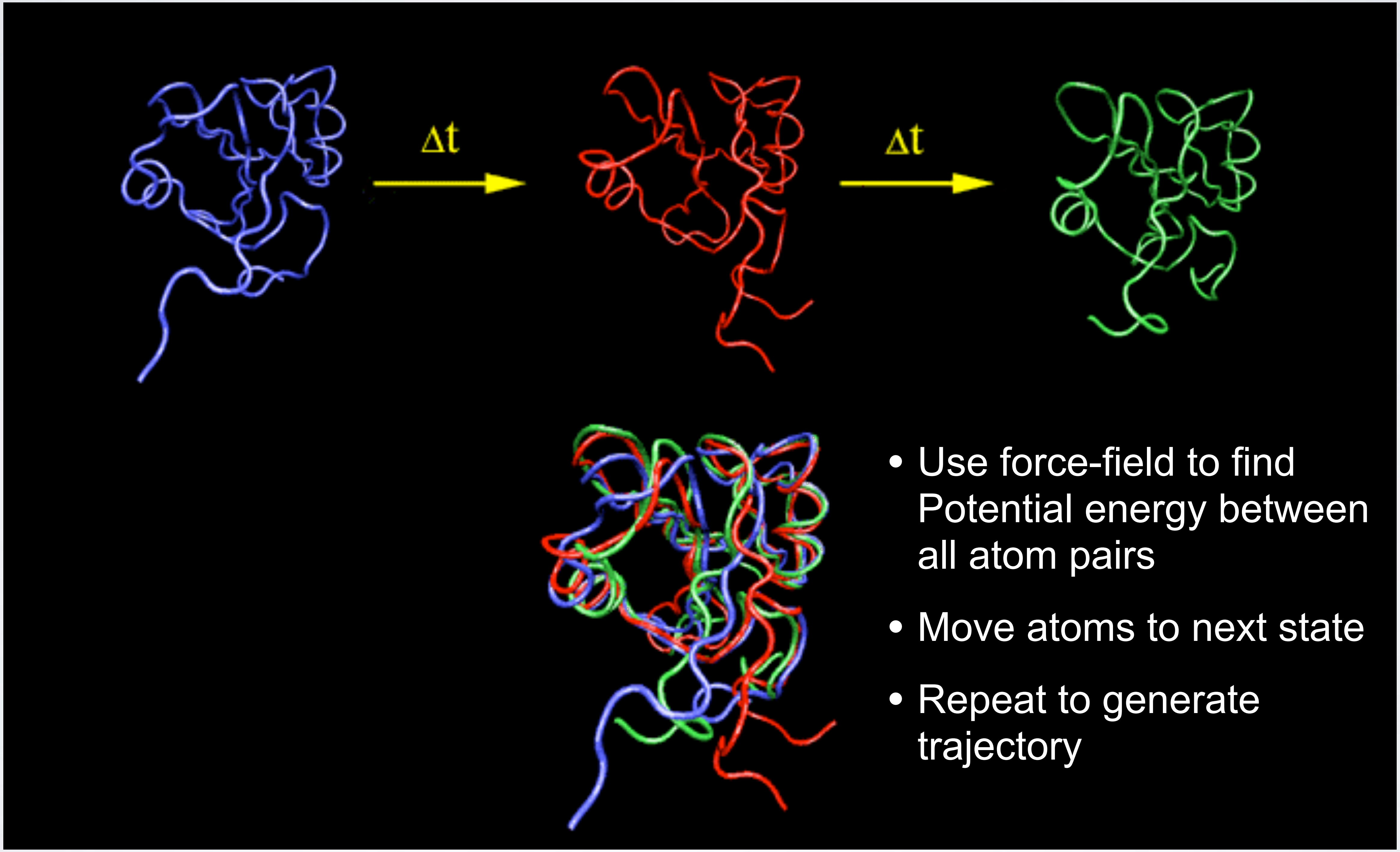
[Muddy Point Assessment]

PREDICTING FUNCTIONAL DYNAMICS

- **Proteins are <u>intrinsically flexible</u> molecules with internal motions that are often intimately coupled to their biochemical function**
  - E.g. ligand and substrate binding, conformational activation, allosteric regulation, etc.

