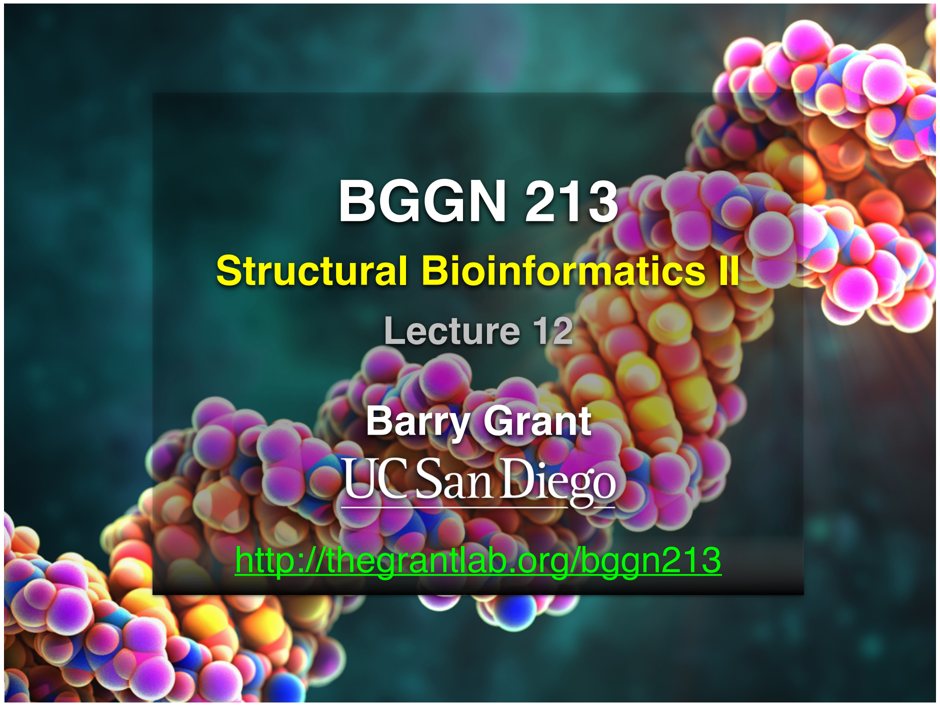


BGGN 213

Structural Bioinformatics II

Lecture 12

Barry Grant

UC San Diego

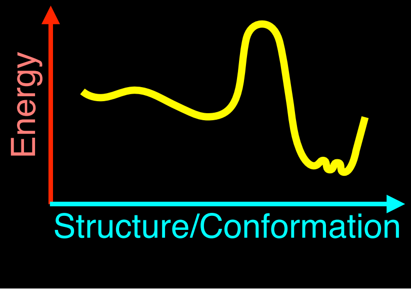
http://thegrantlab.org/bggn213

Next Up:

- **Overview of structural bioinformatics**
  - Motivations, goals and challenges
- **Fundamentals of protein structure**
  - Structure composition, form and forces
- **Representing, interpreting & modeling protein structure**
  - Visualizing and interpreting protein structures
  - Analyzing protein structures
  - Modeling energy as a function of structure
  - Drug discovery & Predicting functional dynamics

Key concept:

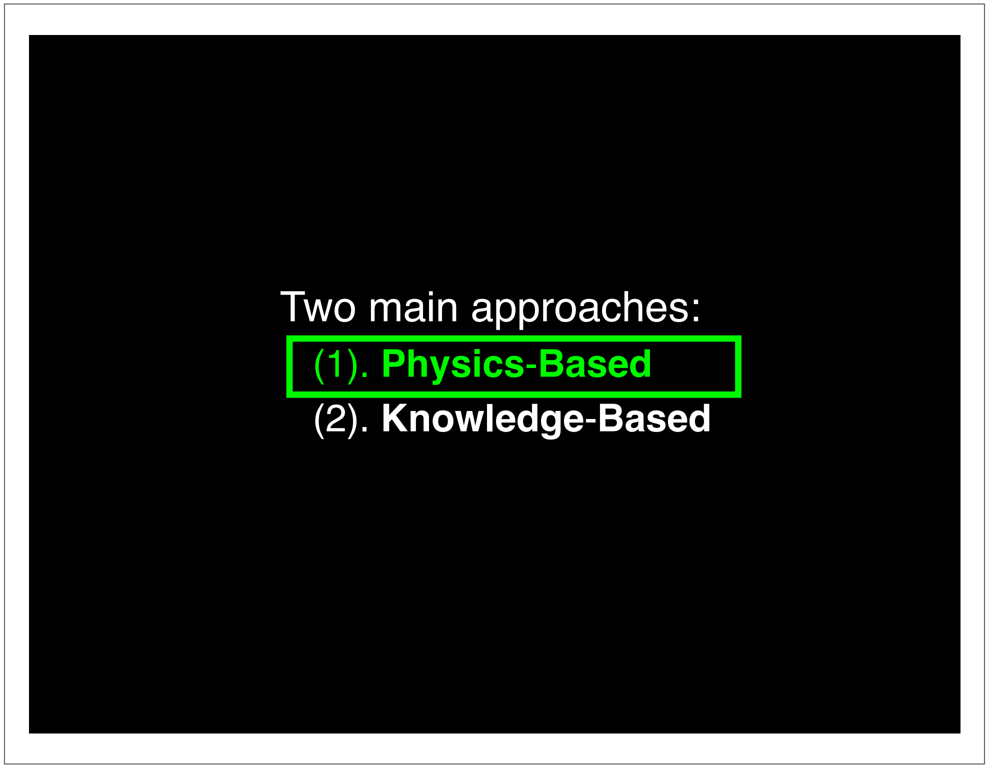
Potential functions describe a systems energy as a function of its structure



Two main approaches:

(1). **Physics-Based**

(2). **Knowledge-Based**



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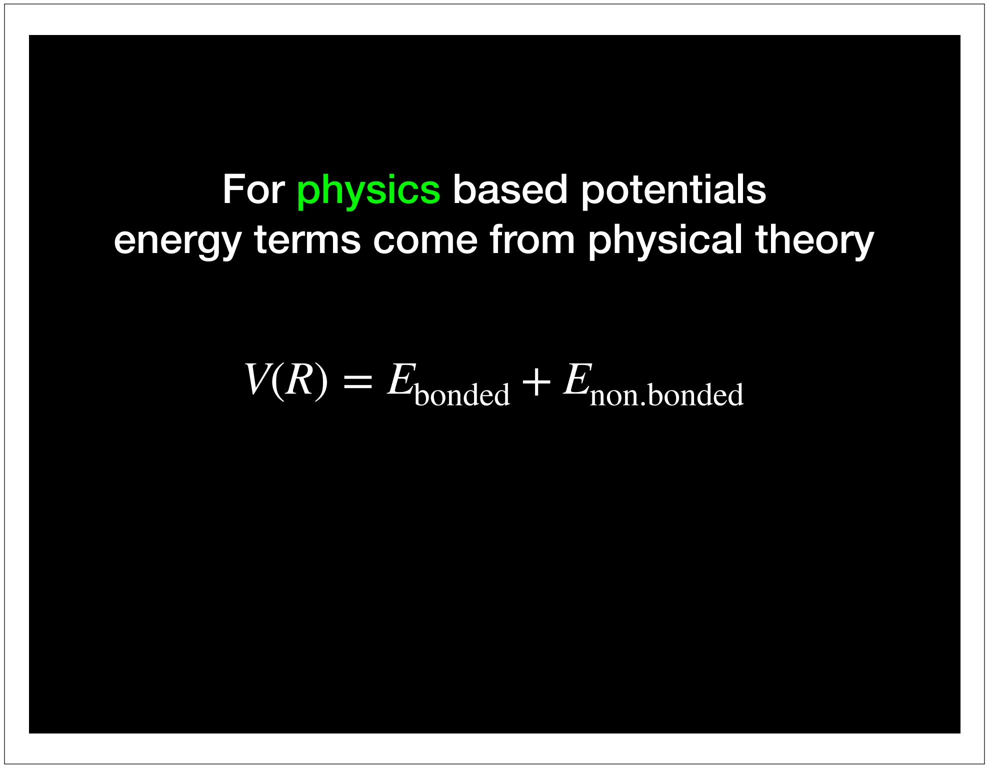
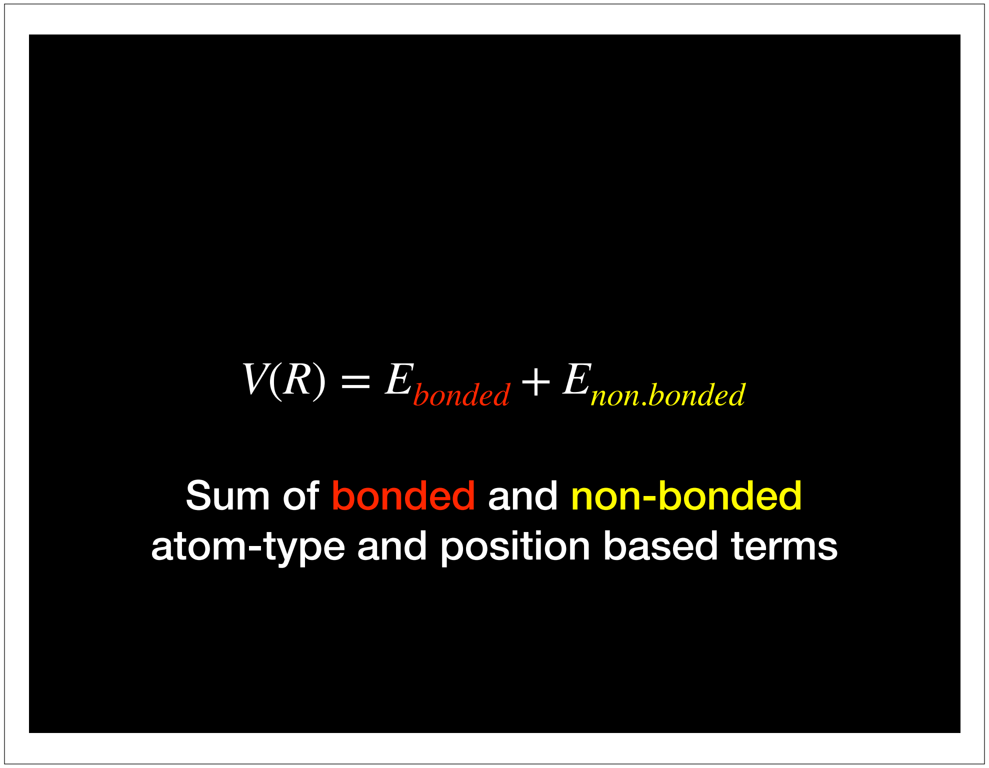


