BGGN 213

Structural Bioinformatics

Lecture 11

Barry Grant

UC San Diego

http://thegrantlab.org/bggn213

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

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Bioinformatics is computer aided biology!

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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

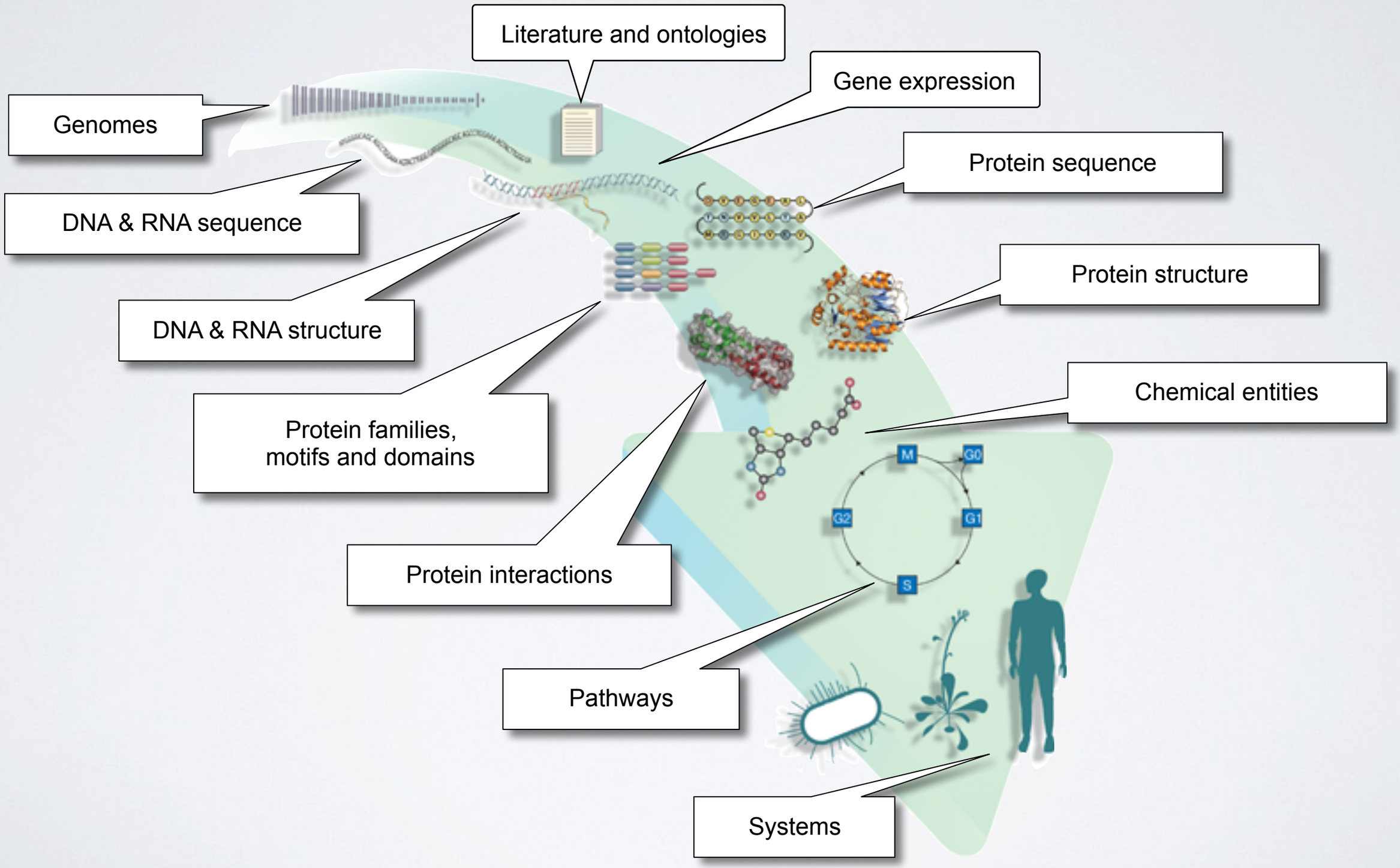
Why should we care?

Why should we care?

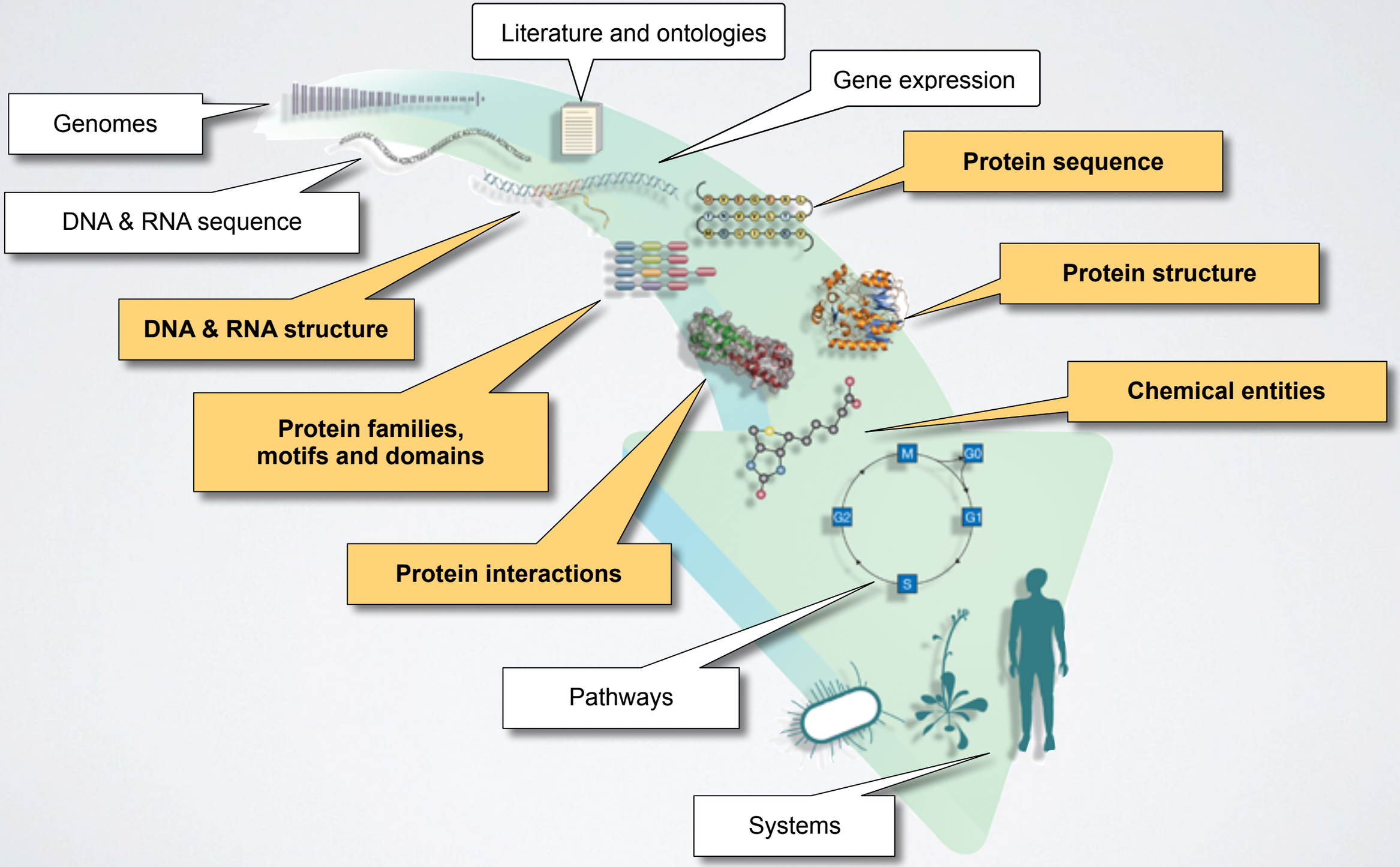
Because biomolecules are “nature’s robots”

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

BIOINFORMATICS DATA



STRUCTURAL DATA IS CENTRAL



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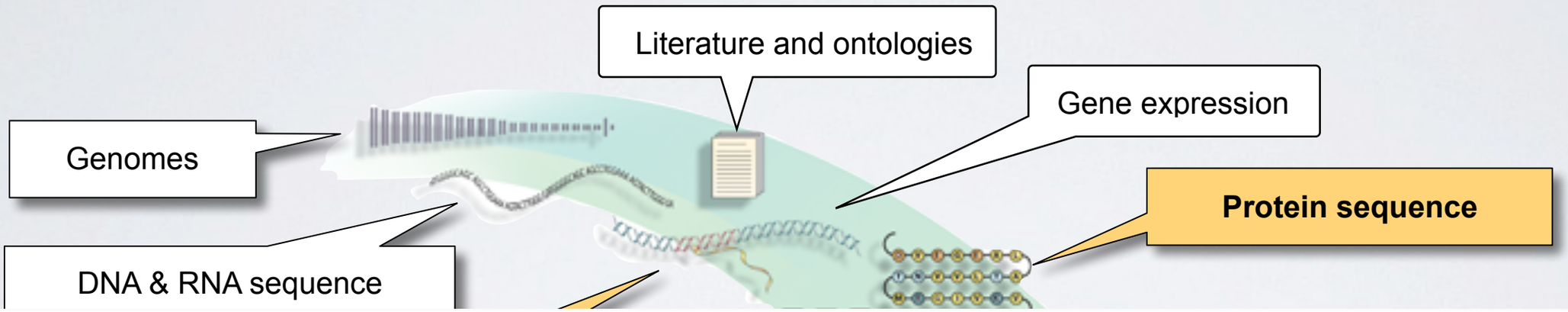
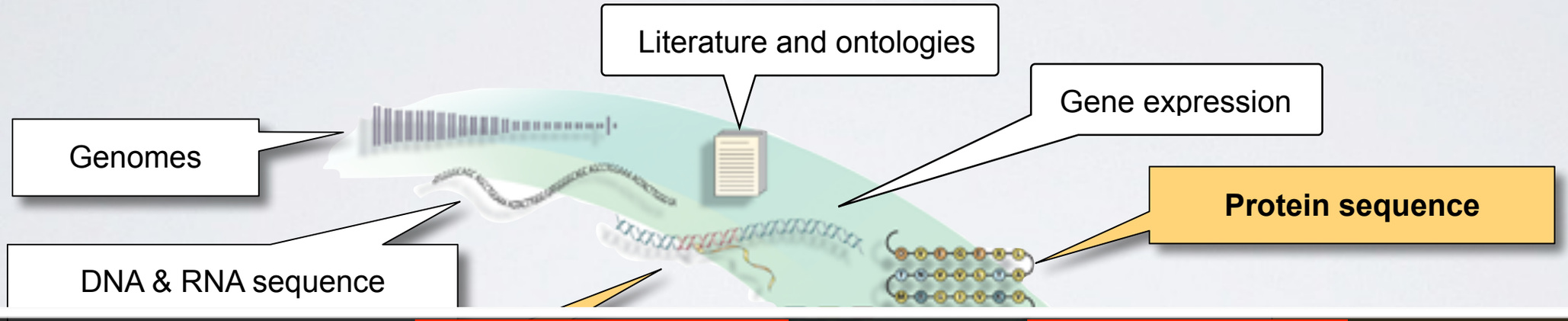
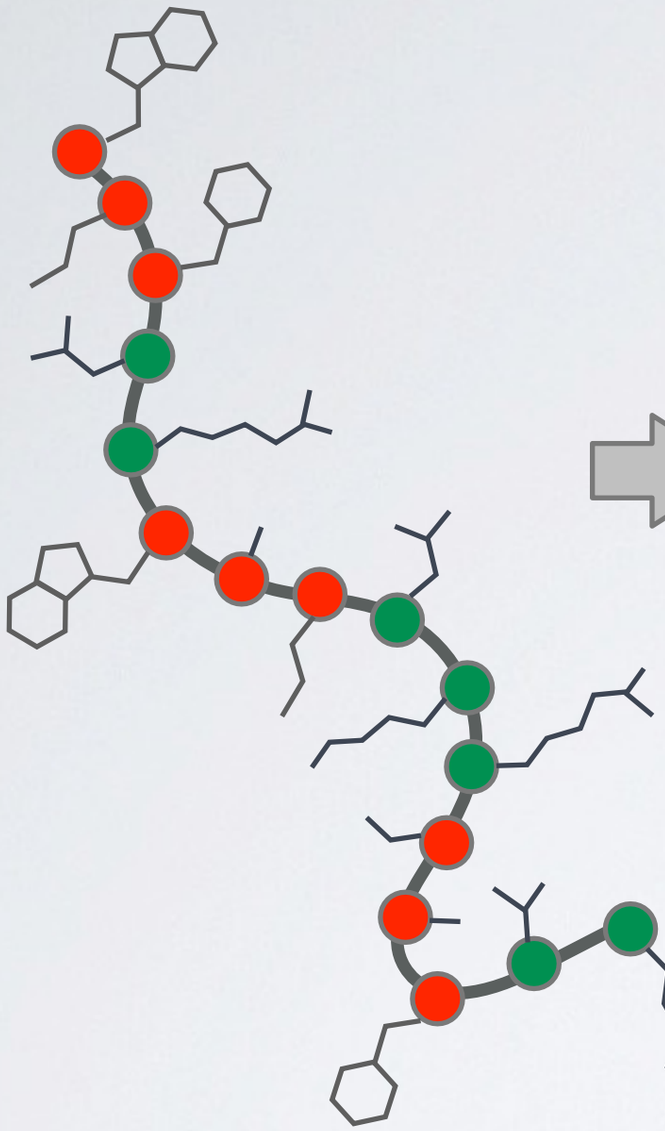
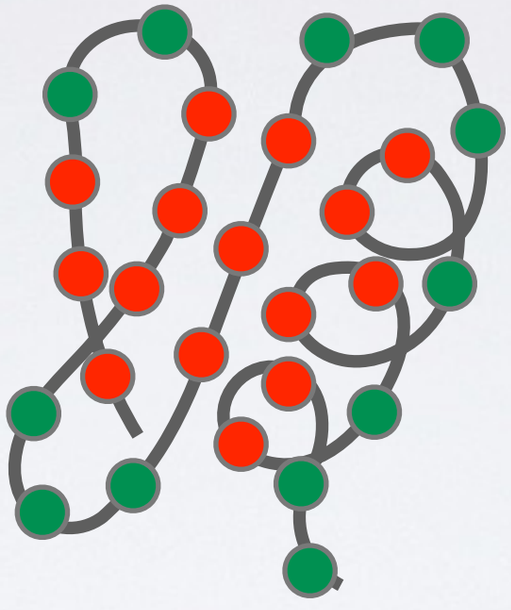


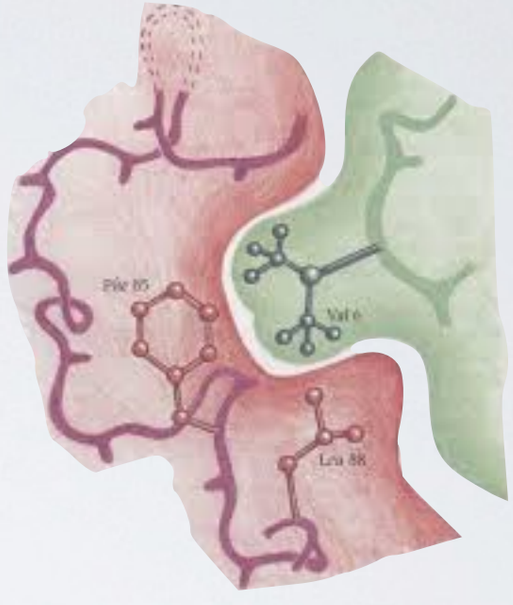
Sequence > Structure > Function

STRUCTURAL DATA IS CENTRAL









Sequence	Structure	Function
• Unfolded chain of amino acid chain • Highly mobile • Inactive	• Ordered in a precise 3D arrangment • Stable but dynamic	• Active in specific “conformations” • Specific associations & precise reactions

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

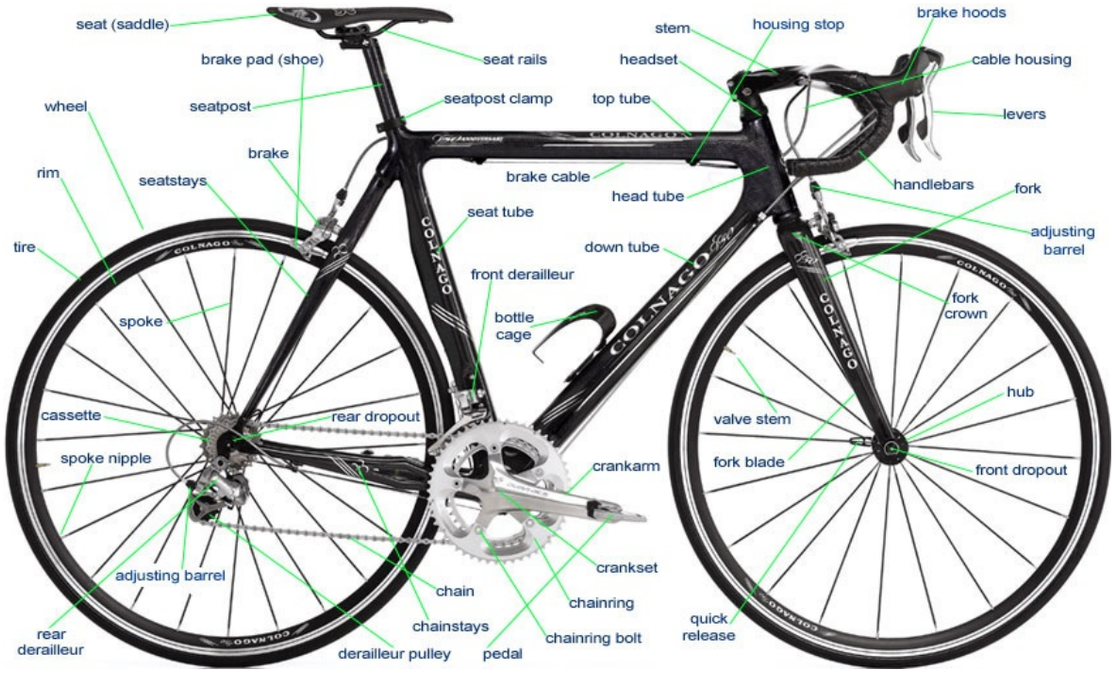
Genomics is a great start ….

Track Bike – DL 175

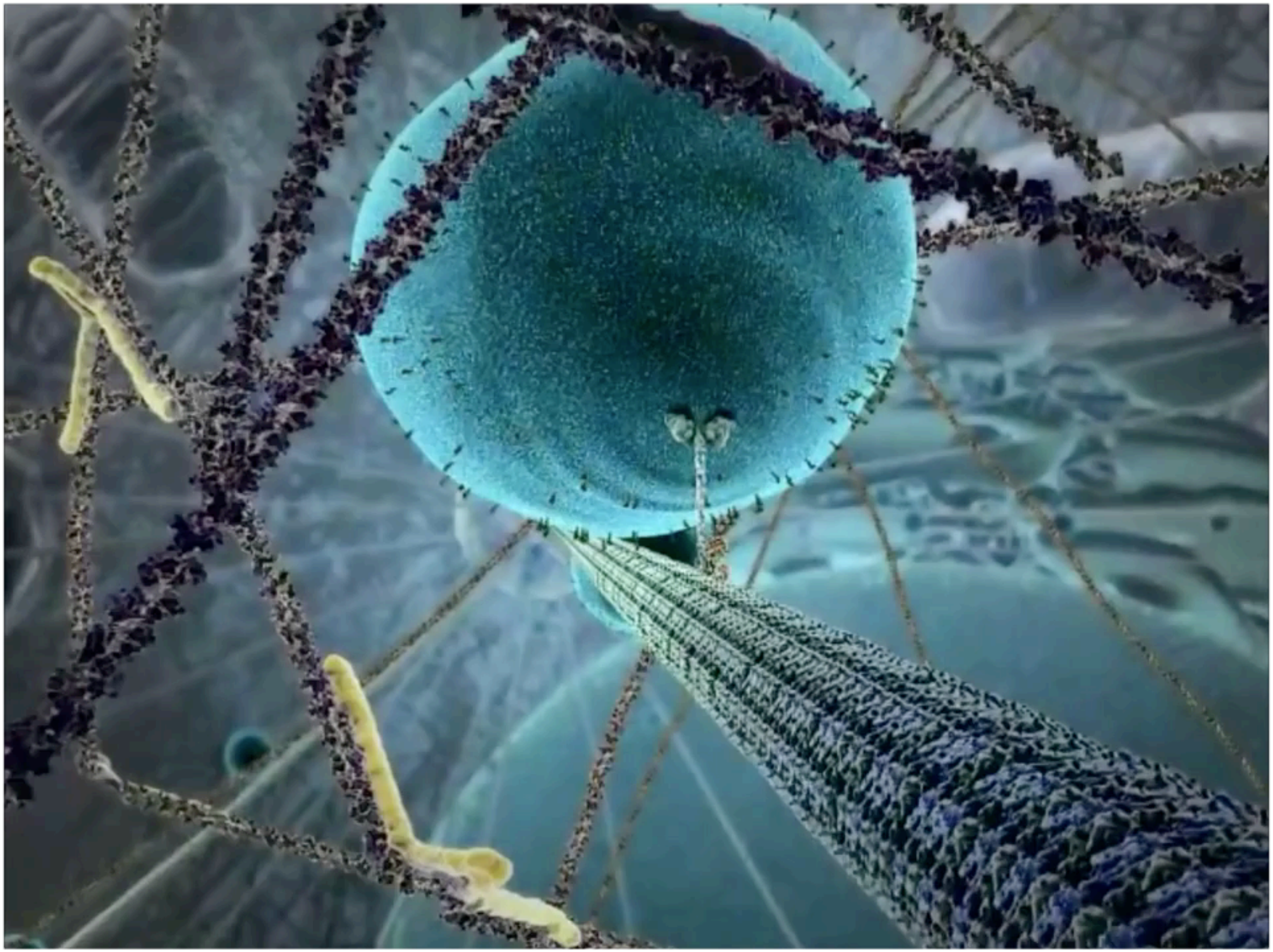
REF. NO.	IBM NO.	DESCRIPTION
1	156011	Track Frame 21", 22", 23", 24", Team Red
2	157040	Fork for 21" Frame
2	157039	Fork for 22" Frame
2	157038	Fork for 23" Frame
2	157037	Fork for 24" Frame
3	191202	Handlebar TTT Competition Track Alloy 15/16"
4		Handlebar Stem, TTT, Specify extension
5	191278	Expander 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