- **Thus knowledge of dynamics can provide a deeper understanding of the <u>mapping of structure to function</u>**
  - **<u>Molecular dynamics</u>** (MD) and **<u>normal mode analysis</u>** (NMA) are two major methods for predicting and characterizing molecular motions and their properties

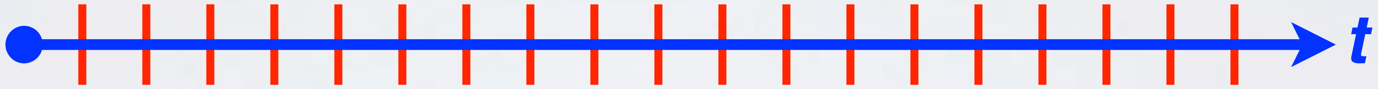
MOLECULAR DYNAMICS SIMULATION



- Use force-field to find Potential energy between all atom pairs
- Move atoms to next state
- Repeat to generate trajectory

McCammon, Gelin & Karplus, *Nature* (1977)
[See: https://www.youtube.com/watch?v=ui1ZysMFcKk]

- Divide **time** into discrete (~1fs) **time steps** (**Δt**) (for integrating equations of motion, see below)



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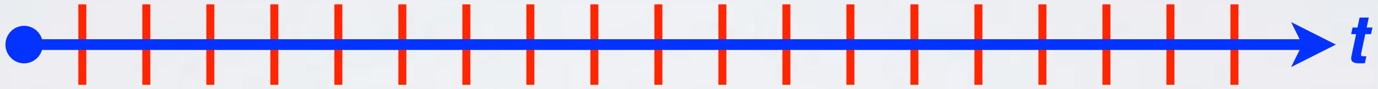
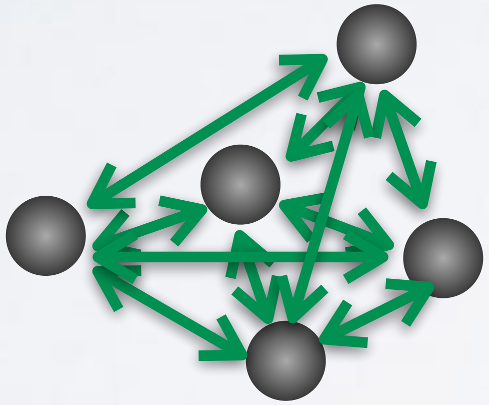


- At each time step calculate pair-wise atomic **forces** (***F(t)***)
(by evaluating **force-field** gradient)



Nucleic motion described classically

$$m_i \frac{d^2}{dt^2}\vec{R}_i = -\vec{\nabla}_i E(\vec{R})$$

Empirical force field

$$E(\vec{R}) = \sum_{\mathrm{bonded}} E_i(\vec{R}) + \sum_{\mathrm{non-bonded}} E_i(\vec{R})$$

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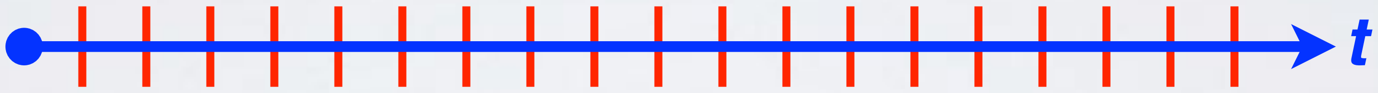

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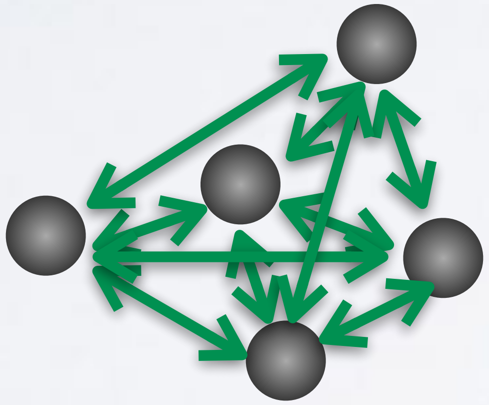

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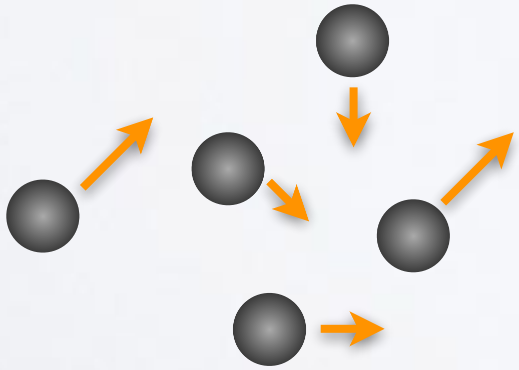
Empirical force field

$$E(\vec{R}) = \sum_{\text{bonded}} E_i(\vec{R}) + \sum_{\text{non-bonded}} E_i(\vec{R})$$

- Use the forces to calculate **velocities** and move atoms to new **positions**
(by integrating numerically via the “leapfrog” scheme)

