STRUCTURAL BIOINFORMATICS

Barry Grant
University of Michigan
www.thegrantlab.org

MODULE OVERVIEW

Objective: Provide an introduction to the practice of bioinformatics as well as a practical guide to using common bioinformatics databases and algorithms

1.1. *Introduction to Bioinformatics*

1.2. *Sequence Alignment and Database Searching*

1.3 *Structural Bioinformatics*

1.4 *Genome Informatics: High Throughput Sequencing Applications and Analytical Methods*

WEEK TWO REVIEW

☑ **Answers to last weeks homework** (19/19):
Answers week 2

☑ **Muddy Point Assessment** (11/19):
Responses

- *"More time to finish the assignment"*
- *"I felt there was too much material to cover in one lab"*
- *"The [NCBI] sites were so slow"*
- *"More time with HMMER would be helpful"*
- *"Very nice lab"*

Q18: NW DYNAMIC PROGRAMMING

Match: +2
Mismatch: -1
Gap: -2

```
ATTGC
| | |
AGTTC

A-TTGC
| || |
AGTT-C
```

		A	G	T	T	C
	0	-2	-4	-6	-8	-10
A	-2	+2	0	-2	-4	-6
T	-4	0	+1	+2	0	-2
T	-6	-2	-1	+3	+4	+2
G	-8	-4	0	+1	+2	+3
C	-10	-6	-2	-1	0	+4

THIS WEEK'S HOMEWORK

☑ Check out the "**Background Reading**" material online:
- Achievements & Challenges in Structural Bioinformatics
- Protein Structure Prediction
- Biomolecular Simulation
- Computational Drug Discovery

☑ Complete the **lecture 1.3 homework questions**:
http://tinyurl.com/bioinf525-quiz3

"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!

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

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

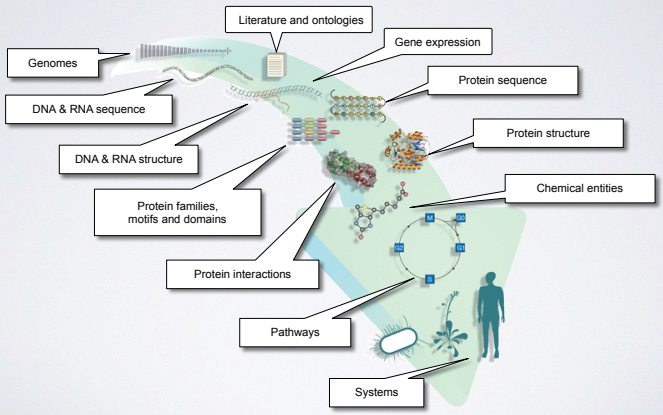
Why should we care?

Why should we care?

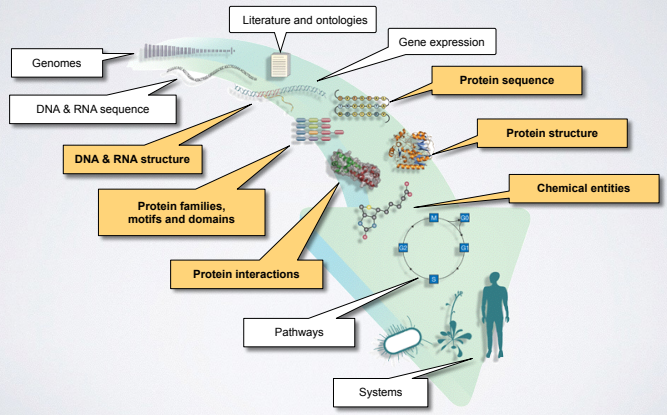
Because biomolecules are "nature's robots"

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

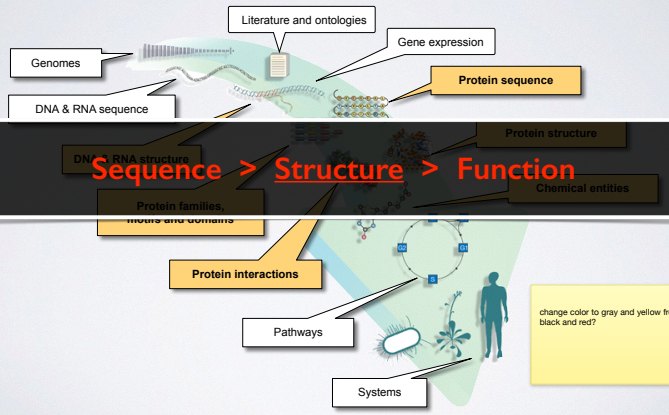
BIOINFORMATICS DATA



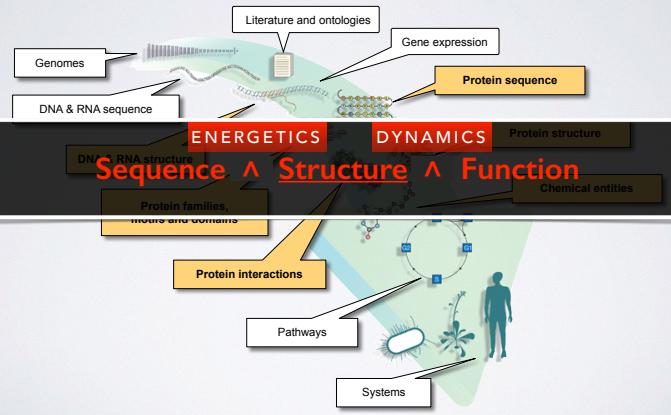
STRUCTURAL DATA IS CENTRAL

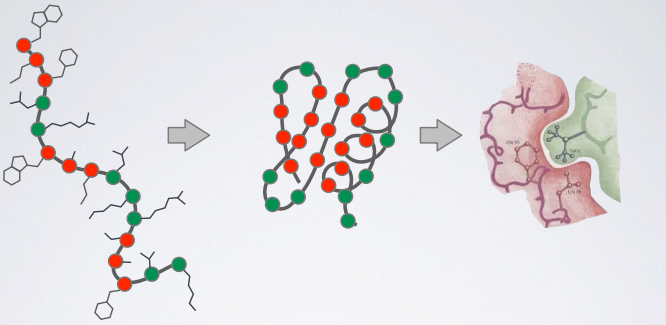


STRUCTURAL DATA IS CENTRAL



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*

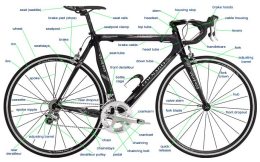
Genomics is a great start ….

Track Bike — DL175

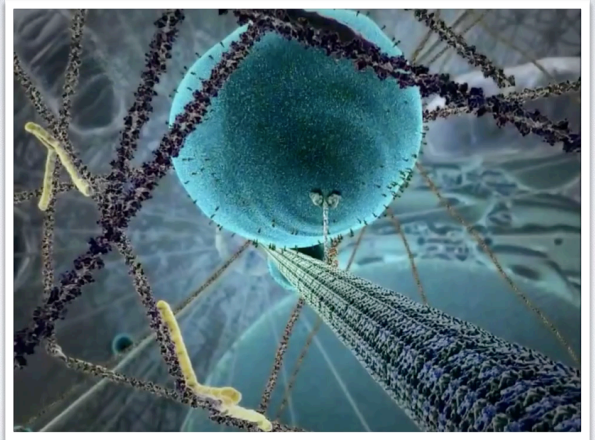
REF. NO.	IBM NO.	DESCRIPTION
1	156011	Track Frame 21", 22", 23", 24", Team Red
2	157040	Fork for 21" Frame
2	157039	Fork for 22" Frame
2	157038	Fork for 23" Frame
2	157037	Fork for 24" Frame
3	191202	Handlebar TTT Competition Track Alloy 15/16"
4		Handlebar Stem, TTT, Specify extension
5	191278	Expander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