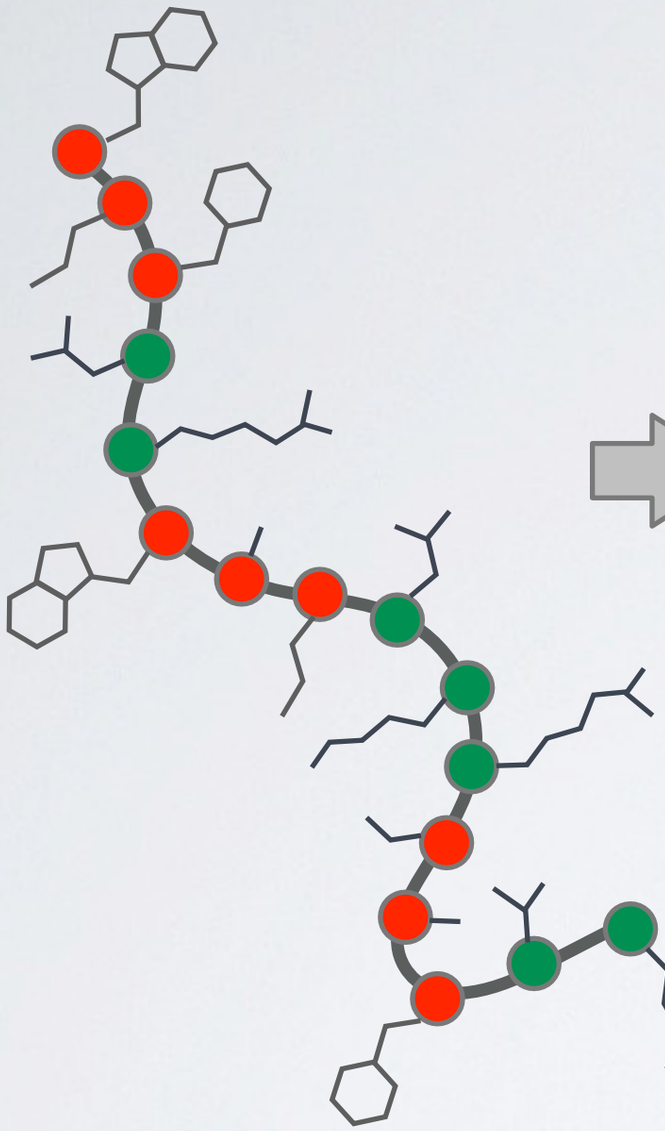
… but not the end

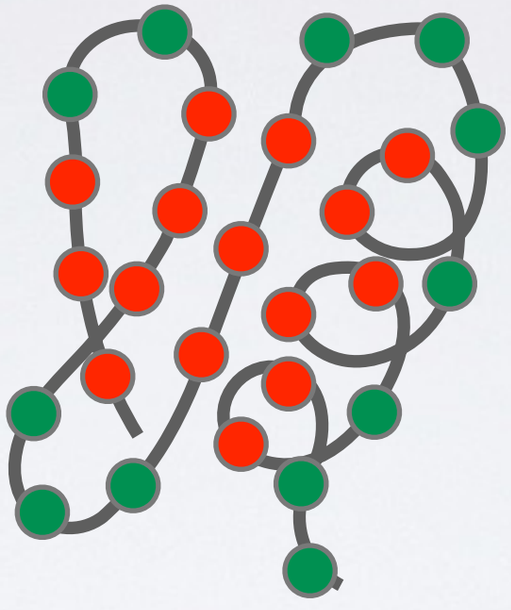


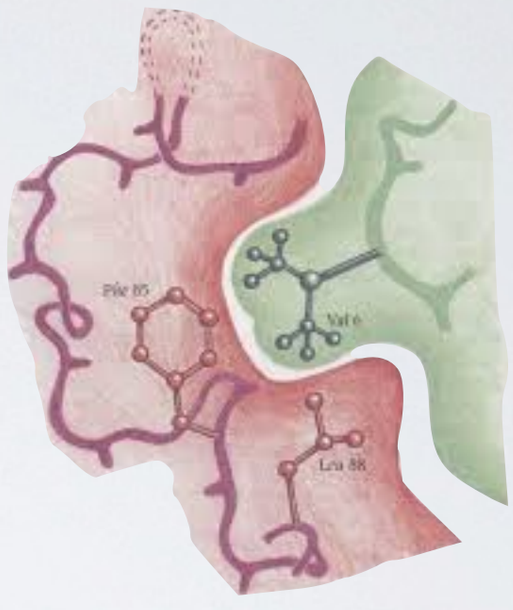
- We want the full spatiotemporal picture, and an ability to control it
- Broad applications, including drug design, medical diagnostics, chemical manufacturing, and energy



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

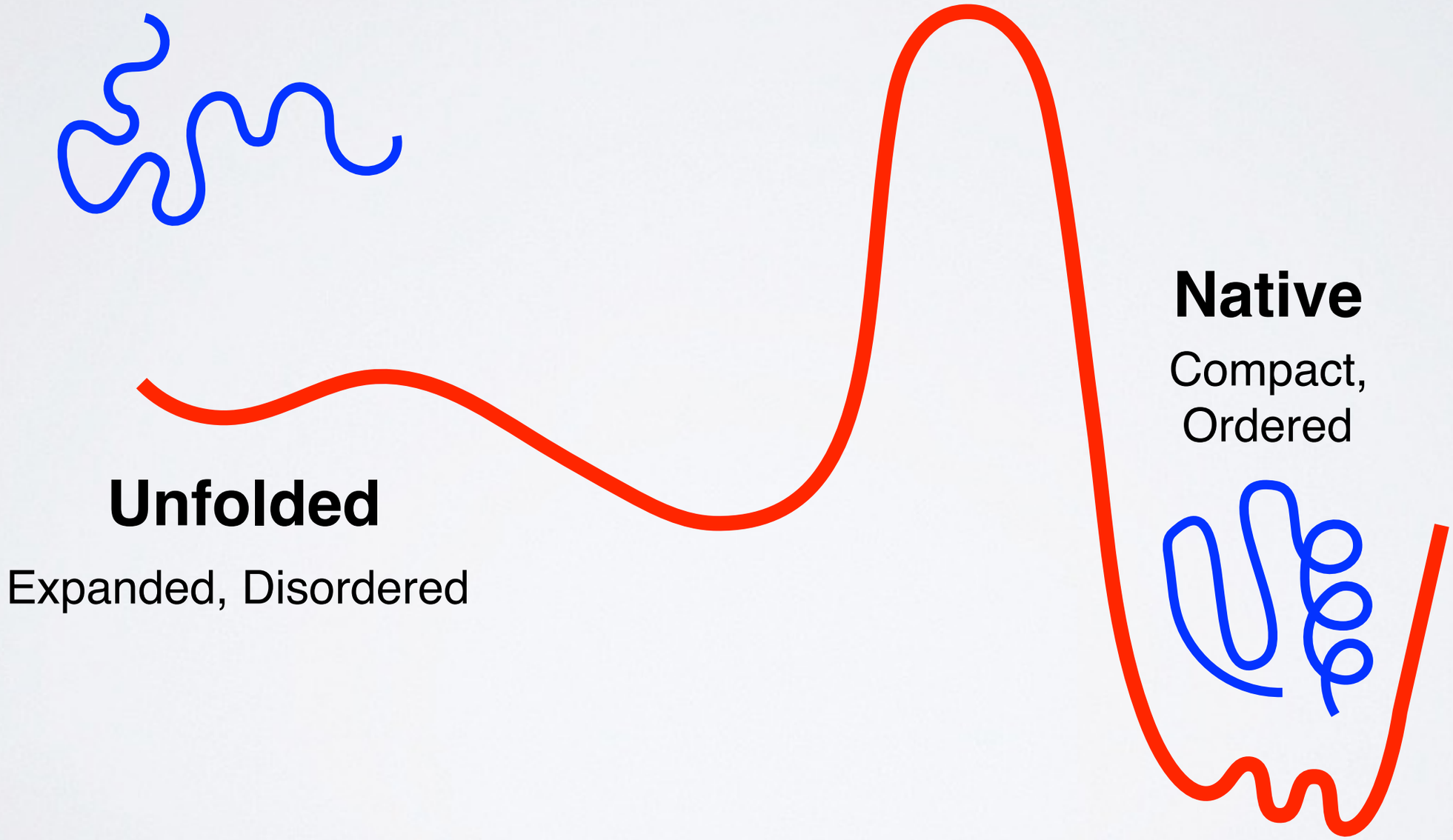






Sequence	Structure	Function
• Unfolded chain of amino acid chain • Highly mobile • Inactive	• Ordered in a precise 3D arrangment • Stable but dynamic	• Active in specific "conformations" • Specific associations & precise reactions

KEY CONCEPT: ENERGY LANDSCAPE



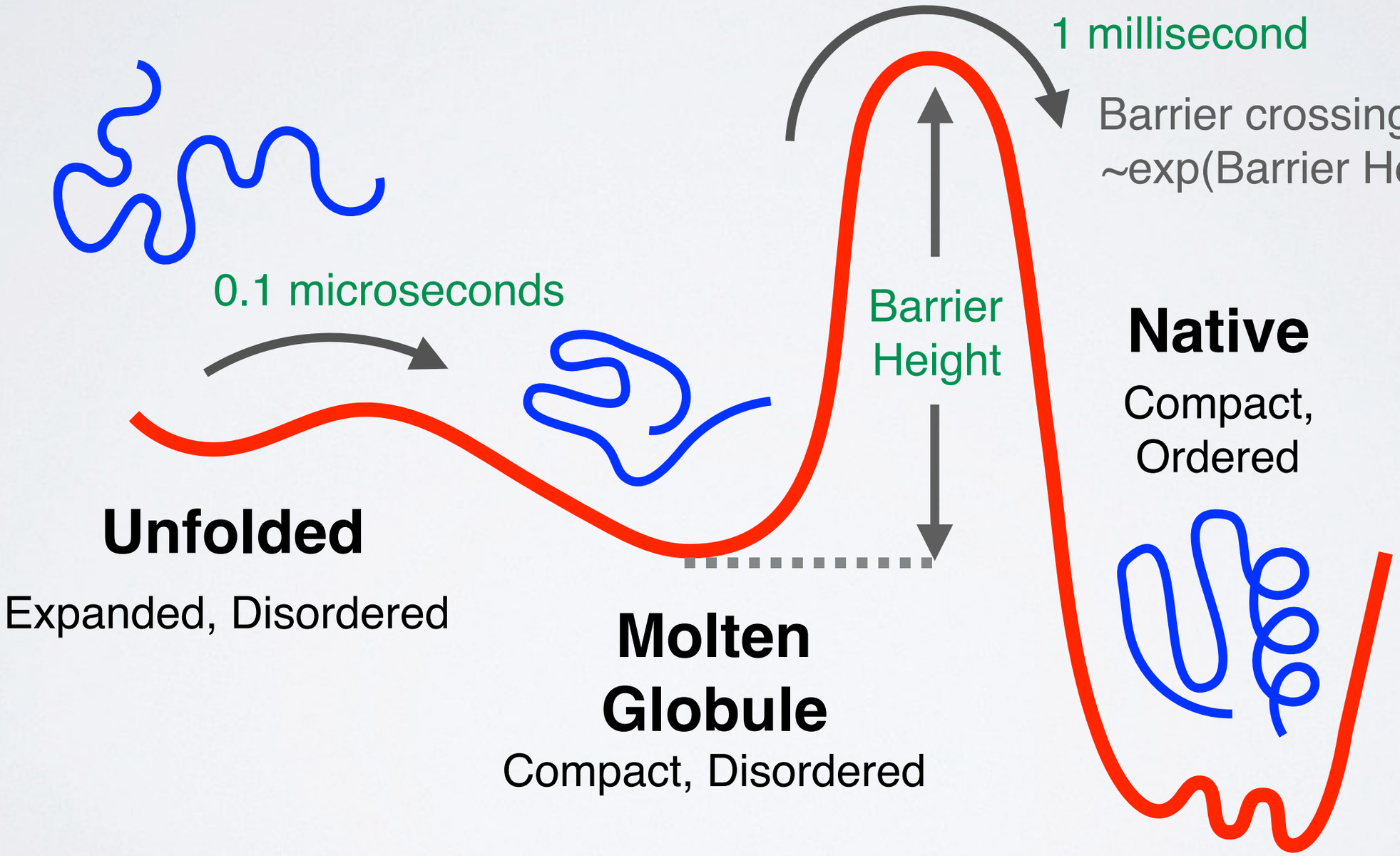
Unfolded

Expanded, Disordered

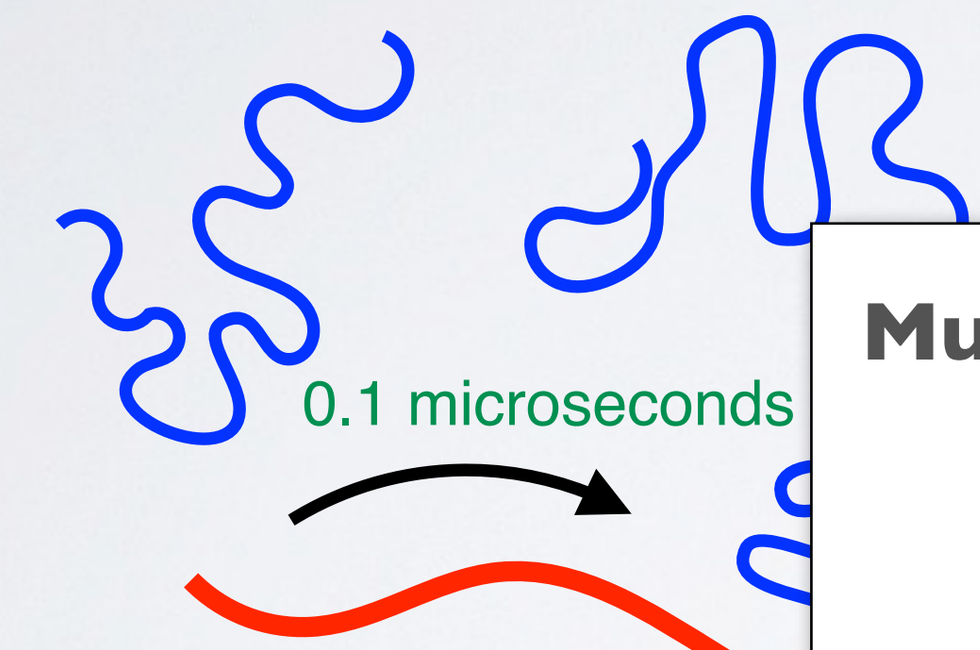
Native

Compact,
Ordered

KEY CONCEPT: ENERGY LANDSCAPE



KEY CONCEPT: **ENERGY LANDSCAPE**



0.1 microseconds

1 millisecond

Barrier crossing time

Unfolded State

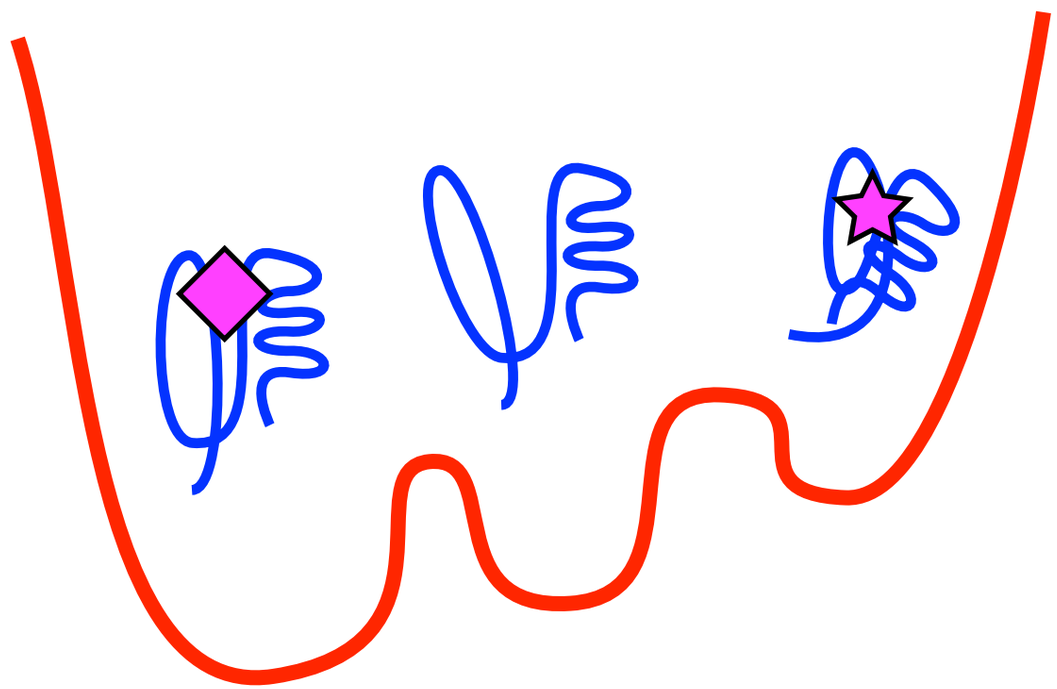
Expanded, Disordered

Mo

Cor

Multiple Native Conformations

(e.g. ligand bound and unbound)



Today's Menu

- **Overview of structural bioinformatics**
  - Motivations, goals and challenges

- **Fundamentals of protein structure**
  - Structure composition, form and forces

- **Representing, interpreting & modeling protein structure**
  - Visualizing & interpreting protein structures
  - Analyzing protein structures
  - Modeling energy as a function of structure

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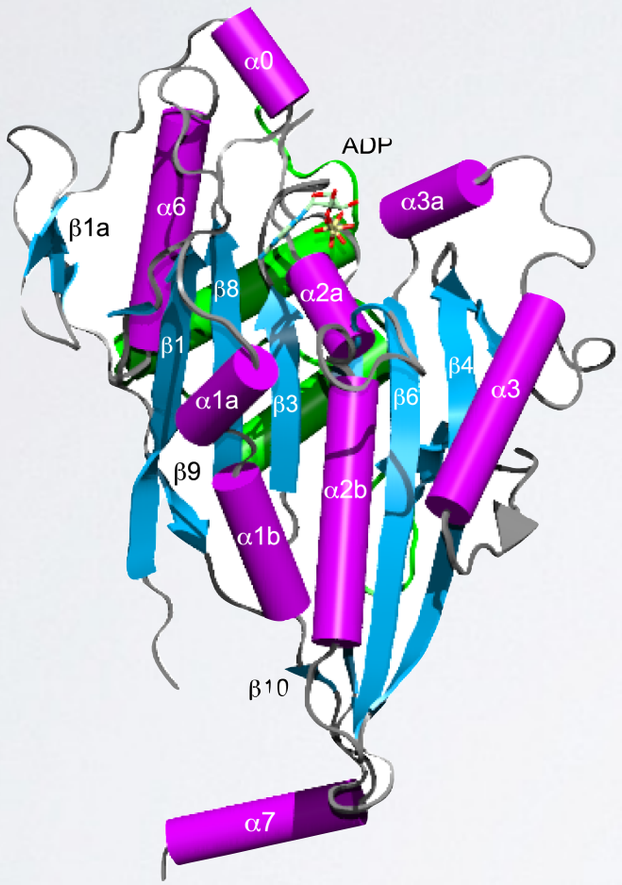
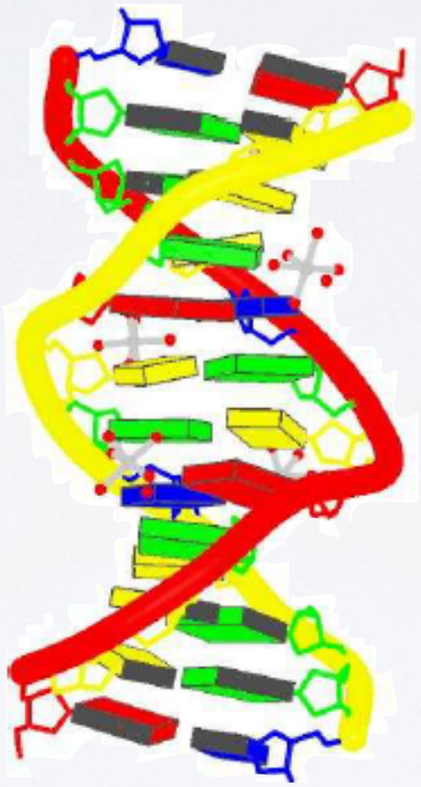
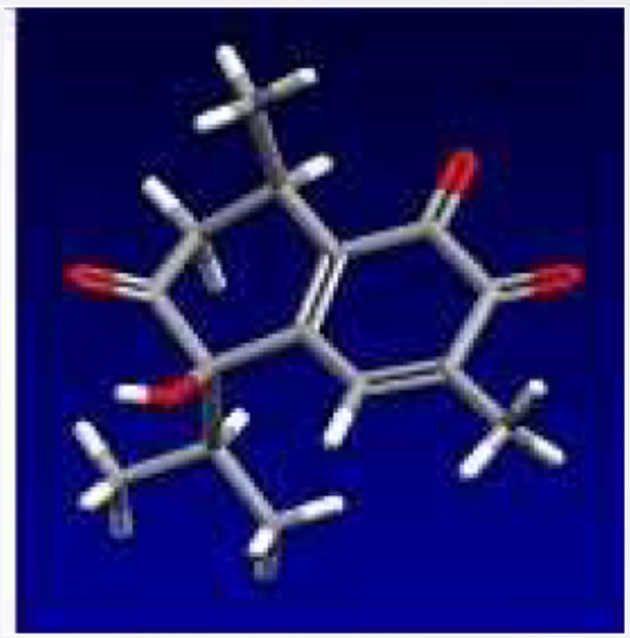
TRADITIONAL FOCUS **PROTEIN**, **DNA** AND **SMALL MOLECULE** DATA SETS WITH **MOLECULAR STRUCTURE**