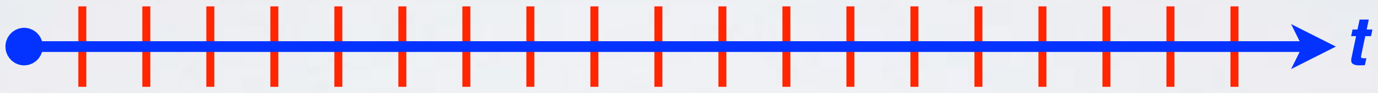


$$\boxed{\boldsymbol{v}(t+\frac{\Delta t}{2})} = \boldsymbol{v}(t-\frac{\Delta t}{2}) + \frac{\boldsymbol{F}(t)}{m}\Delta t$$

$$\boldsymbol{r}(t+\Delta t) = \boldsymbol{r}(t) + \boxed{\boldsymbol{v}(t+\frac{\Delta t}{2})}\Delta t$$

BASIC ANATOMY OF A MD SIMULATION

- Divide **time** into discrete (~1fs) **time steps** (**Δt**)
  (for integrating equations of motion, see below)



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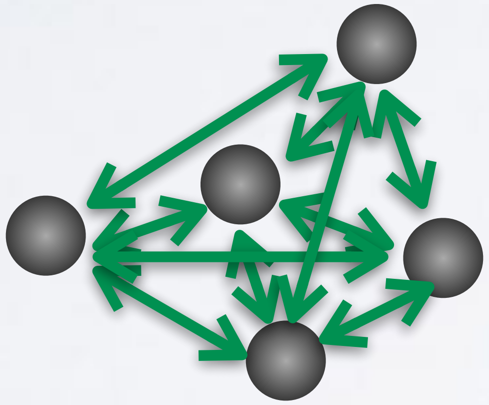
  (by evaluating **force-field** gradient)



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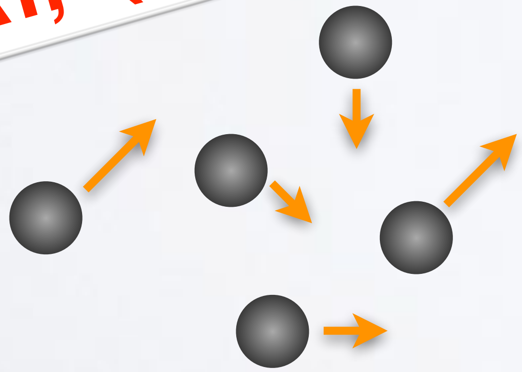
Empirical force fi

$E(\vec{R}) = \sum$ … $E_i(\vec{R})$

non−bonded

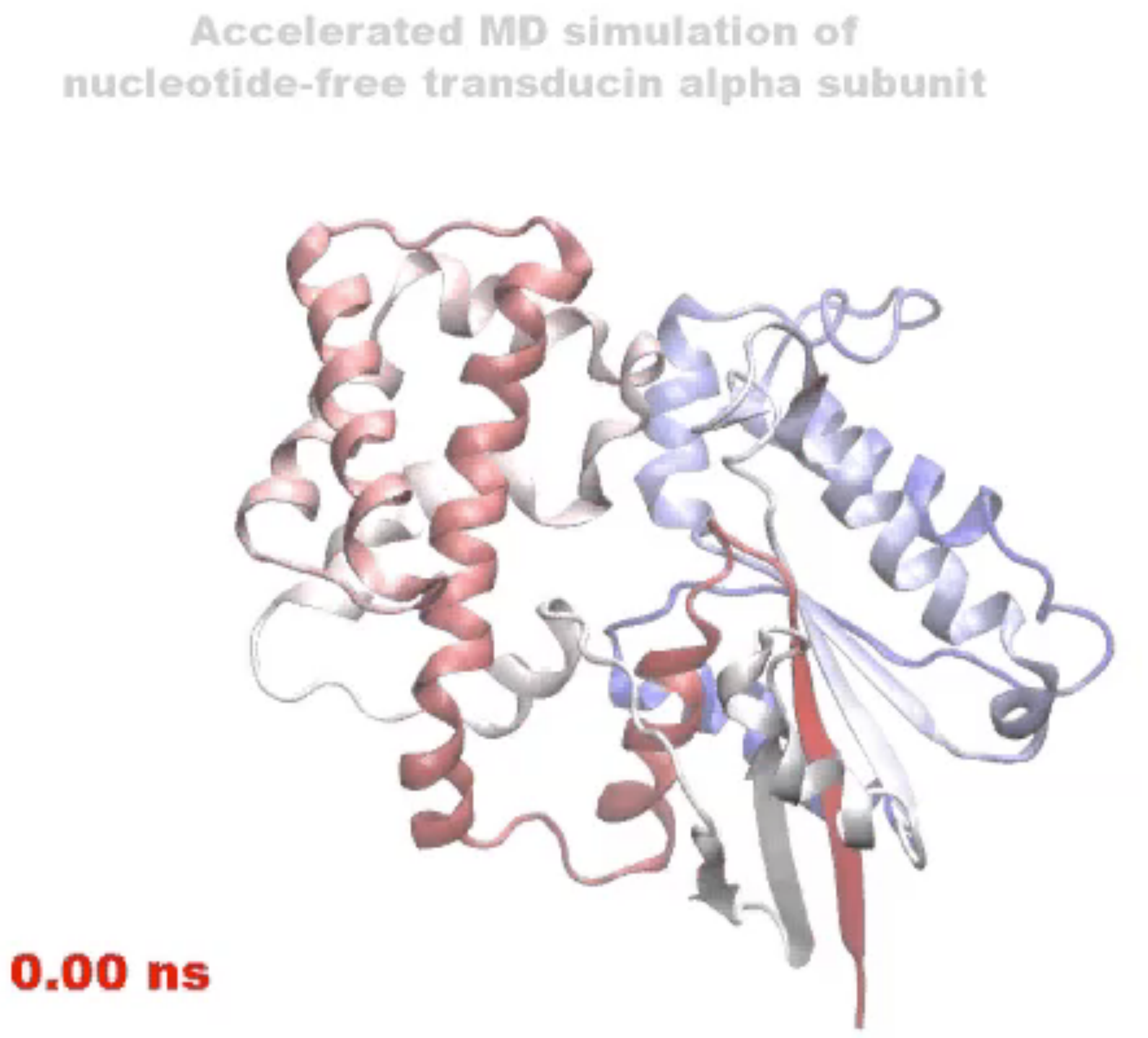
- Use the fo… …ate **velocities** and move atoms to new **positions**
  (b… …g numerically via the “leapfrog” scheme)

