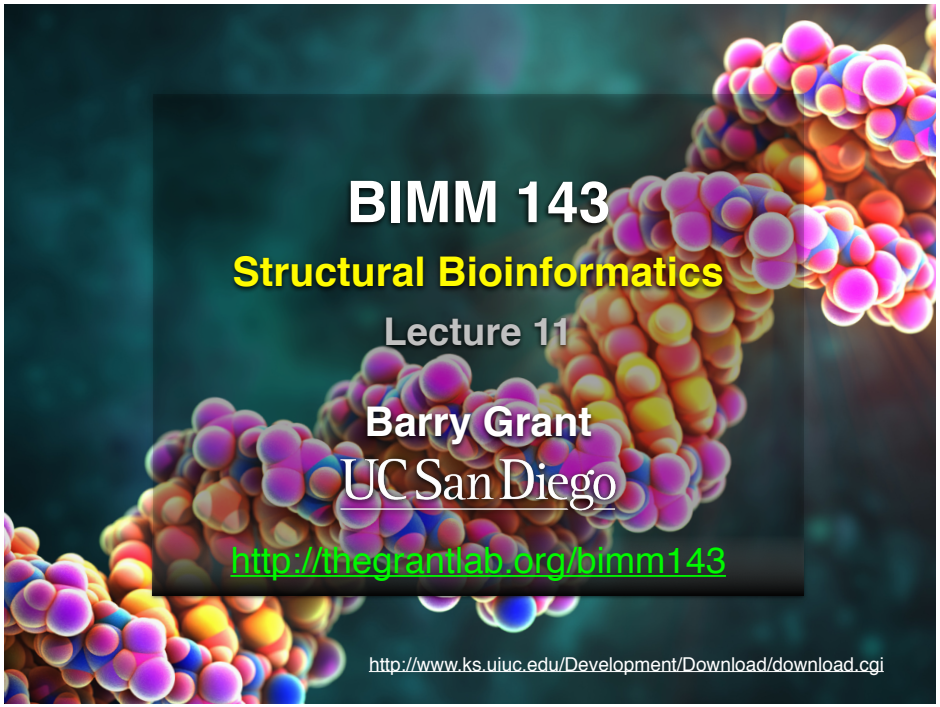

"*Bioinformatics is the application of computers to the collection, archiving, organization, and analysis of biological data.*"

… A hybrid of biology and computer science

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Bioinformatics is computer aided biology!

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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

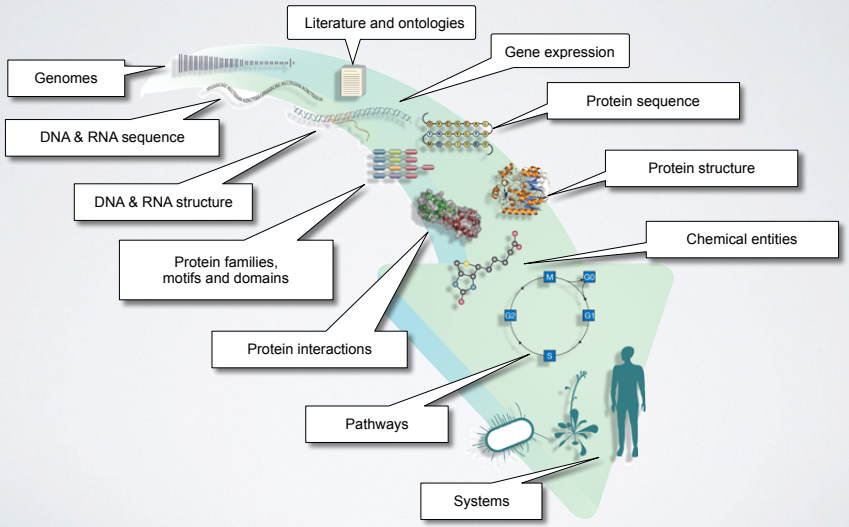
Why should we care?

Why should we care?

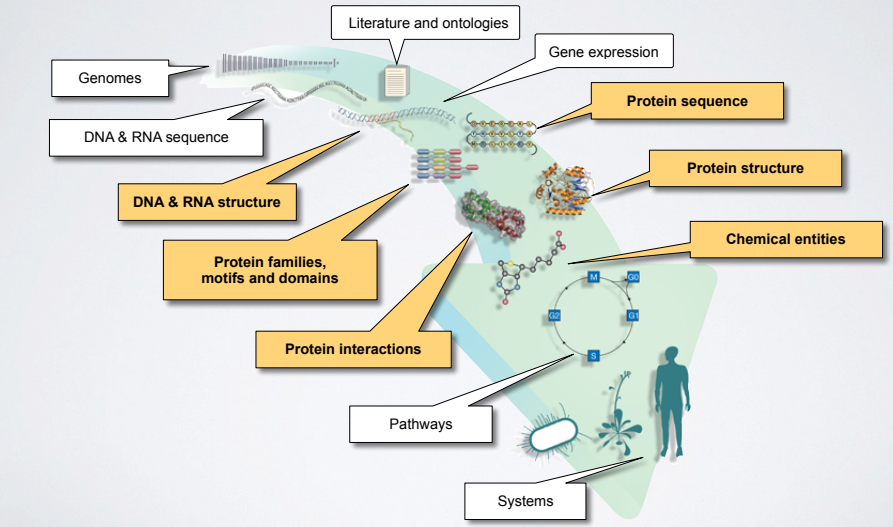
Because biomolecules are “nature’s robots”

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

BIOINFORMATICS DATA



STRUCTURAL DATA IS CENTRAL



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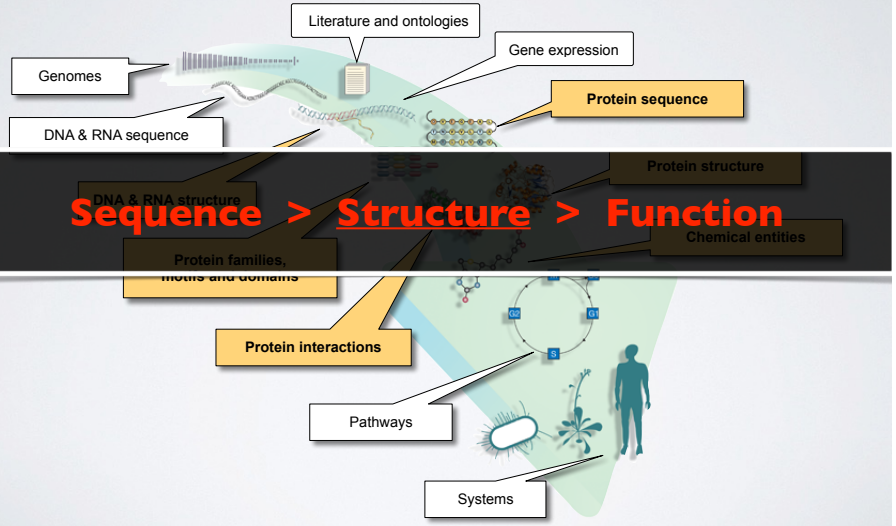

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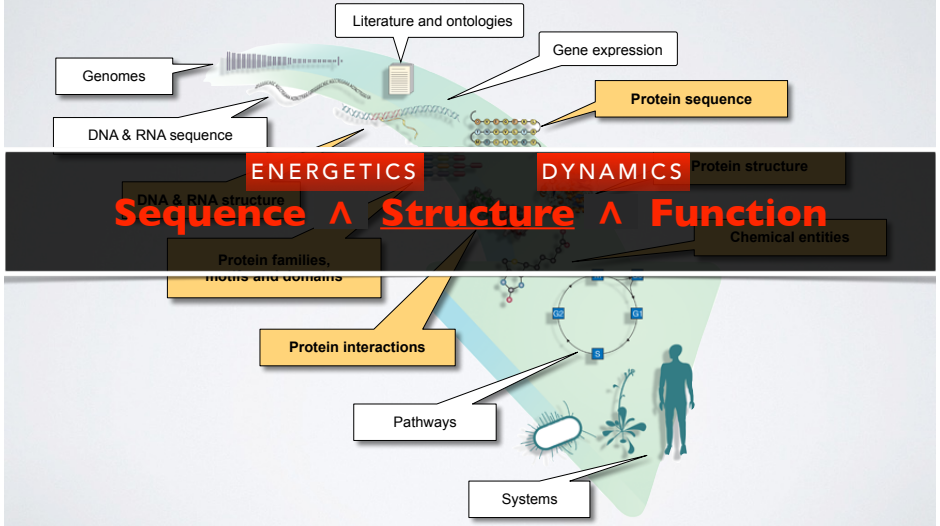
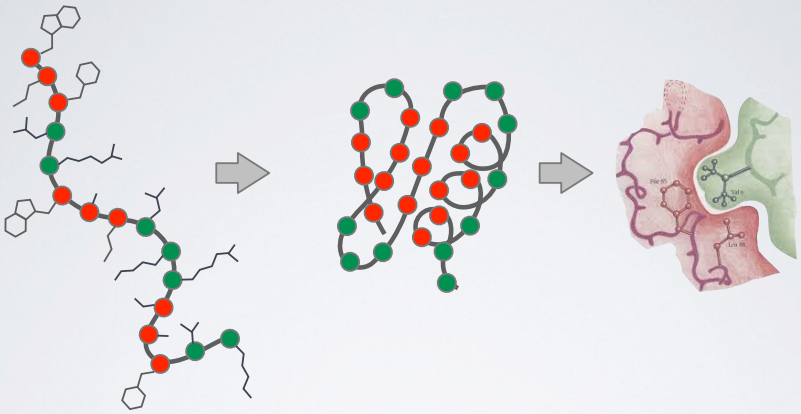




Sequence	Structure	Function
• Unfolded chain of amino acid chain • Highly mobile • Inactive	• Ordered in a precise 3D arrangment • Stable but dynamic	• Active in specific "conformations" • Specific associations & precise reactions

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

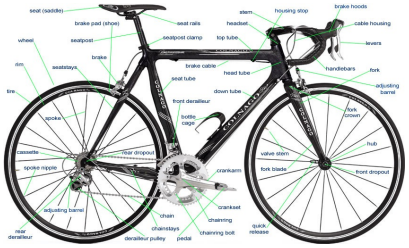
Genomics is a great start ….

