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**
  - **drug discovery** & Predicting functional dynamics

THE TRADITIONAL EMPIRICAL PATH TO DRUG DISCOVERY

Compound library
(commercial, in-house, synthetic, natural)
↘
High throughput screening
(HTS)
↘
Hit confirmation
↘
Lead compounds
(e.g., μM K_d)
↘
Lead optimization
(Medicinal chemistry)
↓
Potent drug candidates
(nM K_d)
←
Animal and clinical evaluation

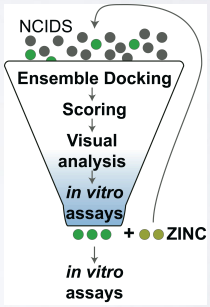
COMPUTER-AIDED LIGAND DESIGN

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**

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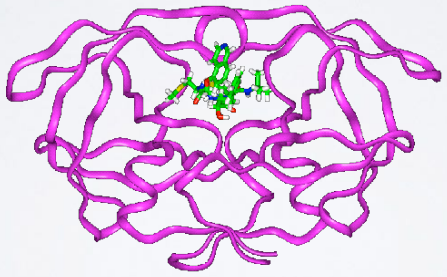
SCENARIO I: RECEPTOR-BASED DRUG DISCOVERY

Structure of Targeted Protein Known: Structure-Based Drug Discovery

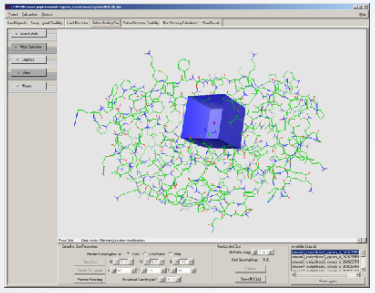


HIV Protease/KNI-272 complex

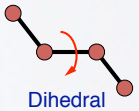
PROTEIN-LIGAND DOCKING

Structure-Based Ligand Design

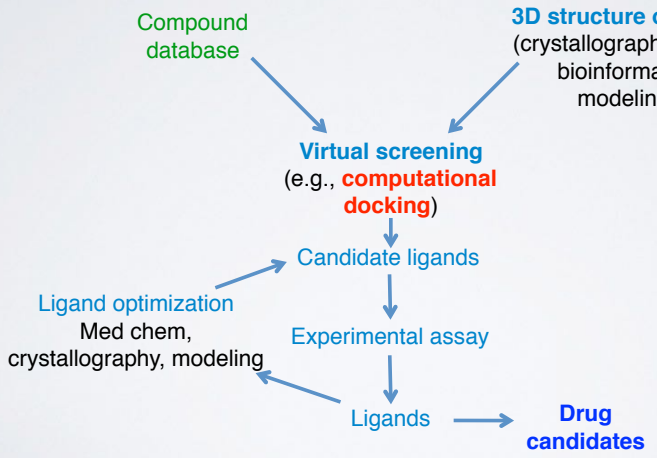
Docking software
Search for structure of lowest energy



Potential function
Energy as function of structure



STRUCTURE-BASED VIRTUAL SCREENING



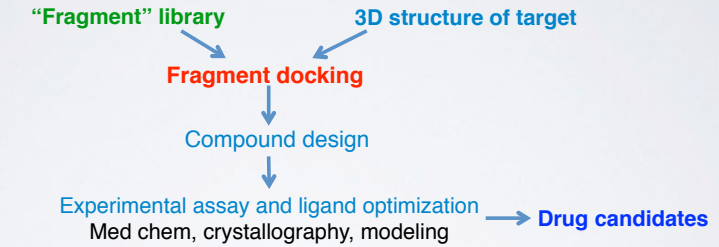
COMPOUND LIBRARIES

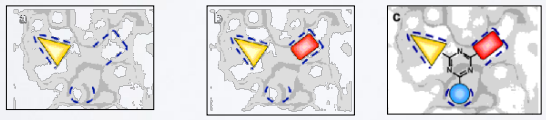
Commercial (in-house pharma)

Government (NIH)