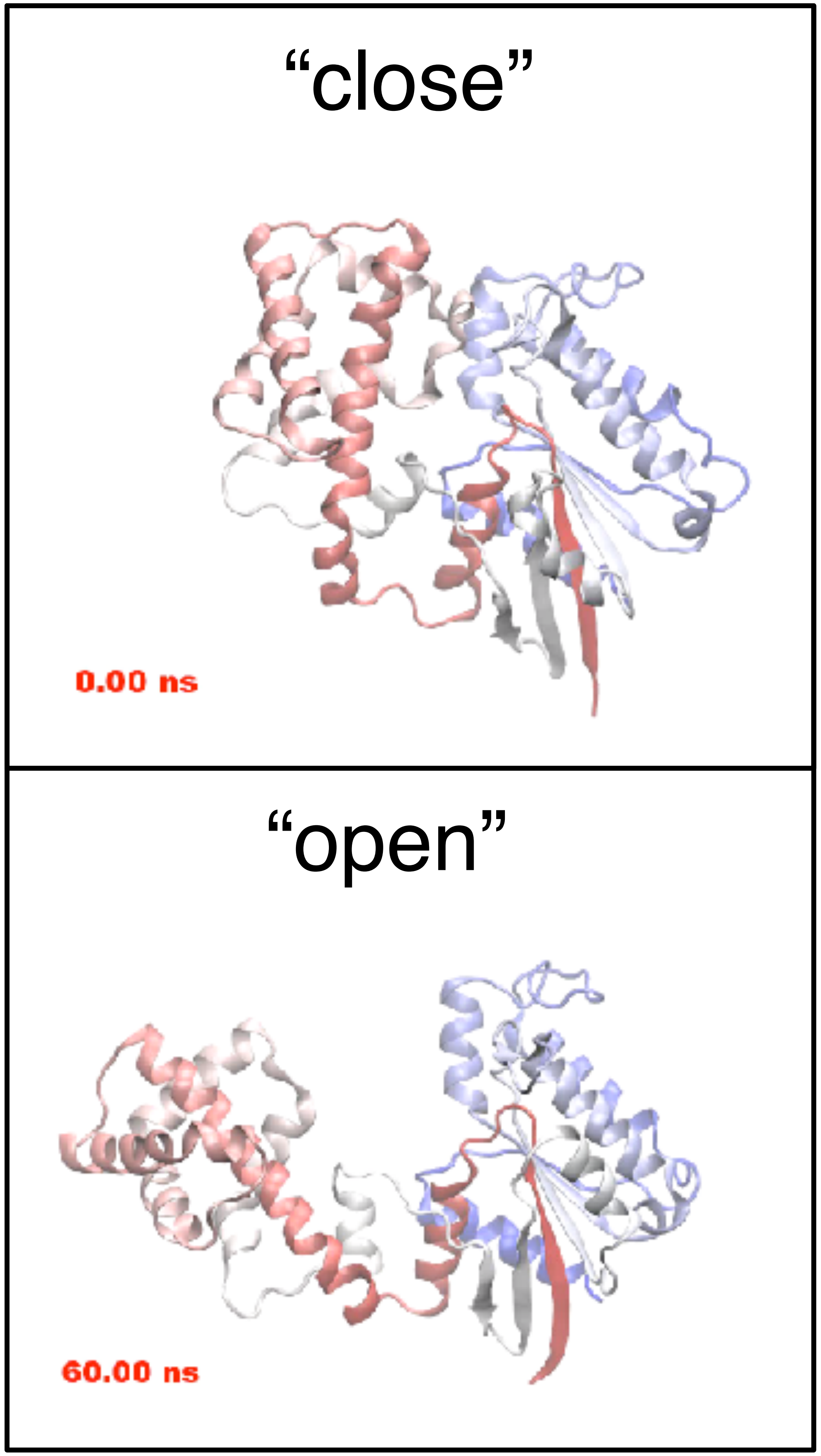


$$\begin{aligned} v(t + \frac{\Delta t}{2}) &= v(t - \frac{\Delta t}{2}) + \frac{F(t)}{m}\Delta t \\ r(t + \Delta t) &= r(t) + v(t + \frac{\Delta t}{2})\Delta t \end{aligned}$$