Protein
(PDB)

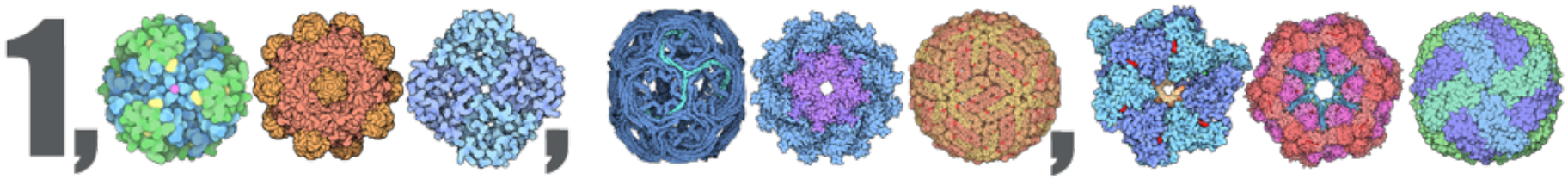


DNA
(NDB)

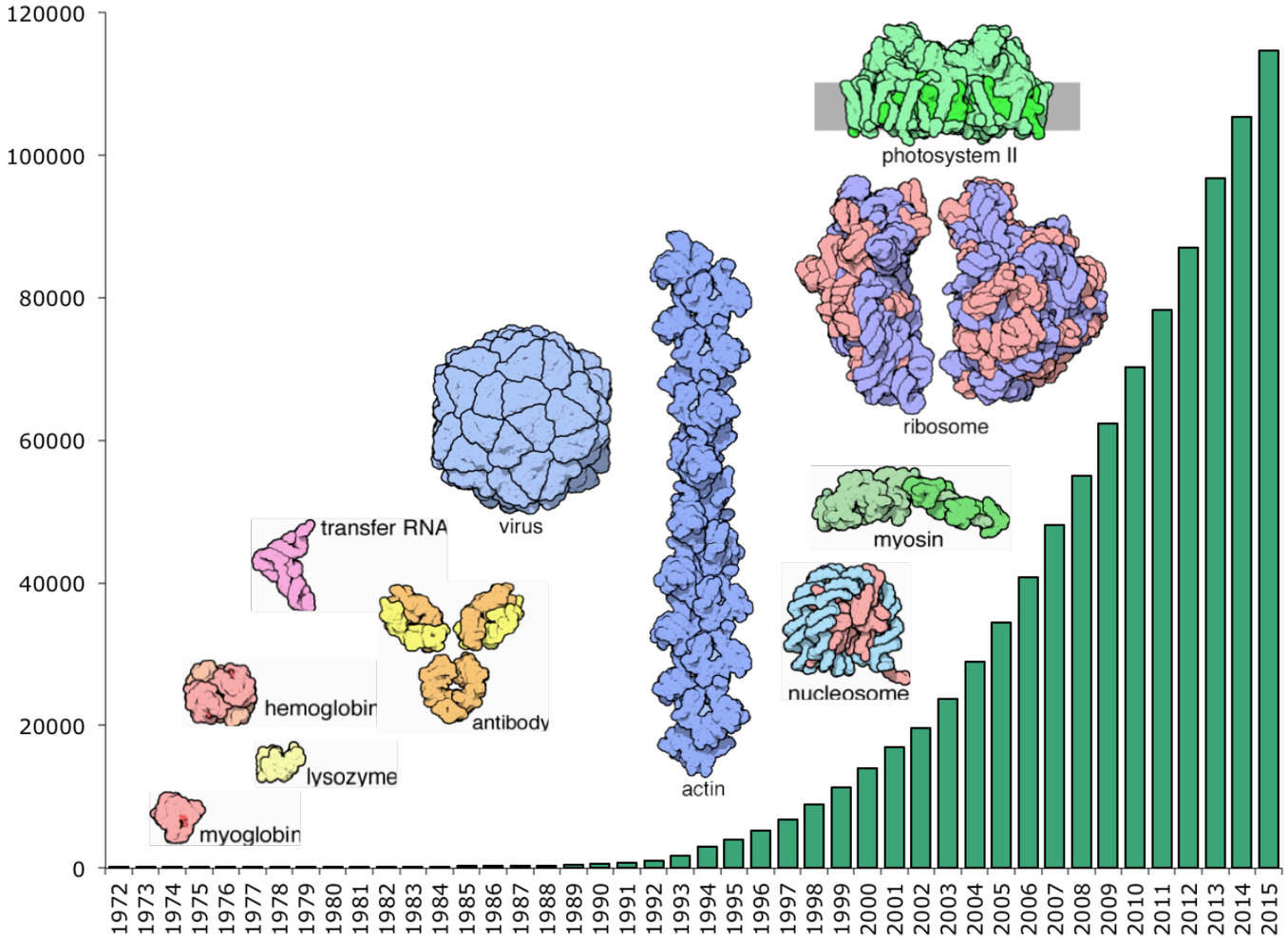


Small Molecules
(CCDB)

PDB – A Billion Atom Archive



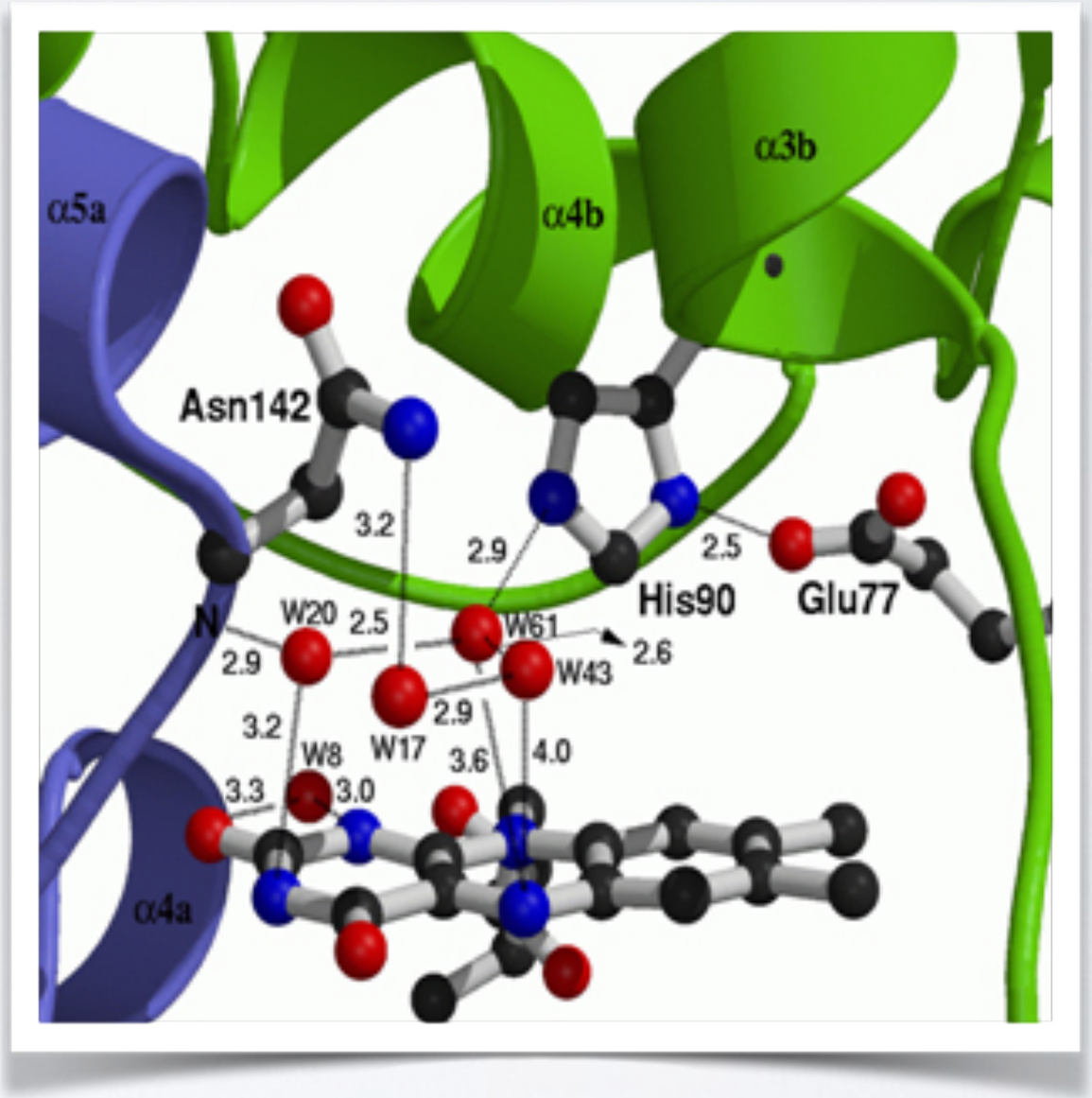
> 1 billion atoms in the asymmetric units



~146,000
Structures as
of Nov 2018

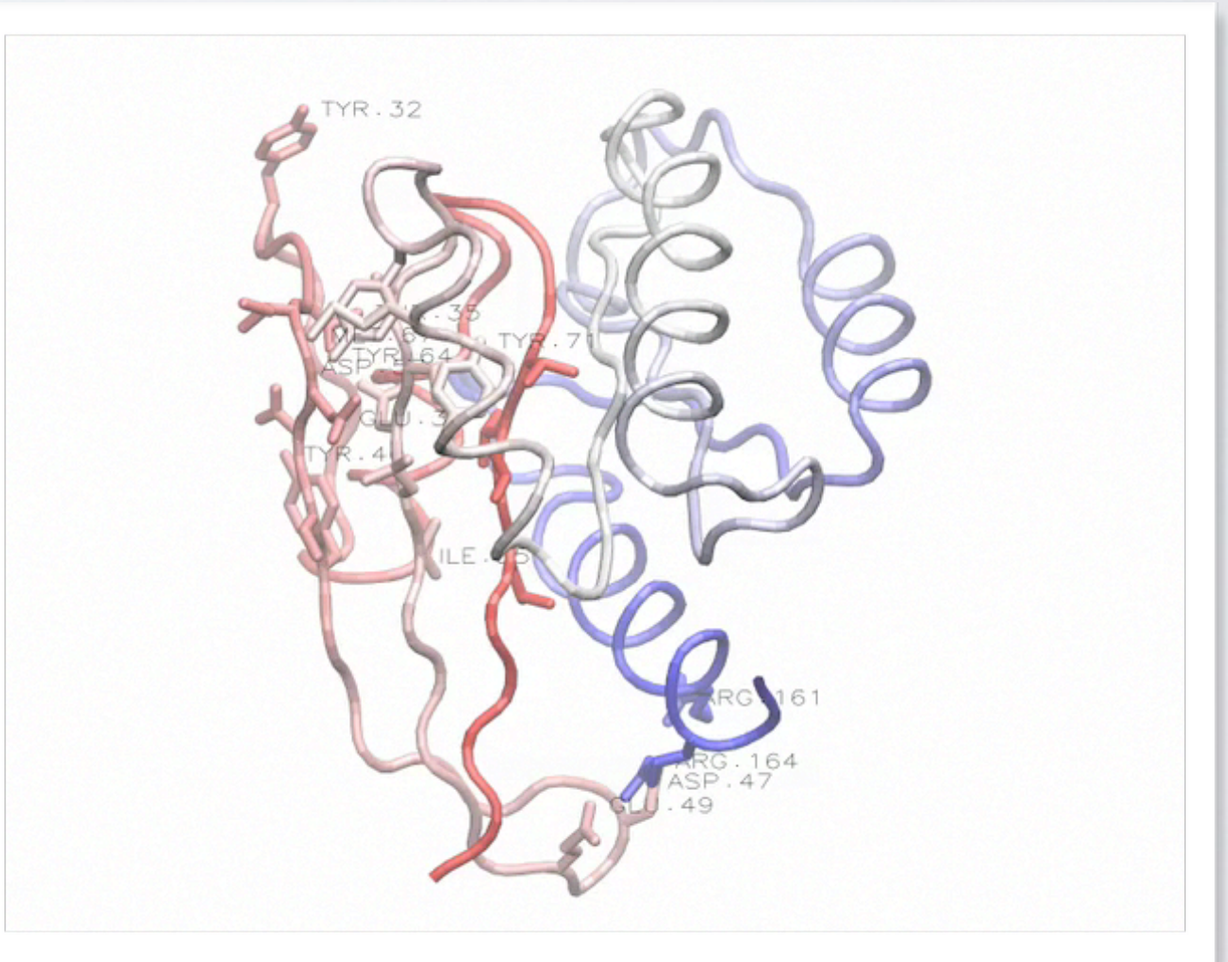
Motivation 1:
Detailed understanding of molecular interactions

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.

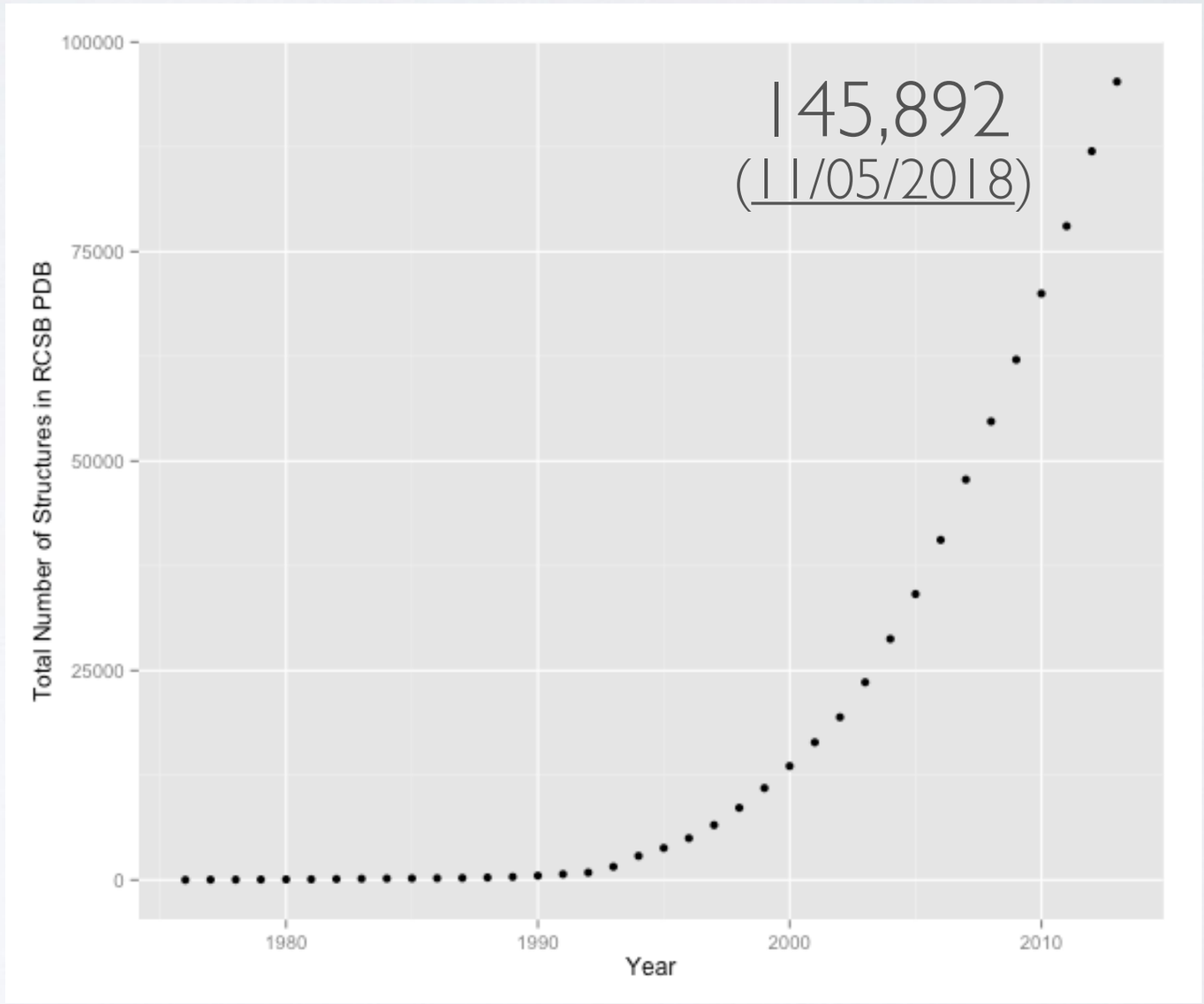


Grant *et al.* PLoS. Comp. Biol. (2010)

Motivation 2:

Lots of structural data is becoming available

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



Data from: https://www.rcsb.org/stats/

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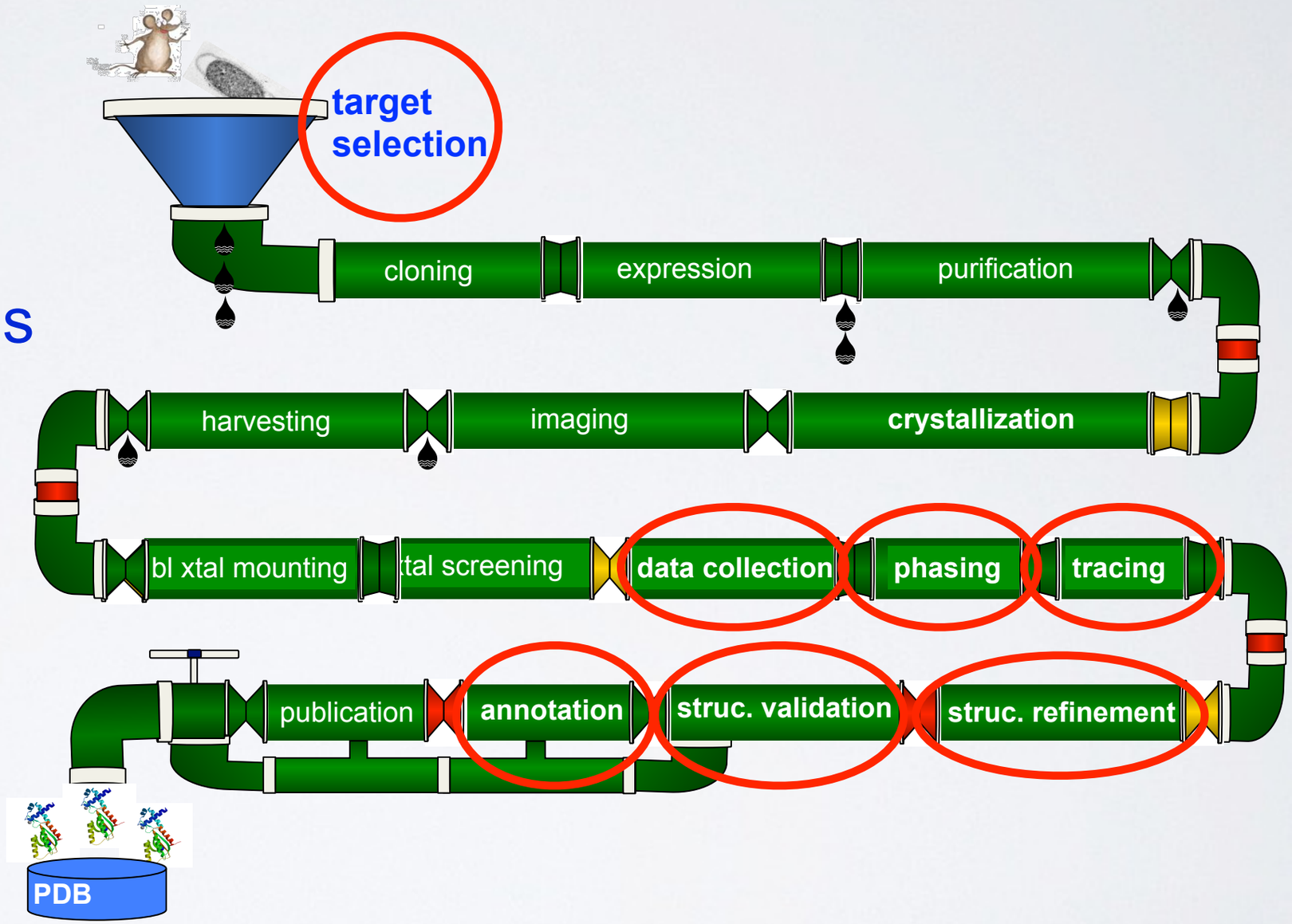
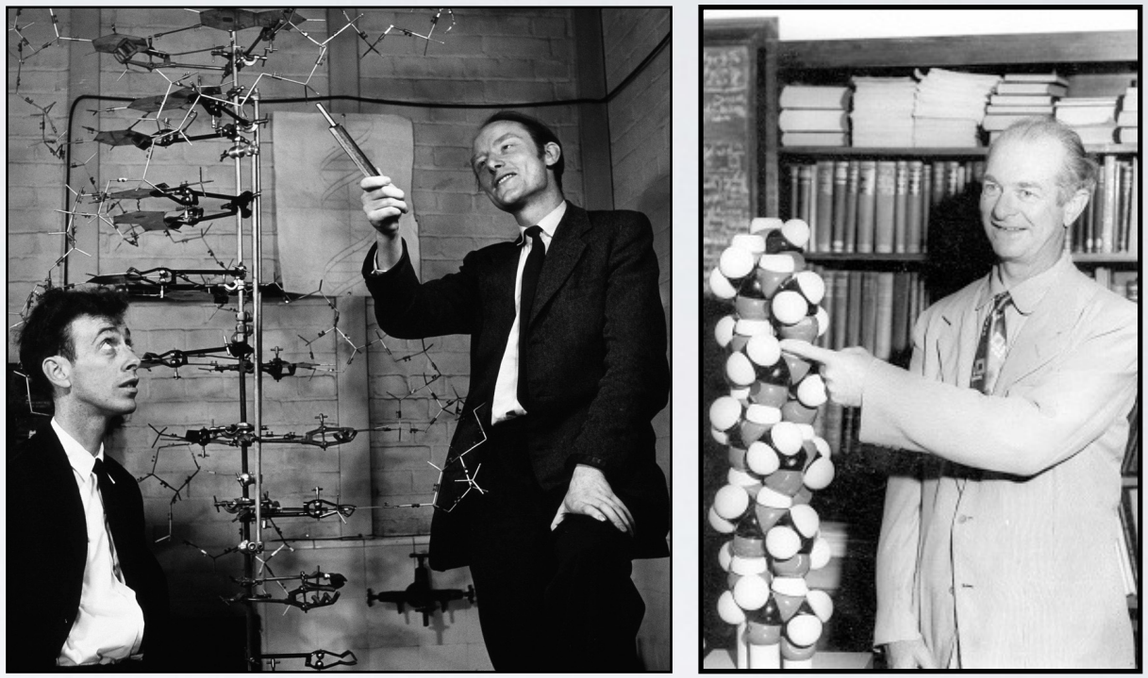