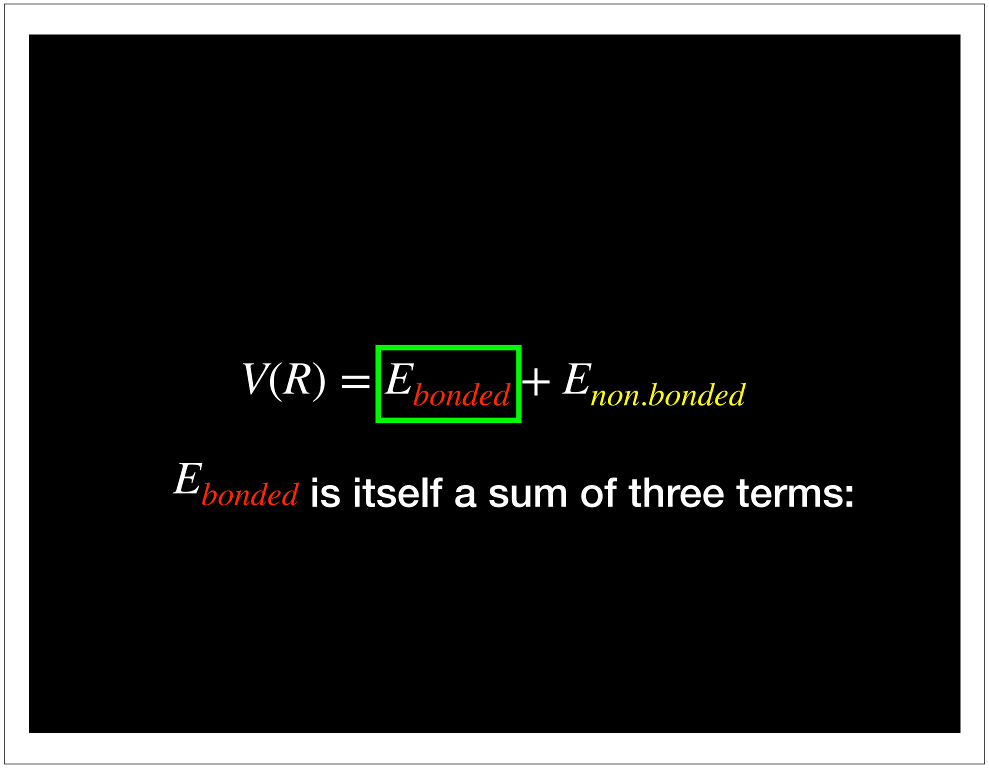
For physics based potentials
energy terms come from physical theory

$$V(R) = E_{\text{bonded}} + E_{\text{non.bonded}}$$



$$V(R) = E_{bonded} + E_{non.bonded}$$

Sum of bonded and non-bonded
atom-type and position based terms



$$V(R) = \boxed{E_{bonded}} + E_{non.bonded}$$

E_{bonded} is itself a sum of three terms:

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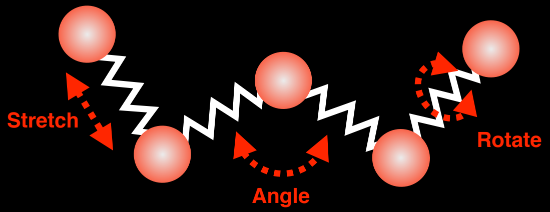
$$\boxed{E_{bond.stretch} + E_{bond.angle} + E_{bond.rotate}}$$



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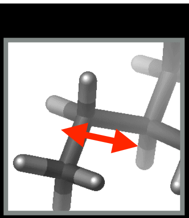
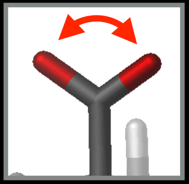