Academia

FRAGMENTAL STRUCTURE-BASED SCREENING

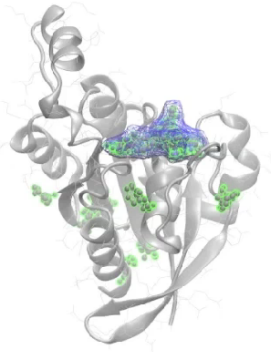


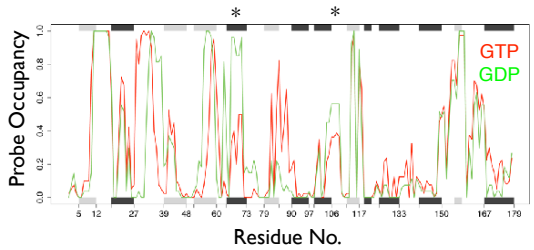


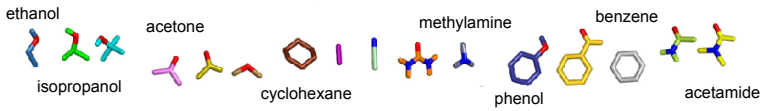
http://www.beilstein-institut.de/bozen2002/proceedings/Jhoti/jhoti.html

Multiple non active-site pockets identified

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



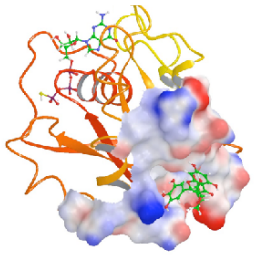


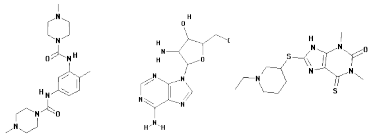


Ensemble docking & candidate inhibitor testing

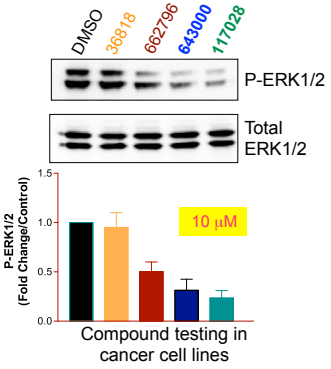
Top hits from ensemble docking against distal pockets were tested for inhibitory effects on basal ERK activity in glioblastoma cell lines.

Ensemble computational docking





Compound effect on U251 cell line



PLoS One (2011, 2012)

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**

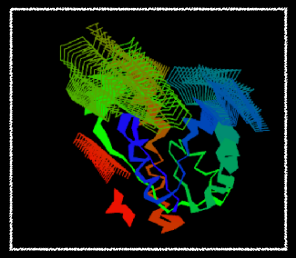
Do it Yourself!

Hand-on time!

https://bioboot.github.io/bggn213_S18/lectures/#12

You can use the classroom computers or your own laptops. If you are using your laptops then you will need to install **VMD** and **MGLTools**

Bio3D view()



- If you want the 3D viewer in your R markdown you can install the development version of Bio3D

- For **MAC**:

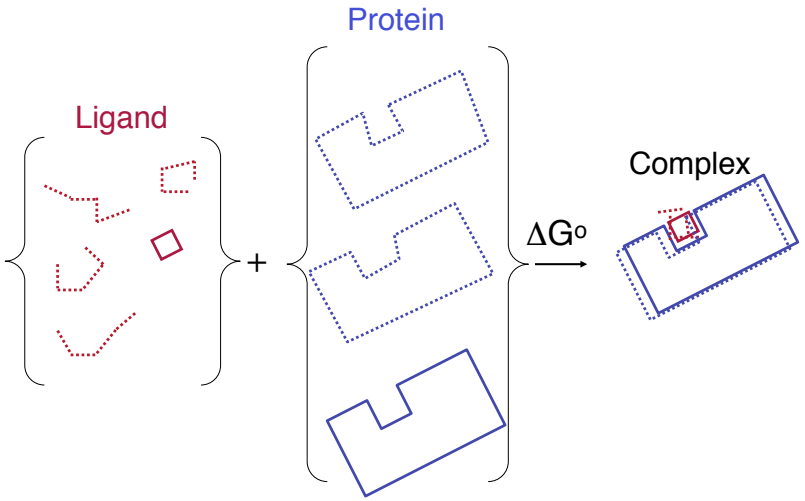
```
> download.file("https://tinyurl.com/bio3d-mac", "bio3d.tar.gz")
> install.packages("bio3d.tar.gz", repos = NULL)
```

- For **Windows**:

```
> install.packages("https://bioboot.github.io/bggn213_S18/class-material/bio3d_2.3-4.9000.zip", repos = NULL)
```

[See: Appendix I in Lab Sheet]

Proteins and Ligand are Flexible



HTTP://129.177.232.111:3848/PCA-APP/

HTTP://BIO3D.UCSD.EDU/PCA-APP/

Two main approaches:

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

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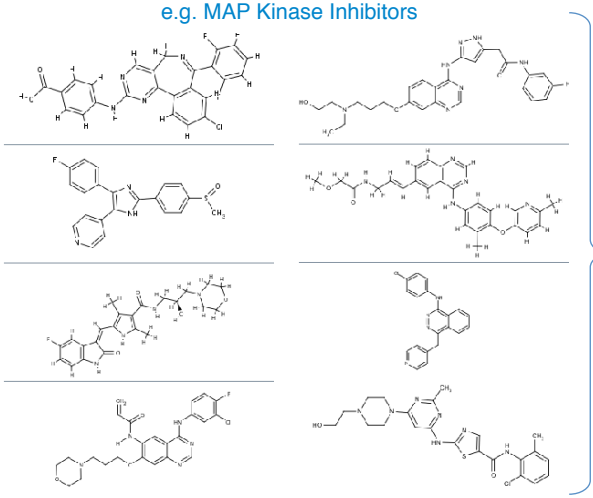
Scenario 2

Structure of Targeted Protein Unknown: Ligand-Based Drug Discovery

e.g. MAP Kinase Inhibitors



Using knowledge of existing inhibitors to discover more

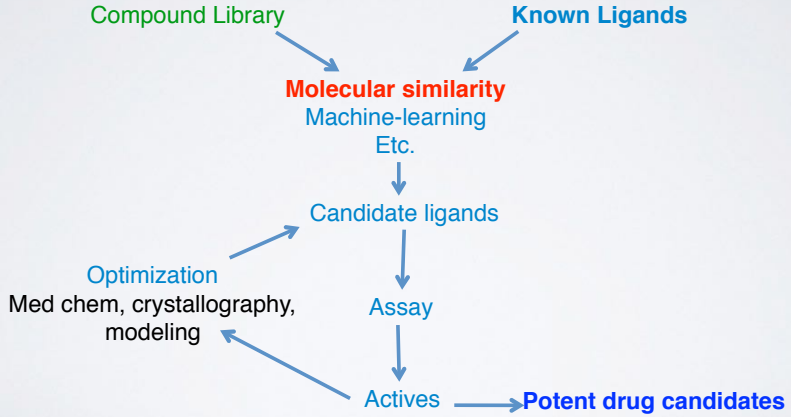
Why Look for Another Ligand if You Already Have Some?

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

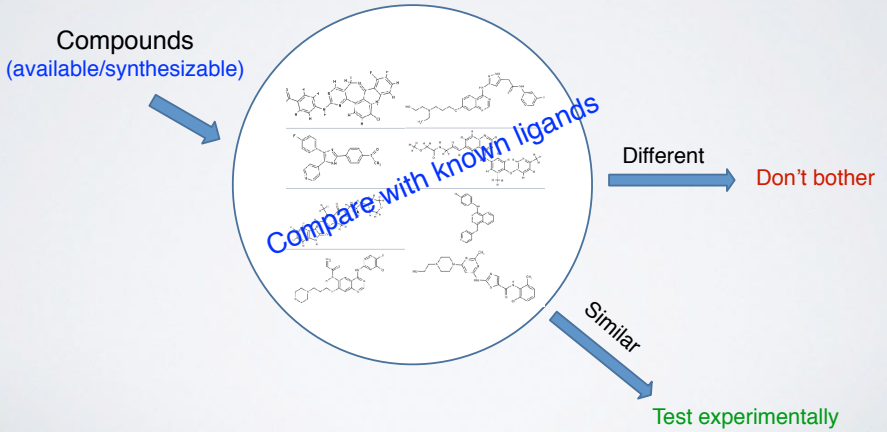
A company wants to work around another company's chemical patents