Image Credit: "Structure determination assembly line" Adam Godzik

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:

- Visualization
- Analysis
- Comparison
- Prediction
- Design

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

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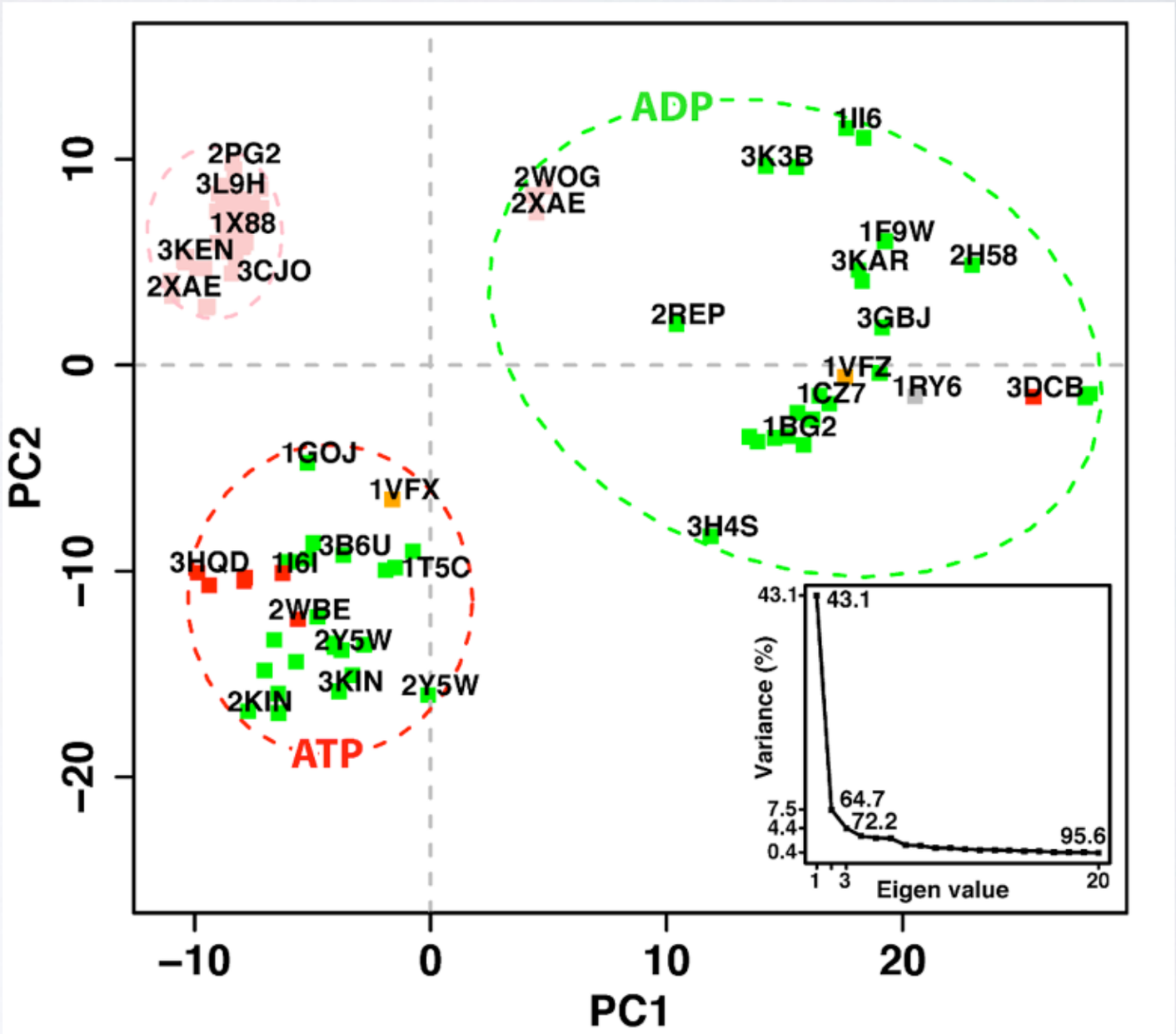

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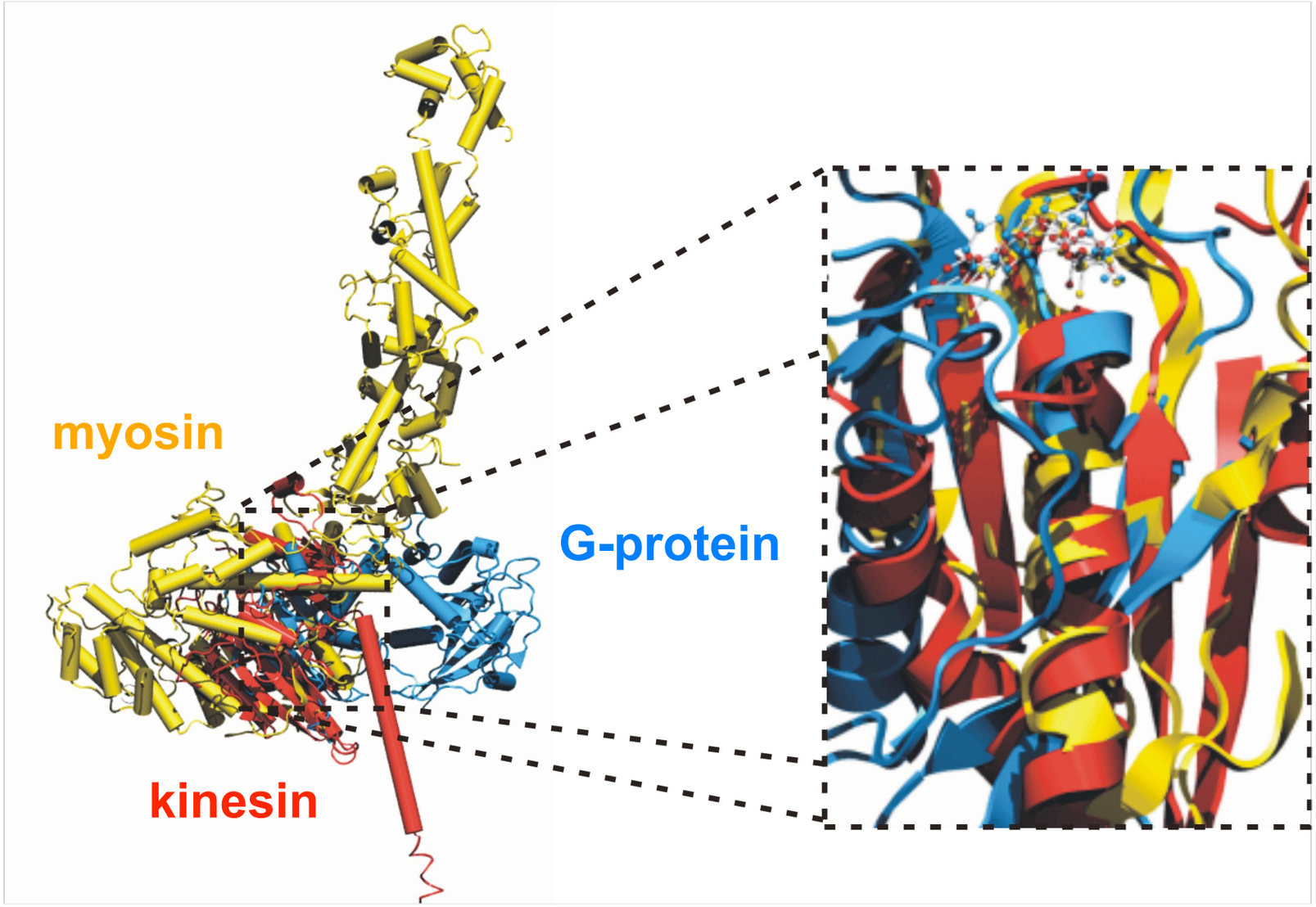

Grant *et al.* unpublished

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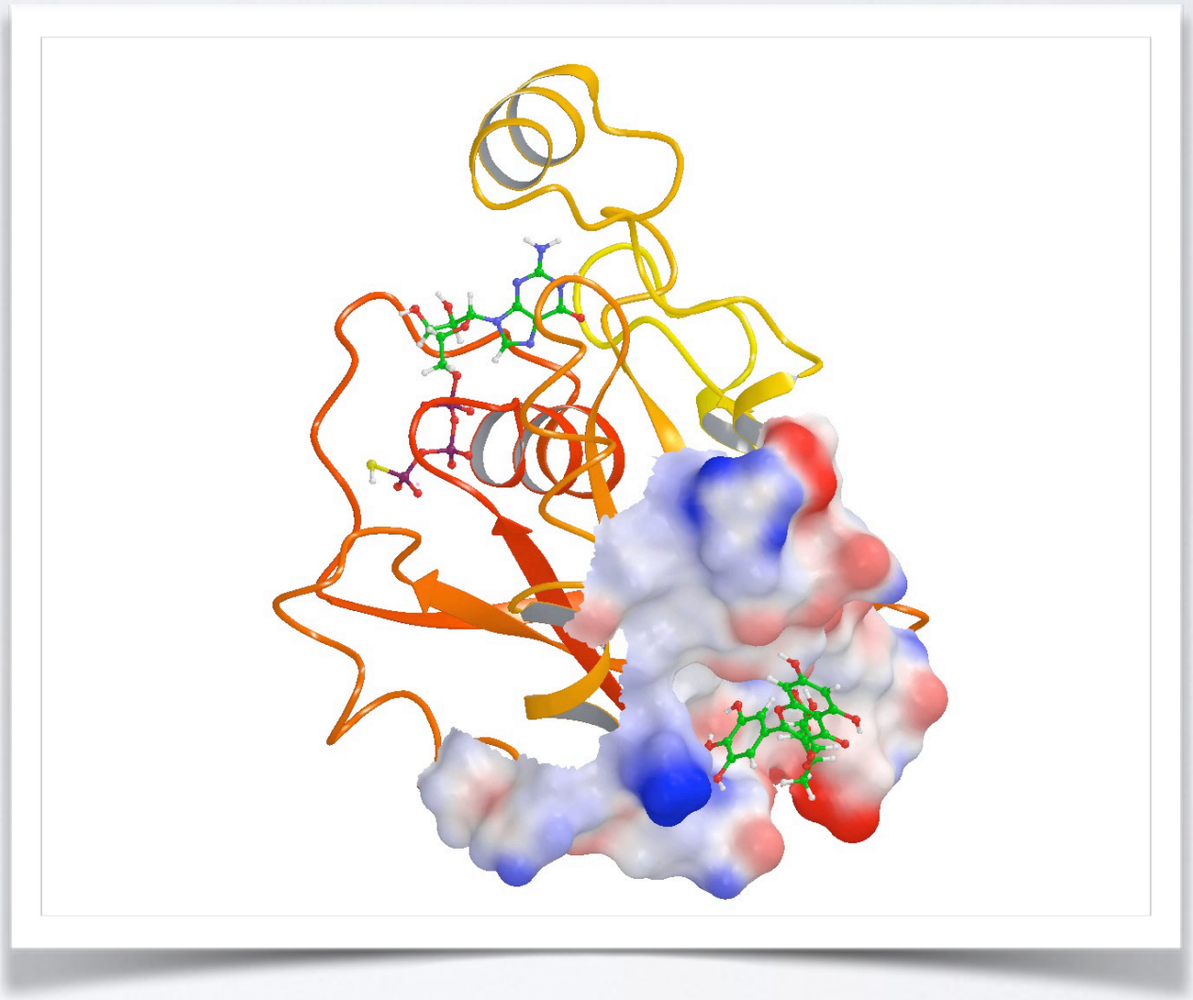

Grant *et al.* PLoS One (2011, 2012)

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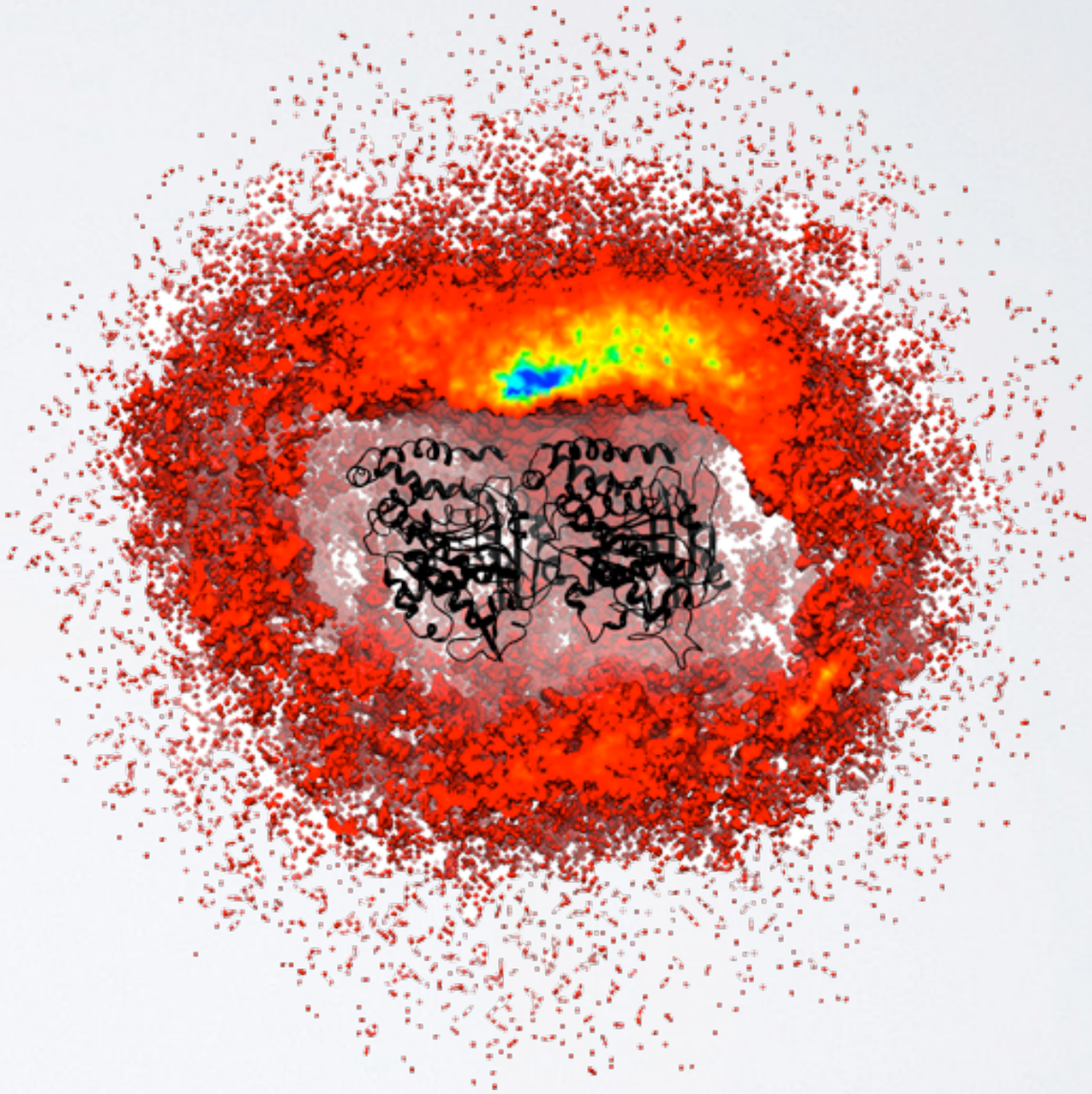

Grant *et al.* PLoS Biology (2011)

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

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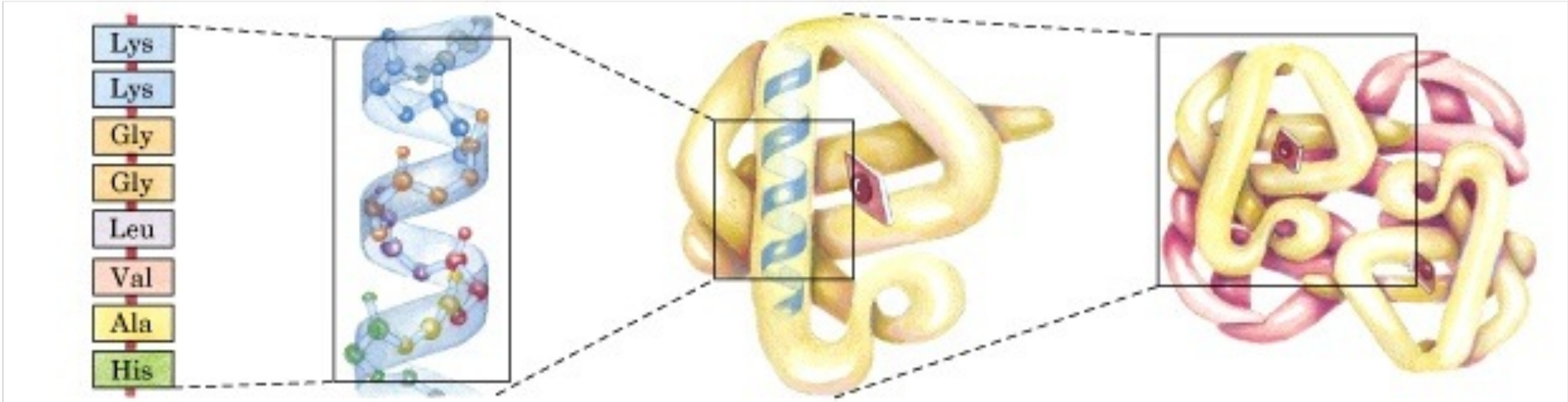
HIERARCHICAL STRUCTURE OF PROTEINS