Track Bike — DL 175

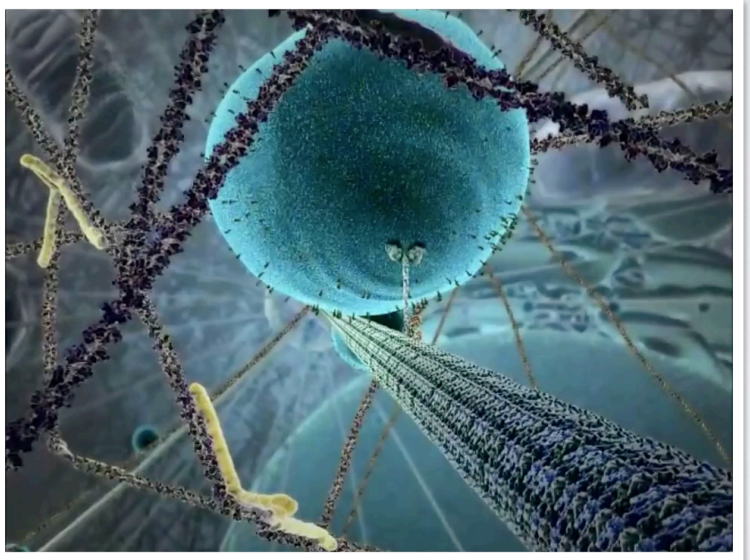
REF. NO.	IBM NO.	DESCRIPTION
1	156011	Track Frame 21", 22", 23", 24", Team Red
2	157040	Fork for 21" Frame
2	157039	Fork for 22" Frame
2	157038	Fork for 23" Frame
2	157037	Fork for 24" Frame
3	191202	Handlebar TTT Competition Track Alloy 15/16"
4		Handlebar Stem, TTT, Specify extension
5	191278	Expander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

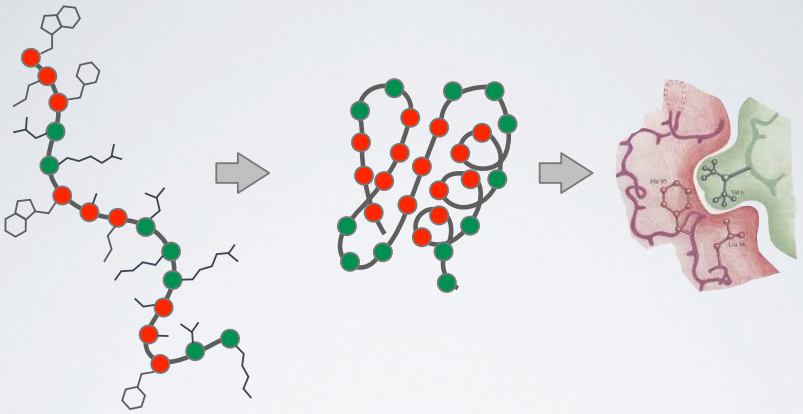
… but not the end



- 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]



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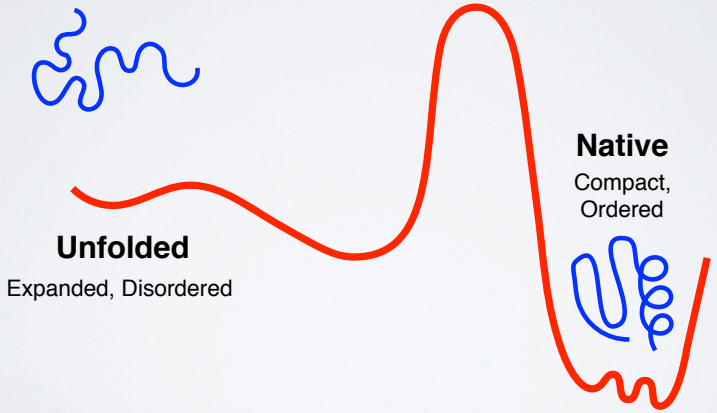
KEY CONCEPT: ENERGY LANDSCAPE



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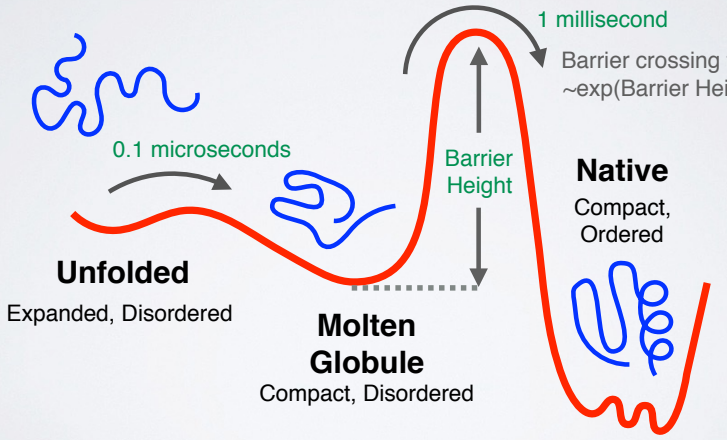

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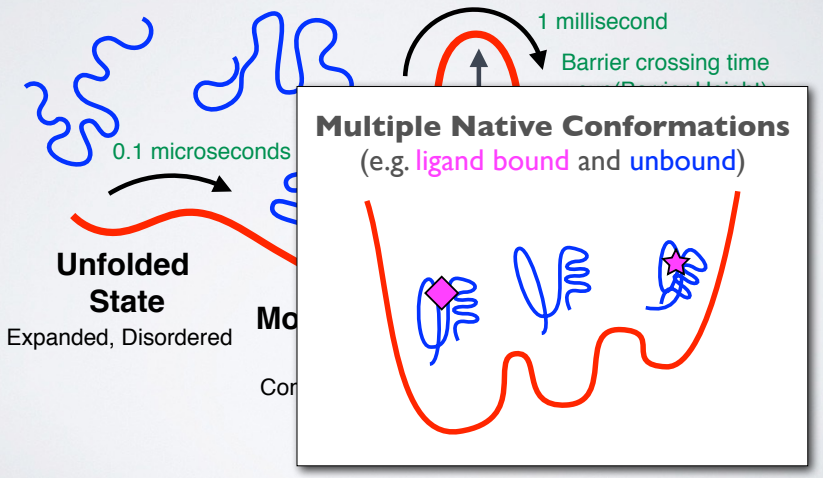

Today's Menu

- **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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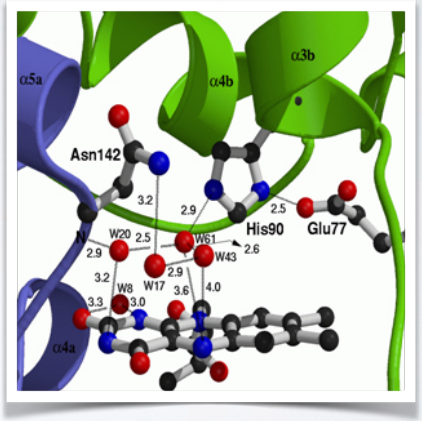
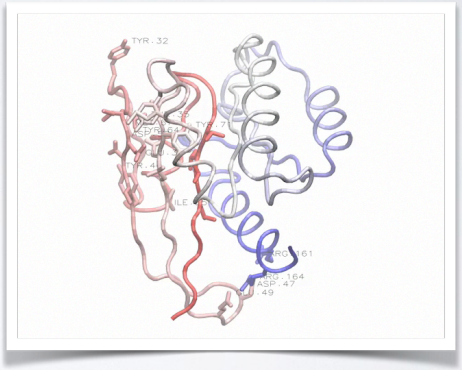
Motivation 1:
Detailed understanding of molecular interactions

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



Motivation 1:
Detailed understanding of molecular interactions

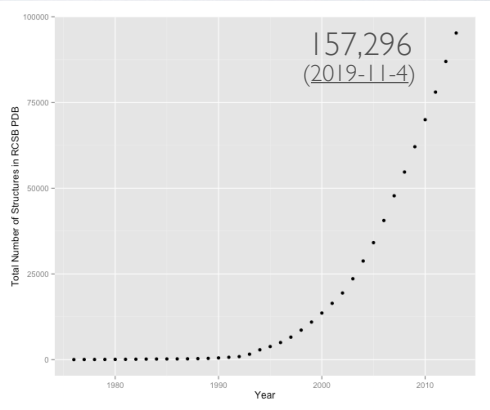
Computational modeling can provide detailed insight into functional interactions, their regulation and potential consequences of perturbation.