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

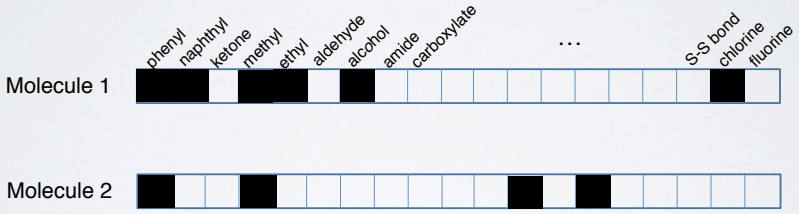
LIGAND-BASED VIRTUAL SCREENING



CHEMICAL SIMILARITY LIGAND-BASED DRUG-DISCOVERY



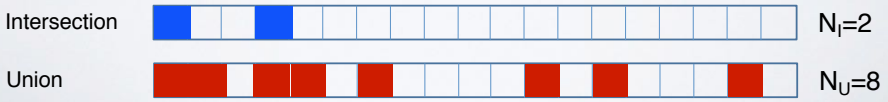
CHEMICAL FINGERPRINTS
BINARY STRUCTURE KEYS



CHEMICAL SIMILARITY FROM FINGERPRINTS

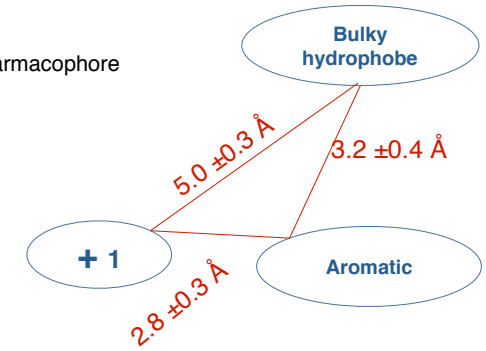
Tanimoto Similarity (or Jaccard Index), T

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



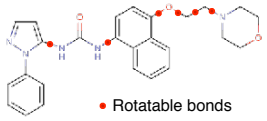
Pharmacophore Models
Φάρμακο (drug) + Φορά (carry)

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)



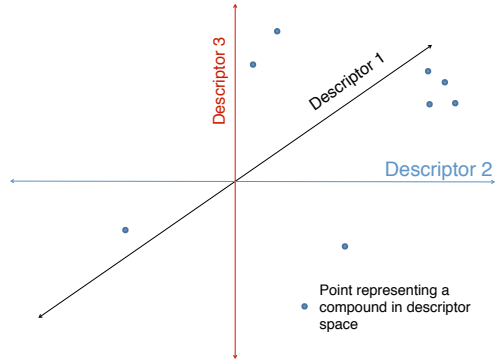
Topological
- branching index
- measures of linearity vs interconnectedness

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, PCA, support vector machines, random forest, deep learning etc.)

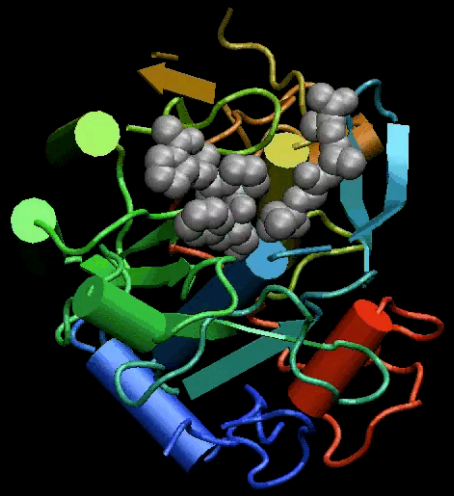
Rules for drug discovery success

- Set of approved drugs or medicinal chemistry compounds and their targets can be used to derive rules for drug discovery success (or failure):
  - What features make a successful drug target?
  - What features make a protein druggable by small molecules?
  - What features of a compound contribute to good oral bioavailability?
  - What chemical groups may be associated with toxicity?

Optional:
Stop here for Today!

[Muddy Point Assessment]

NMA models the protein as a network of elastic strings



Proteinase K

NEXT UP:

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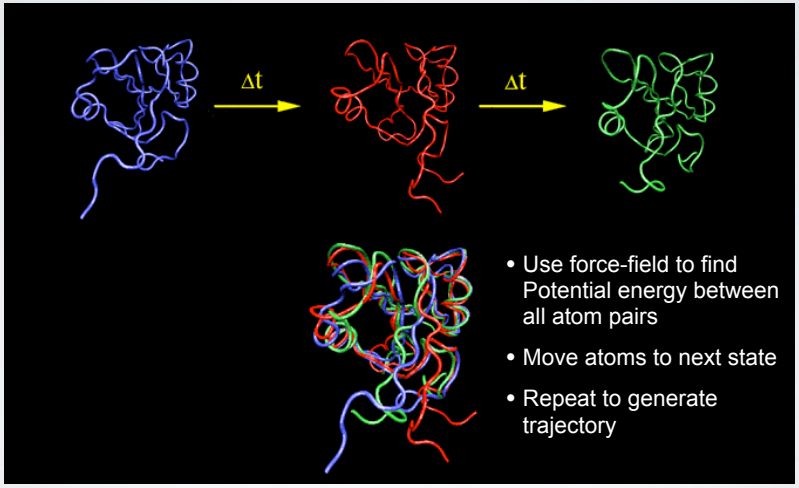
  - Major motivations, goals and challenges
- **Fundamentals of protein structure**
  - Composition, form, forces and dynamics
- **Representing and interpreting protein structure**
  - Modeling energy as a function of structure
- **Example application areas**
  - Drug discovery & predicting **functional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