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

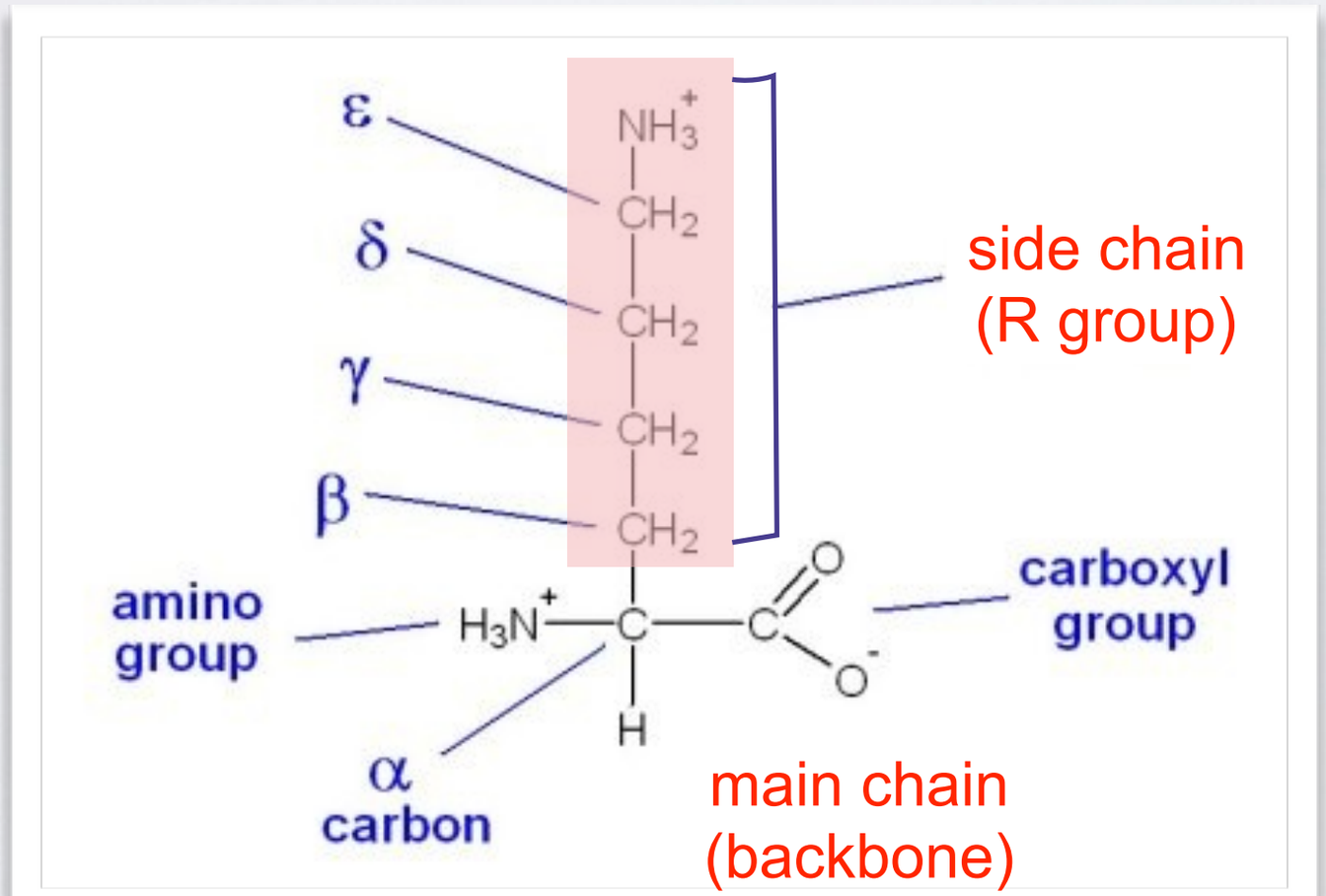
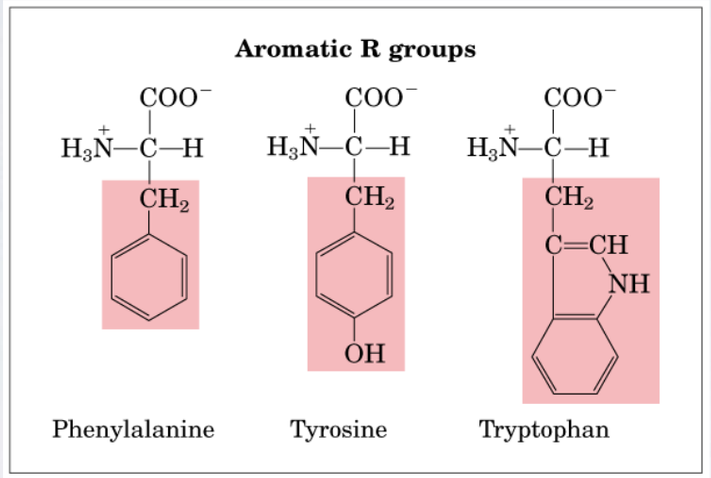
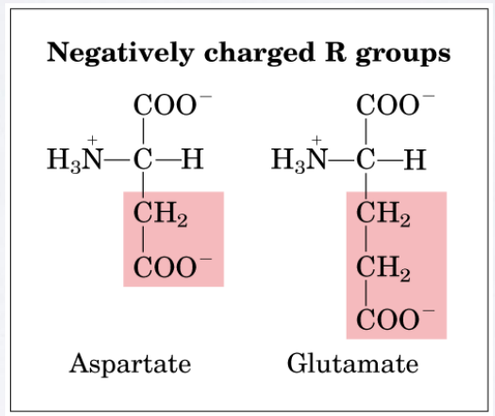
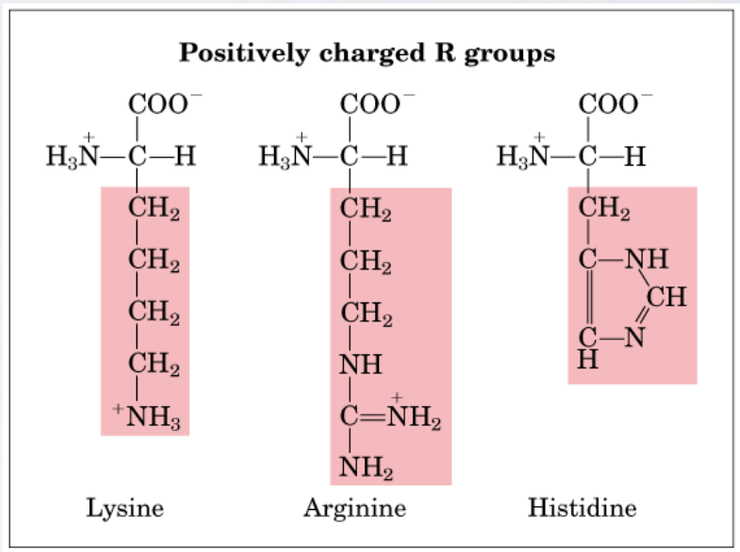


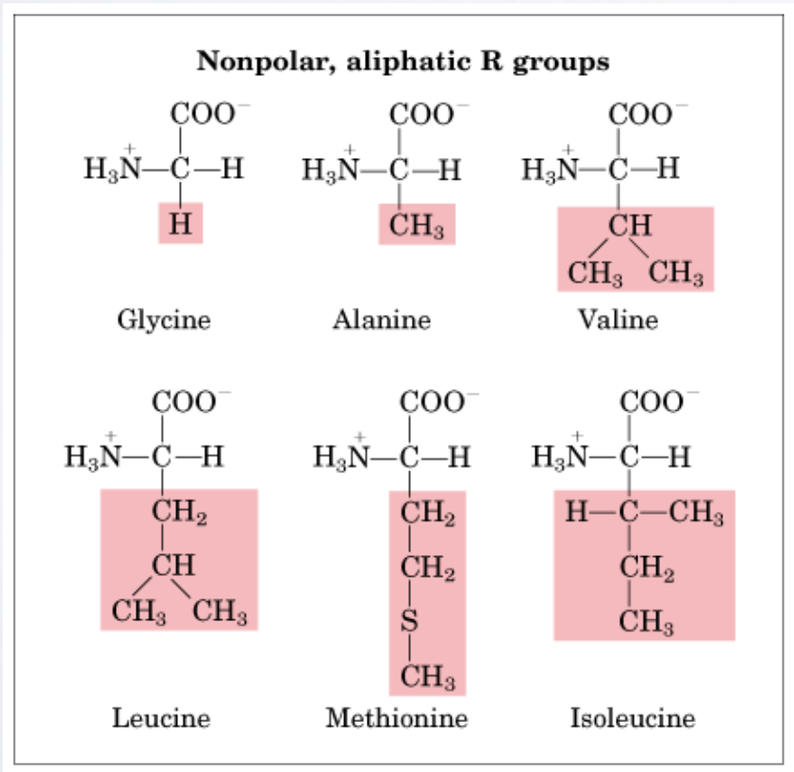
Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

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









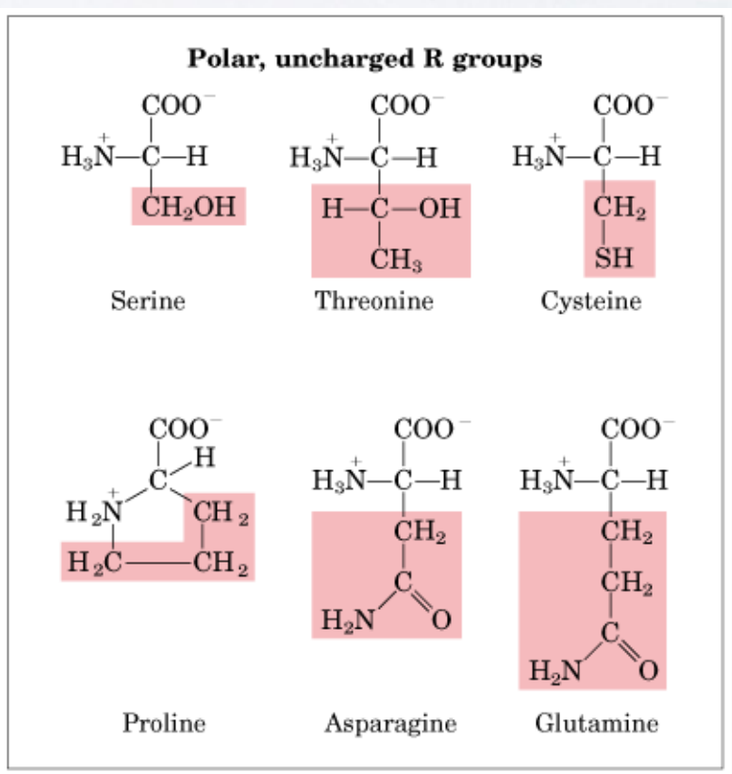
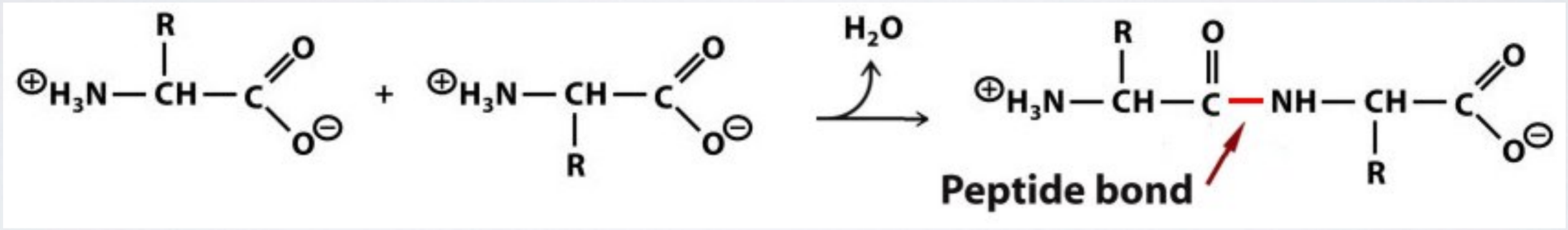


Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

AMINO ACIDS POLYMERIZE THROUGH **PEPTIDE BOND** FORMATION



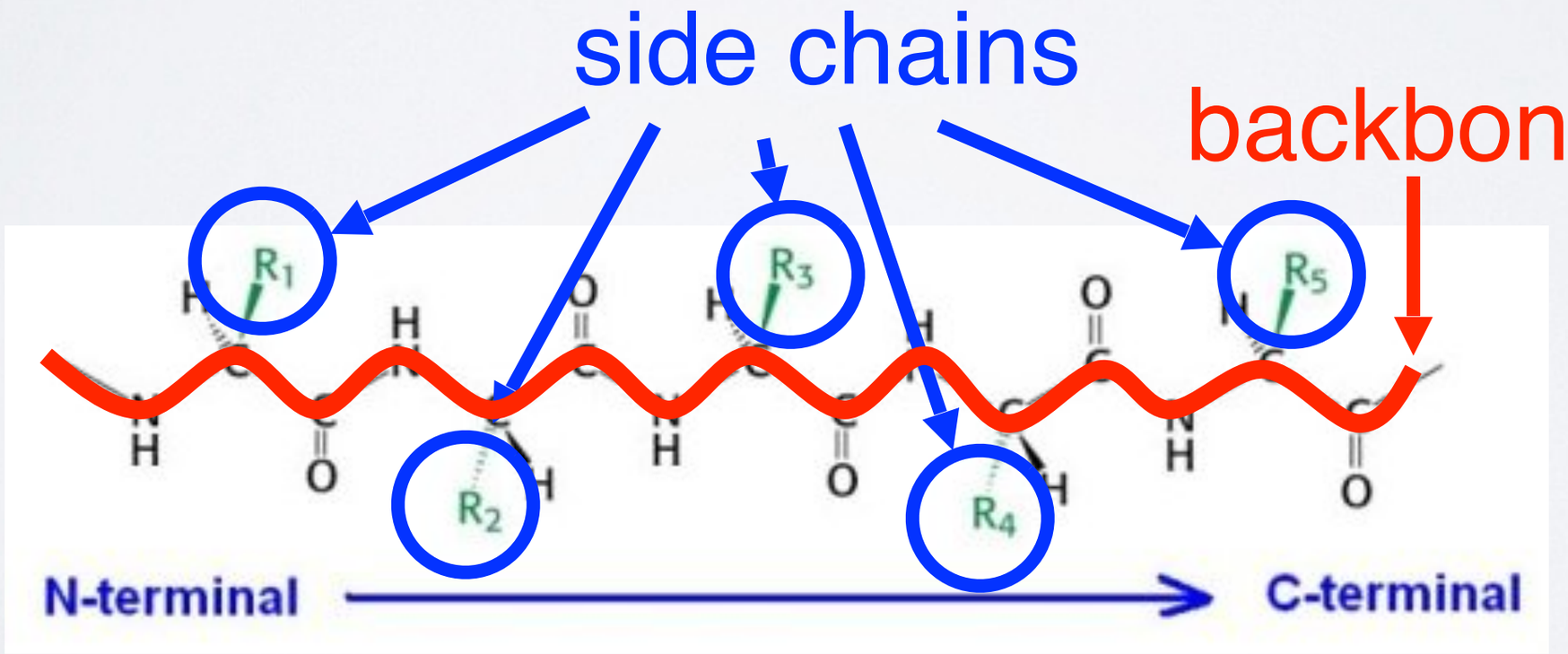
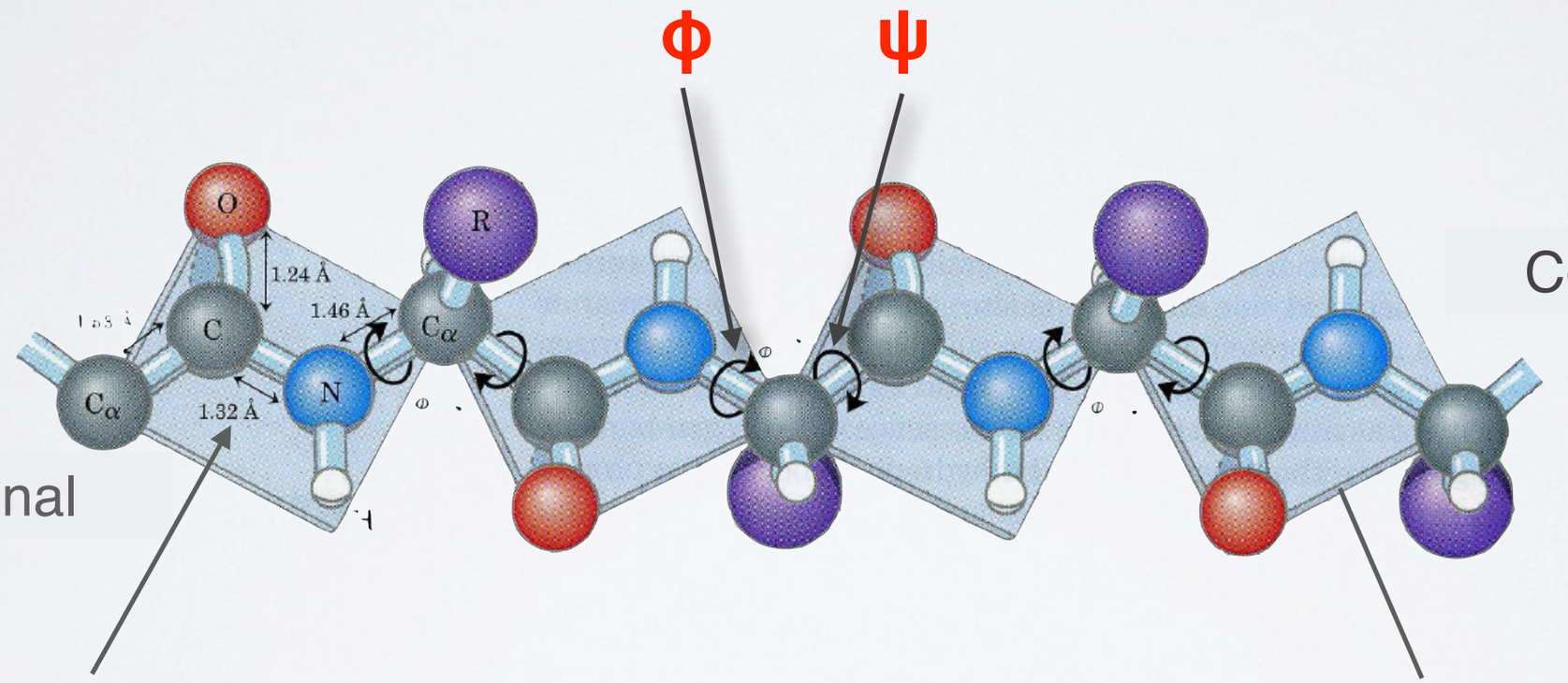


Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

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



C-terminal

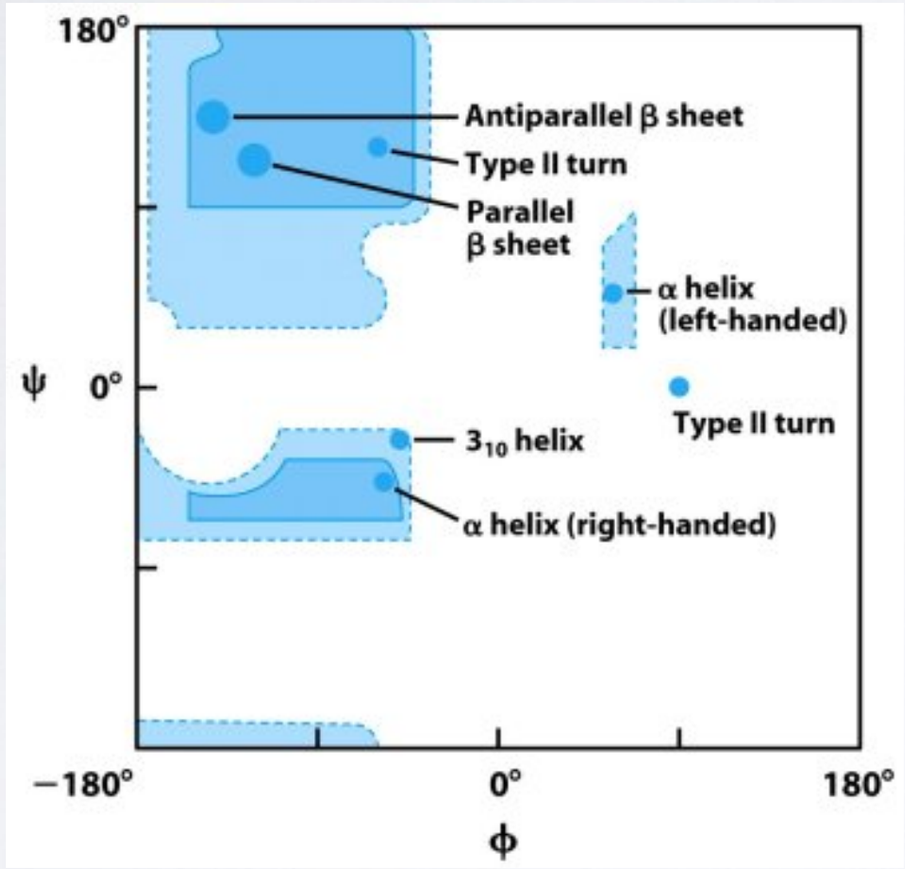
N-terminal

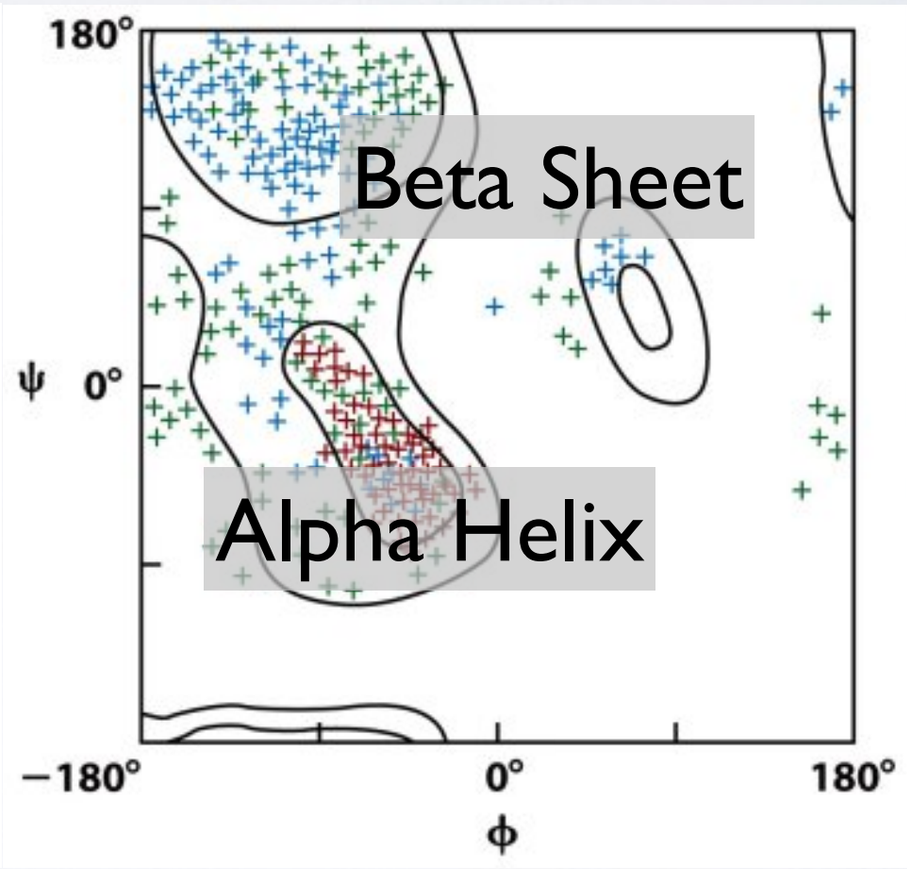
Bond angles and lengths are largely invariant