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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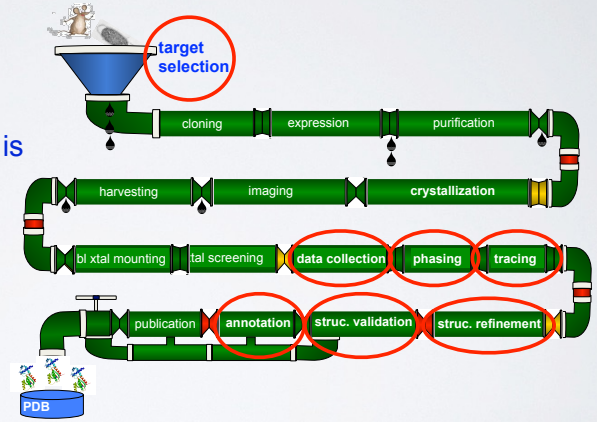
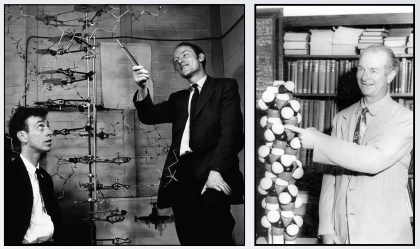


Image Credit: "Structure determination assembly line" Adam Godzik

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)

Goals:

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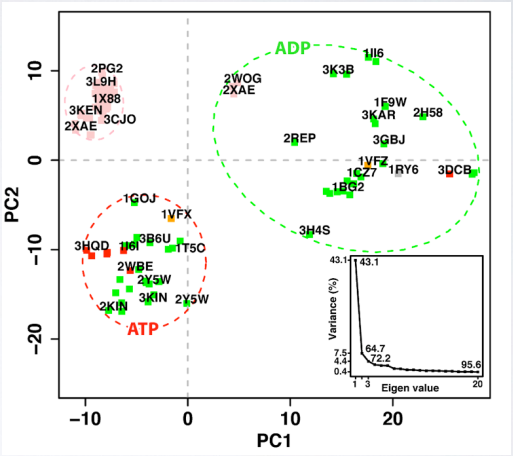

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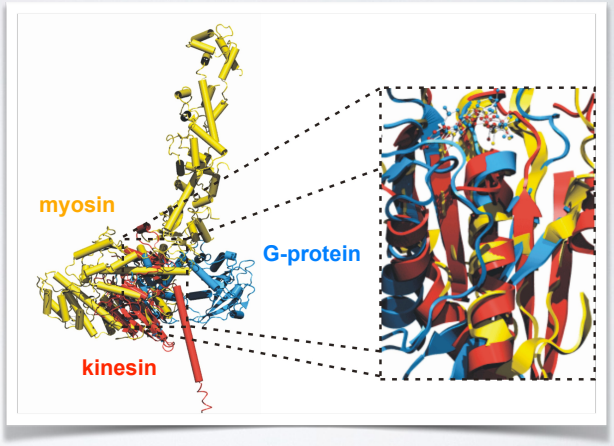

Grant *et al.* unpublished

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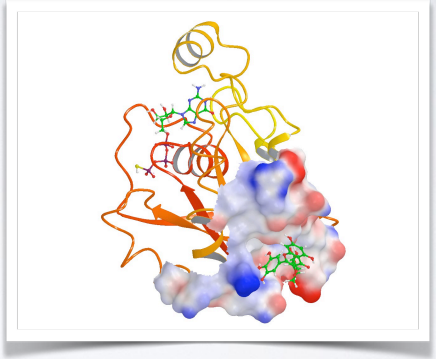

Grant *et al.* PLoS One (2011, 2012)

Goals:
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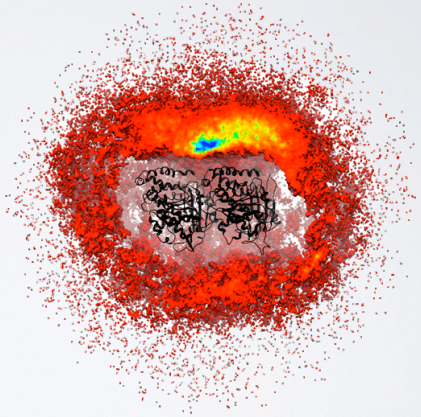

Grant *et al.* PLoS Biology (2011)

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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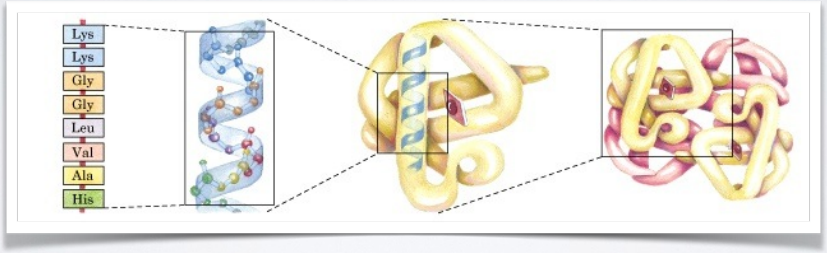
HIERARCHICAL STRUCTURE OF PROTEINS

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

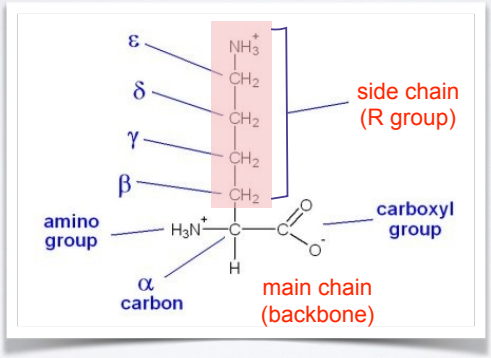


Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

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

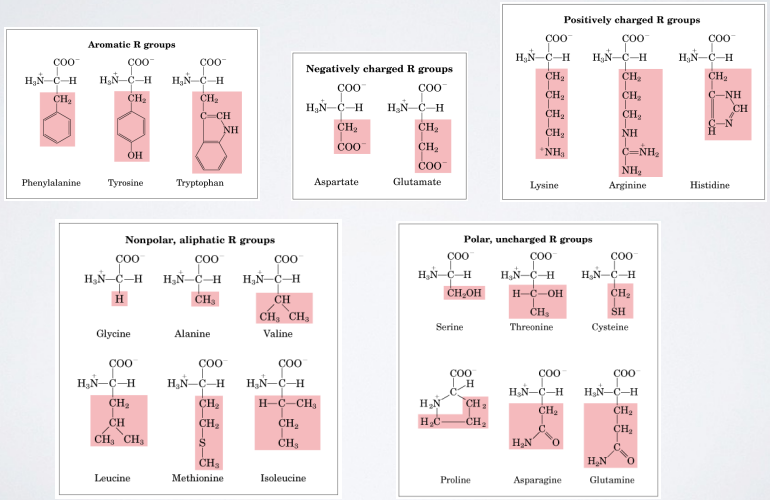
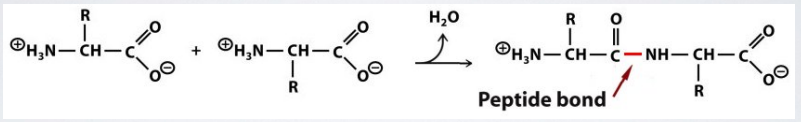


Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

AMINO ACIDS POLYMERIZE THROUGH **PEPTIDE BOND** FORMATION



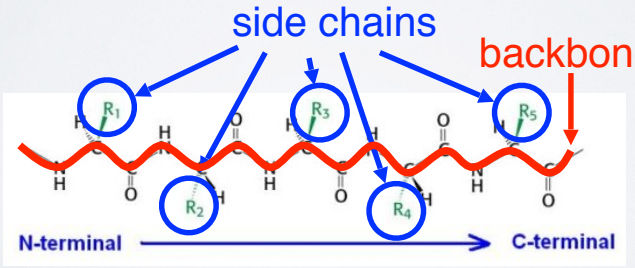
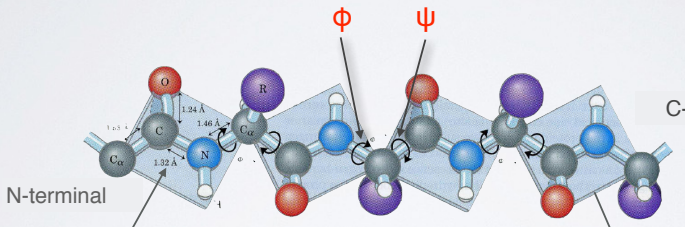


Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

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

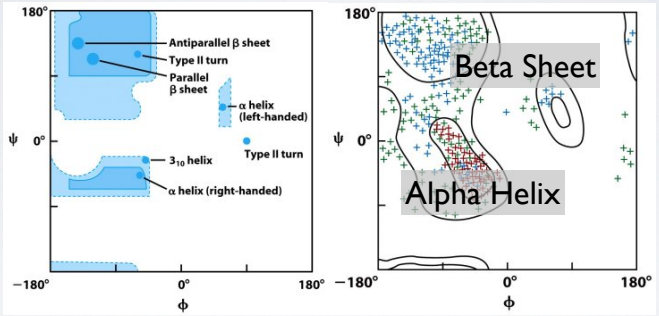


Bond angles and lengths are largely invariant

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/

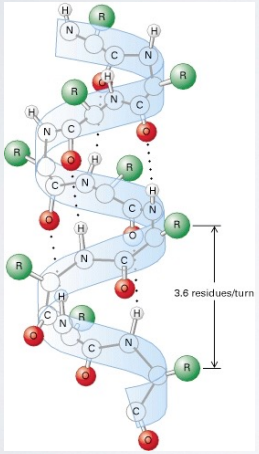
PHI vs PSI PLOTS ARE KNOWN AS **RAMACHANDRAN DIAGRAMS**



- 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

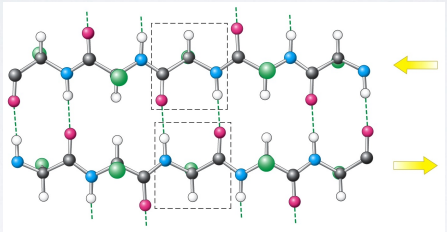


α-helix

- 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 antiparallel 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**