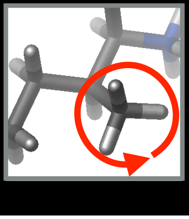
Bond Stretch

$$E_{bond.stretch}$$



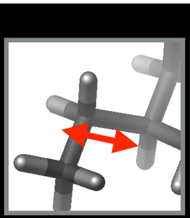
Bond Angle

$$E_{bond.angle}$$



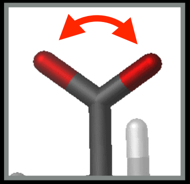
Bond Rotate

$$E_{bond.rotate}$$



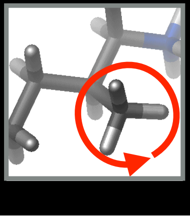
Bond Stretch

$$\sum_{bonds} K_i^{bs}(b_i - b_o)$$



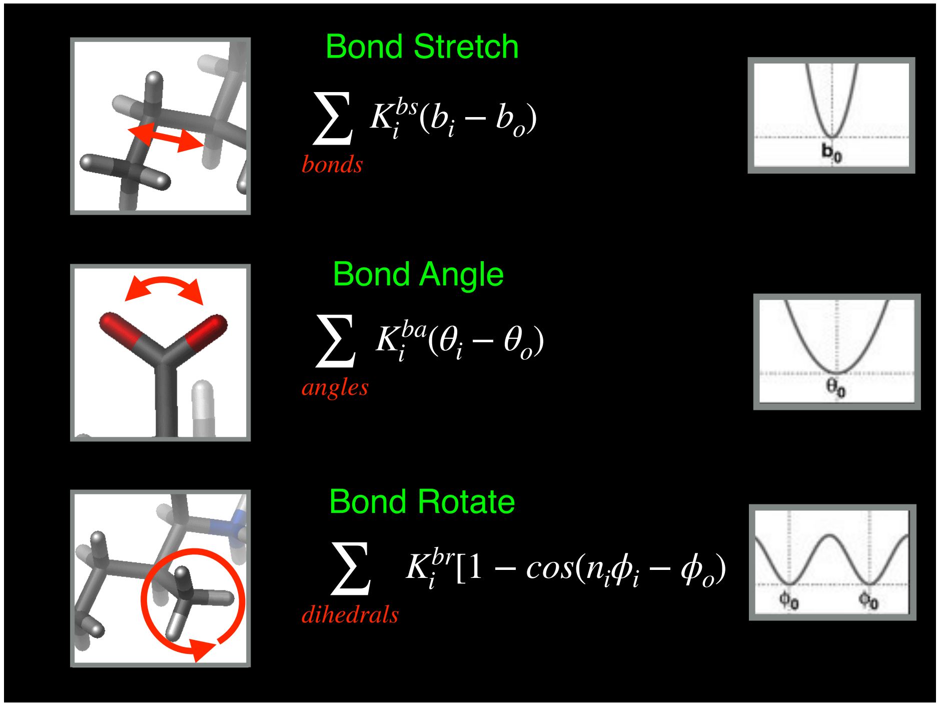
Bond Angle

$$\sum_{angles} K_i^{ba}(\theta_i - \theta_o)$$



Bond Rotate

$$\sum_{dihedrals} K_i^{br}[1 - cos(n_i\phi_i - \phi_o)$$



Bond Stretch

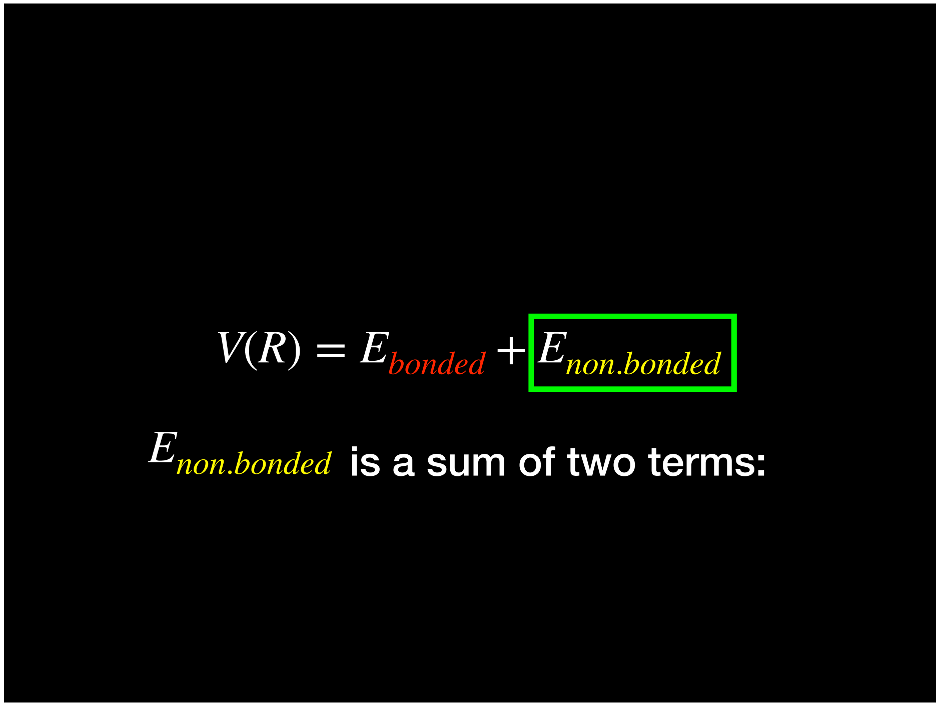
$$\sum_{bonds} K_i^{bs}(b_i - b_o)$$

Bond Angle

$$\sum_{angles} K_i^{ba}(\theta_i - \theta_o)$$

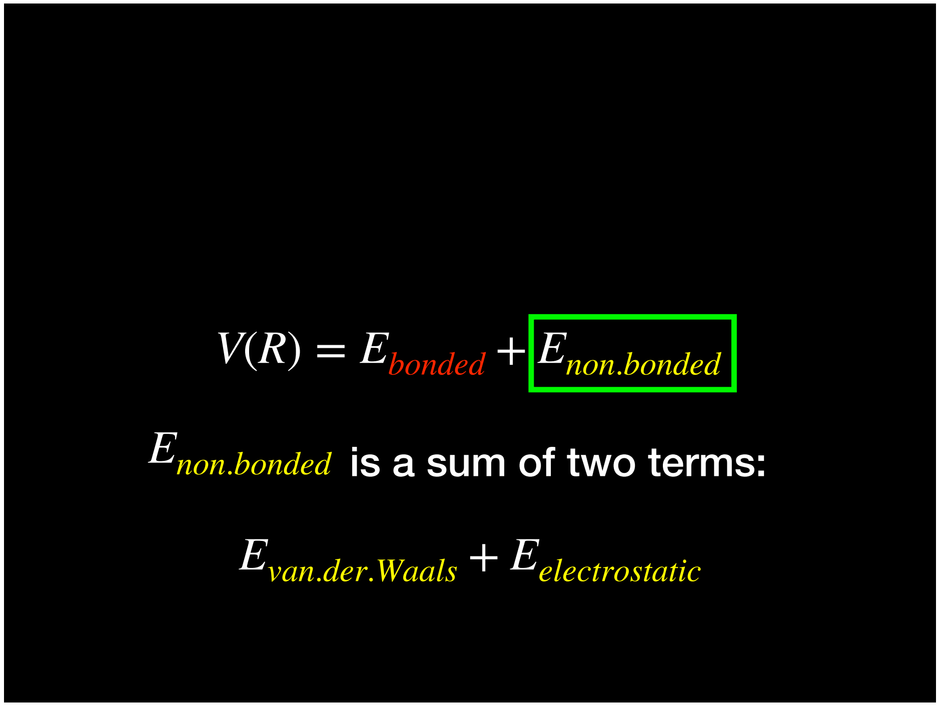
Bond Rotate

$$\sum_{dihedrals} K_i^{br}[1 - cos(n_i\phi_i - \phi_o)]$$



$$V(R) = E_{bonded} + \boxed{E_{non.bonded}}$$

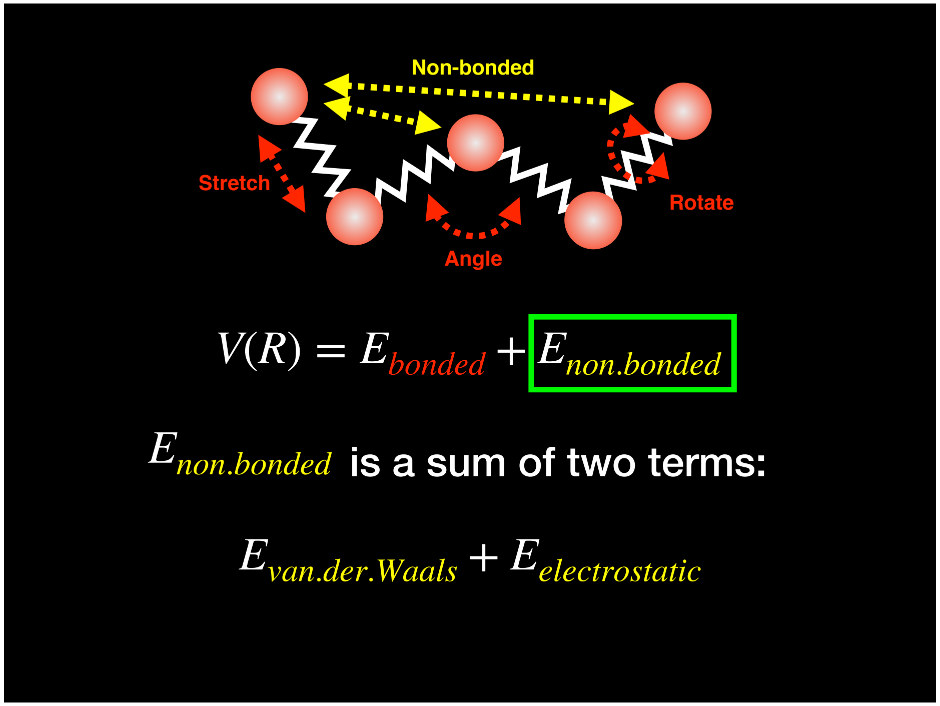
$E_{non.bonded}$ is a sum of two terms:



$$V(R) = E_{bonded} + \boxed{E_{non.bonded}}$$

$E_{non.bonded}$ is a sum of two terms:

$$E_{van.der.Waals} + E_{electrostatic}$$



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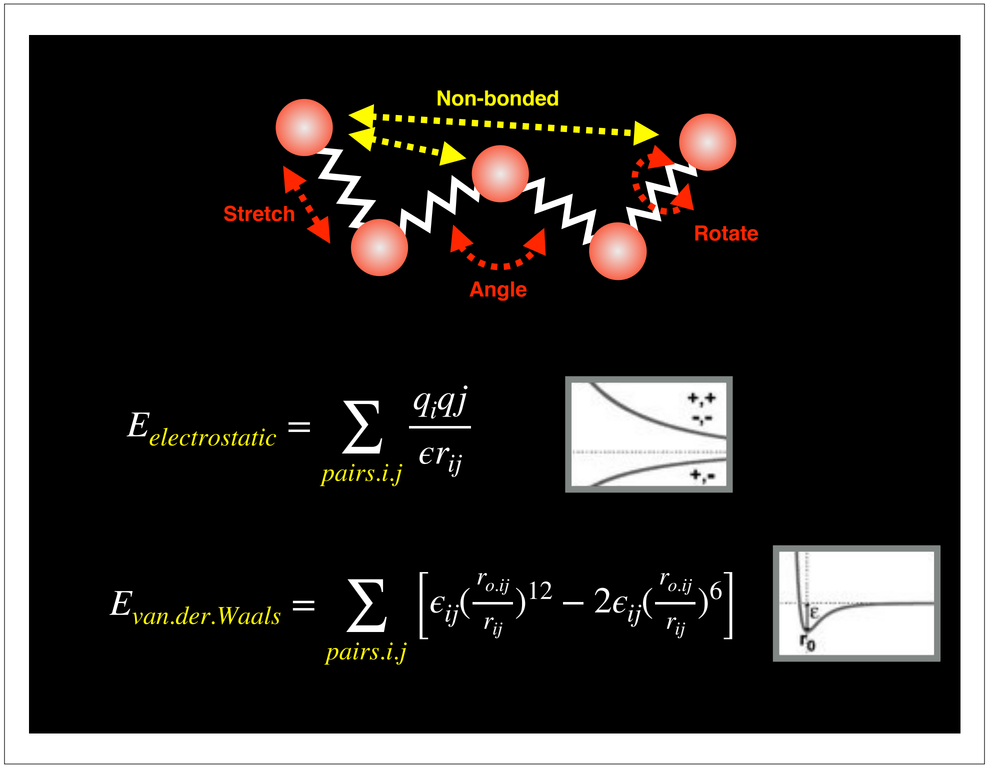
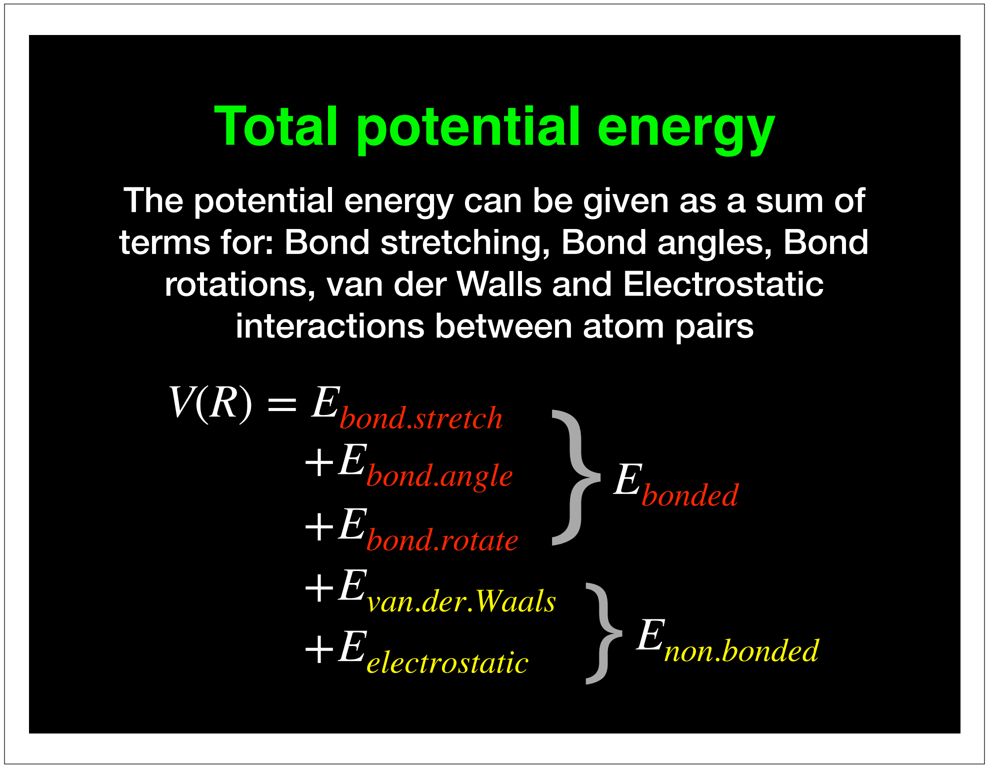


$$E_{electrostatic} = \sum_{pairs.i.j} \frac{q_i qj}{\epsilon r_{ij}}$$

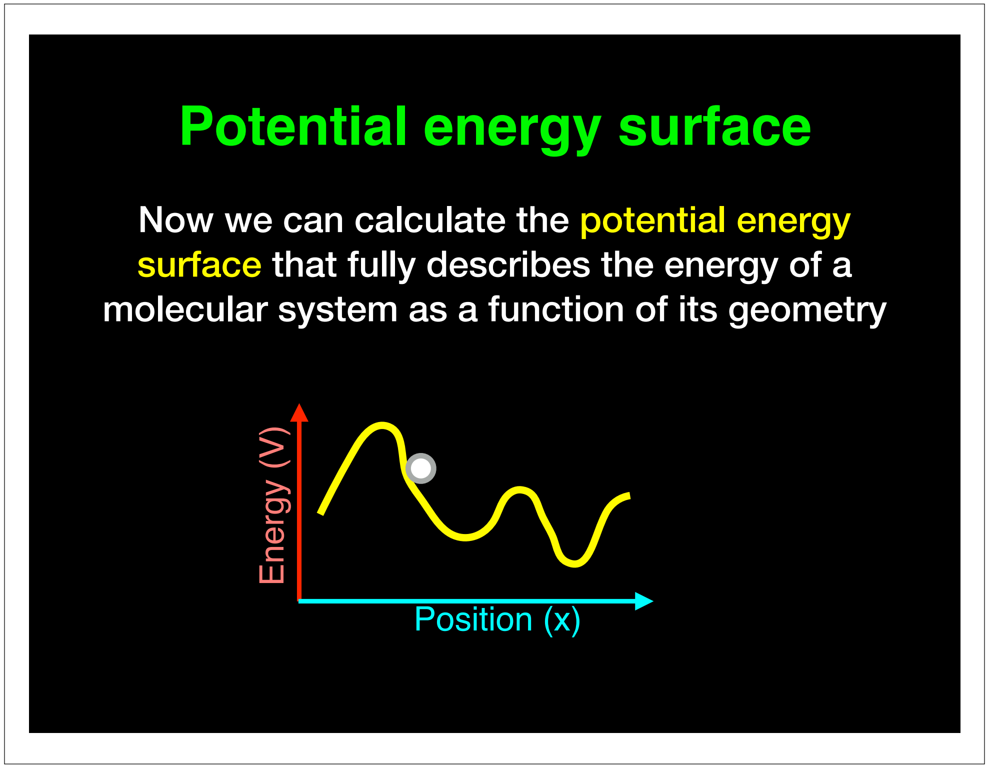
$$E_{van.der.Waals} = \sum_{pairs.i.j} \left[\epsilon_{ij}(\frac{r_{o.ij}}{r_{ij}})^{12} - 2\epsilon_{ij}(\frac{r_{o.ij}}{r_{ij}})^{6}\right]$$



Total potential energy

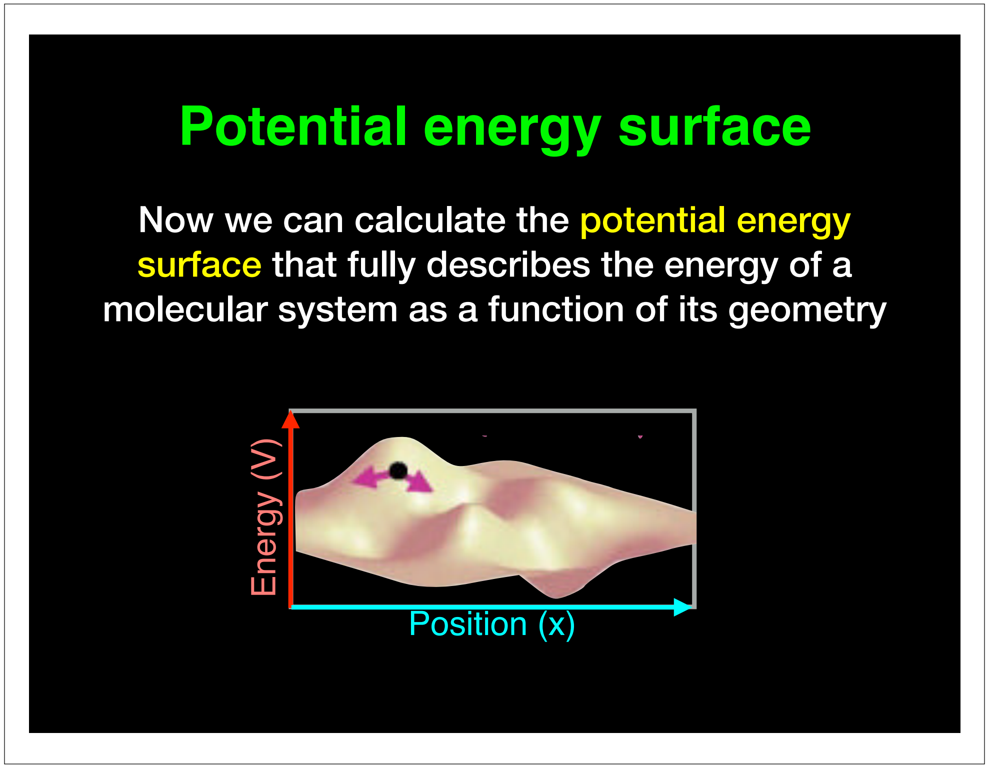
The potential energy can be given as a sum of terms for: Bond stretching, Bond angles, Bond rotations, van der Walls and Electrostatic interactions between atom pairs