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**

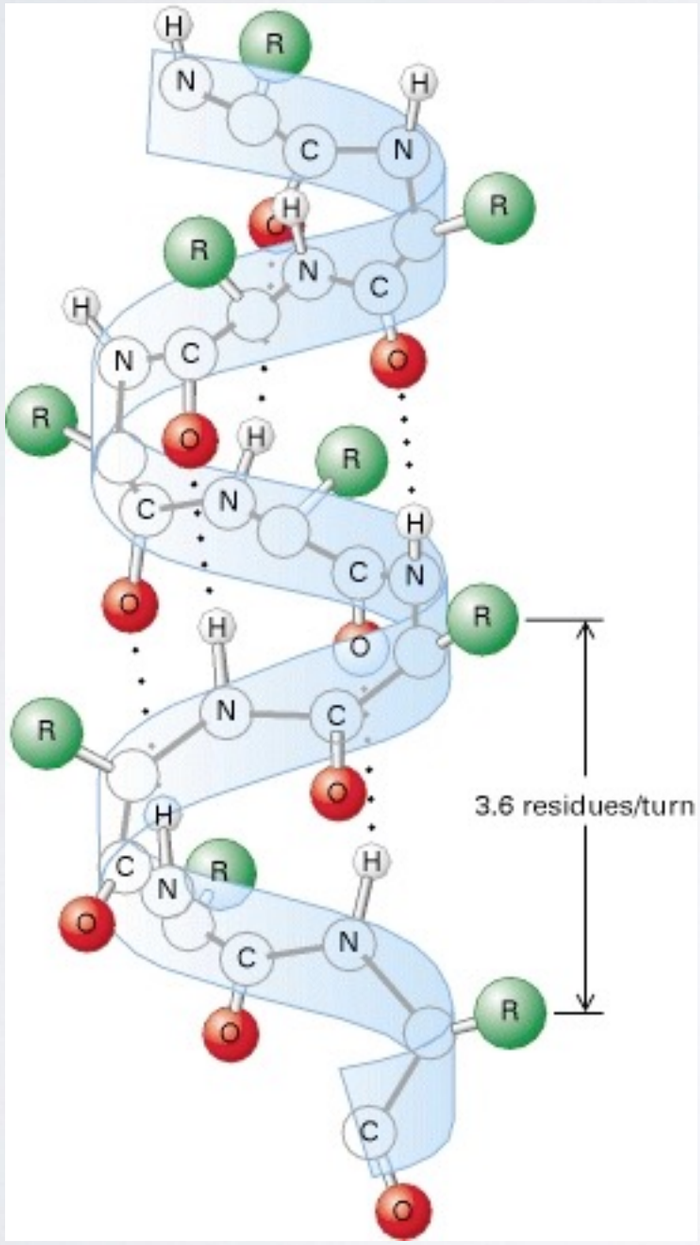




- Steric hindrance dictates torsion angle preference
- Ramachandran plot show preferred regions of ϕ and ψ dihedral angles which correspond to major forms of **secondary structure**

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

MAJOR SECONDARY STRUCTURE TYPES
ALPHA HELIX & BETA SHEET

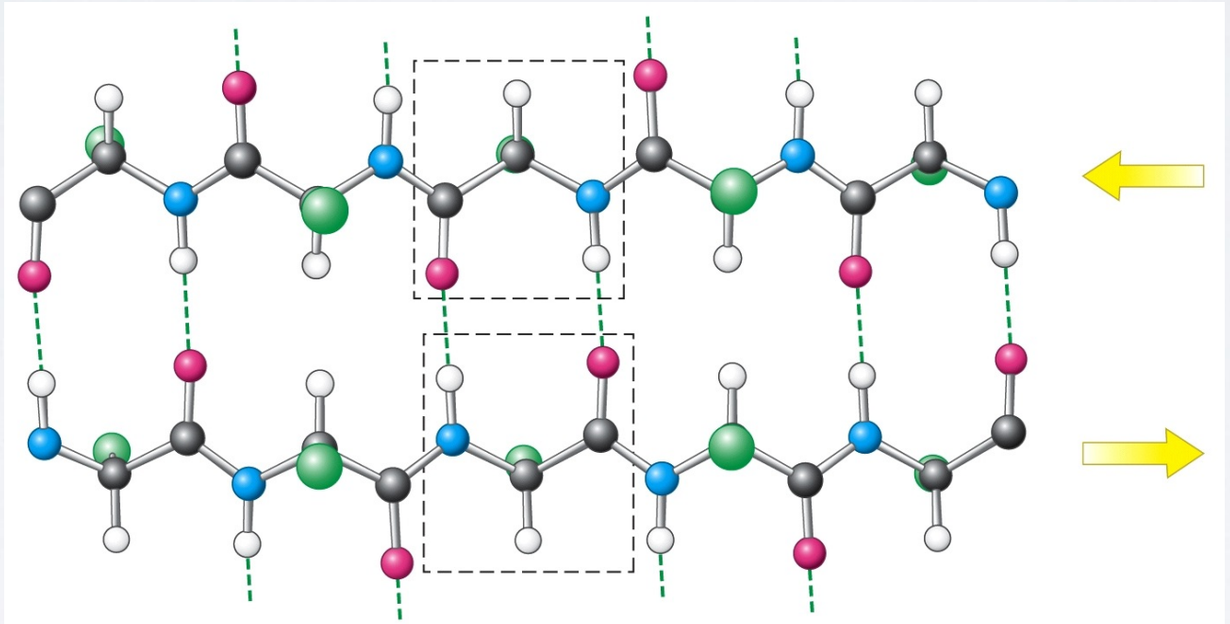


α-helix

- Most common from has <u>3.6 residues per turn</u> (number of residues in one full rotation)
- Hydrogen bonds (dashed lines) between residue <u>*i* and *i+4*</u> 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**

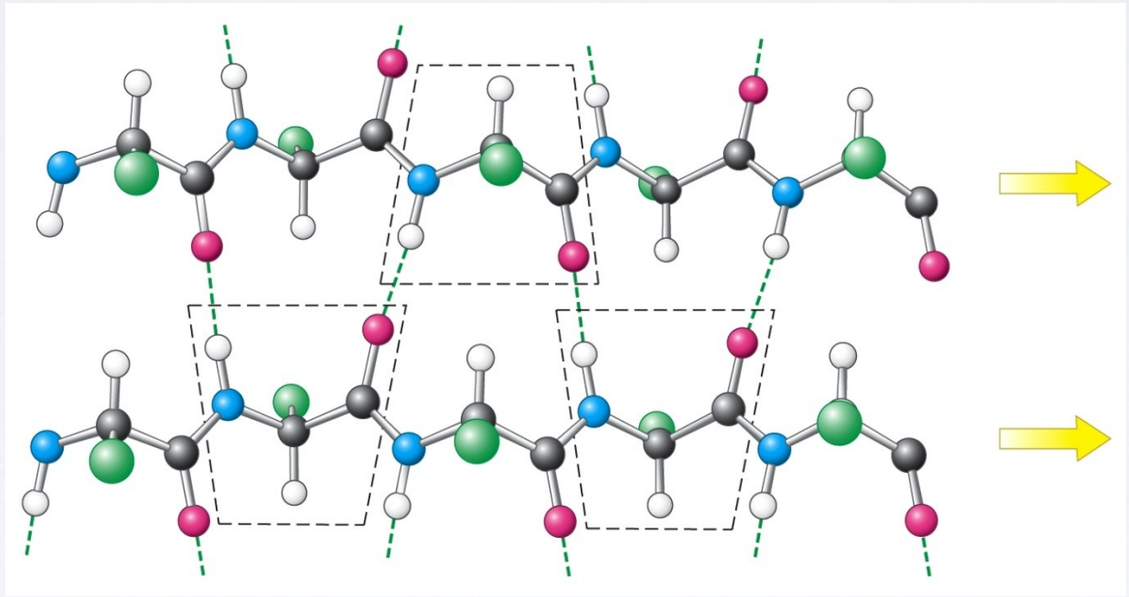


In **<u>antiparallel</u>** β**-sheets**

- Adjacent β-strands run in <u>opposite</u> 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: <u>http://www.ncbi.nlm.nih.gov/books/NBK21581/</u>

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

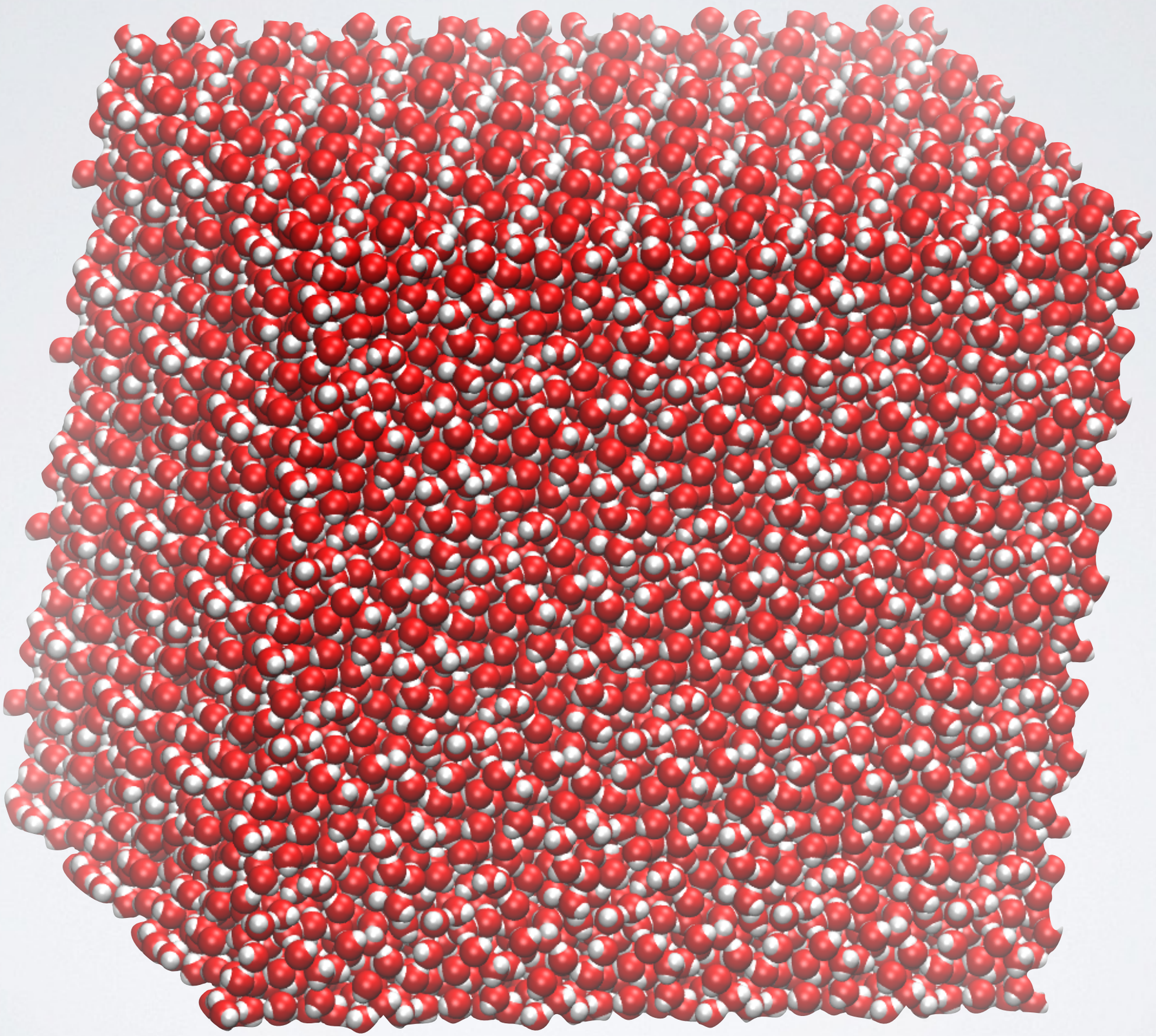


In **<u>parallel</u> β-sheets**

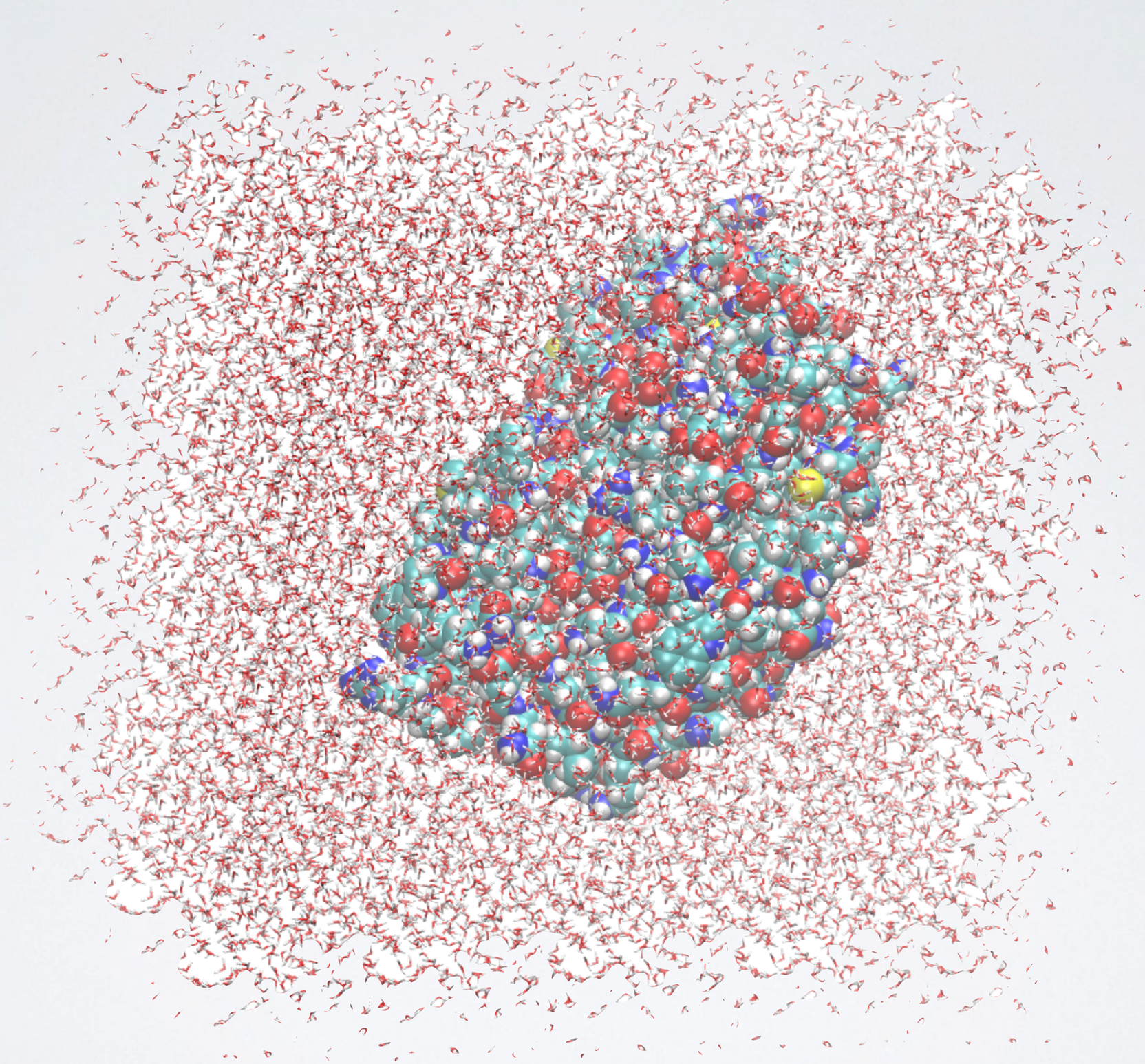
- Adjacent β-strands run in <u>same</u> direction
- Hydrogen bonds (dashed lines) between NH and CO stabilize the structure
- The side chains (in green) are above and below the sheet

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

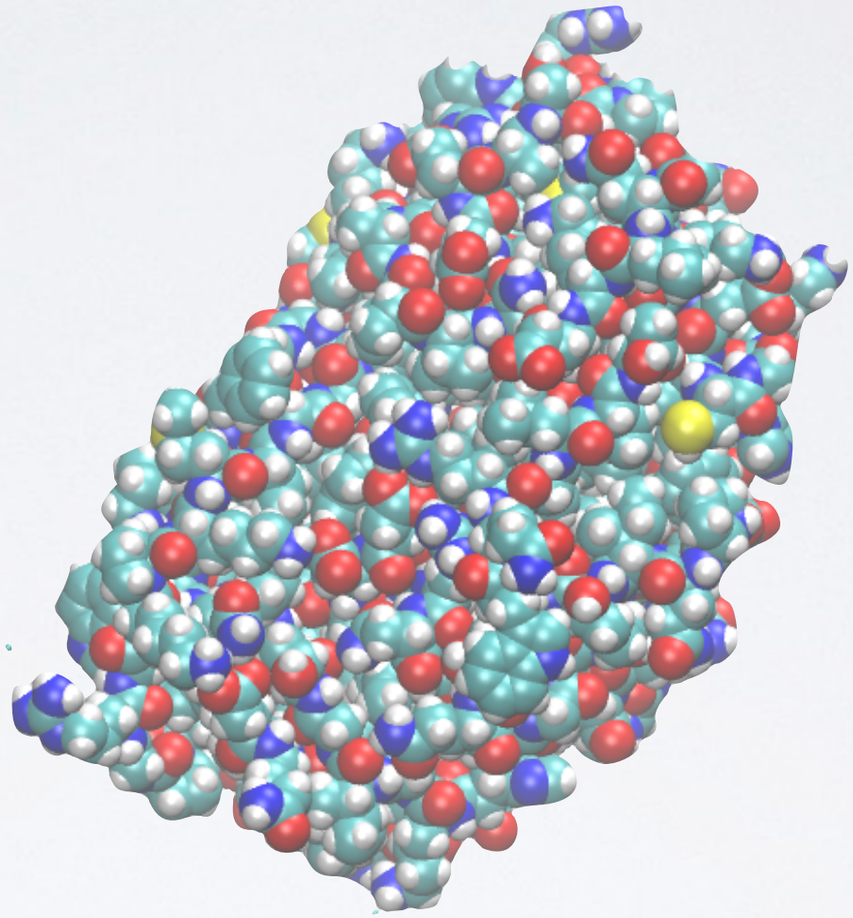
What Does a Protein Look like?



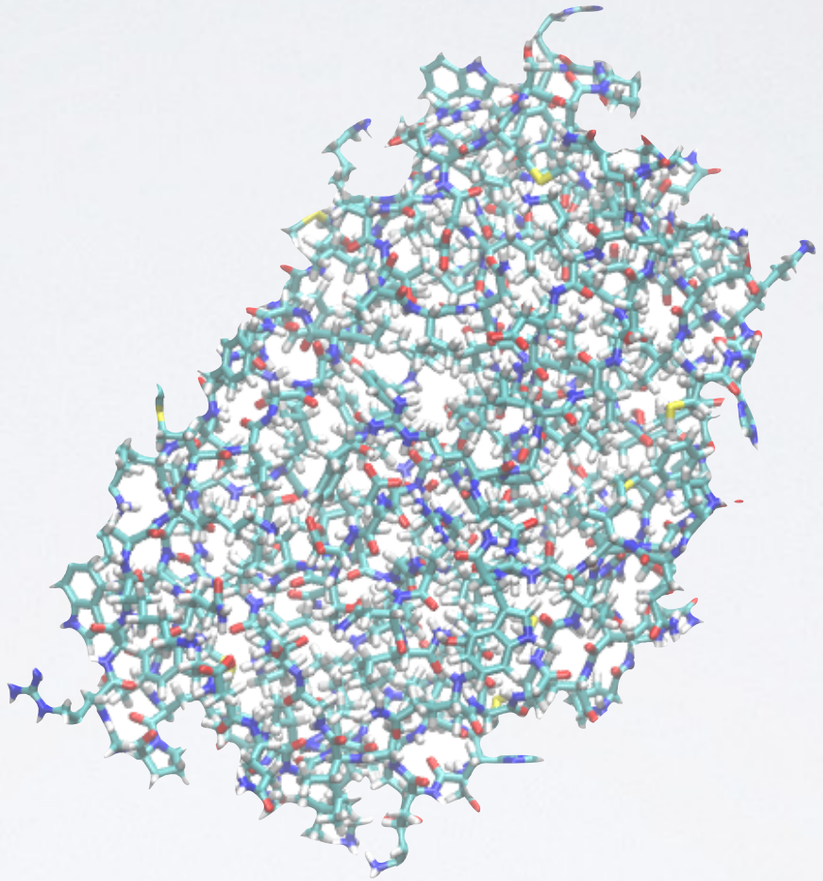
- Proteins are stable (and hidden) in water