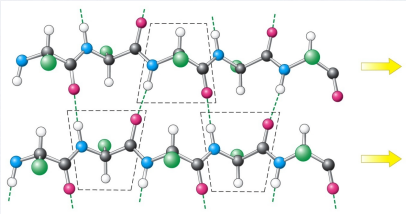


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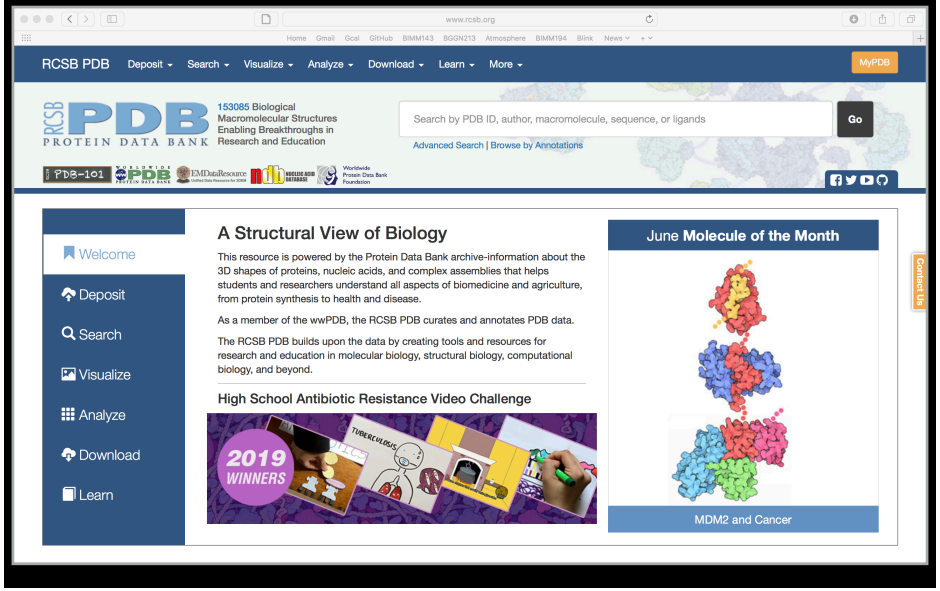
Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

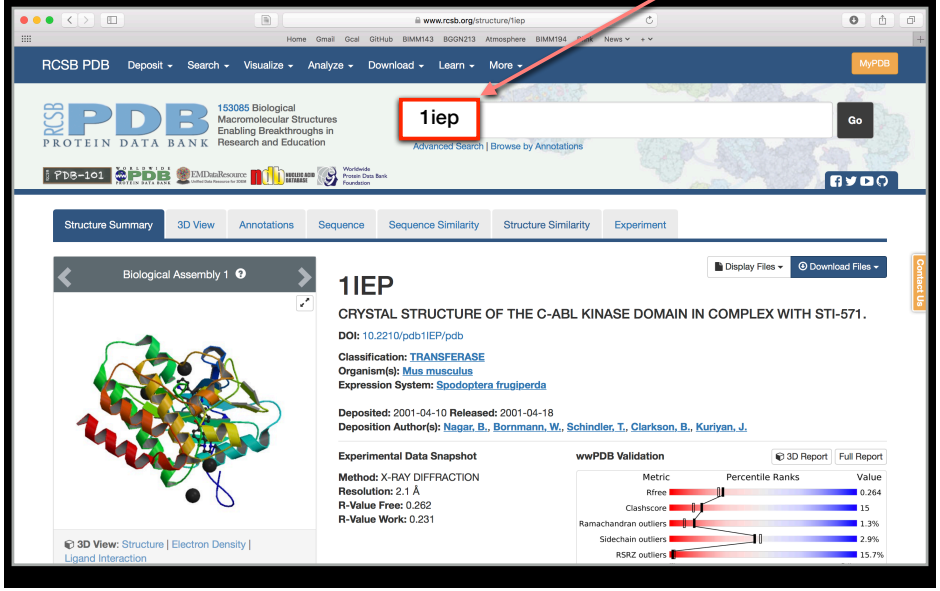
Protein Data Bank (PDB) is the main repository for Biomolecular structure data

http://www.rcsb.org



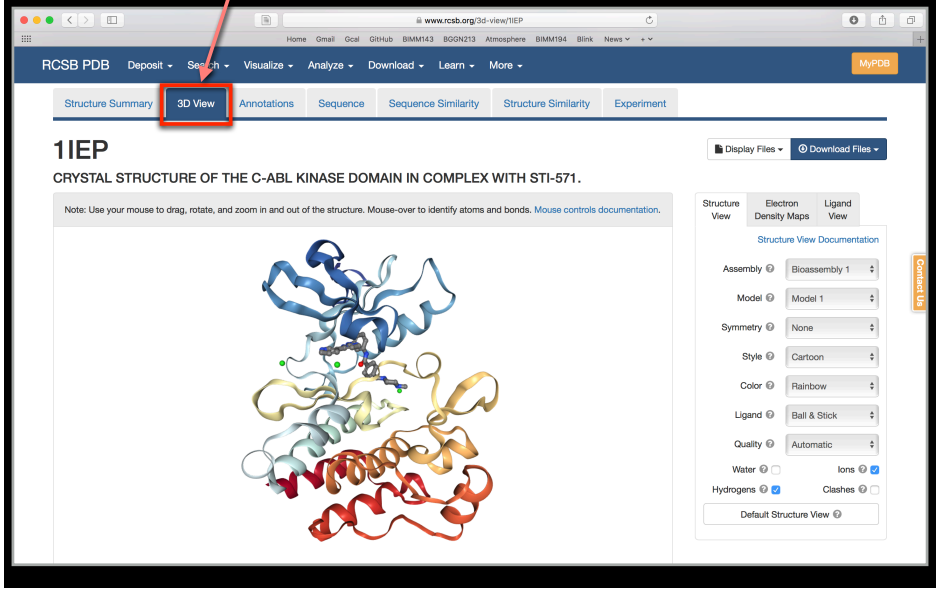
You can search by text (e.g. "ABL kinase"), PDB code (e.g. "1iep") or sequence

http://www.rcsb.org



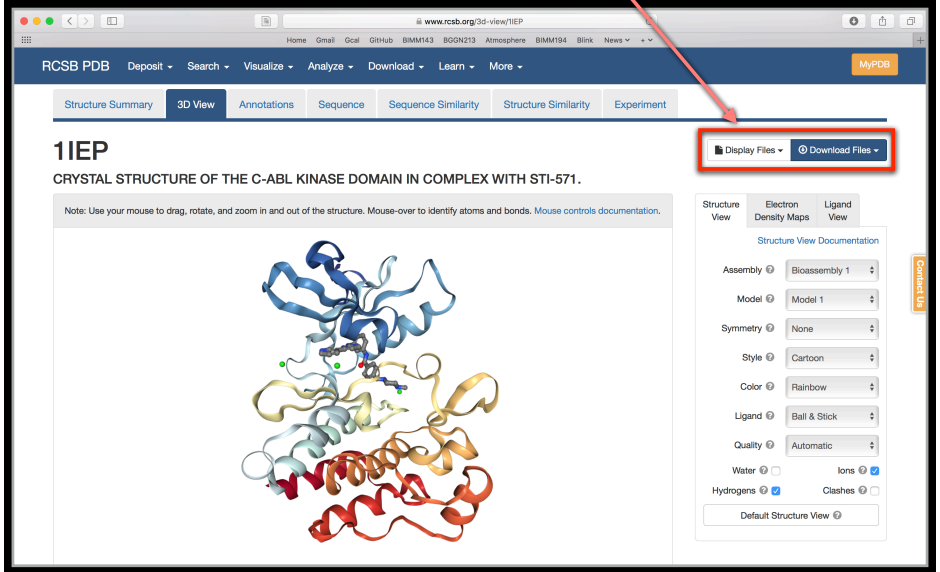
You can get a 3D View of and read details about the experiment and molecule

http://www.rcsb.org



You can display or download PDB format files for a particular entry

http://www.rcsb.org



Side-Note: PDB File Format

- PDB files contains atomic coordinates and associated information.

		Element	Amino Acid	Chain	Sequence/Residue Number	Coordinates X	Y	Z	(etc.)
ATOM	1	N	MET	A	1	19.353	41.547	-3.887	...
ATOM	2	CA	MET	A	1	20.513	40.939	-4.592	...
ATOM	3	C	MET	A	1	20.150	39.658	-5.355	...
ATOM	4	O	MET	A	1	19.053	39.551	-5.903	...
ATOM	5	CB	MET	A	1	21.642	40.678	-3.592	...
ATOM	6	CG	MET	A	1	21.233	39.903	-2.360	...
ATOM	7	SD	MET	A	1	22.533	39.928	-1.113	...
ATOM	8	CE	MET	A	1	23.771	38.881	-1.885	...
ATOM	9	N	ASP	A	2	21.068	38.694	-5.390	...
ATOM	10	CA	ASP	A	2	20.856	37.440	-6.117	...
ATOM	11	C	ASP	A	2	20.124	36.371	-5.299	...
ATOM	12	O	ASP	A	2	20.680	35.818	-4.351	...

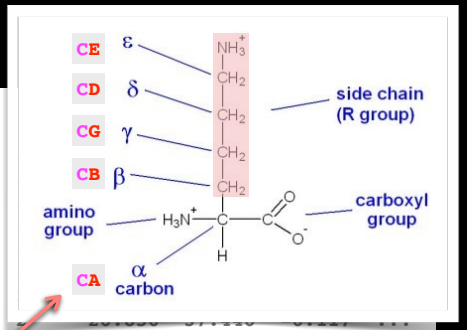
Element position within amino acid

Side-Note: PDB File Format

- PDB files contains atomic coordinates and associated information.