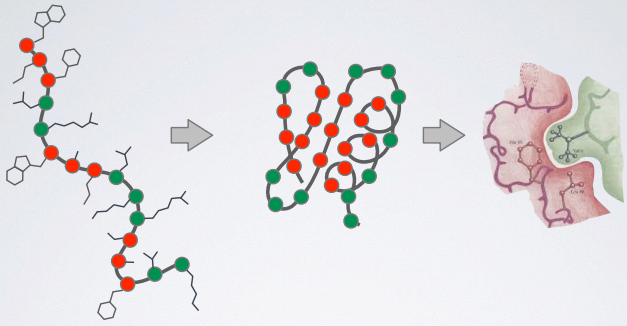
… but not the end



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

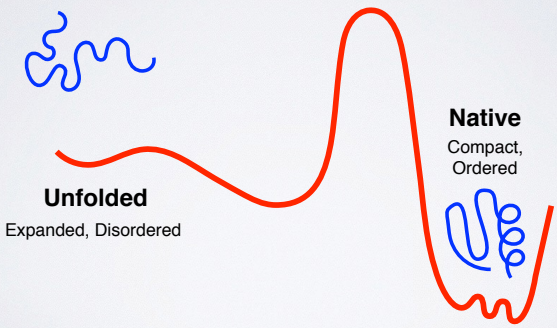


Extracted from The Inner Life of a Cell by Cellular Visions and Harvard
[YouTube link: https://www.youtube.com/watch?v=y-uuk4Pr2i8]

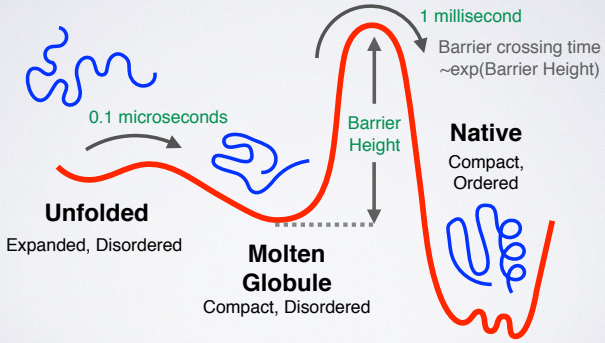


Sequence	Structure	Function
• Unfolded chain of amino acid chain • Highly mobile • Inactive	• Ordered in a precise 3D arrangment • Stable but dynamic	• Active in specific "conformations" • Specific associations & precise reactions

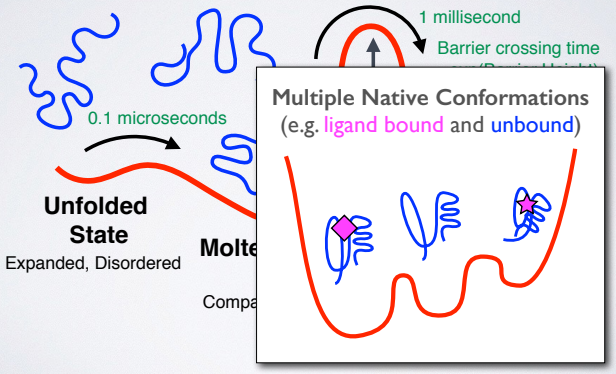
KEY CONCEPT: ENERGY LANDSCAPE



KEY CONCEPT: ENERGY LANDSCAPE



KEY CONCEPT: **ENERGY LANDSCAPE**



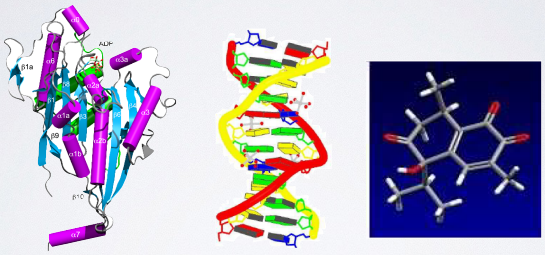
OUTLINE:

- **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

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

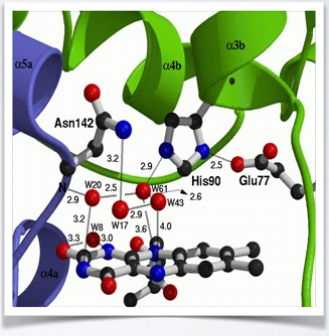
TRADITIONAL FOCUS **PROTEIN**, **DNA** AND **SMALL MOLECULE** DATA SETS WITH **MOLECULAR STRUCTURE**



Protein (PDB) | DNA (NDB) | Small Molecules (CCDB)

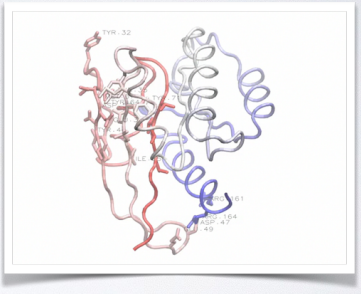
Motivation 1:
Detailed understanding of molecular interactions

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



Motivation 1:
Detailed understanding of molecular interactions

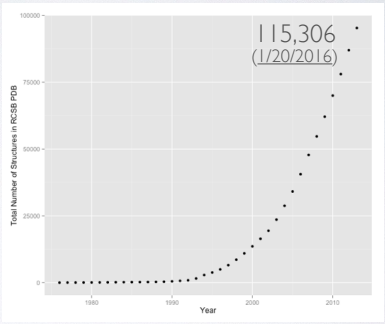
Computational modeling can provide detailed insight into functional interactions, their regulation and potential consequences of perturbation.



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

Motivation 2:
Lots of structural data is becoming available

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

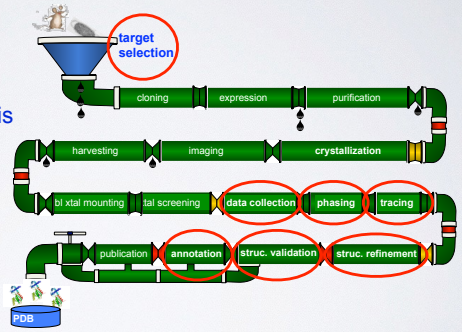
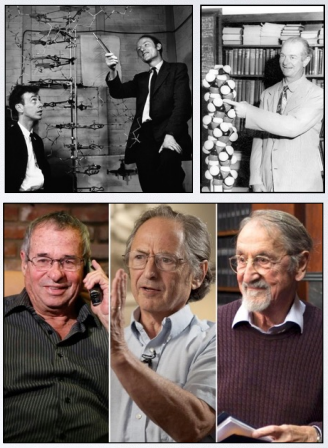


Image Credit: "Structure determination assembly line" Adam Godzik

Motivation 3:
Theoretical and computational predictions have been, and continue to be, enormously valuable and influential!



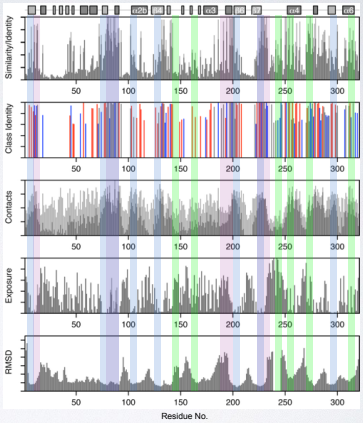
SUMMARY OF KEY **MOTIVATIONS**

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

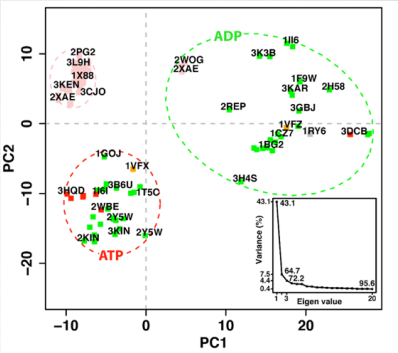


Grant *et al.* JMB. (2007)