- **REPEAT, (iterate many, many times… 1ms = 10^{12} time steps)**

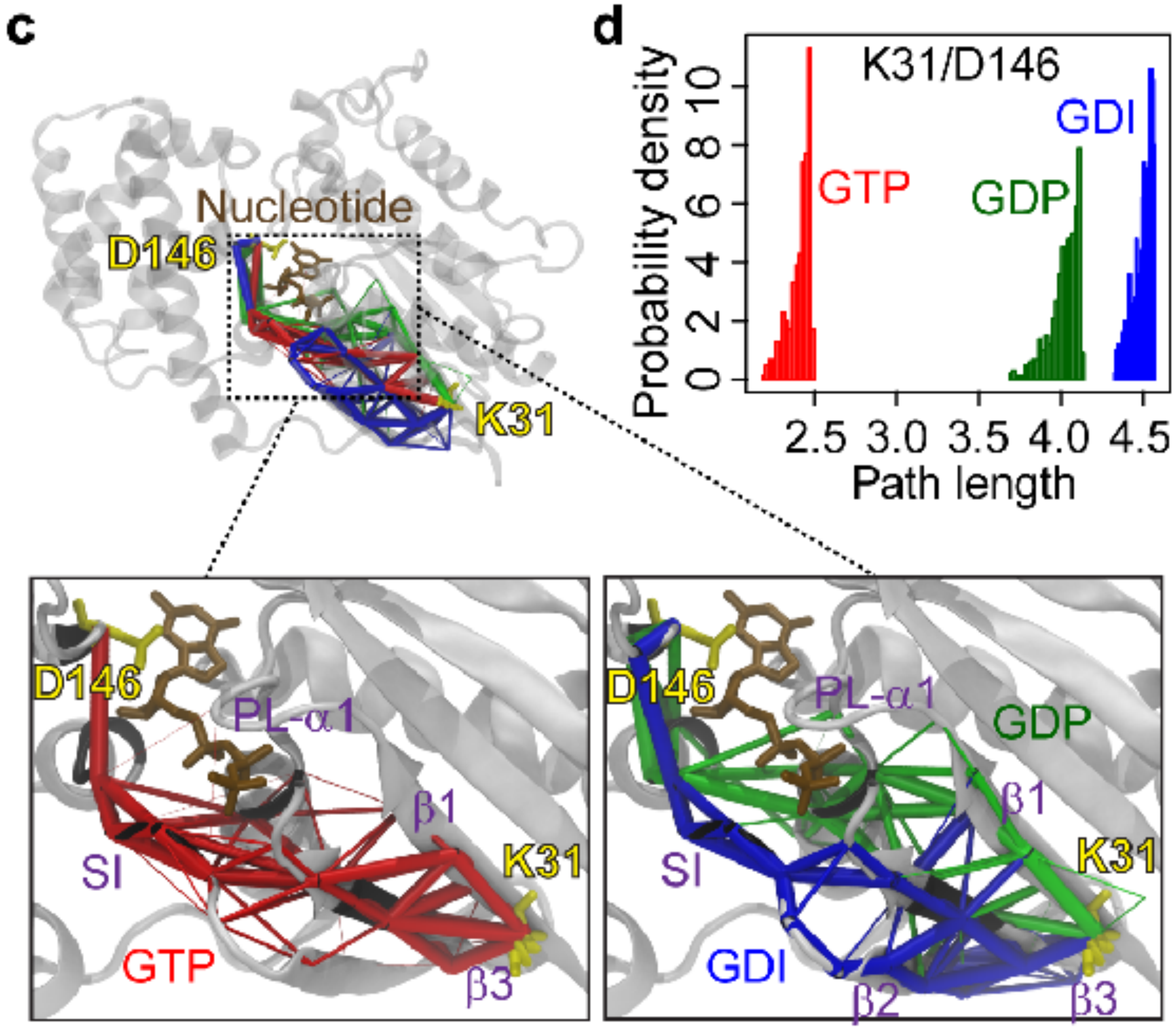
MD Prediction of Functional Motions