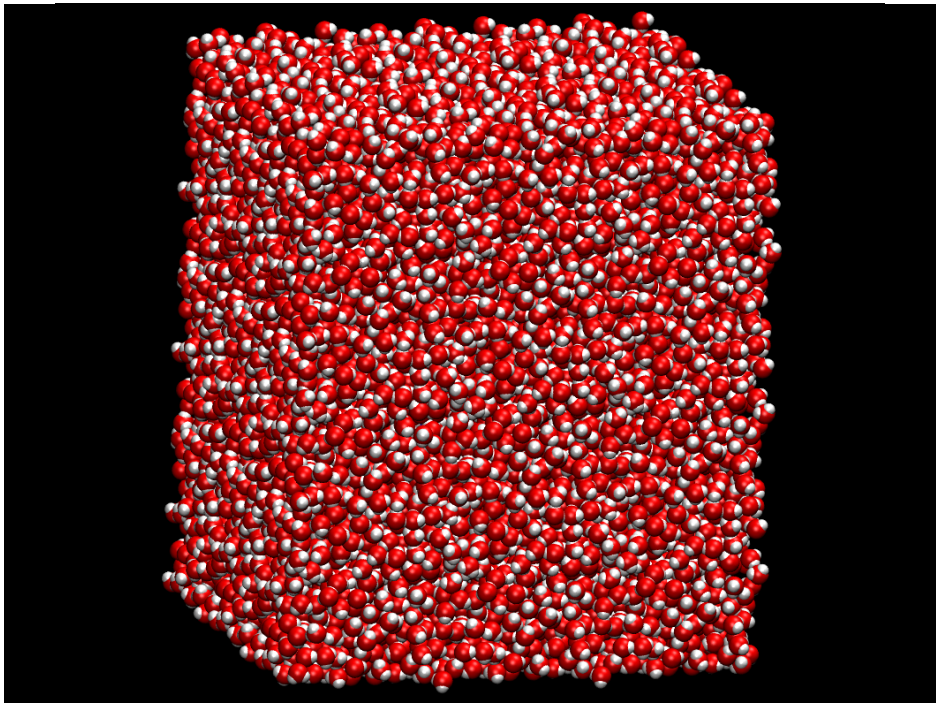
Element

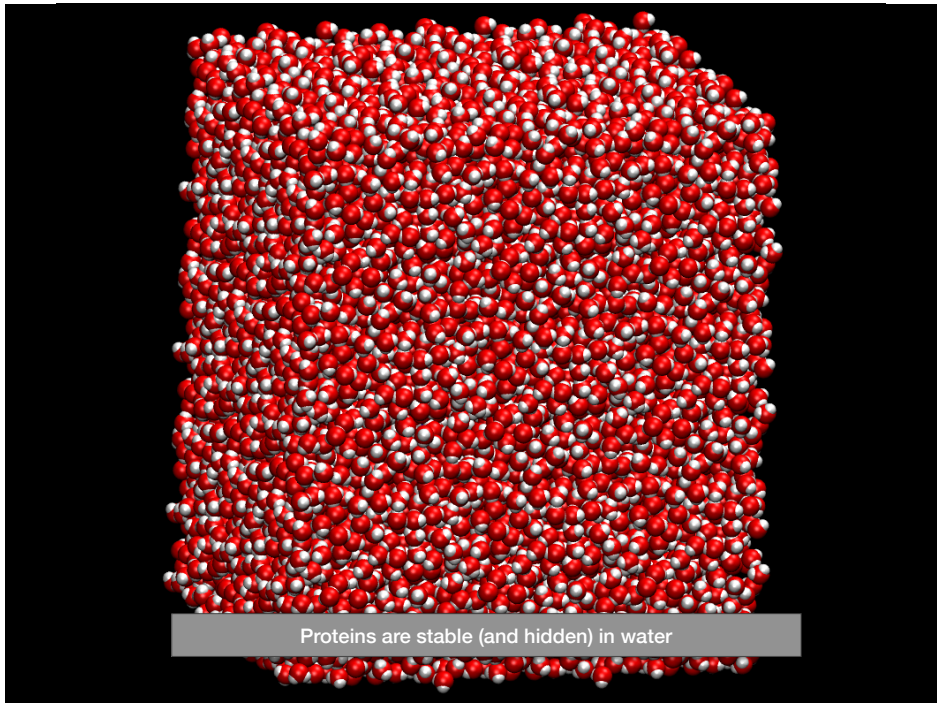
ATOM	1	N	MET	A					
ATOM	2	CA	MET	A					
ATOM	3	C	MET	A					
ATOM	4	O	MET	A					
ATOM	5	CB	MET	A					
ATOM	6	CG	MET	A					
ATOM	7	SD	MET	A					
ATOM	8	CE	MET	A					
ATOM	9	N	ASP	A	2	21.068	38.694	-5.390	...
ATOM	10	CA	ASP	A	2	20.856	37.440	-6.117	...
ATOM	11	C	ASP	A	2	20.124	36.371	-5.299	...
ATOM	12	O	ASP	A	2	20.680	35.818	-4.351	...

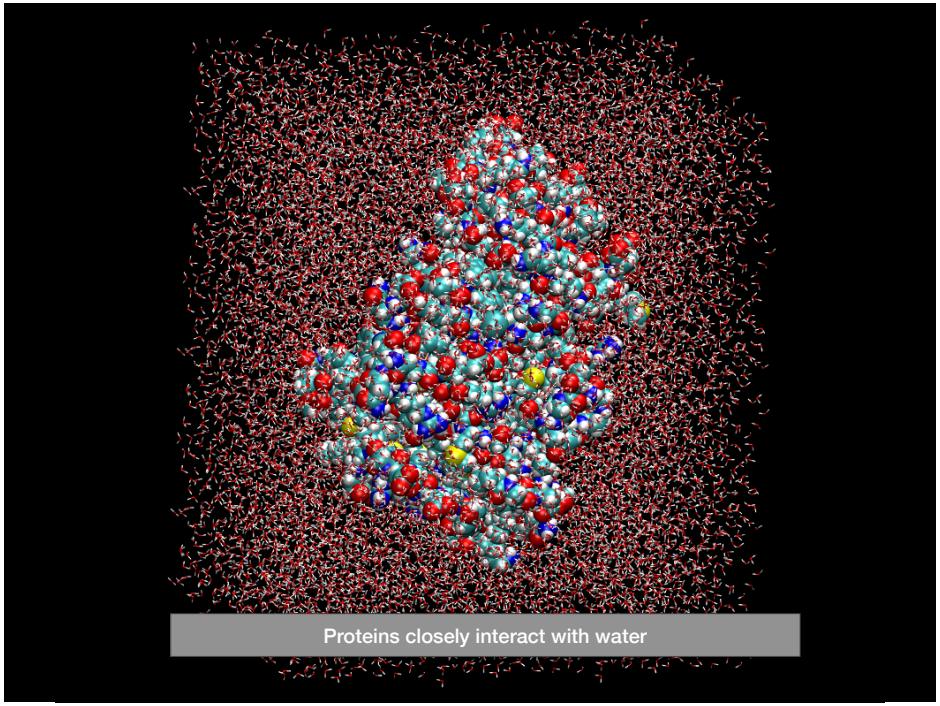


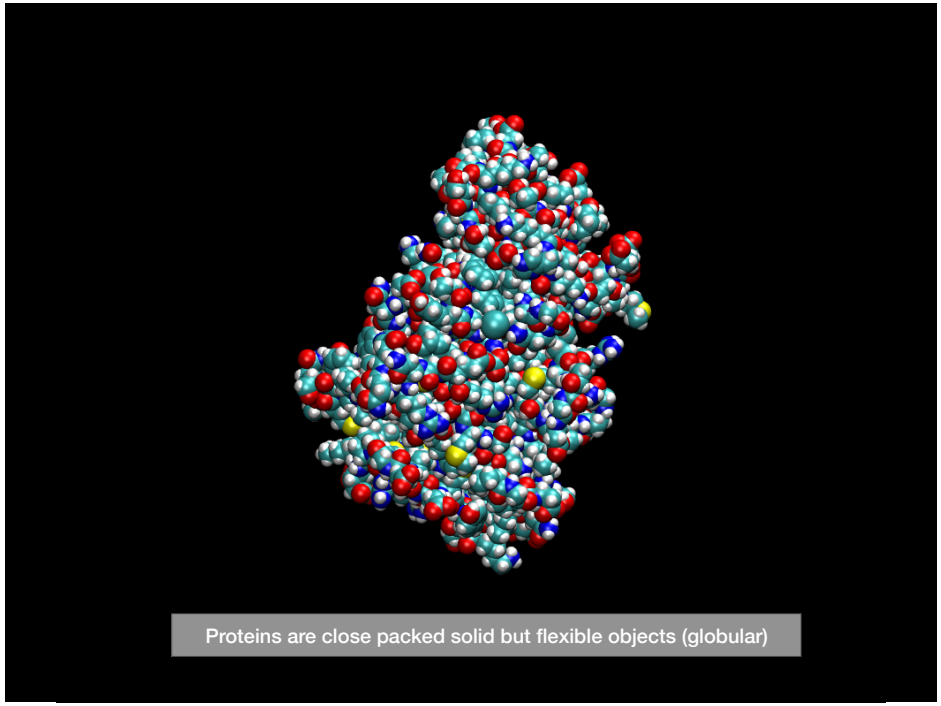
Element position within amino acid

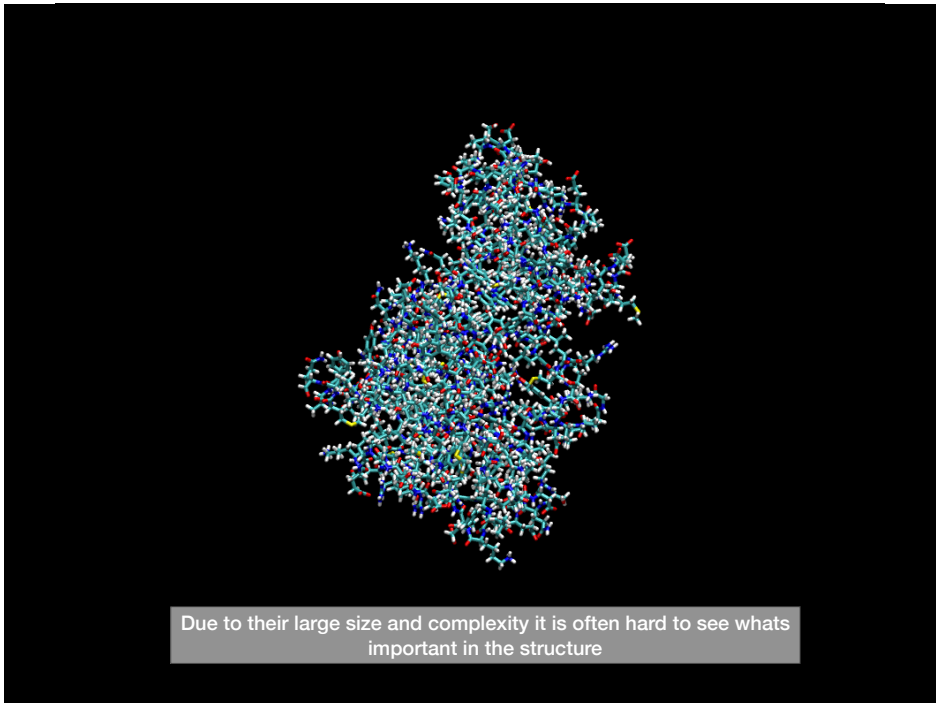
What Does a Protein Look like?