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]

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**

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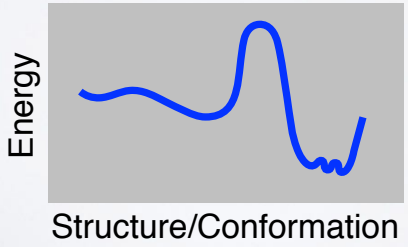

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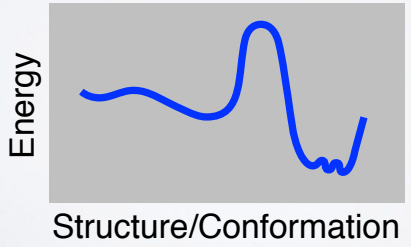
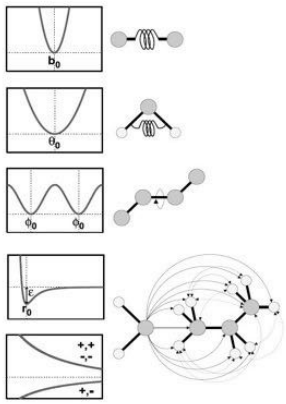


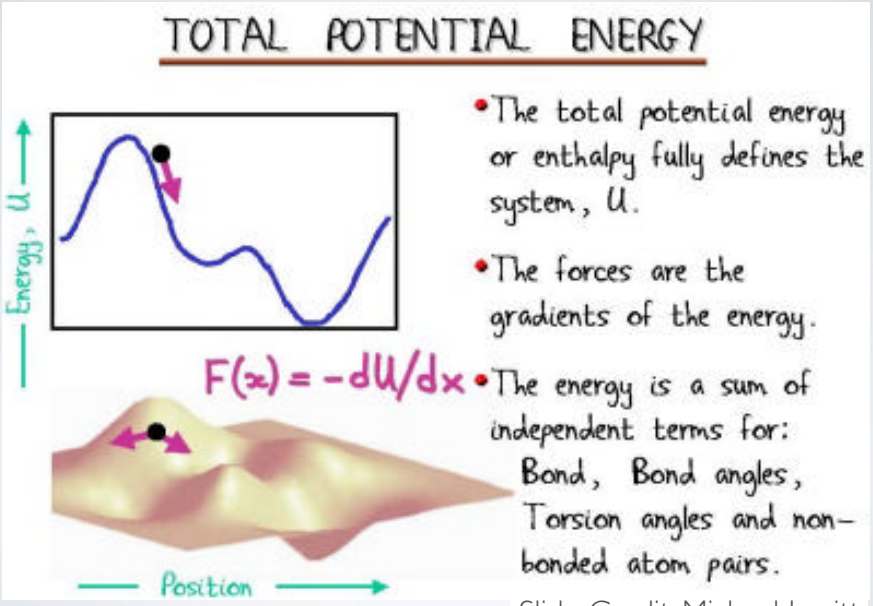
PHYSICS-BASED POTENTIALS
ENERGY TERMS FROM PHYSICAL THEORY

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

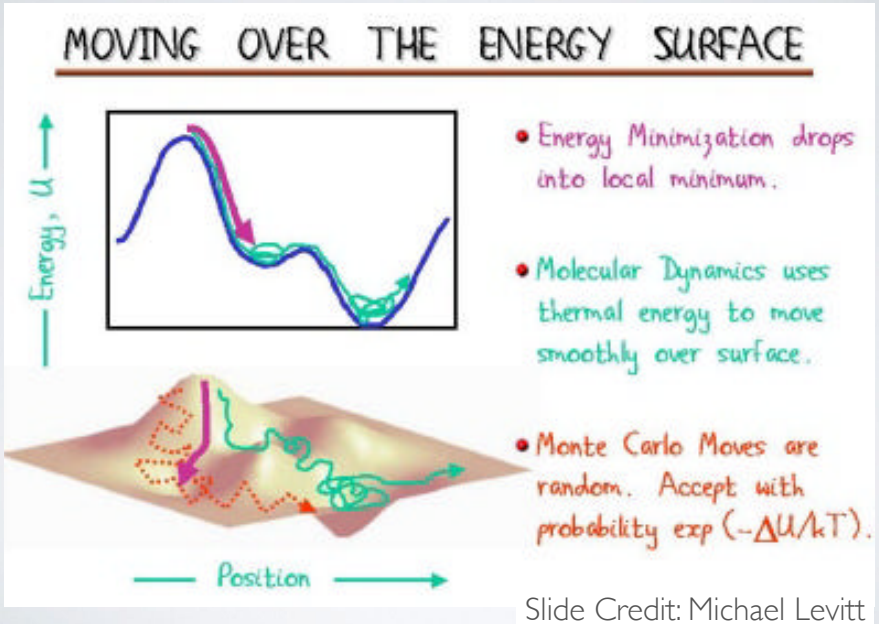


U_{bond} = oscillations about the equilibrium bond length
U_{angle} = oscillations of 3 atoms about an equilibrium bond angle
$U_{dihedral}$ = torsional rotation of 4 atoms about a central bond