Goals:
- Analysis
- Visualization
- Comparison
- Prediction
- Design

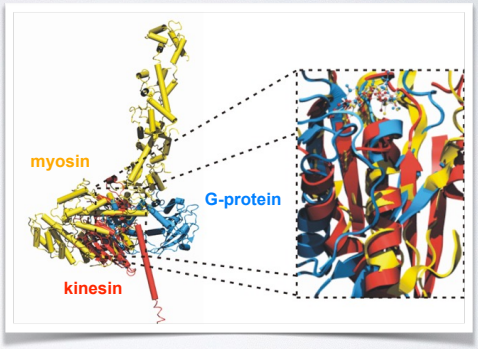
Scarabelli and Grant. PLoS. Comp. Biol. (2013)

Goals:
- Analysis
- Visualization
- Comparison
- Prediction
- Design



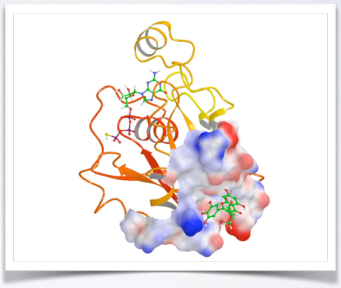
Scarabelli and Grant. PLoS. Comp. Biol. (2013)

Goals:
- Analysis
- Visualization
- Comparison
- Prediction
- Design



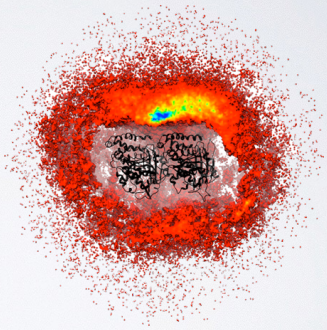
Grant *et al.* unpublished

Goals:
- Analysis
- Visualization
- Comparison
- Prediction
- Design



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...

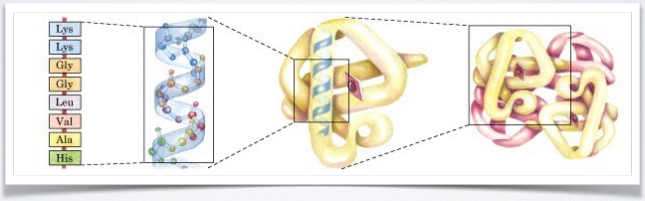
With applications to Biology, Medicine, Agriculture and Industry

NEXT UP:

- **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

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

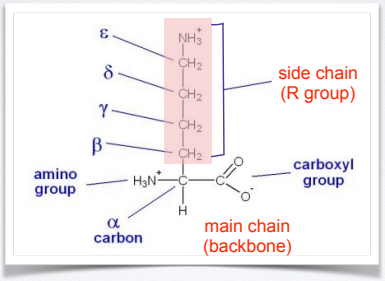


Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

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

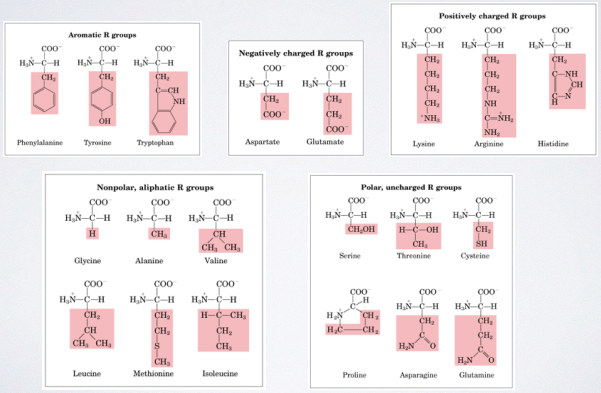
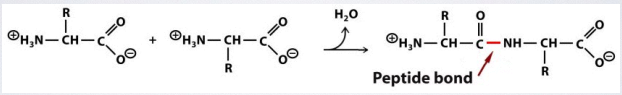


Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

AMINO ACIDS POLYMERIZE THROUGH **PEPTIDE BOND** FORMATION



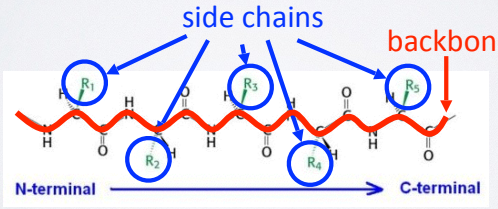
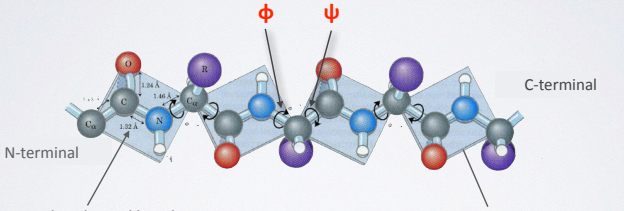


Image from: http://www.ncbi.nlm.nih.gov/books/NBK21581/

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

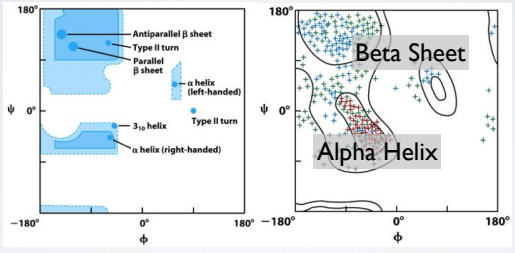


Bond angles and lengths are largely invariant

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/

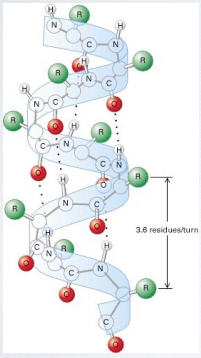
PHI vs PSI PLOTS ARE KNOWN AS **RAMACHANDRAN DIAGRAMS**



- 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



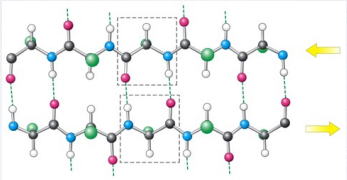
α-helix

- 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

Hydrogen bond: **i→i+4**

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

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

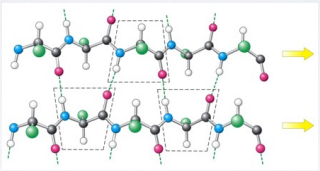


In **antiparallel** β**-sheets**

- 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**

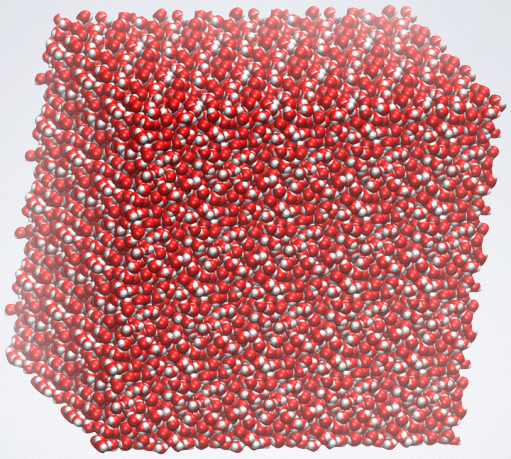


In **parallel** β**-sheets**

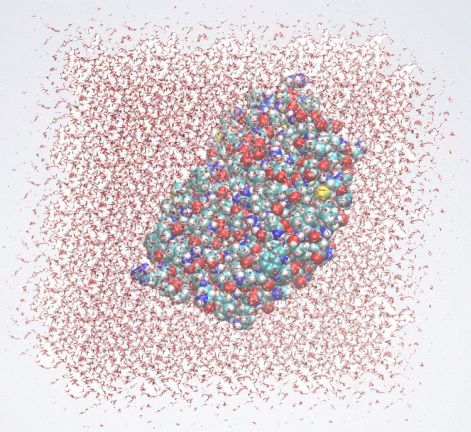
- Adjacent β-strands run in same direction
- Hydrogen bonds (dashed lines) between NH and CO stabilize the structure
- The side chains (in green) are above and below the sheet

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

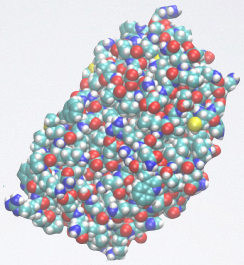
What Does a Protein Look like?