$$\begin{aligned} V(R) = & \left.\begin{aligned} &E_{bond.stretch} \\ &+E_{bond.angle} \\ &+E_{bond.rotate} \end{aligned}\right\} E_{bonded} \\ & \left.\begin{aligned} &+E_{van.der.Waals} \\ &+E_{electrostatic} \end{aligned}\right\} E_{non.bonded} \end{aligned}$$



Potential energy surface

Now we can calculate the potential energy surface that fully describes the energy of a molecular system as a function of its geometry

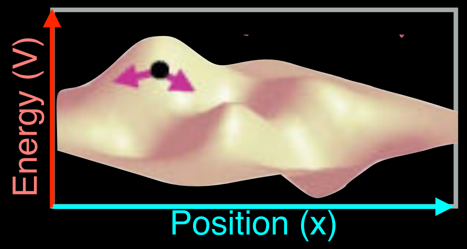


Potential energy surface

Now we can calculate the potential energy surface that fully describes the energy of a molecular system as a function of its geometry

Key concept:

Now we can calculate the potential energy surface that fully describes the energy of a molecular system as a function of its geometry



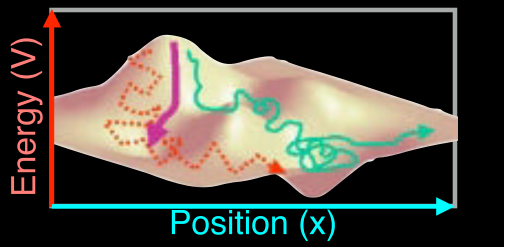
- The **forces** are the gradients of the energy

$$F(x) = -dV/dx$$

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:

$$exp(-\Delta V/dx)$$



PHYSICS-ORIENTED APPROACHES

Weaknesses

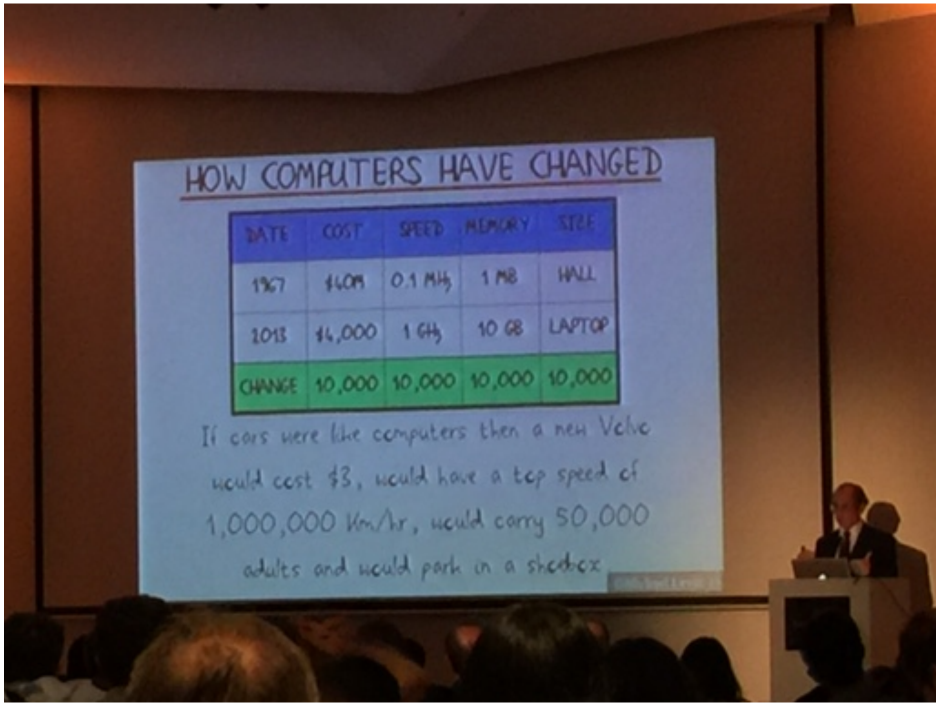
Fully physical detail becomes computationally intractable
Approximations are unavoidable
(Quantum effects approximated classically, water may be treated crudely)
Parameterization still required

Strengths

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

Status

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

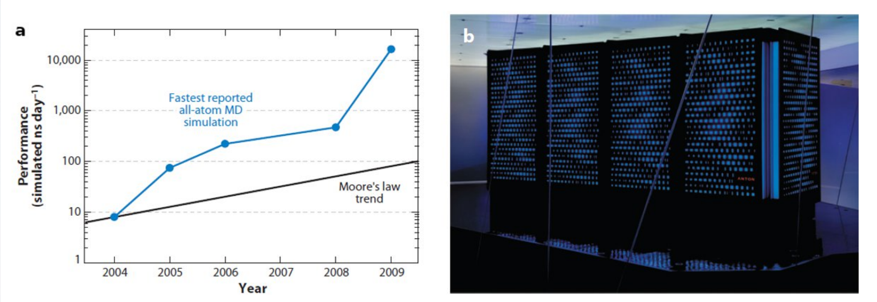


HOW COMPUTERS HAVE CHANGED

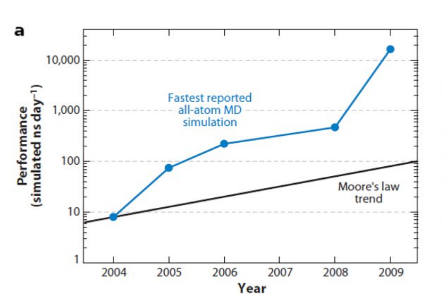
DATE	COST	SPEED	MEMORY	SIZE
1967	$40M	0.1 MHz	1 MB	HALL
2013	$4,000	1 GHz	10 GB	LAPTOP
CHANGE	10,000	10,000	10,000	10,000

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

SIDE-NOTE: GPUS AND ANTON SUPERCOMPUTER



SIDE-NOTE: GPUS AND ANTON SUPERCOMPUTER



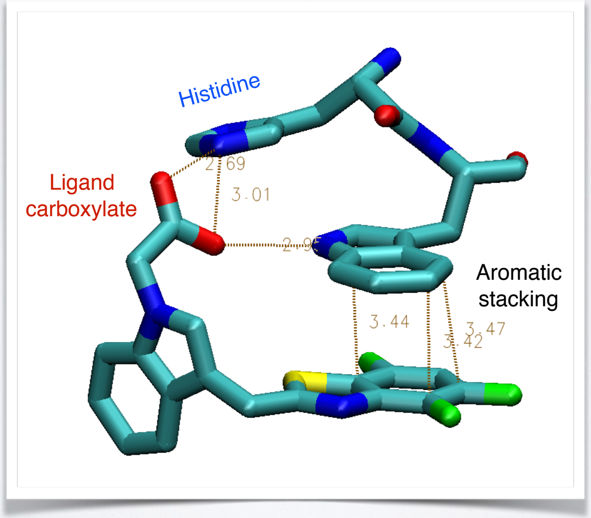
POTENTIAL FUNCTIONS DESCRIBE A SYSTEMS **ENERGY** AS A FUNCTION OF ITS **STRUCTURE**

Two main approaches:

(1). **Physics-Based**

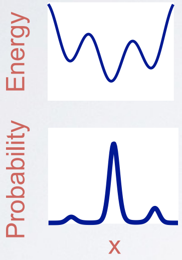
(2). **Knowledge-Based**

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 POTENTIALS

Weaknesses

Accuracy limited by availability of data

Strengths

Relatively easy to implement
Computationally fast

Status

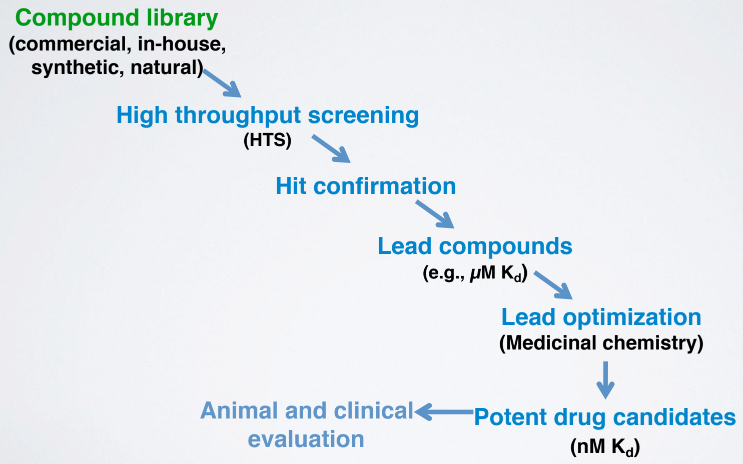
Useful, far from perfect
May be at point of diminishing returns
(not always clear how to make improvements)

Computer Aided Drug Discovery

Next Up:

- **Overview of structural bioinformatics**
  - Motivations, goals and challenges
- **Fundamentals of protein structure**
  - Structure composition, form and forces
- **Representing, interpreting & modeling protein structure**
  - Visualizing and interpreting protein structures
  - Analyzing protein structures
  - Modeling energy as a function of structure
  - 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

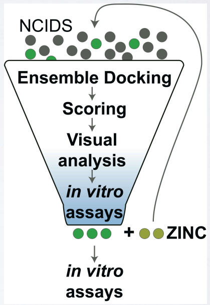
COMPUTER-AIDED LIGAND DESIGN

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**

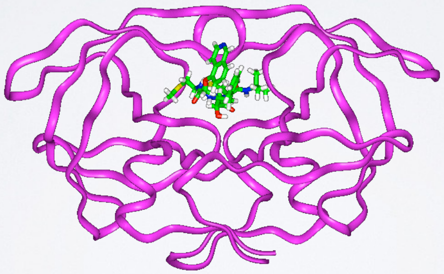
Two main approaches:

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

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

SCENARIO 1: RECEPTOR-BASED DRUG DISCOVERY

Structure of Targeted Protein Known: Structure-Based Drug Discovery

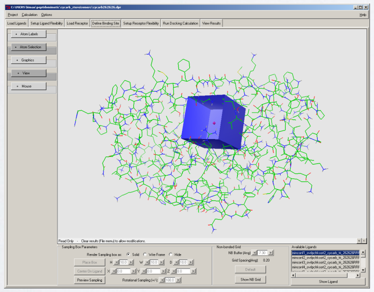


HIV Protease/KNI-272 complex

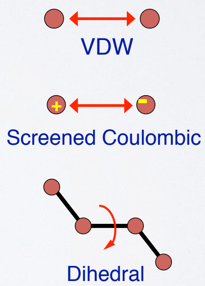
PROTEIN-LIGAND DOCKING

Structure-Based Ligand Design

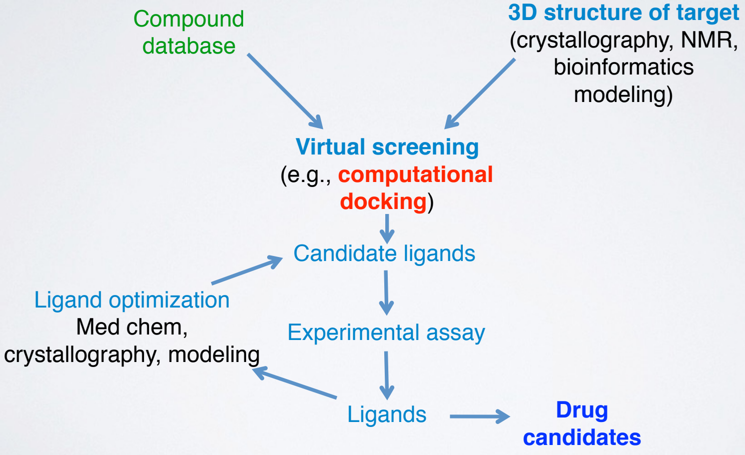
Docking software
Search for structure of lowest energy



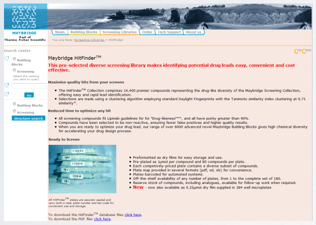
Potential function
Energy as function of structure



STRUCTURE-BASED VIRTUAL SCREENING



COMPOUND LIBRARIES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You are here: Screening Libraries > HitFinder
Search center
Building Blocks
Screening
Go
Structure search

Maybridge HitFinder™

This pre-selected diverse screening library makes identifying potential drug leads easy, convenient and cost effective.

Maximise quality hits from your screens

- The HitFinder™ Collection comprises 14,400 premier compounds representing the drug-like diversity of the Maybridge Screening Collection, offering easy and rapid lead identification.
- Selections are made using a clustering algorithm employing standard Daylight Fingerprints with the Tanimoto similarity index clustering at 0.71 similarity*.

Reduced time to optimize any hit

- All screening compounds fit Lipinski guidelines for for "Drug-likeness"**, and all have purity greater than 90%.
- Compounds have been selected to be non-reactive, ensuring fewer false positives and higher quality results.
- When you are ready to optimize your drug lead, our range of over 6000 advanced novel Maybridge Building Blocks gives high chemical diversity for accelerating your drug design process.

Ready to Screen

- Preformatted as dry films for easy storage and use.
- Pre-plated as 1μmol per compound and 80 compounds per plate.
- Each competively-priced plate contains a diverse subset of compounds.
- Plate map provided in several formats (pdf, sd, xls) for convenience.
- Plates barcoded for automated systems.
- Off-the-shelf availability of any number of plates, from 1 to the complete set of 180.
- Reserve stock of compounds, including analogues, available for follow-up work when required.
- New - now also available as 0.25μmol dry film supplied in 384 well microplates

All HitFinder™ plates are securely sealed and carry both a clear plate number and bar-code for convenient use and storage.

To download the HitFinder™ database files click here.
To download the PDF flier click here.

Commercial
(in-house pharma)

Welcome

NIH Molecular Libraries Small Molecule Repository collects samples for high throughput biological screening and distributes them to the NIH Molecular Libraries Probe Production Centers Network. Learn more.

MLSMR is a key component of the Molecular Libraries Initiative, an NIH Roadmap project supporting New Pathways to Discovery in the 21st century. The project is funded in whole with Federal funds from the National Institutes of Health, Department of Health and Human Services, under Contract No. HHS-N-278-2004-41001C.

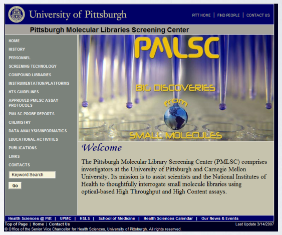
In the news:

Behind the Scenes at the NIH Molecular Libraries Small Molecule Repository

The NIH Molecular Libraries Small Molecule Repository is now selling the NIH Clinical Collection

BioFocus, a Galapagos company operates MLSMR in South San Francisco.

Government (NIH)


University of Pittsburgh
PITT HOME | FIND PEOPLE | CONTACT US
Pittsburgh Molecular Libraries Screening Center
HOME
HISTORY
PERSONNEL
SCREENING TECHNOLOGY
COMPOUND LIBRARIES
INSTRUMENTATION/PLATFORMS
HTS GUIDELINES
APPROVED PMLSC ASSAY PROTOCOLS
PMLSC PROBE REPORTS
CHEMISTRY
DATA ANALYSIS/INFORMATICS
EDUCATIONAL ACTIVITIES
PUBLICATIONS
LINKS
CONTACTS
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Welcome

The Pittsburgh Molecular Library Screening Center (PMLSC) comprises investigators at the University of Pittsburgh and Carnegie Mellon University. Its mission is to assist scientists and the National Institutes of Health to thoughtfully interrogate small molecule libraries using optical-based High Throughput and High Content assays.

Academia

COMMON SIMPLIFICATIONS USED IN PHYSICS-BASED DOCKING

Quantum effects approximated classically

Protein often held rigid

Configurational entropy neglected

Influence of water treated crudely

Do it Yourself!