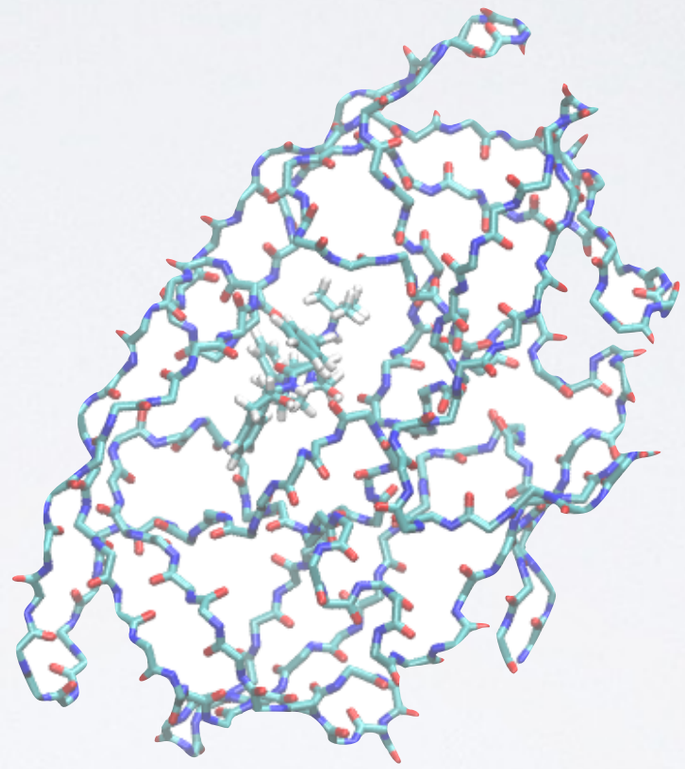
- Proteins closely interact with water



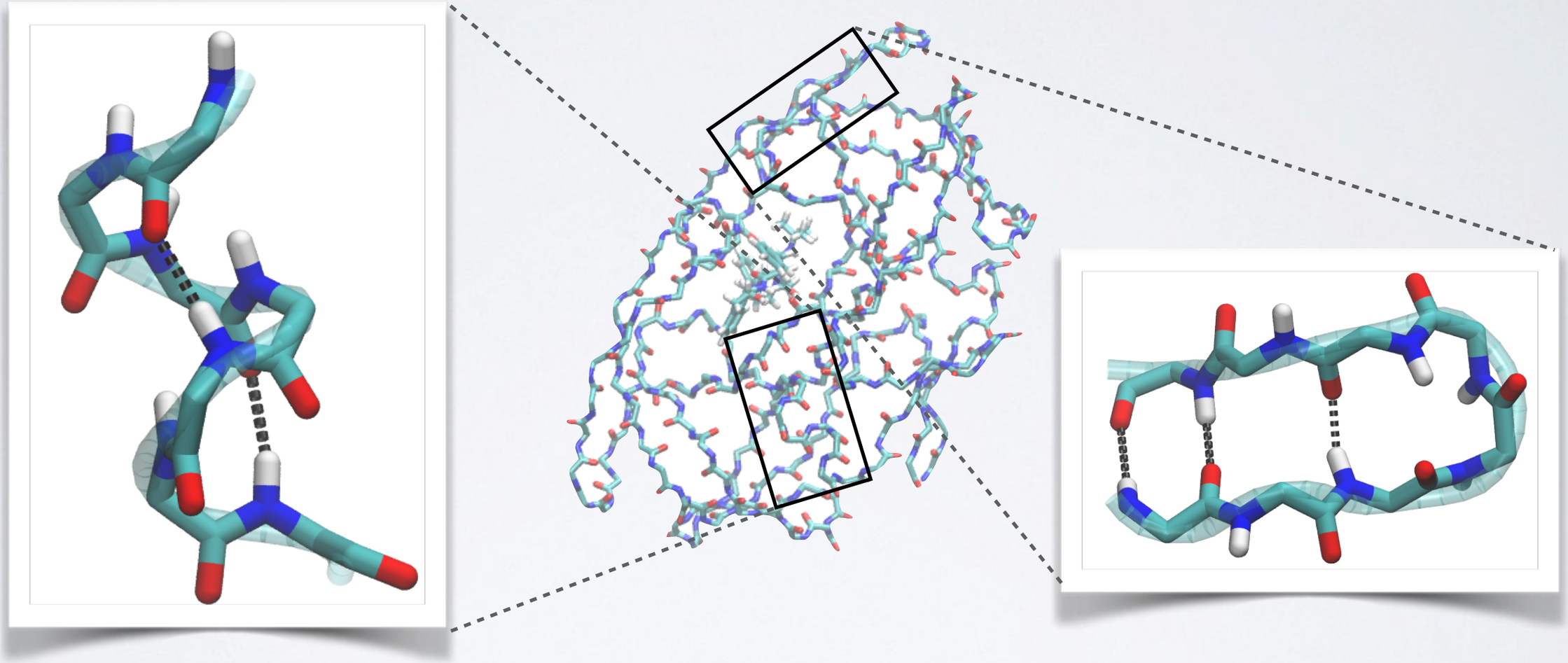
- Proteins are close packed solid but flexible objects (globular)



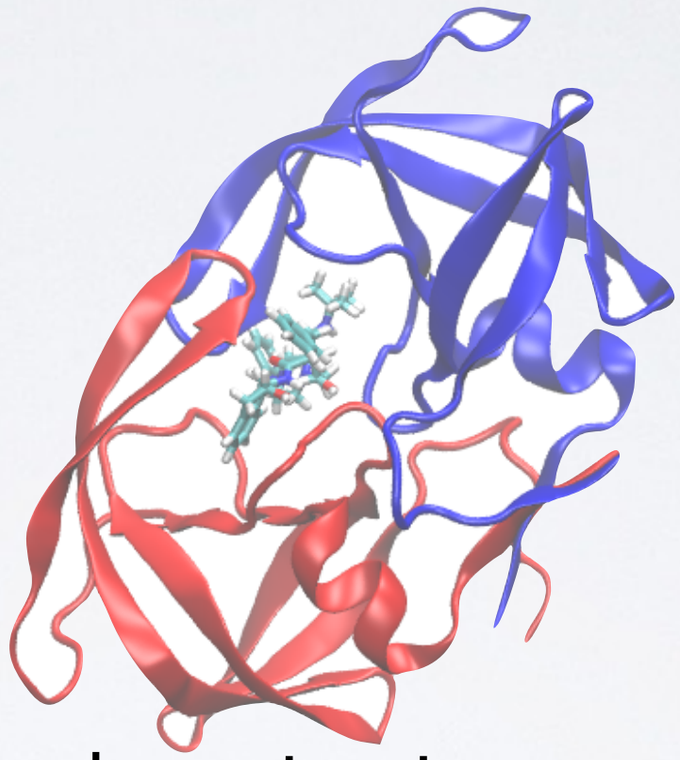
- Due to their large size and complexity it is often hard to see whats important in the structure



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

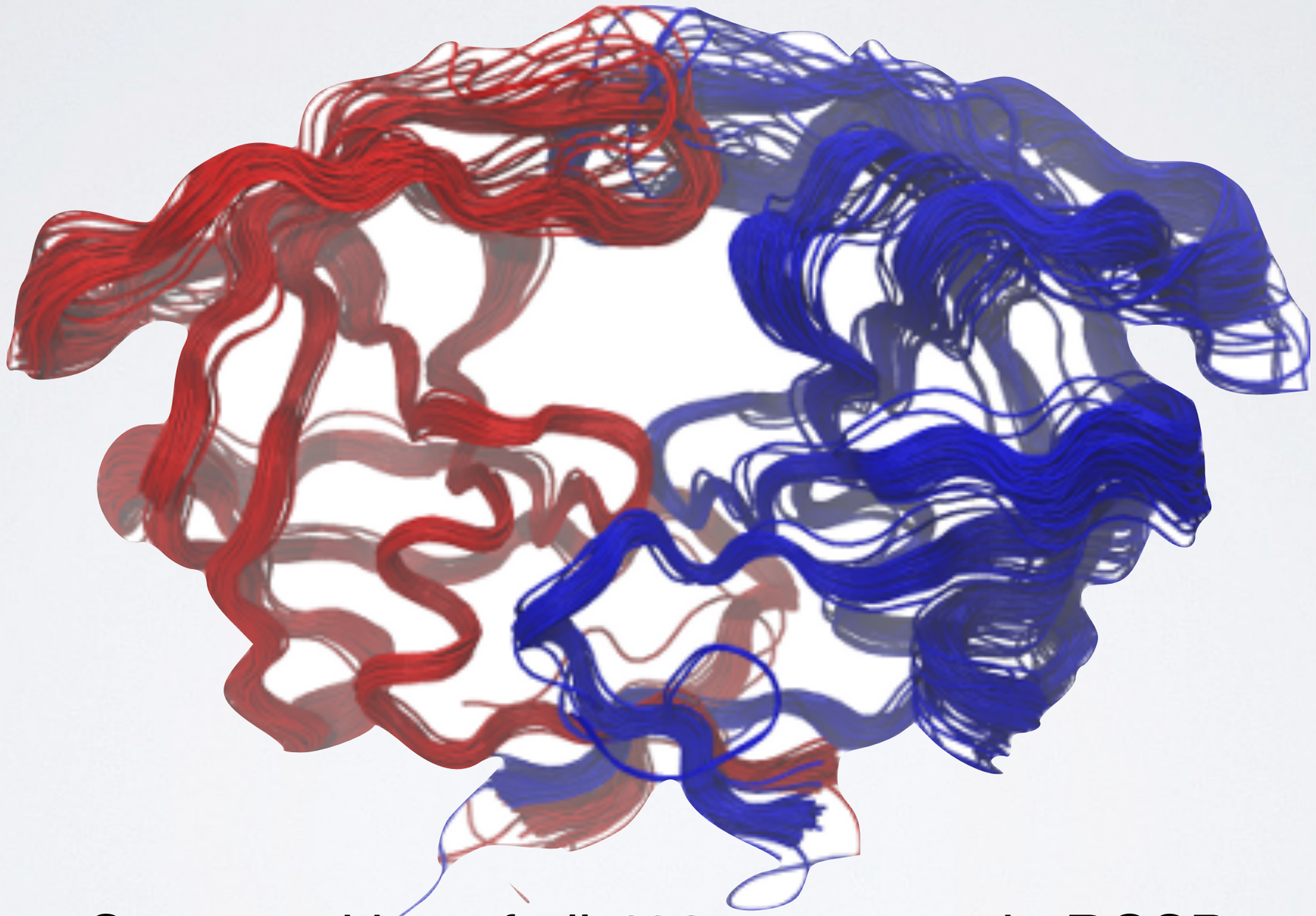


- Backbone or main-chain representation can help trace chain topology & reveal secondary structure



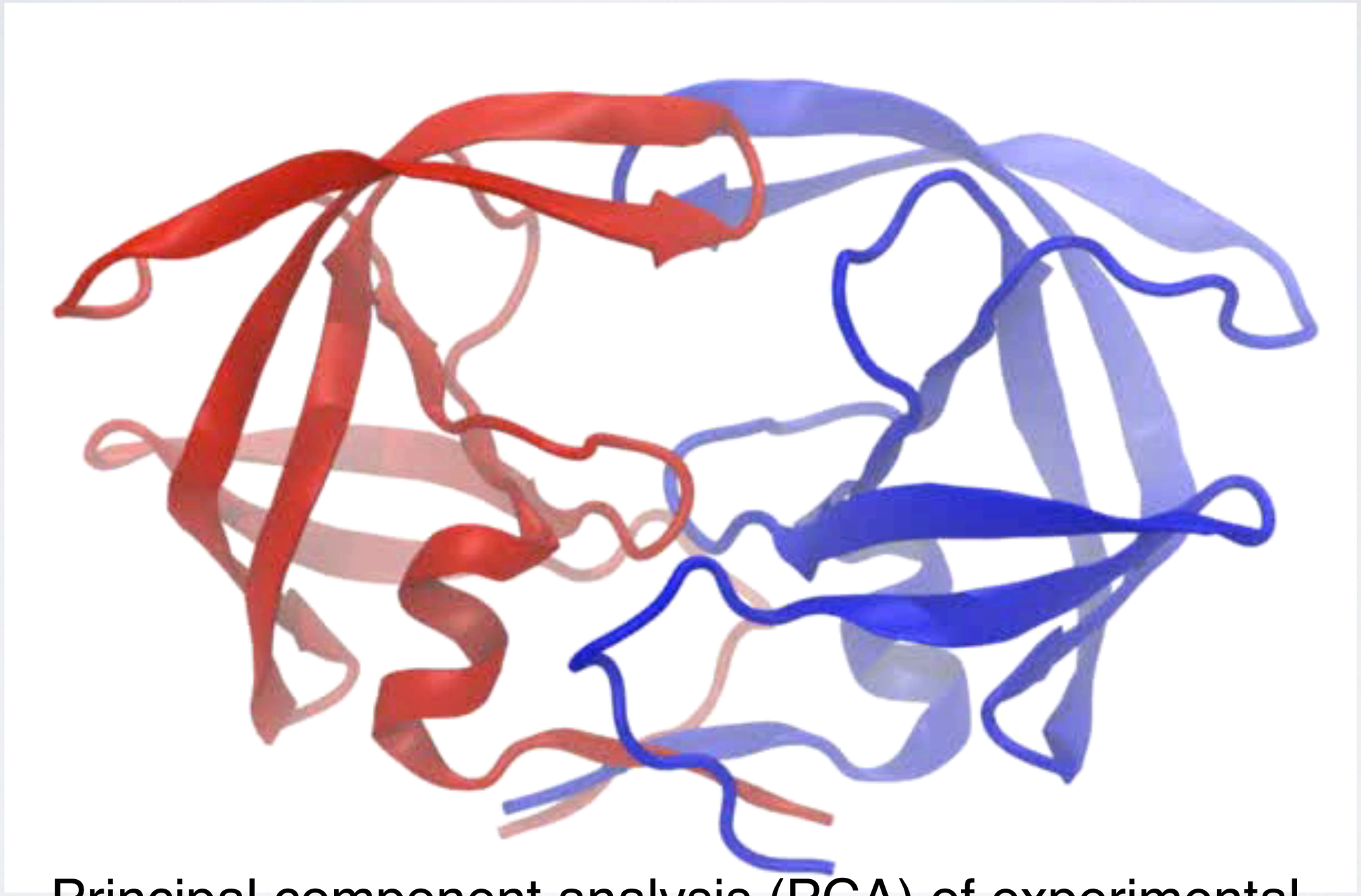
- Simplified secondary structure representations are commonly used to communicate structural details
- Now we can clearly see 2^{o}, 3^{o} and 4^{o} structure
- Coiled chain of connected secondary structures

DISPLACEMENTS REFLECT INTRINSIC FLEXIBILITY



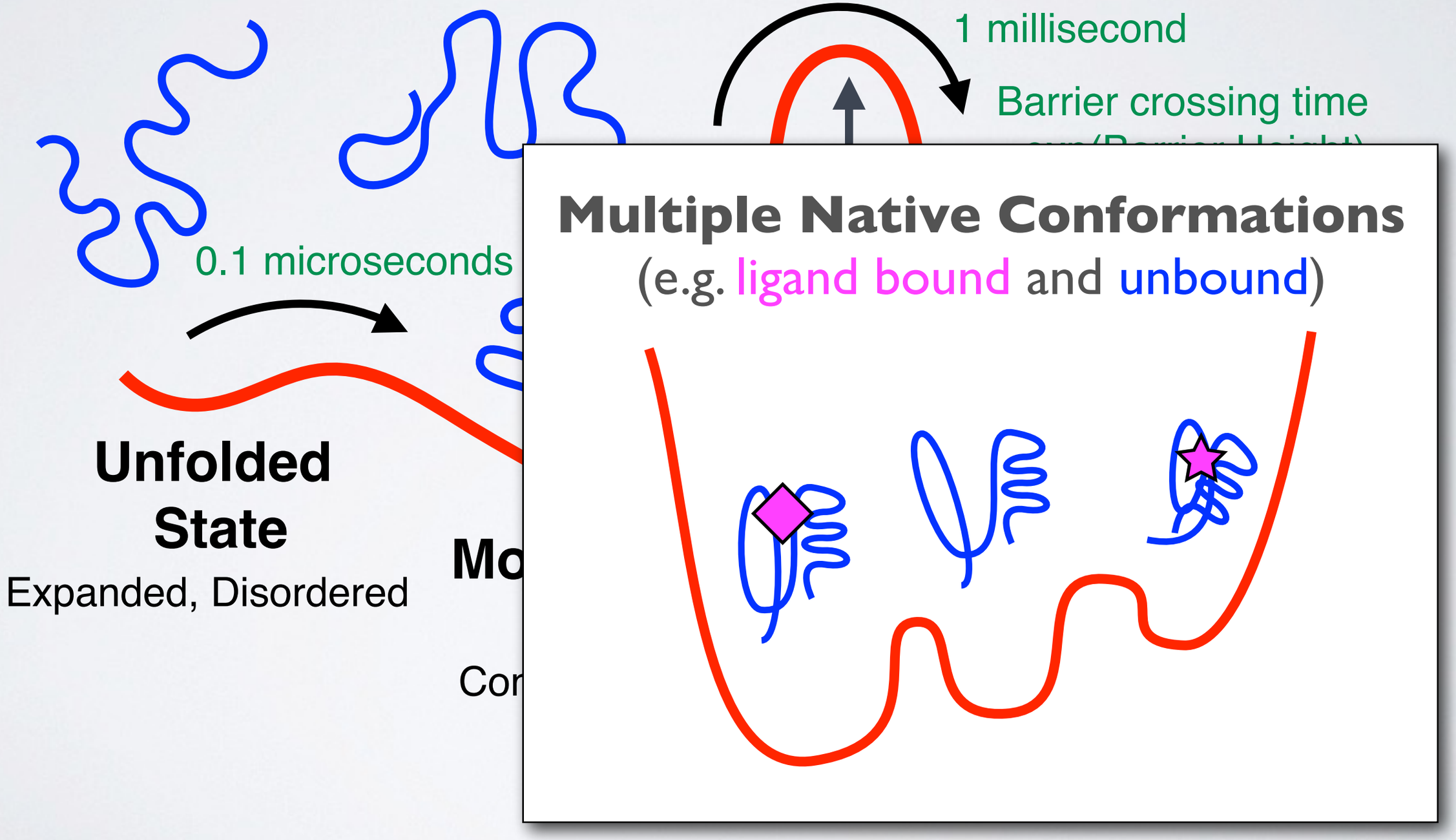
Superposition of all 482 structures in RCSB PDB (23/09/2015)

DISPLACEMENTS REFLECT INTRINSIC FLEXIBILITY

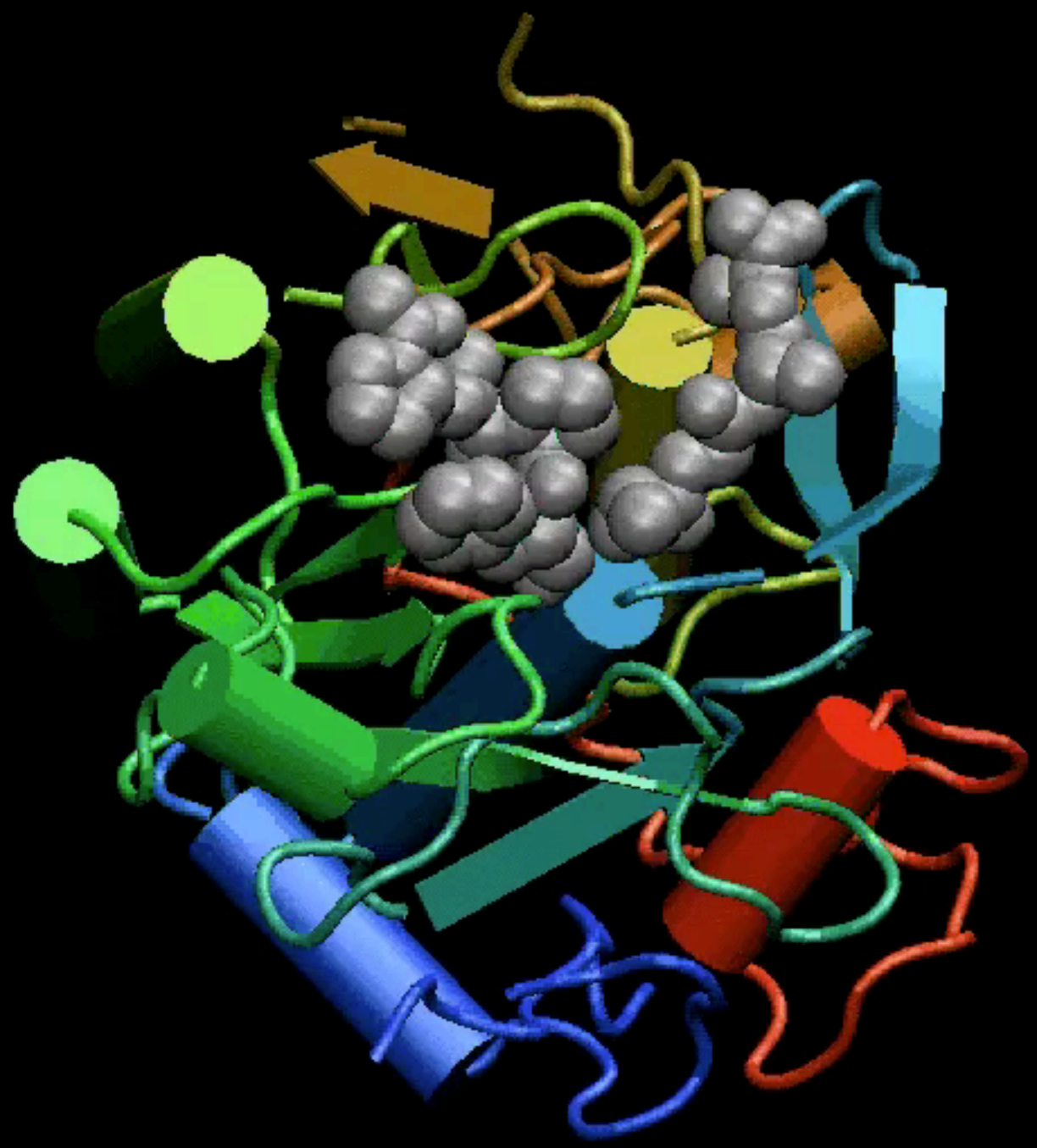


Principal component analysis (PCA) of experimental structures

KEY CONCEPT: **ENERGY LANDSCAPE**



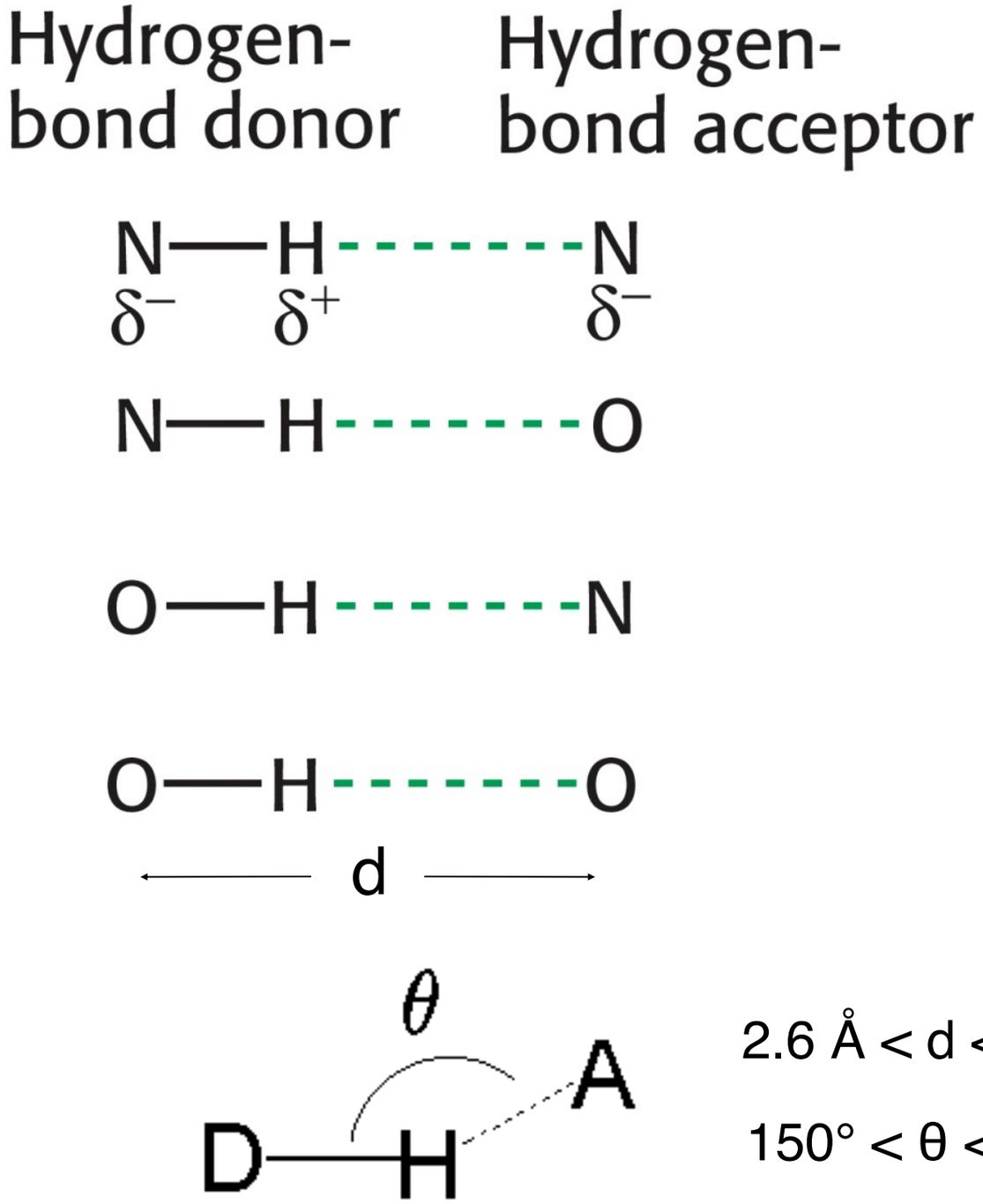
Normal **M**ode **A**nalysis (NMA) models the protein as a network of elastic strings