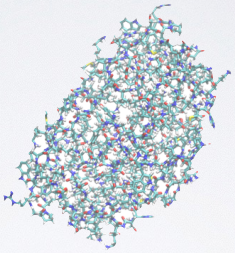
- Proteins are stable (and hidden) in water



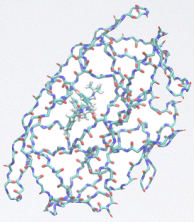
- Proteins closely interact with water



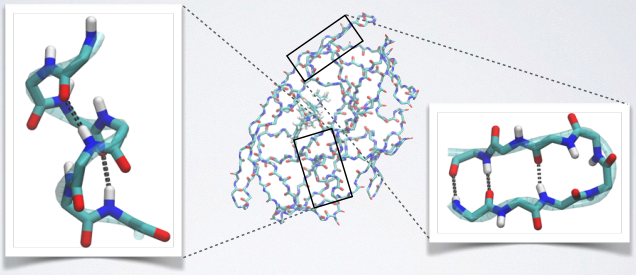
- Proteins are close packed solid but flexible objects (globular)



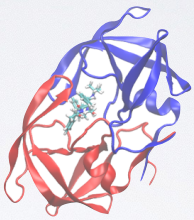
- Due to their large size and complexity it is often hard to see whats important in the structure



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

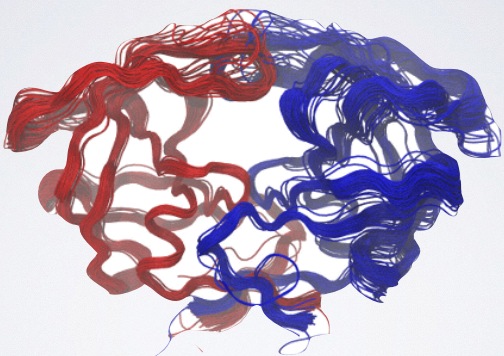


- Backbone or main-chain representation can help trace chain topology & reveal secondary structure



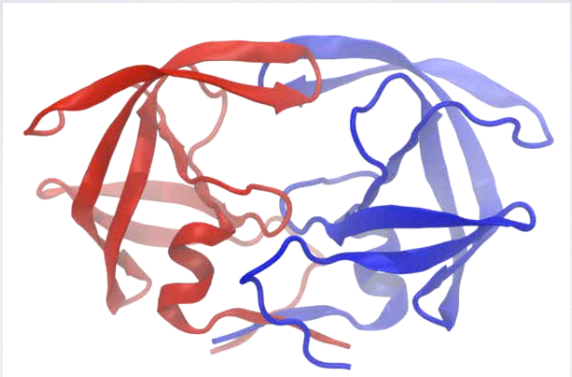
- Simplified secondary structure representations are commonly used to communicate structural details
- Now we can clearly see 2^o, 3^o and 4^o structure
- Coiled chain of connected secondary structures

DISPLACEMENTS REFLECT INTRINSIC FLEXIBILITY



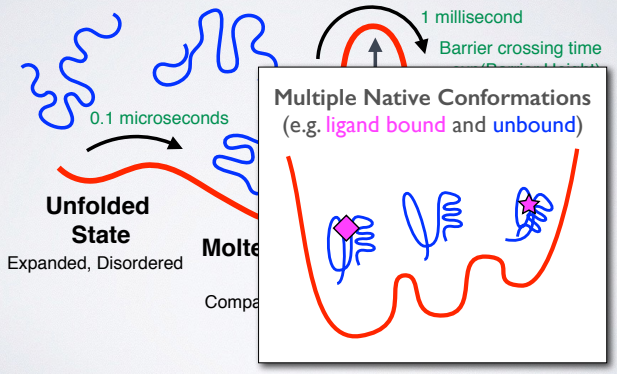
Superposition of all 482 structures in RCSB PDB (23/09/2015)

DISPLACEMENTS REFLECT INTRINSIC FLEXIBILITY



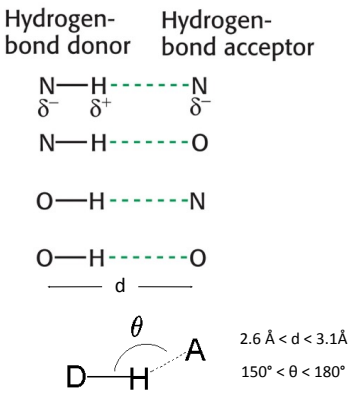
Principal component analysis (PCA) of experimental structures

KEY CONCEPT: **ENERGY LANDSCAPE**



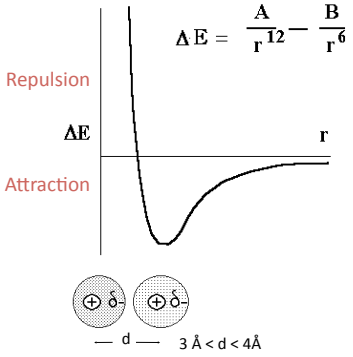
Key forces affecting structure:

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



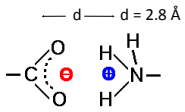
Key forces affecting structure:

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



Key forces affecting structure:

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



carboxyl group and amino group

(some time called IONIC BONDs or SALT BRIDGEs)

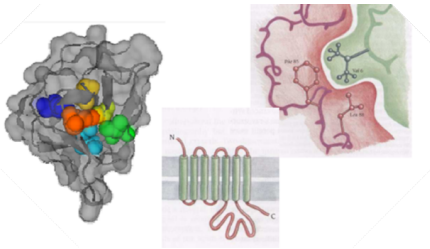
Coulomb's law

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

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
- Disulfide Bridges

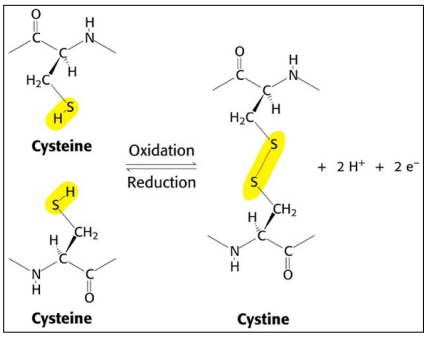


The force that causes hydrophobic molecules or nonpolar portions of molecules to aggregate together rather than to dissolve in water is called Hydrophobicity (*Greek, "water fearing"*). This is not a separate bonding force; rather, it is the result of the energy required to insert a nonpolar molecule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

Forces affecting structure:

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

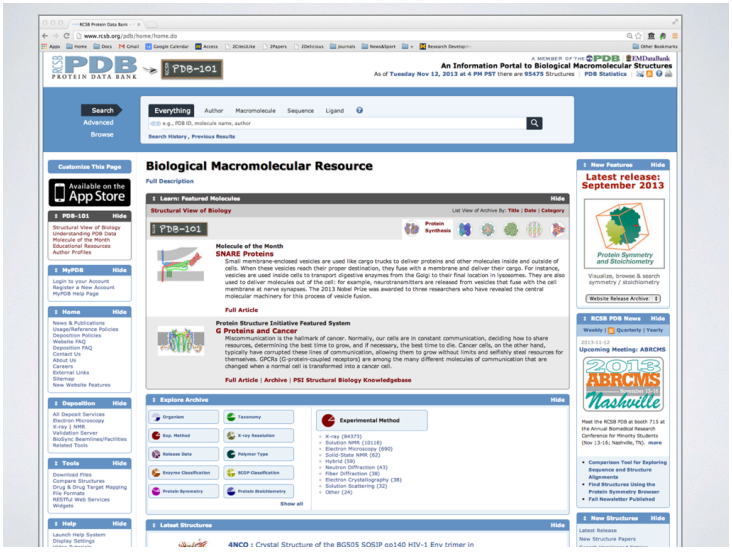
Other names:
cystine bridge
disulfide bridge