Accelerated MD simulation of
nucleotide-free transducin alpha subunit
0.00 ns



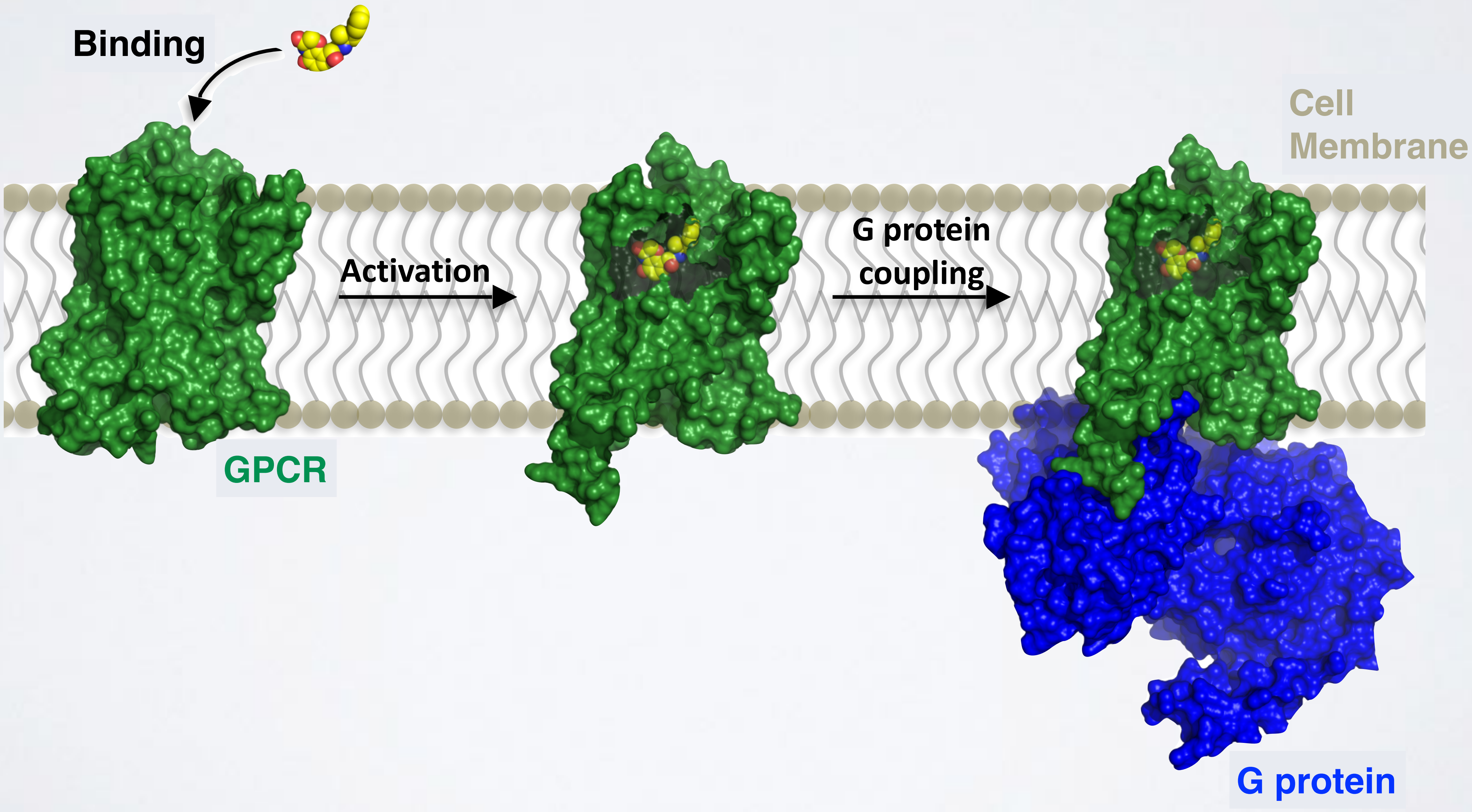
Yao and Grant, Biophys J. (2013)