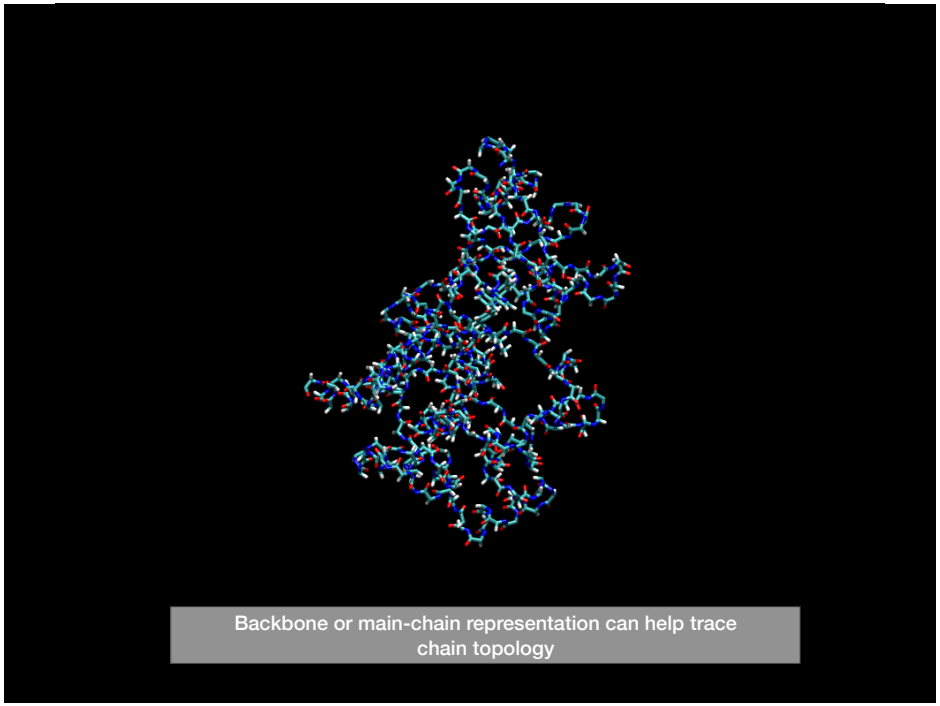

Proteins are stable (and hidden) in water


Proteins closely interact with water

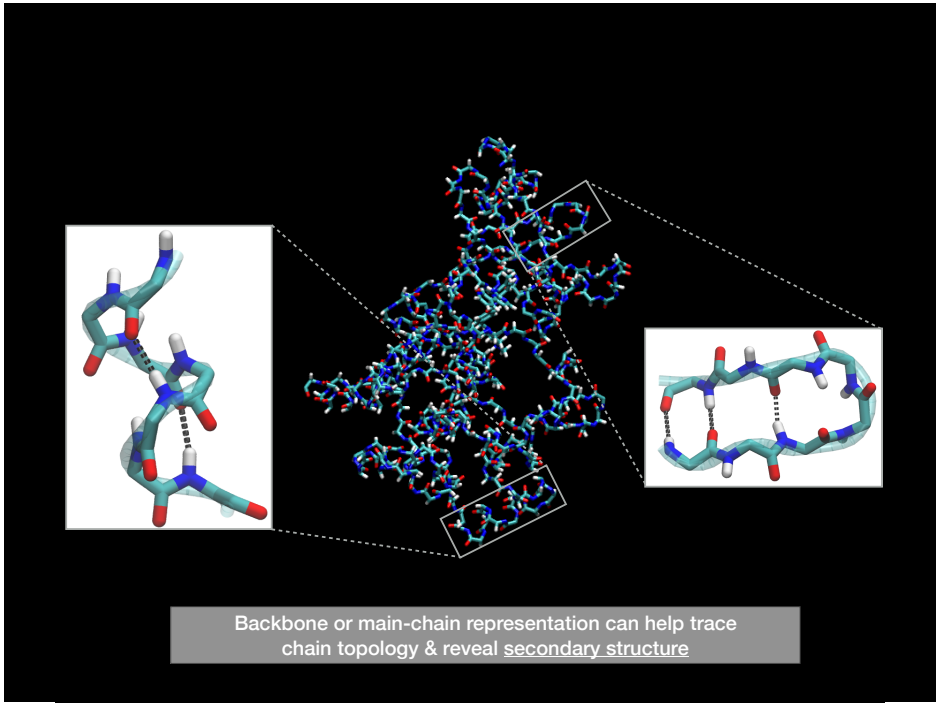

Proteins are close packed solid but flexible objects (globular)



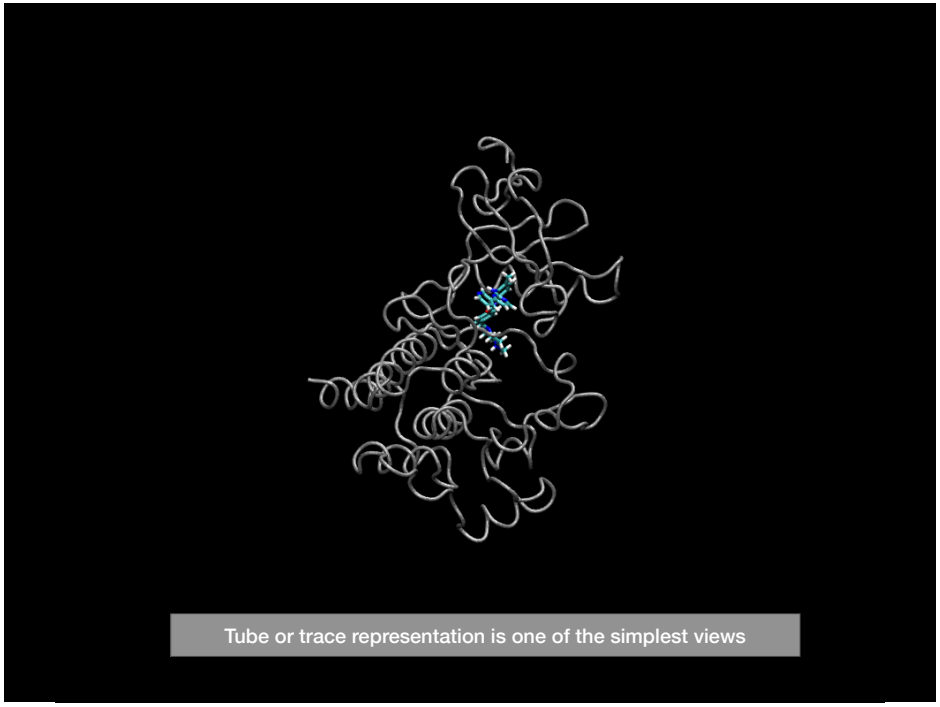
Due to their large size and complexity it is often hard to see whats important in the structure



Backbone or main-chain representation can help trace chain topology

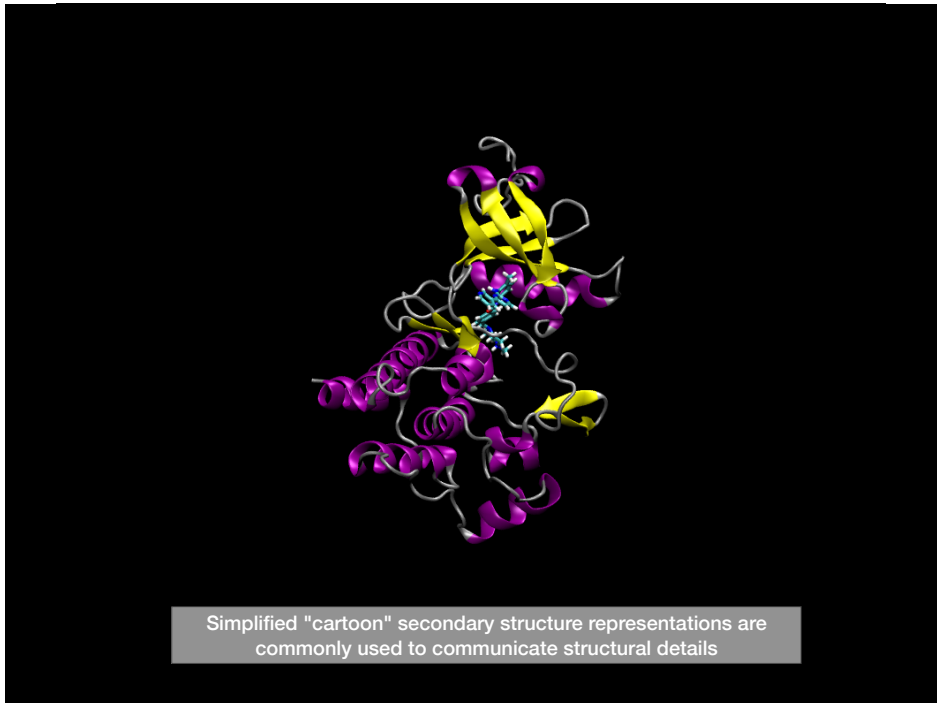


Backbone or main-chain representation can help trace chain topology & reveal secondary structure