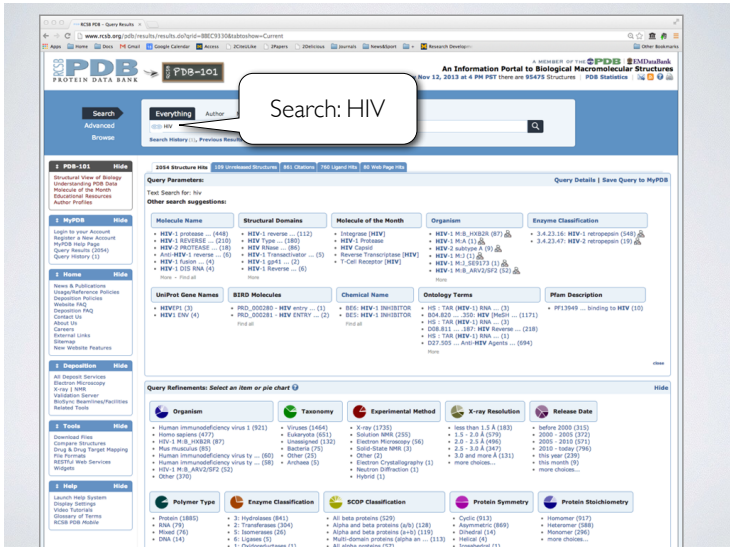


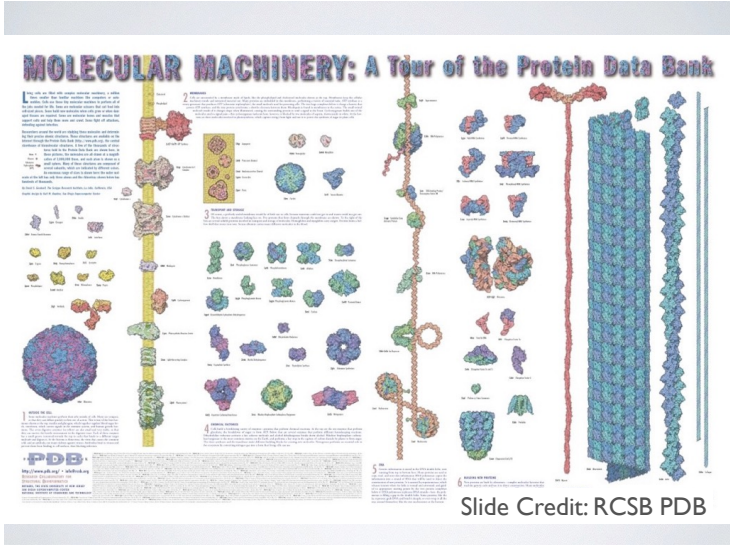
Hair contains lots of disulfide bonds which are broken and reformed by heat

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







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.

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

Two main approaches:

(1). **Physics-Based**

(2). **Knowledge-Based**

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

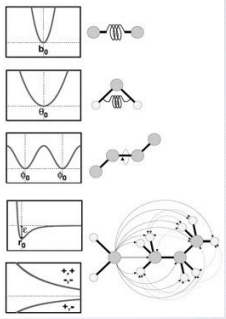
Two main approaches:

(1). **Physics-Based**

(2). **Knowledge-Based**

PHYSICS-BASED POTENTIALS
ENERGY TERMS FROM PHYSICAL THEORY

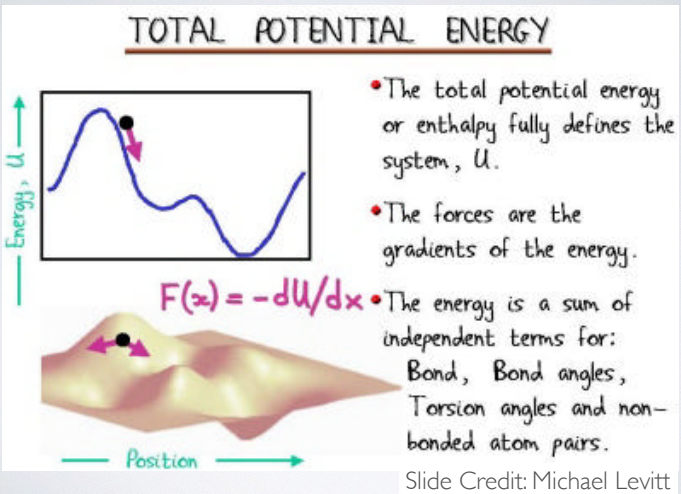
$$U(\vec{R}) = \underbrace{\sum_{bonds} k_i^{bond}(r_i - r_0)^2}_{U_{bond}} + \underbrace{\sum_{angles} k_i^{angle}(\theta_i - \theta_0)^2}_{U_{angle}} + \underbrace{\sum_{dihedrals} k_i^{dihe}[1 + \cos(n_i\phi_i + \delta_i)]}_{U_{dihedral}} + \underbrace{\sum_i \sum_{j \neq i} 4\epsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \sum_i \sum_{j \neq i} \frac{q_i q_j}{\epsilon r_{ij}}}_{U_{nonbond}}$$



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 PE. function, see: http://www.charmm.org/

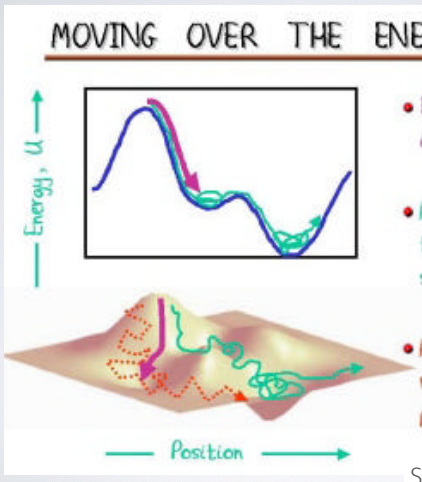
TOTAL POTENTIAL ENERGY



- 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 $\exp(-\Delta U/kT)$.

Slide Credit: Michael Levitt

PHYSICS-ORIENTED APPROACHES

Weaknesses

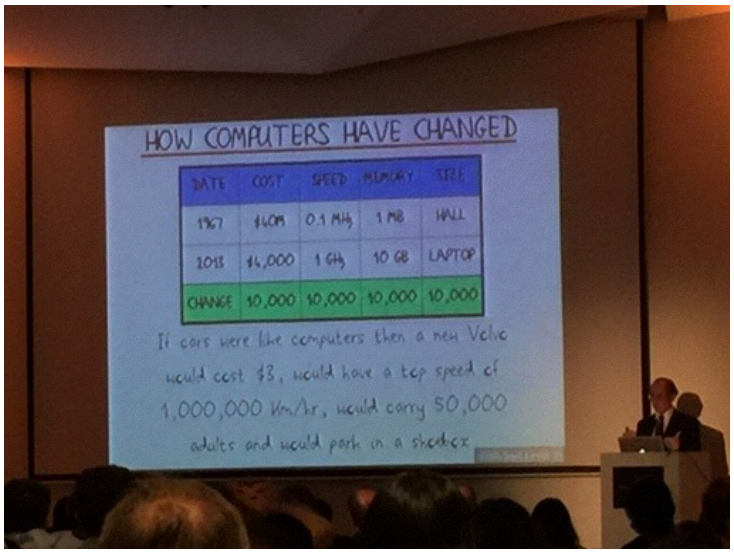
- Fully physical detail becomes computationally intractable
- Approximations are unavoidable
  - (Quantum effects approximated classically, water may be treated crudely)
- Parameterization still required

Strengths

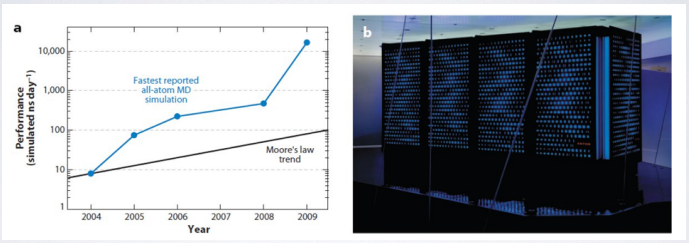
- Interpretable, provides guides to design
- Broadly applicable, in principle at least
- Clear pathways to improving accuracy