Simulations Identify Key Residues Mediating Dynamic Activation

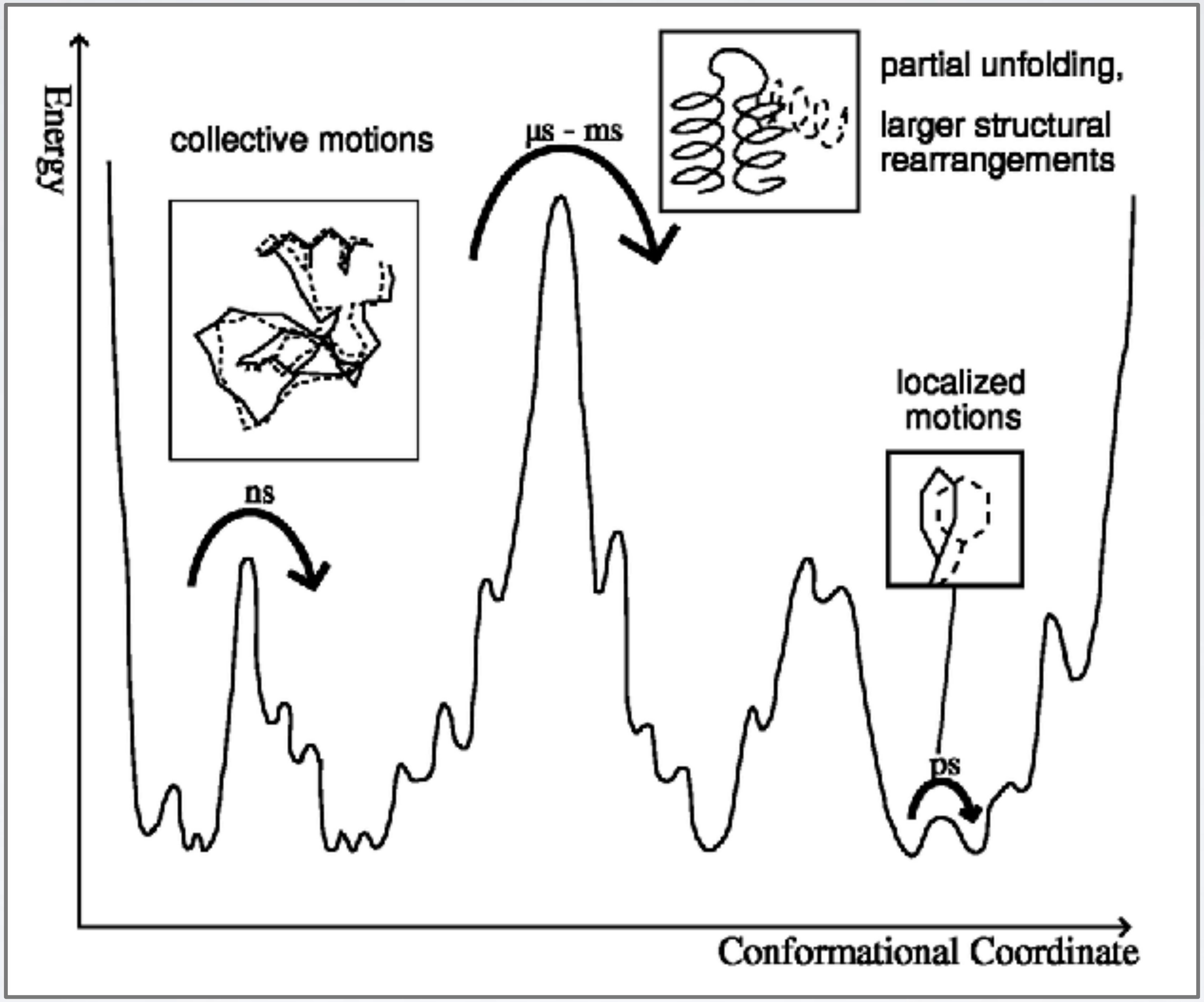


Yao … Grant, Journal of Biological Chemistry (2016)

EXAMPLE APPLICATION OF MOLECULAR SIMULATIONS TO GPCRS



PROTEINS JUMP BETWEEN MANY, HIERARCHICALLY ORDERED “CONFORMATIONAL SUBSTATES”



H. Frauenfelder et al., *Science* **229** (1985) 337

Improve this slide

MOLECULAR DYNAMICS IS VERY

Example: F_1-ATPase in water (183,674 atoms) for 1 nanosecond:

=> 10^6 integration steps
=> $8.4 * 10^{11}$ floating point operations/step
[n(n-1)/2 interactions]