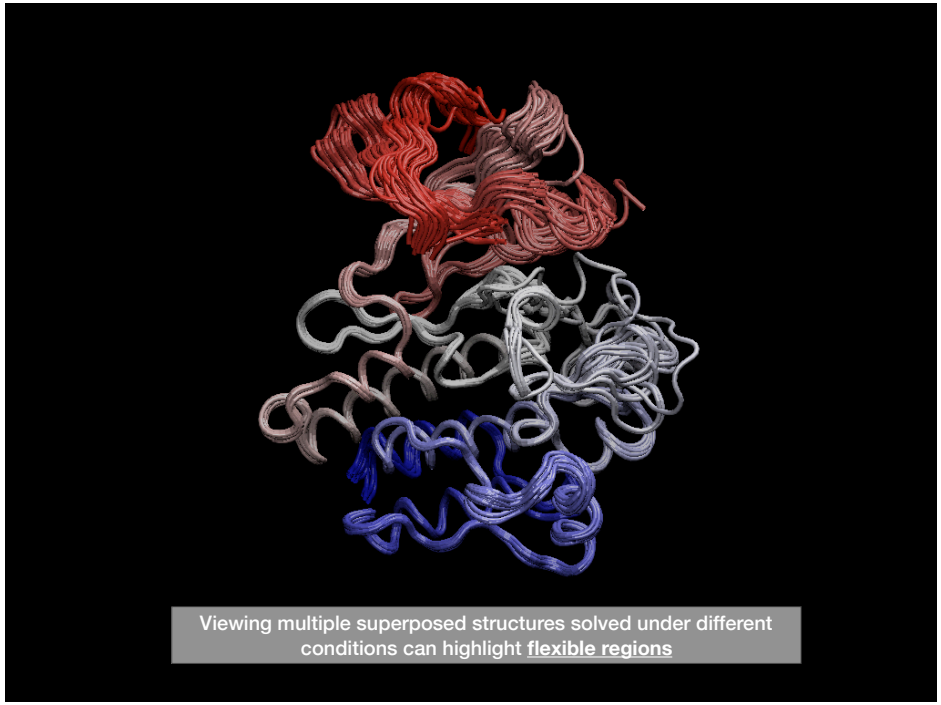
Tube or trace representation is one of the simplest views

Tube with added colors to highlight secondary structure

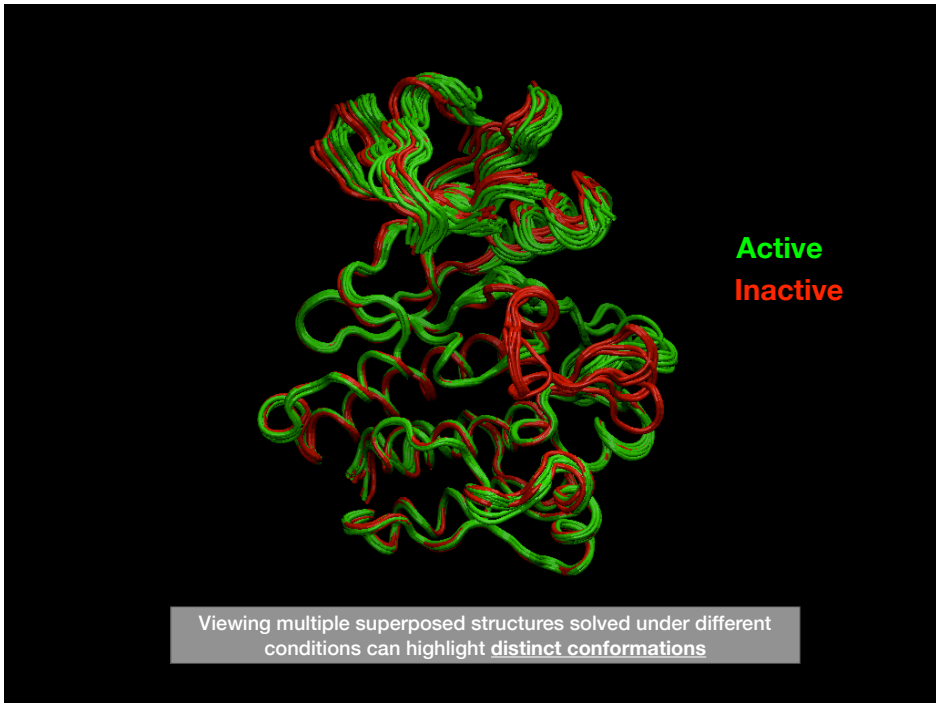


Simplified "cartoon" secondary structure representations are commonly used to communicate structural details

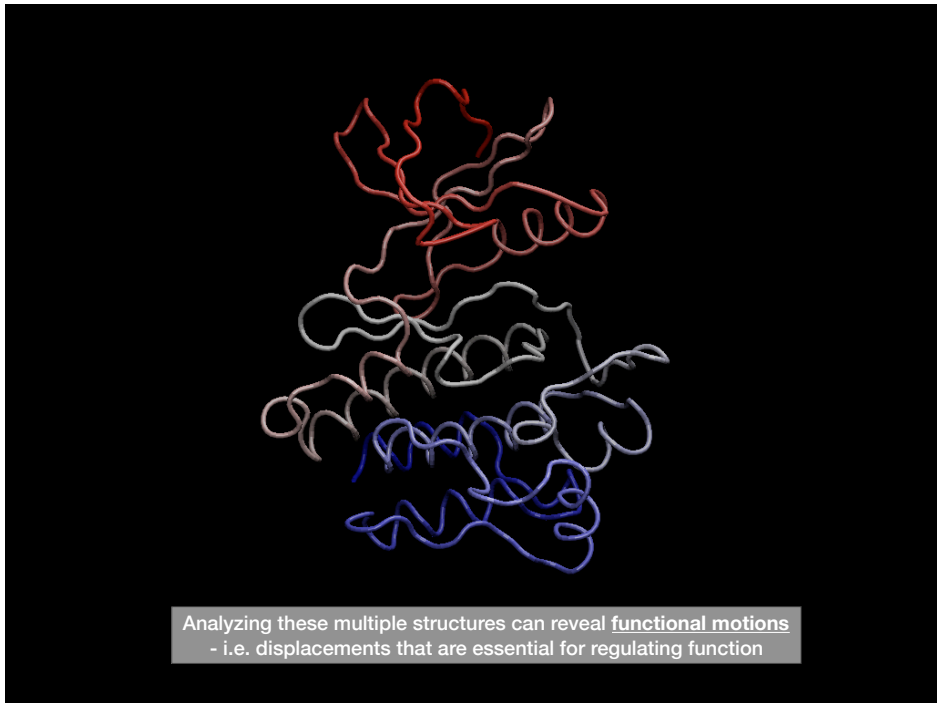
Viewing in 3D is often essential for interpretation.
Now we can clearly see 2° and 3° structure - the coiled chain of connected secondary structures



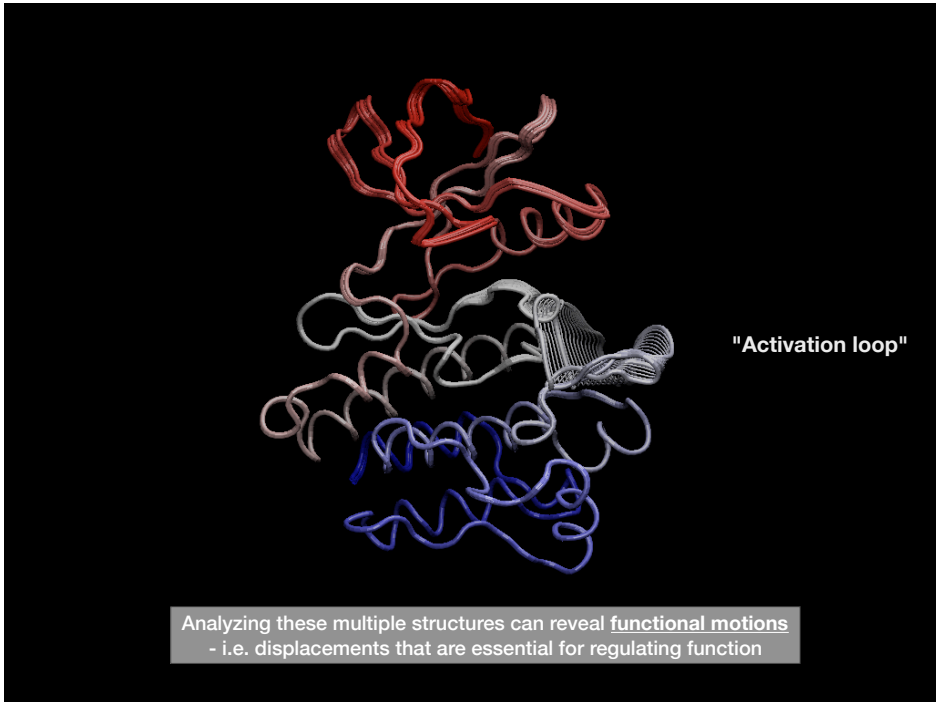
Viewing multiple superposed structures solved under different conditions can highlight **flexible regions**



Viewing multiple superposed structures solved under different conditions can highlight distinct conformations



Analyzing these multiple structures can reveal functional motions - i.e. displacements that are essential for regulating function