Status

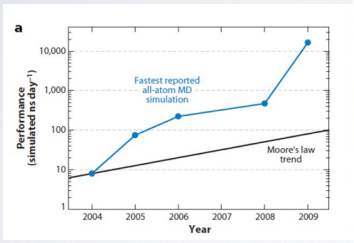
- Useful, widely adopted but far from perfect
- Multiple groups working on fewer, better approxs
  - Force fields, quantum
  - entropy, water effects
- Moore's law: hardware improving



SIDE-NOTE: GPUS AND ANTON SUPERCOMPUTER



SIDE-NOTE: GPUS AND ANTON SUPERCOMPUTER



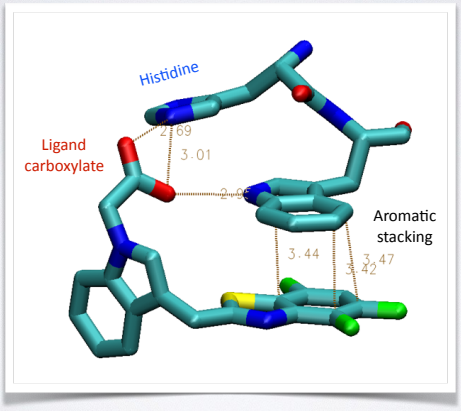
KEY CONCEPT: POTENTIAL FUNCTIONS DESCRIBE A SYSTEMS **ENERGY** AS A FUNCTION OF ITS **STRUCTURE**

Two main approaches:

(1). **Physics-Based**

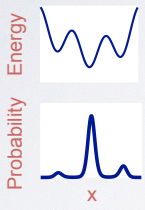
(2). **Knowledge-Based**

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

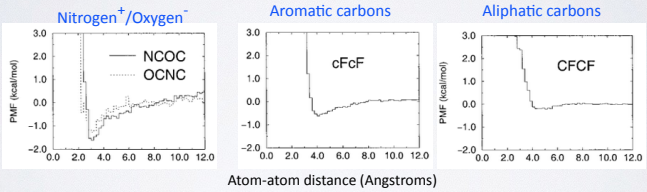
Find all protein-ligand structures in the PDB with a ligand carboxylate O

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



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

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)

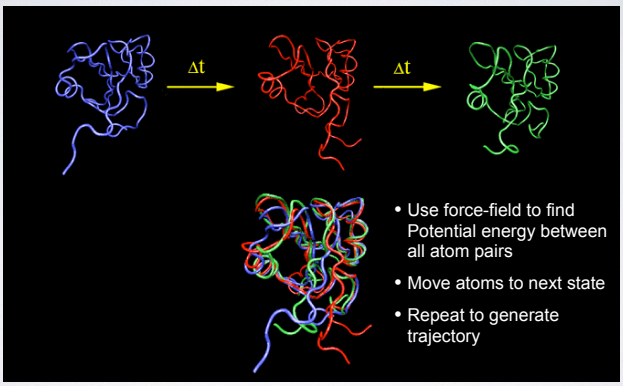
NEXT UP:

- **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

PREDICTING FUNCTIONAL DYNAMICS

- **Proteins are intrinsically flexible 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 mapping of structure to function**
  - **Molecular dynamics** (MD) and **normal mode analysis** (NMA) are two major methods for predicting and characterizing molecular motions and their properties

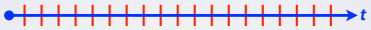
MOLECULAR DYNAMICS SIMULATION



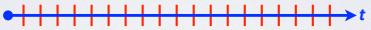
McCammon, Gelin & Karplus, *Nature* (1977)

[See: https://www.youtube.com/watch?v=ui1ZysMFcKk]

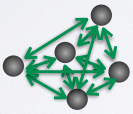
- Divide **time** into discrete (~1fs) **time steps** (**Δt**)
  (for integrating equations of motion, see below)



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



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



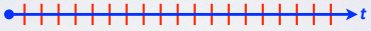
Nucleic motion described classically

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

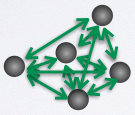
Empirical force field

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

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



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



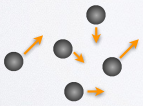
Nucleic motion described classically

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

Empirical force field

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

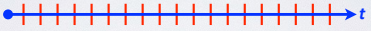
- Use the forces to calculate **velocities** and move atoms to new **positions**
  (by integrating numerically via the "leapfrog" scheme)



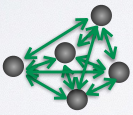
$$\begin{aligned} \boldsymbol{v}(t+\tfrac{\Delta t}{2}) &= \boldsymbol{v}(t-\tfrac{\Delta t}{2}) + \frac{\boldsymbol{F}(t)}{m}\Delta t \\ \boldsymbol{r}(t+\Delta t) &= \boldsymbol{r}(t) + \boldsymbol{v}(t+\tfrac{\Delta t}{2})\Delta t \end{aligned}$$

BASIC ANATOMY OF A MD SIMULATION

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



- 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

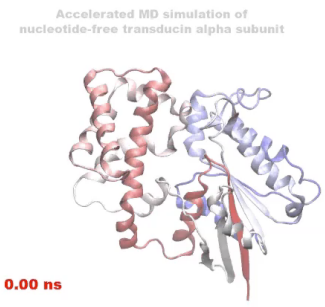
$$E(\vec{R}) = \sum_{\text{bonded}} E_i(\vec{R}) + \sum_{\text{non-bonded}} E_i(\vec{R})$$

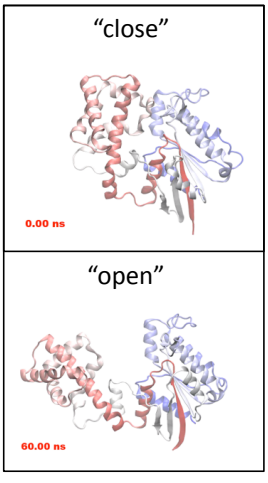
- Use the forces to calculate **velocities** and move atoms to new **positions**
  (by integrating numerically via the "leapfrog" scheme)

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

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

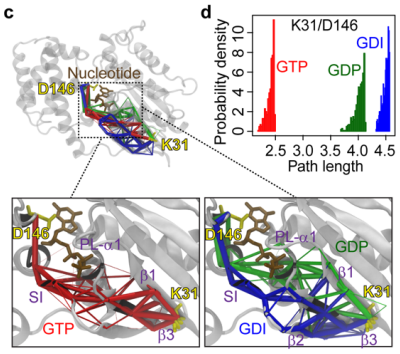
MD Prediction of Functional Motions





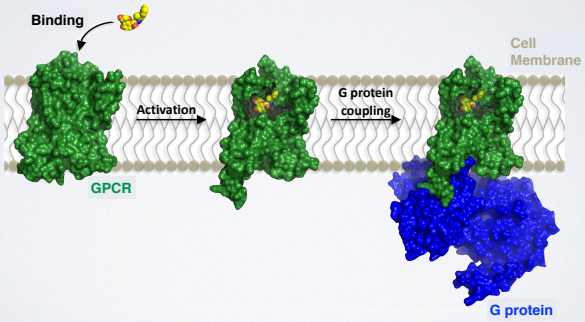
Yao and Grant, Biophys J. (2013)

Simulations Identify Key Residues Mediating Dynamic Activation

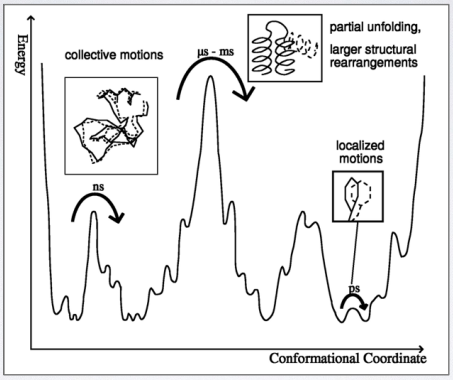


Yao … Grant, Journal of Biological Chemistry (2016)