Hand-on time!

https://bioboot.github.io/bggn213_W19/lectures/#12

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

Two main approaches:

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

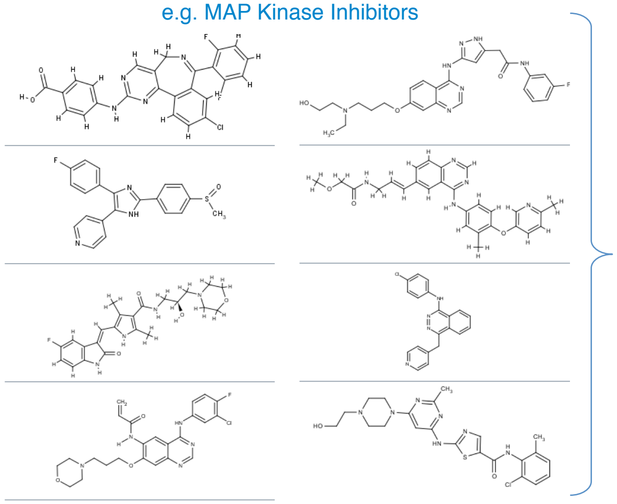
(2). **Ligand/Drug-Based**

Scenario 2

Structure of Targeted Protein Unknown:

Ligand-Based Drug Discovery

e.g. MAP Kinase Inhibitors



Using knowledge of existing inhibitors to discover more

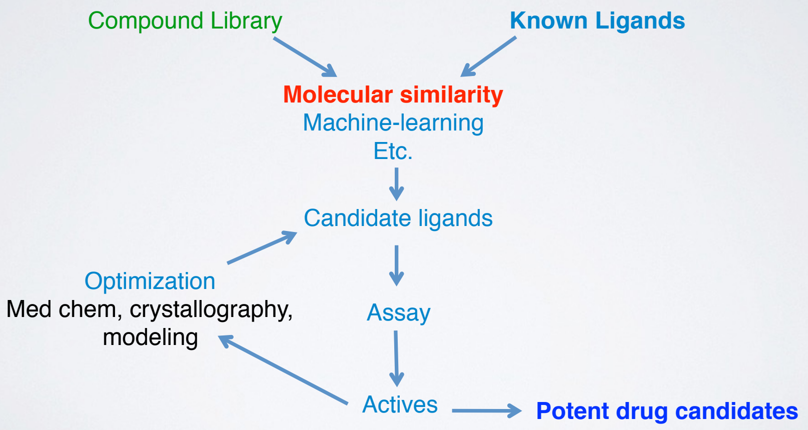
Why Look for Another Ligand if You Already Have Some?

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

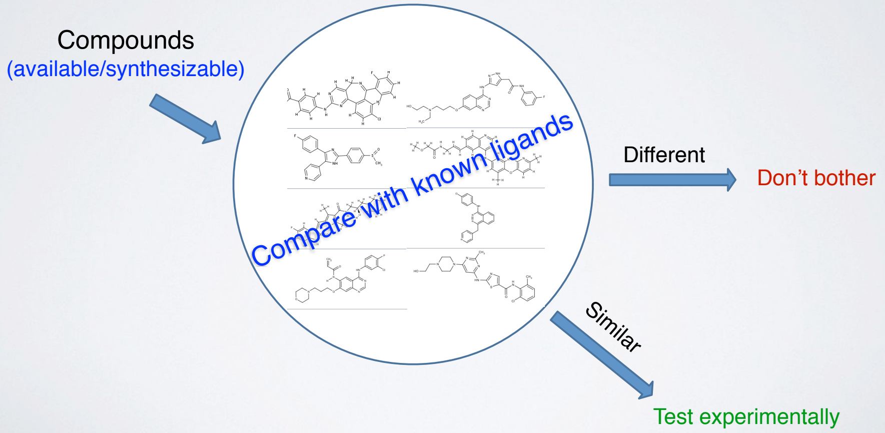
A company wants to work around another company's chemical patents

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

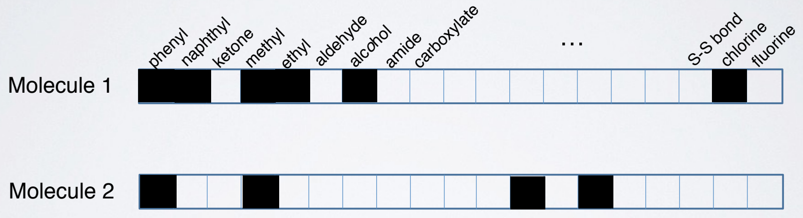
LIGAND-BASED VIRTUAL SCREENING



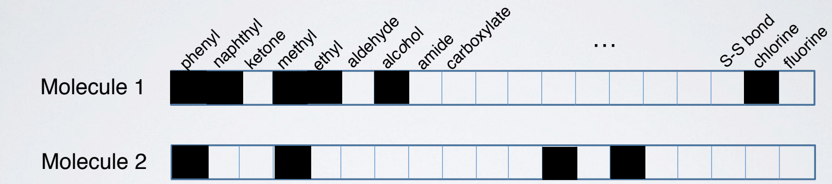
CHEMICAL SIMILARITY
LIGAND-BASED DRUG-DISCOVERY



CHEMICAL FINGERPRINTS
BINARY STRUCTURE KEYS

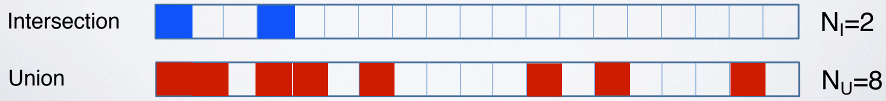


CHEMICAL SIMILARITY FROM FINGERPRINTS



Tanimoto Similarity (or Jaccard Index), T

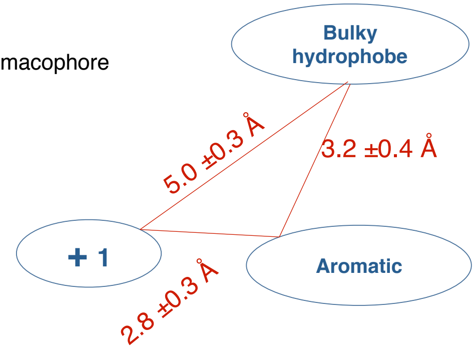
$$T \equiv \frac{N_I}{N_U} = 0.25$$



Pharmacophore Models

Φάρμακο (drug) + Φορά (carry)

A 3-point pharmacophore

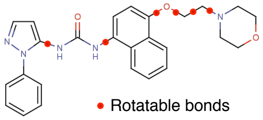


Molecular Descriptors

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

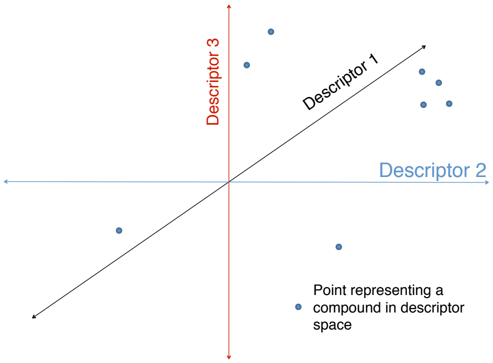
- branching index
- measures of linearity vs interconnectedness

Etc. etc.

A High-Dimensional “Chemical Space”

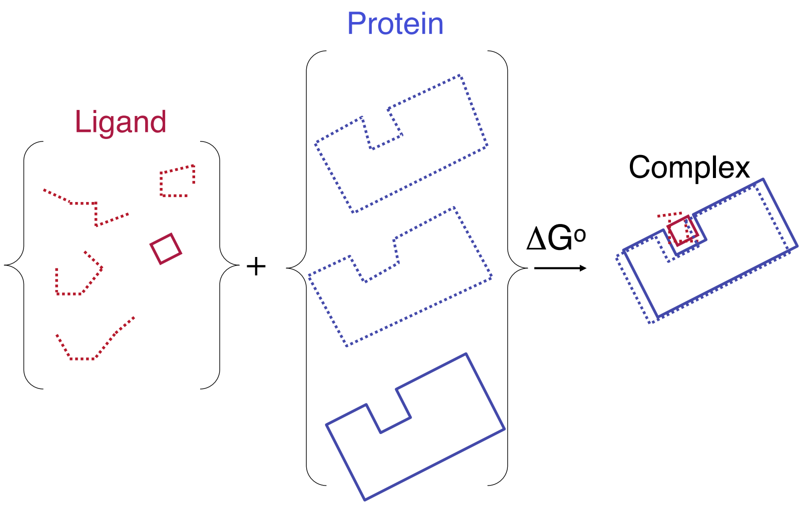
Each compound is a point in an n-dimensional space

Compounds with similar properties are near each other



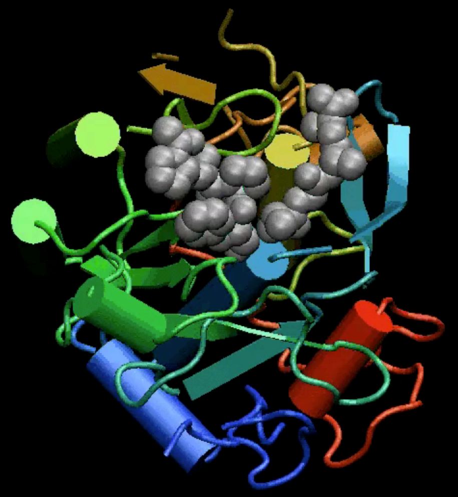
Apply **multivariate statistics** and **machine learning** for descriptor-selection. (e.g. partial least squares, PCA, support vector machines, random forest, deep learning etc.)