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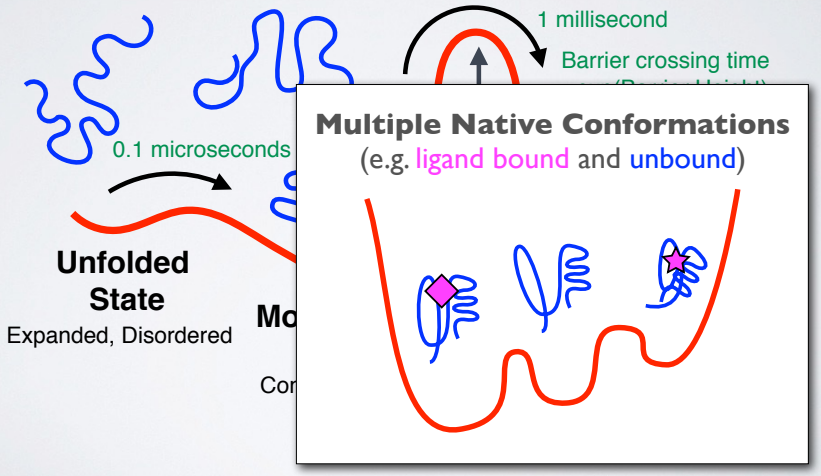
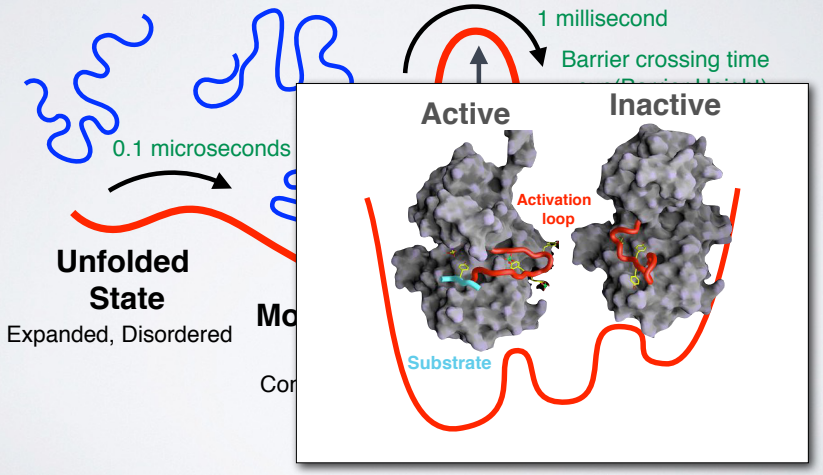
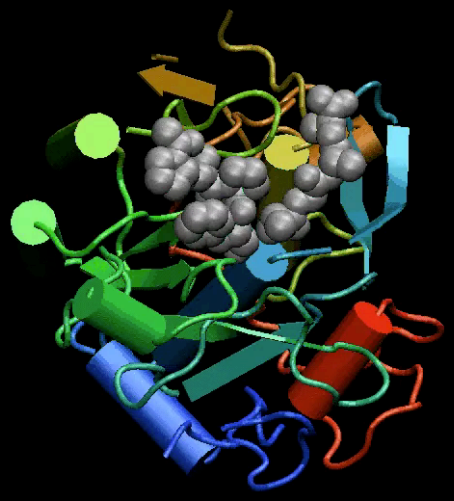
KEY CONCEPT: **ENERGY LANDSCAPE**



KEY CONCEPT: **ENERGY LANDSCAPE**



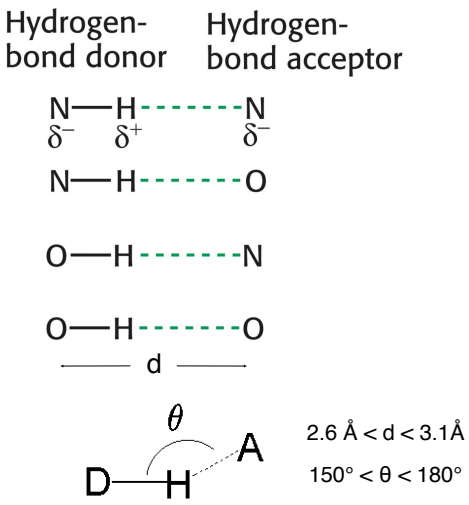
Normal **M**ode **A**nalysis (NMA) models the protein as a network of elastic strings



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

Key forces affecting structure:

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



2.6 Å < d < 3.1Å

150° < θ < 180°

Key forces affecting structure:

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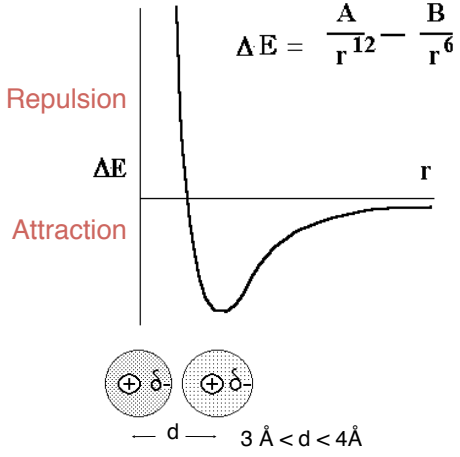
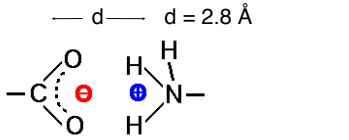
- Van der Waals
- Electrostatics
- Hydrophobicity



3 Å < d < 4Å

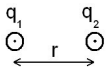
Key forces affecting structure:

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



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
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- Electrostatics
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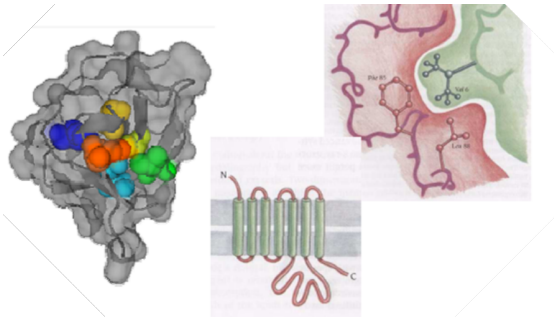

The force that causes hydrophobic molecules or nonpolar portions of molecules to aggregate together rather than to dissolve in water is called Hydrophobicity (Greek, "water fearing"). This is not a separate bonding force; rather, it is the result of the energy required to insert a nonpolar molecule into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

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

- PDB files contains atomic coordinates and associated information.

Amino Acid | Sequence/Residue Number | Coordinates

Element | Chain | X | Y | Z | (etc.)

```
ATOM      1  N   MET A   1      19.353  41.547  -3.887  ...
ATOM      2  CA  MET A   1      20.513  40.939  -4.592  ...
ATOM      3  C   MET A   1      20.150  39.658  -5.355  ...
ATOM      4  O   MET A   1      19.053  39.551  -5.903  ...
ATOM      5  CB  MET A   1      21.642  40.678  -3.592  ...
ATOM      6  CG  MET A   1      21.233  39.903  -2.360  ...
ATOM      7  SD  MET A   1      22.533  39.928  -1.113  ...
ATOM      8  CE  MET A   1      23.771  38.881  -1.885  ...
ATOM      9  N   ASP A   2      21.068  38.694  -5.390  ...
ATOM     10  CA  ASP A   2      20.856  37.440  -6.117  ...
ATOM     11  C   ASP A   2      20.124  36.371  -5.299  ...
ATOM     12  O   ASP A   2      20.680  35.818  -4.351  ...
```

Element position within amino acid

Side-Note: PDB File Format

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Element

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ATOM      1  N   MET A
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ATOM      3  C   MET A
ATOM      4  O   MET A
ATOM      5  CB  MET A
ATOM      6  CG  MET A
ATOM      7  SD  MET A
ATOM      8  CE  MET A
ATOM      9  N   ASP A
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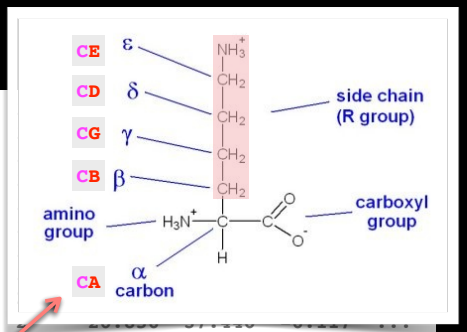
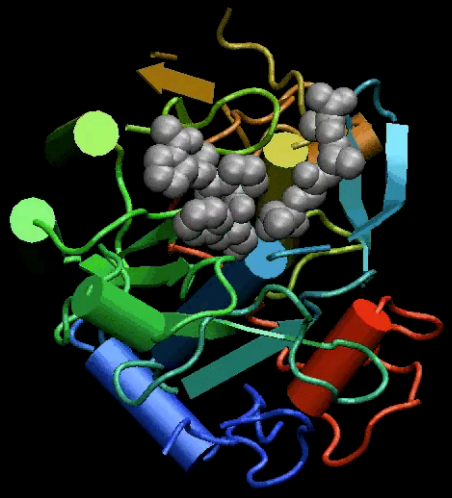
```



Element position within amino acid

Download VMD



Hands-on Time!

Focus on **section 2** of "*Lab Sheet*" (using VMD)

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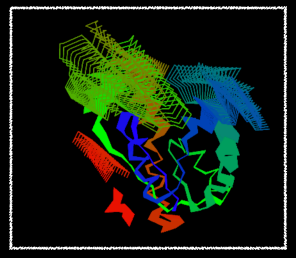
Do it Yourself!

Hand-on time!

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

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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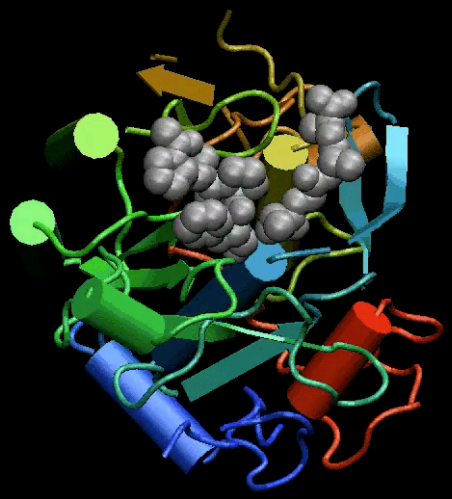
NMA models the protein as a network of elastic strings



Proteinase K

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)))
```

Bio3D 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)
```

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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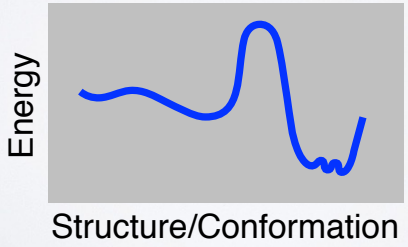
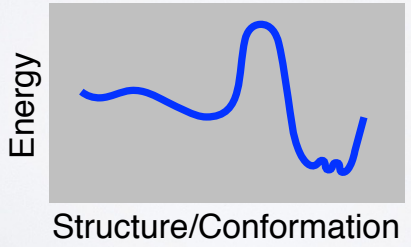


This will be the focus of the next class!



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]