EXAMPLE APPLICATION OF MOLECULAR SIMULATIONS TO GPCRS



PROTEINS JUMP BETWEEN MANY, HIERARCHICALLY ORDERED "CONFORMATIONAL SUBSTATES"



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

MOLECULAR DYNAMICS IS VERY E

Improve this slide

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]

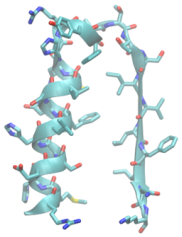
Total: 8.4 * 10^{17} flop
(on a 100 Gflop/s cpu: **ca 25 years!**)

… 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)**

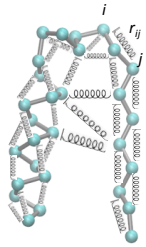
COARSE GRAINING: **NORMAL MODE ANALYSIS** (NMA)

- 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

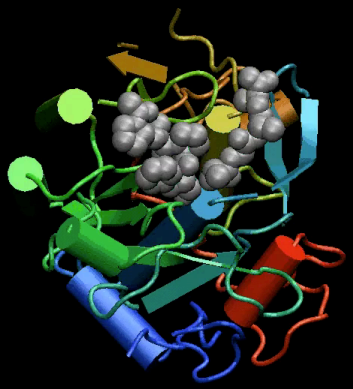
C. G.



Coarse Grained

- 1 bead / 1 amino acid
- Connected by springs

NMA models the protein as a network of elastic strings

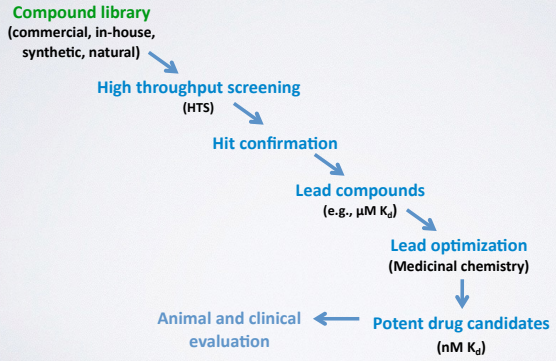


Proteinase K

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**

THE TRADITIONAL EMPIRICAL PATH TO DRUG DISCOVERY



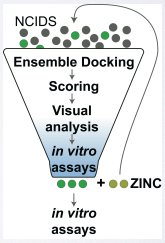
COMPUTER-AIDED LIGAND DESIGN

Aims to reduce number of compounds synthesized and assayed

Lower costs

Reduce chemical waste

Facilitate faster progress



Two main approaches:

(1). **Receptor/Target-Based**

(2). **Ligand/Drug-Based**

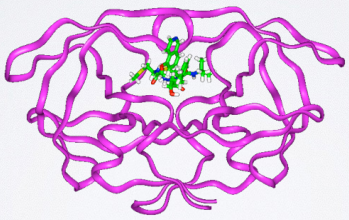
Two main approaches:

(1). **Receptor/Target-Based**

(2). **Ligand/Drug-Based**

SCENARIO I: RECEPTOR-BASED DRUG DISCOVERY

Structure of Targeted Protein Known: Structure-Based Drug Discovery



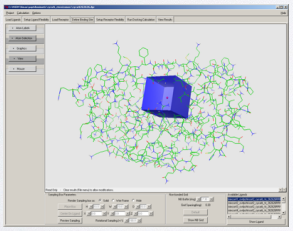
HIV Protease/KNI-272 complex

PROTEIN-LIGAND DOCKING

Structure-Based Ligand Design

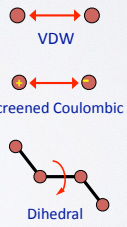
Docking software

Search for structure of lowest energy

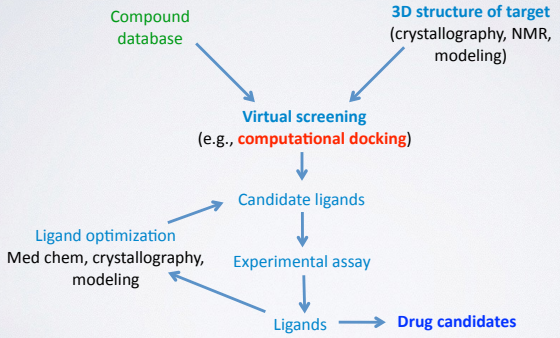


Potential function

Energy as function of structure



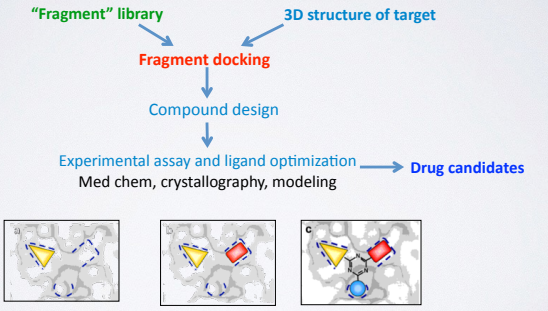
STRUCTURE-BASED VIRTUAL SCREENING



COMPOUND LIBRARIES

Commercial (in-house pharma) | Government (NIH) | Academia

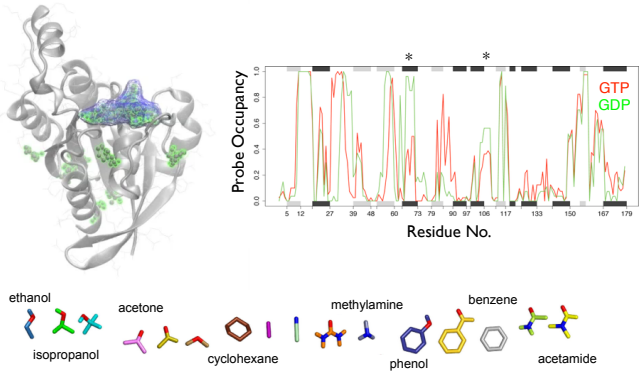
FRAGMENTAL STRUCTURE-BASED SCREENING



http://www.beilstein-institut.de/bozen2002/proceedings/jhoti/jhoti.html

Multiple non active-site pockets identified

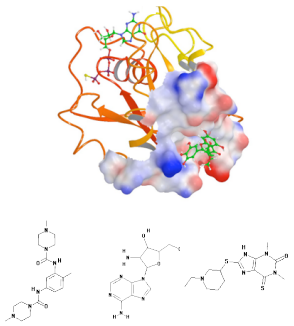
Small organic probe fragment affinities map multiple potential binding sites across the structural ensemble.



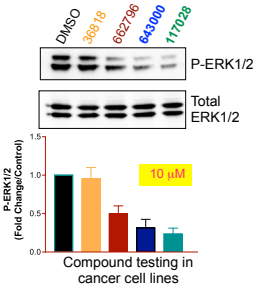
Ensemble docking & candidate inhibitor testing

Top hits from ensemble docking against distal pockets were tested for inhibitory effects on basal ERK activity in glioblastoma cell lines.