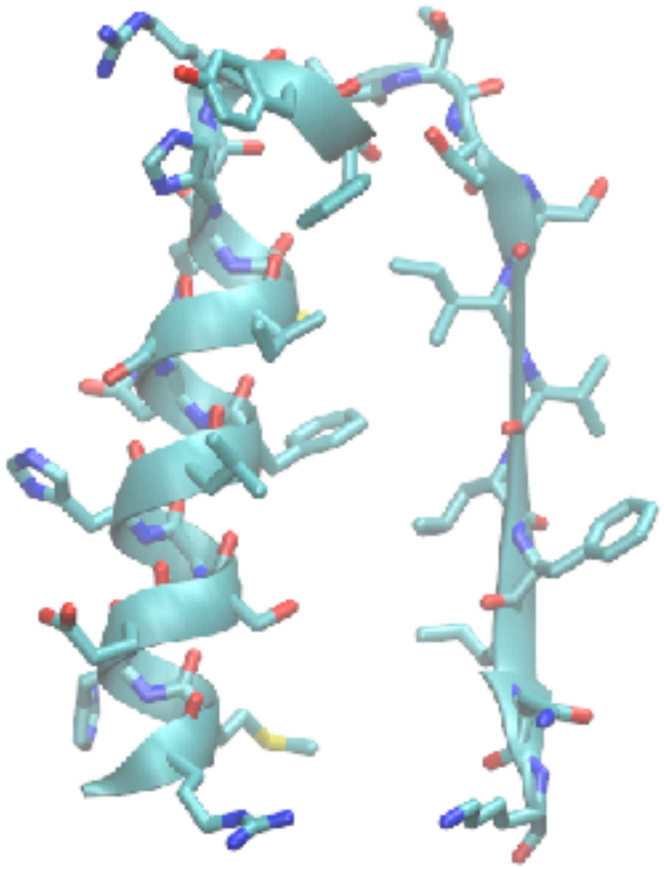
Total: $8.4 * 10^{17}$ flop
(on a 100 Gflop/s cpu: **ca 25 years!**)

… but performance has been improved by use of:

multiple time stepping	ca. 2.5 years
fast multipole methods	ca. 1 year
parallel computers	ca. 5 days
modern GPUs	**ca. 1 day**
(Anton supercomputer	**ca. minutes)**

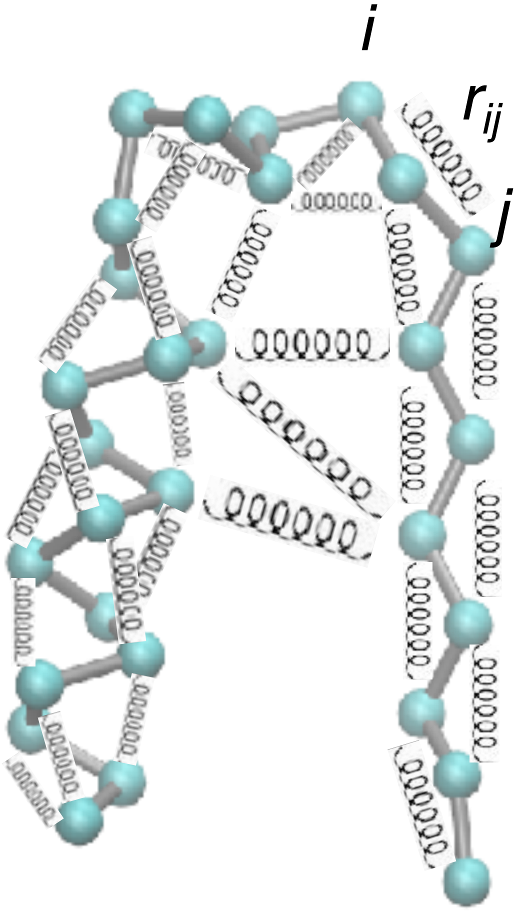
COARSE GRAINING: **NORMAL MODE ANALYSIS** (NMA)

- MD is still time-consuming for large systems
- Elastic network model NMA (ENM-NMA) is an example of a lower resolution approach that finishes in seconds even for large systems.



Atomistic

C. G.



Coarse Grained

- 1 bead / 1 amino acid
- Connected by springs

NMA models the protein as a network of elastic strings

Proteinase K

Do it Yourself!

Hand-on time!

https://bioboot.github.io/bimm143_S18/lectures/#11

Focus on **section 6** to **7**

SUMMARY

- Structural bioinformatics is computer aided structural biology
- Described major motivations, goals and challenges of structural bioinformatics
- Reviewed the fundamentals of protein structure
- Introduced both physics and knowledge based modeling approaches for describing the structure, energetics and dynamics of proteins computationally