$U_{nonbond}$ = non-bonded energy terms (electrostatics and Lenard-Jones)

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



Slide Credit: Michael Levitt



Slide Credit: Michael Levitt

PHYSICS-ORIENTED APPROACHES

Weaknesses

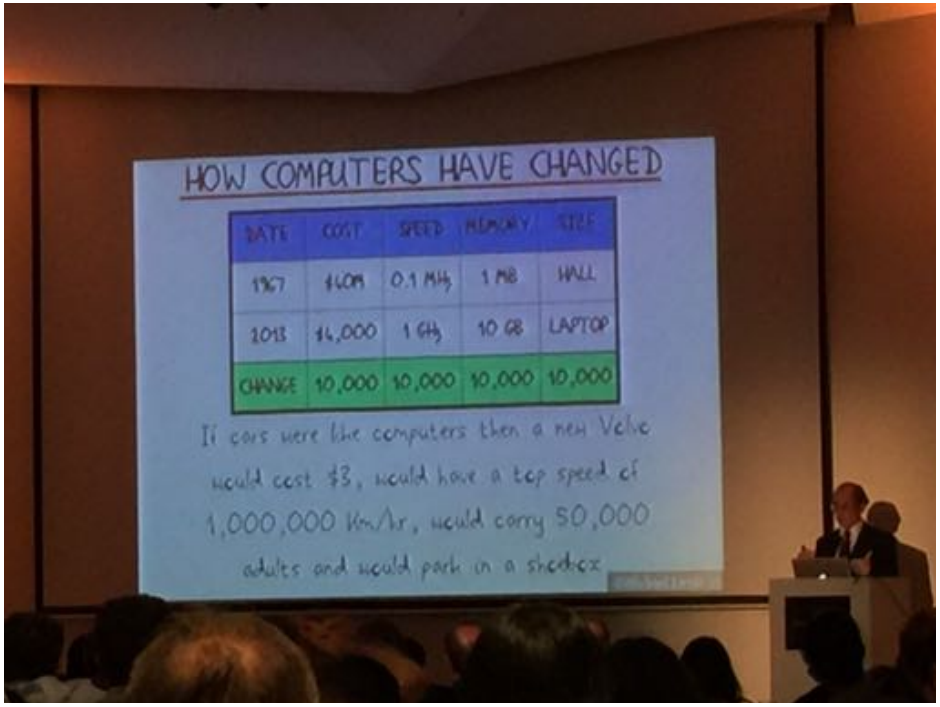
- Fully physical detail becomes computationally intractable
- Approximations are unavoidable
  - (Quantum effects approximated classically, water may be treated crudely)
- Parameterization still required

Strengths

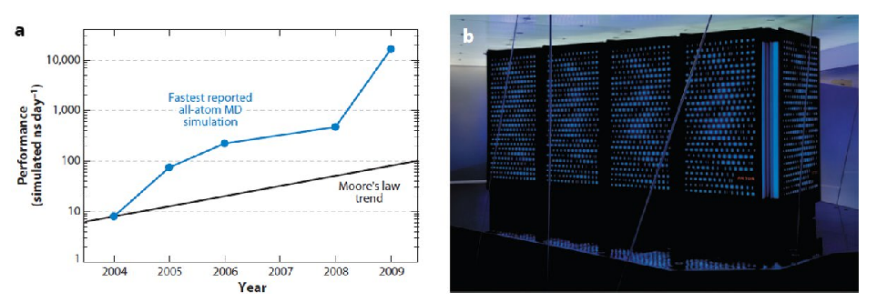
- Interpretable, provides guides to design
- Broadly applicable, in principle at least
- Clear pathways to improving accuracy

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



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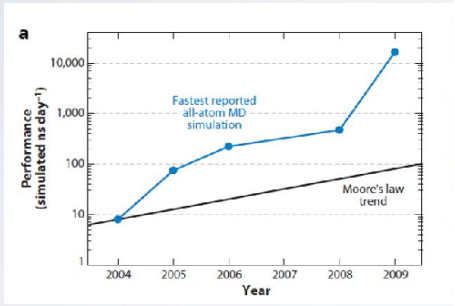