Ensemble computational docking

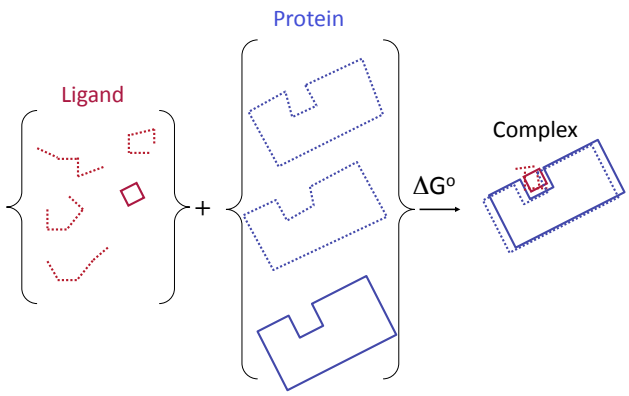


Compound effect on U251 cell line



PLoS One (2011, 2012)

Proteins and Ligand are Flexible



COMMON SIMPLIFICATIONS USED IN PHYSICS-BASED DOCKING

Quantum effects approximated classically

Protein often held rigid

Configurational entropy neglected

Influence of water treated crudely

Two main approaches:

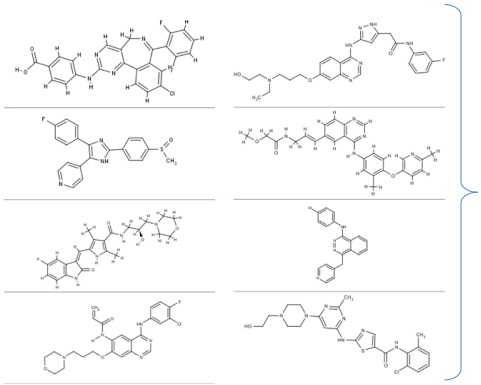
(1). **Receptor/Target-Based**

(2). **Ligand/Drug-Based**

Scenario 2

Structure of Targeted Protein Unknown: Ligand-Based Drug Discovery

e.g. MAP Kinase Inhibitors



Using knowledge of existing inhibitors to discover more

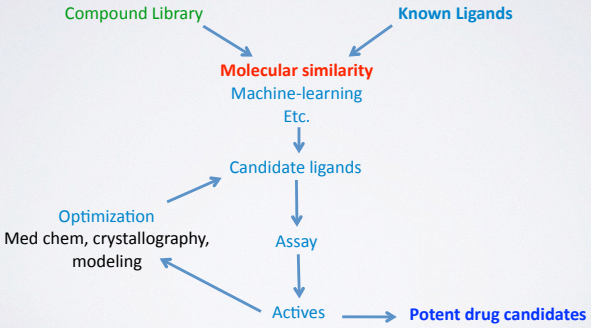
Why Look for Another Ligand if You Already Have Some?

Experimental screening generated some ligands, but they don't bind tightly

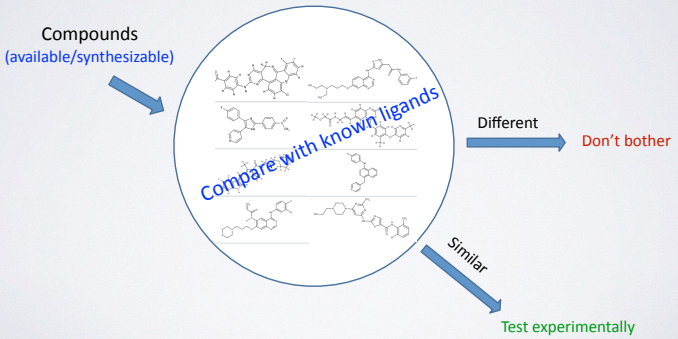
A company wants to work around another company's chemical patents

An high-affinity ligand is toxic, is not well-absorbed, etc.

LIGAND-BASED VIRTUAL SCREENING



CHEMICAL SIMILARITY LIGAND-BASED DRUG-DISCOVERY

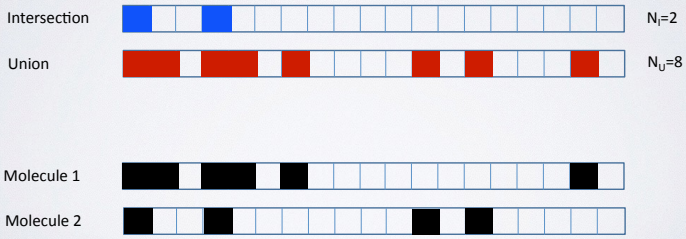


CHEMICAL FINGERPRINTS
BINARY STRUCTURE KEYS

CHEMICAL SIMILARITY FROM FINGERPRINTS

Tanimoto Similarity or Jaccard Index, T

$$T \equiv \frac{N_I}{N_U} = 0.25$$

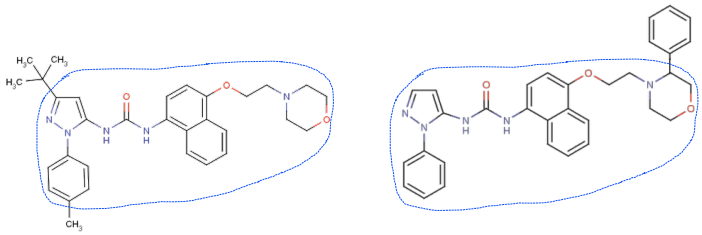


POTENTIAL DRAWBACKS OF PLAIN CHEMICAL SIMILARITY

May miss good ligands by being overly conservative

May put too much weight on irrelevant details
- Examine ligand shape and common substructures
- Build pharmacophore models
- Statistics and machine learning on chemical descriptors

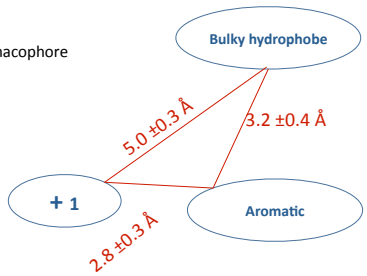
Maximum Common Substructure



N_{common}=34

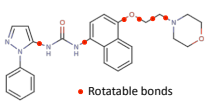
Pharmacophore Models
Φάρμακο (drug) + Φορά (carry)

A 3-point pharmacophore



Molecular Descriptors
More abstract than chemical fingerprints

Physical descriptors
- molecular weight
- charge
- dipole moment
- number of H-bond donors/acceptors
- number of rotatable bonds
- hydrophobicity (log P and clogP)



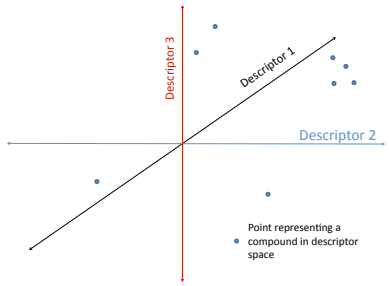
Topological
- branching index
- measures of linearity vs interconnectedness

Etc. etc.

A High-Dimensional "Chemical Space"

Each compound is at a point in an n-dimensional space

Compounds with similar properties are near each other



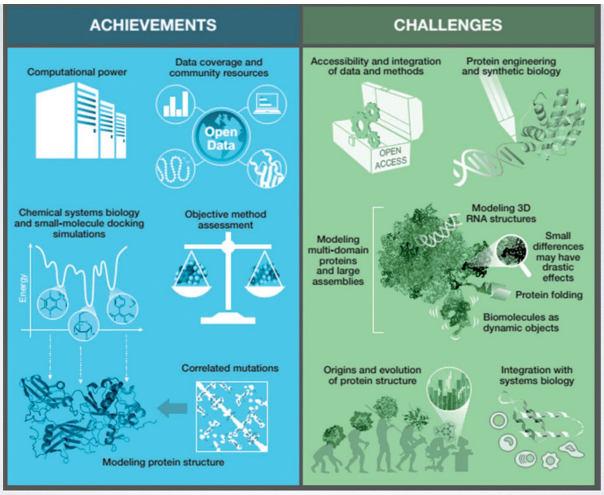
Apply **multivariate statistics** and **machine learning** for descriptor-selection.
(e.g. partial least squares, support vector machines, random forest, etc.)

CAUTIONARY NOTES

- **"Everything should be made as simple as it can be but not simpler"**
  A model is **never perfect**. A model that is not quantitatively accurate in every respect does not preclude one from establishing results relevant to our understanding of biomolecules as long as the biophysics of the model are properly understood and explored.
- **Calibration of the parameters is an ongoing and imperfect process**
  Questions and hypotheses should always be designed such that they do not depend crucially on the precise numbers used for the various parameters.
- **A computational model is rarely universally right or wrong**
  A model may be accurate in some regards, inaccurate in others. These subtleties can only be uncovered by comparing to all available experimental data.

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



Ilan Samish et al. Bioinformatics 2015;31:146-150

INFORMING SYSTEMS BIOLOGY?