NMA is a bioinformatics method to predict the intrinsic dynamics of biomolecules

Key forces affecting structure:

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



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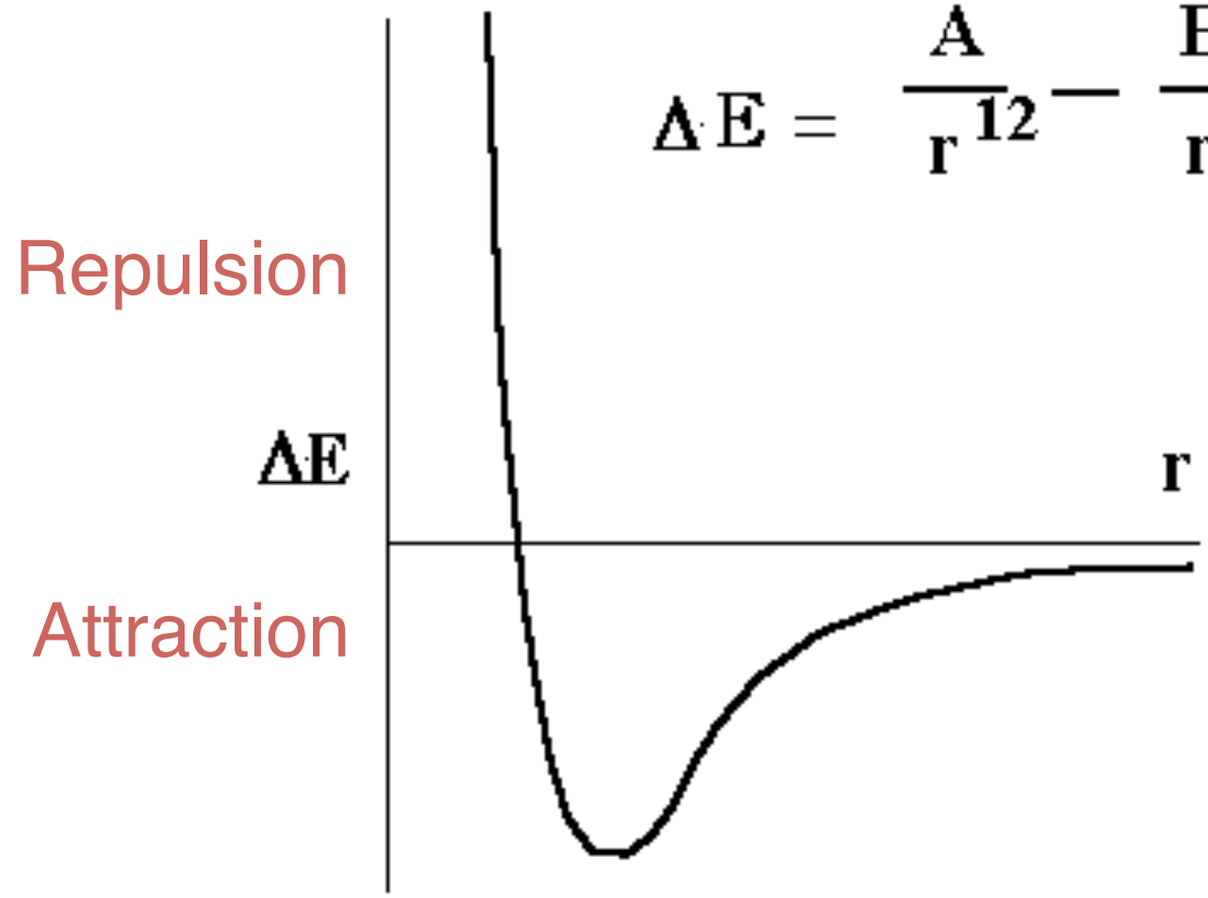

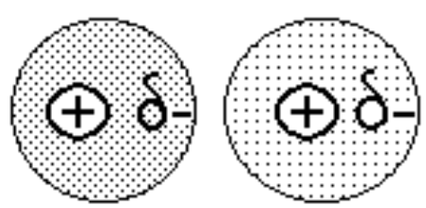

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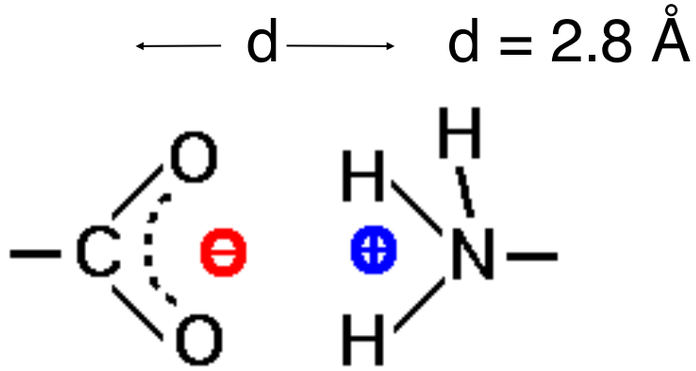
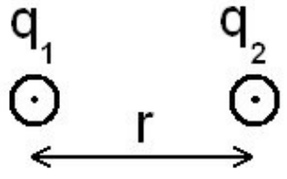


carboxyl group and amino group

- Hydrophobicity

(some time called IONIC BONDs or SALT BRIDGEs)



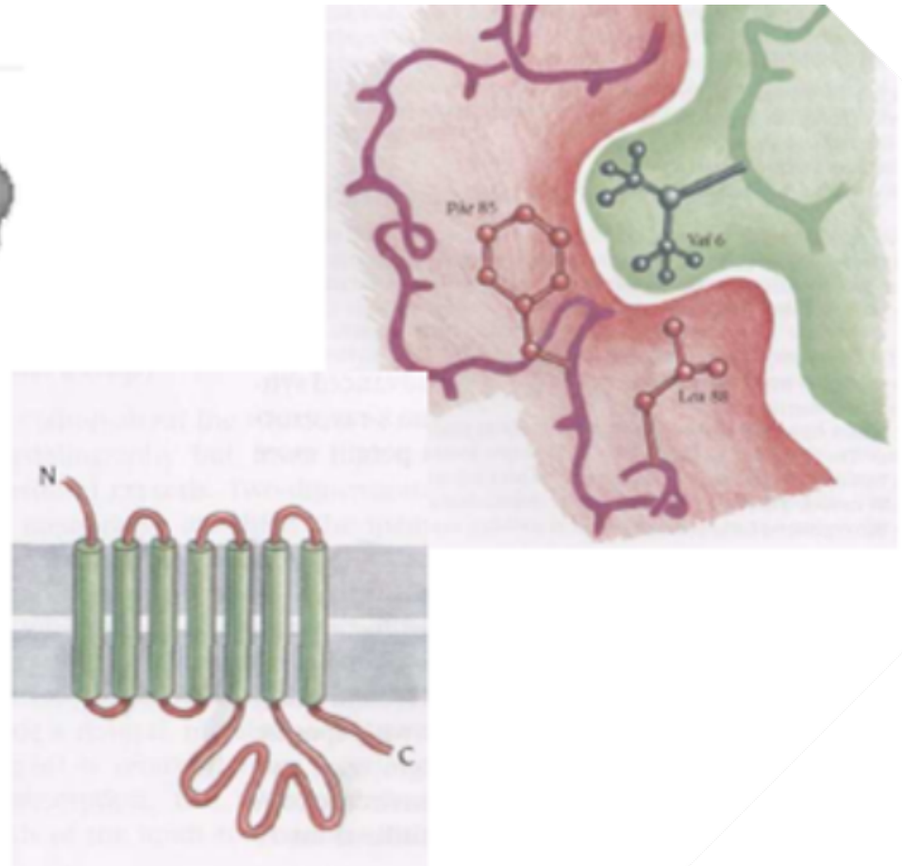
Coulomb's law

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

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.

Today's Menu

- **Overview of structural bioinformatics**
  - Motivations, goals and challenges

- **Fundamentals of protein structure**
  - Structure composition, form and forces

- **Representing, interpreting & modeling protein structure**
  - Visualizing & interpreting protein structures
  - Analyzing protein structures
  - Modeling energy as a function of structure

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Do it Yourself!

Hand-on time!

https://bioboot.github.io/bggn213_W19/lectures/#11

Focus on **section 1** only please!

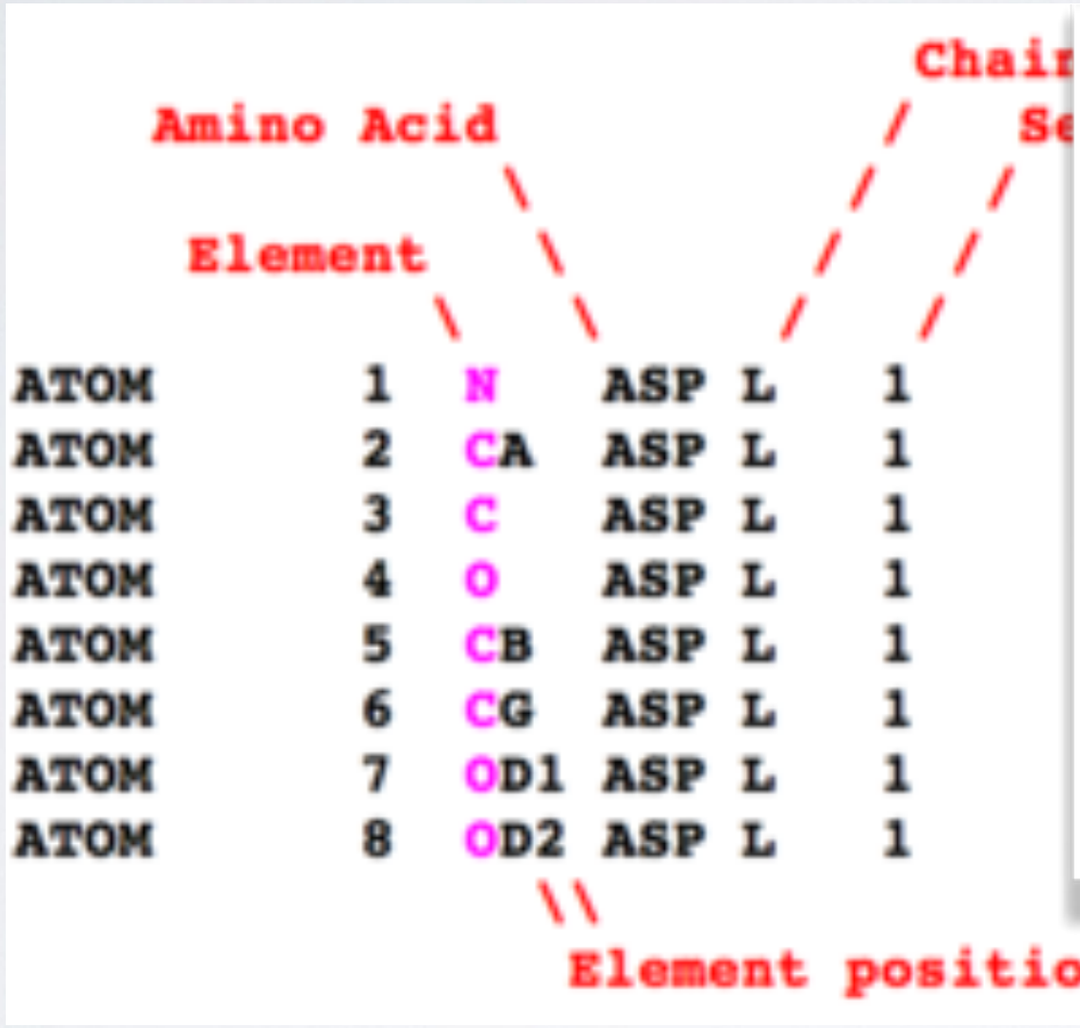
N.B. Remember to make your new **class11** RStudio project inside your GitHub tracked directory from last day and **UNCHECK** the "Create a Git repository" option...

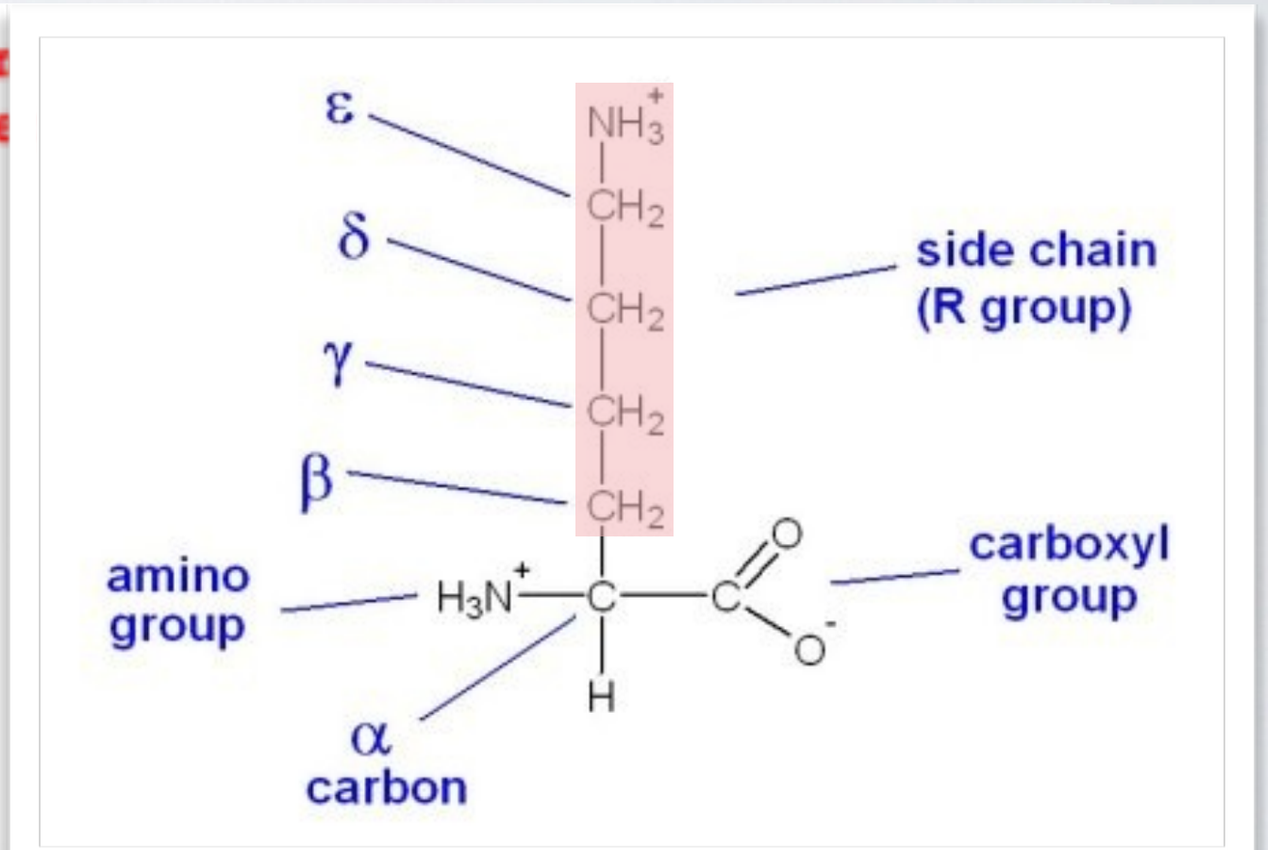
SIDE-NOTE: **PDB FILE FORMAT**

```
                                  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.

SIDE-NOTE: **PDB FILE FORMAT**





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

Do it Yourself!

Hand-on time!

https://bioboot.github.io/bggn213_W19/lectures/#11

Focus on **section 2** please!

N.B. You will need to have VMD installed on your computer (see class website and hands-on sheet for details)

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Focus on **section 3** to **5**

Side Note: Section 6.1

- Download MUSCLE for your OS from:
  https://www.drive5.com/muscle/downloads.htm

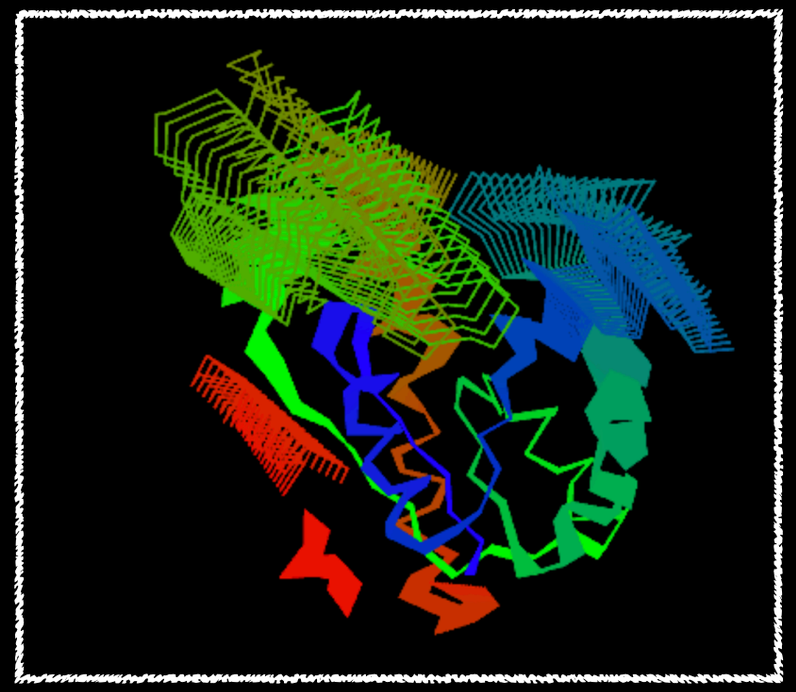
- On **MAC** use your TERMINAL to enter the commands:

```
> tar -xvf ~/Downloads/muscle3.8.31_i86darwin32.tar
> sudo mv muscle3.8.31_i86darwin32 /usr/local/bin/muscle
```

- On **Windows** use file explorer to:
  - Move the downloaded **muscle3.8.31_i86win32.exe** from your *Downloads* folder to your *Project* folder.
  - Then right click to rename to **muscle.exe**

```
> ./muscle.exe -version
```

Bio3D view()



- If you want the 3D viewer in your R markdown you can install the development version of bio3d.view

- In your R console:

```
> install.packages("devtools")
> devtools::install_bitbucket("Grantlab/bio3d-view")
```

- To use in your R session:

```
> library("bio3d.view")
> pdb <- read.pdb("5p21")
> view(pdb)
> view(pdb, "overview", col="sse")
```

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NMA in Bio3D

- Normal Mode Analysis (NMA) is a bioinformatics method that can predict the major motions of biomolecules.

```{r}
library(bio3d)
library(bio3d.view)
```

```{r}
pdb <- read.pdb("1hel")
modes <- nma( pdb )
m7 <- mktrj(modes, mode=7, file="mode_7.pdb")

view(m7, col=vec2color(rmsf(m7)))
```

SideNote: view()

- If you want the interactive 3D viewer in **Rmd** rendered to output: html_output document:

````
```{r}
library(bio3d.view)
library(rgl)
```
````

````
```{r}
modes <- nma( read.pdb("1hel") )
m7 <- mktrj(modes, mode=7, file="mode_7.pdb")

view(m7, col=vec2color(rmsf(m7)))
rglwidget(width=500, height=500)
```
````

Optional:
Stop here for Today!

[Muddy Point Assessment]

SUMMARY

- Structural bioinformatics is computer aided structural biology
- Described major motivations, goals and challenges of structural bioinformatics
- Reviewed the fundamentals of protein structure
- Explored how to use R to perform advanced custom structural bioinformatics analysis!
- Introduced both physics and knowledge based modeling approaches for describing the structure, energetics and dynamics of proteins computationally

[Muddy Point Assessment]