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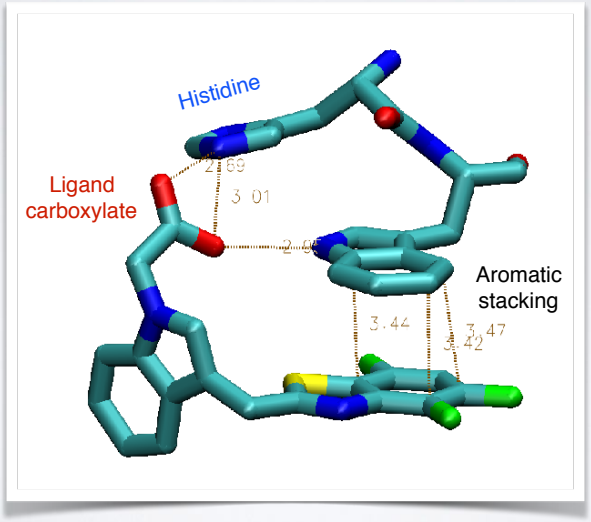
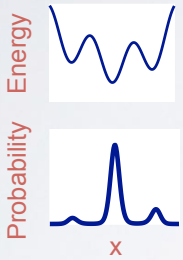
KNOWLEDGE-BASED DOCKING POTENTIALS



ENERGY DETERMINES **PROBABILITY** (STABILITY)

Basic idea: Use probability as a proxy for energy



Boltzmann:

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

Inverse Boltzmann:

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

Example: ligand carboxylate O to protein histidine N

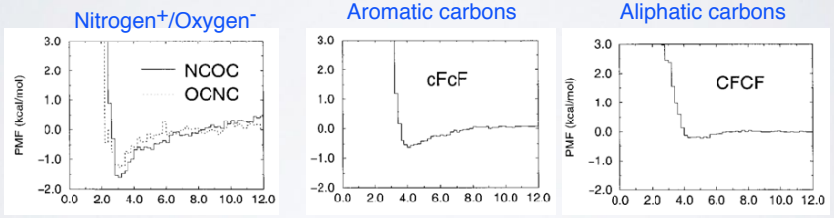
Find all protein-ligand structures in the PDB with a ligand carboxylate O

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

KNOWLEDGE-BASED DOCKING POTENTIALS

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

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



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

KNOWLEDGE-BASED POTENTIALS

Weaknesses

Accuracy limited by availability of data

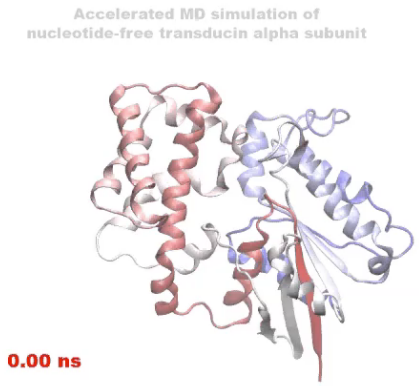
Strengths

Relatively easy to implement
Computationally fast

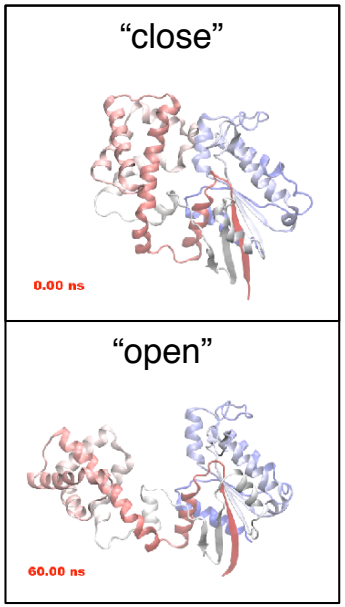
Status

Useful, far from perfect
May be at point of diminishing returns
(not always clear how to make improvements)

MD Prediction of Functional Motions

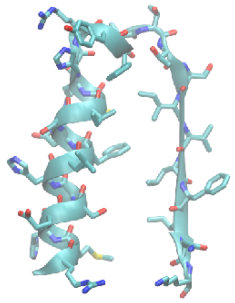


Yao and Grant, Biophys J. (2013)



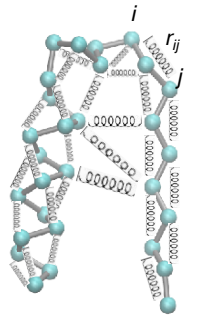
COARSE GRAINING: **NORMAL MODE ANALYSIS** (NMA)

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



Atomistic

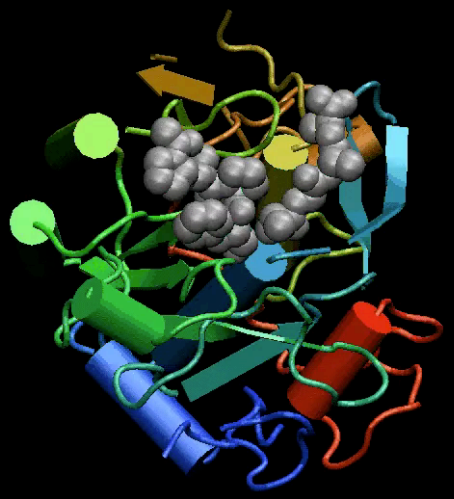
C. G.



Coarse Grained

- 1 bead / 1 amino acid
- Connected by springs

NMA models the protein as a network of elastic strings



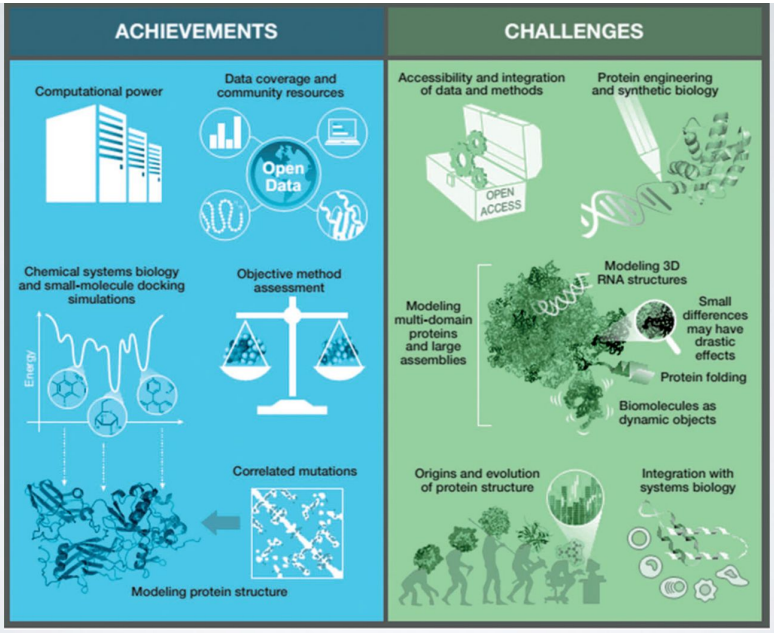
Proteinase K

Do it Yourself!

Hand-on time!

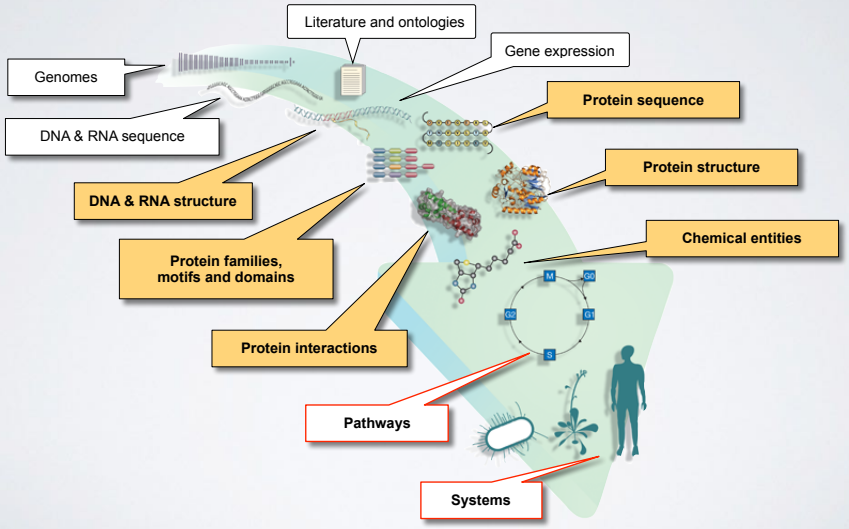
https://bioboot.github.io/bggn213_S18/lectures/#12

Focus on **section 3** & **4** exploring **PCA** and **NMA apps**



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

INFORMING SYSTEMS BIOLOGY?



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
- Introduced both structure and ligand based bioinformatics approaches for drug discovery and design