Proteins and Ligand are Flexible



NMA (Normal Mode Analysis) is a bioinformatics method to predict the intrinsic dynamics of biomolecules

Do it Yourself!



https://bioboot.github.io/bggn213_W19/lectures/#12

Reference Slides

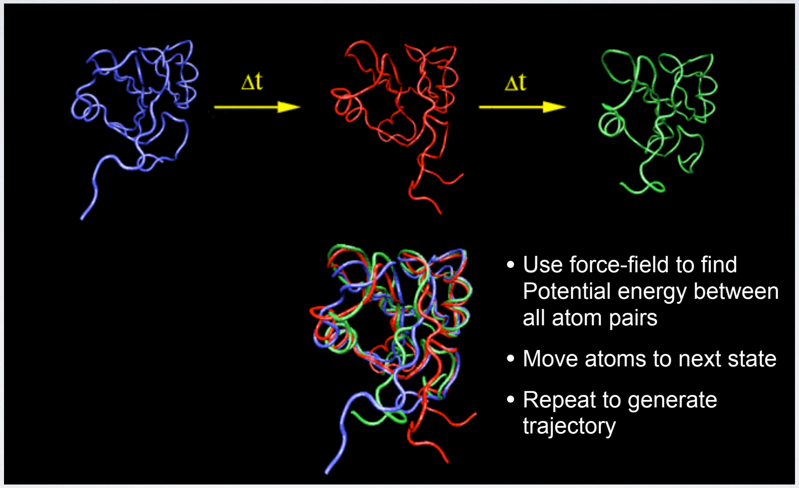
Molecular Dynamics (MD) and Normal Mode Analysis (NMA) Background and Cautionary Notes

[Muddy Point Assessment]

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

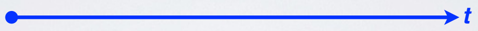
MOLECULAR DYNAMICS SIMULATION



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

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

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



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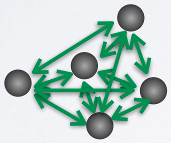
(for integrating equations of motion, see below)

- 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

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

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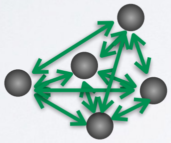


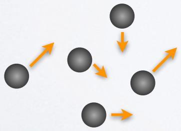
Nucleic motion described classically

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

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)

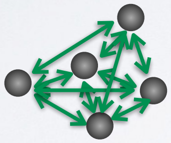


$$\begin{aligned} \boldsymbol{v}(t+\frac{\Delta t}{2}) &= \boldsymbol{v}(t-\frac{\Delta t}{2}) + \frac{\boldsymbol{F}(t)}{m}\Delta t \\ \boldsymbol{r}(t+\Delta t) &= \boldsymbol{r}(t) + \boldsymbol{v}(t+\frac{\Delta t}{2})\Delta t \end{aligned}$$

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)



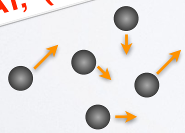
Nucleic motion described classically

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

Empirical force f

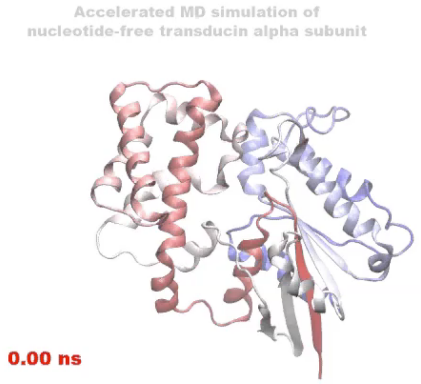
- Use the fo **velocities** and move atoms to new **posit ons**
  numerically via the “leapfrog” scheme)

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



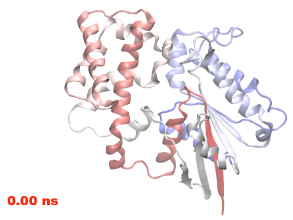
$$\begin{aligned} \boldsymbol{v}(t+\frac{\Delta t}{2}) &= \boldsymbol{v}(t-\frac{\Delta t}{2}) + \frac{\boldsymbol{F}(t)}{m}\Delta t \\ \boldsymbol{r}(t+\Delta t) &= \boldsymbol{r}(t) + \boldsymbol{v}(t+\frac{\Delta t}{2})\Delta t \end{aligned}$$

MD Prediction of Functional Motions

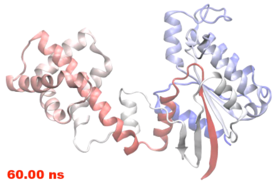

Accelerated MD simulation of nucleotide-free transducin alpha subunit
0.00 ns

Yao and Grant, Biophys J. (2013)

“close”

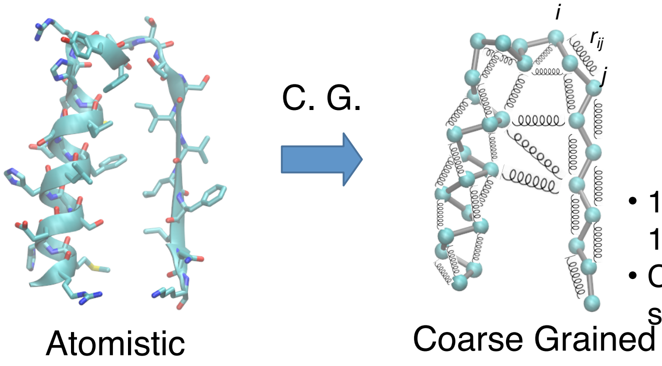


“open”

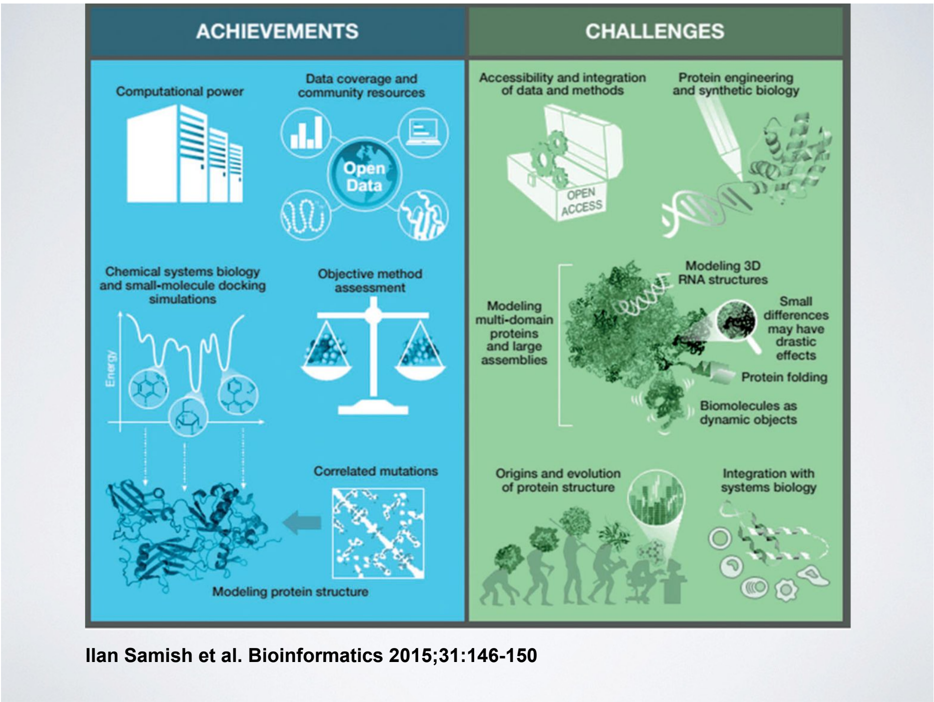


COARSE GRAINING: **NORMAL MODE ANALYSIS** (NMA)

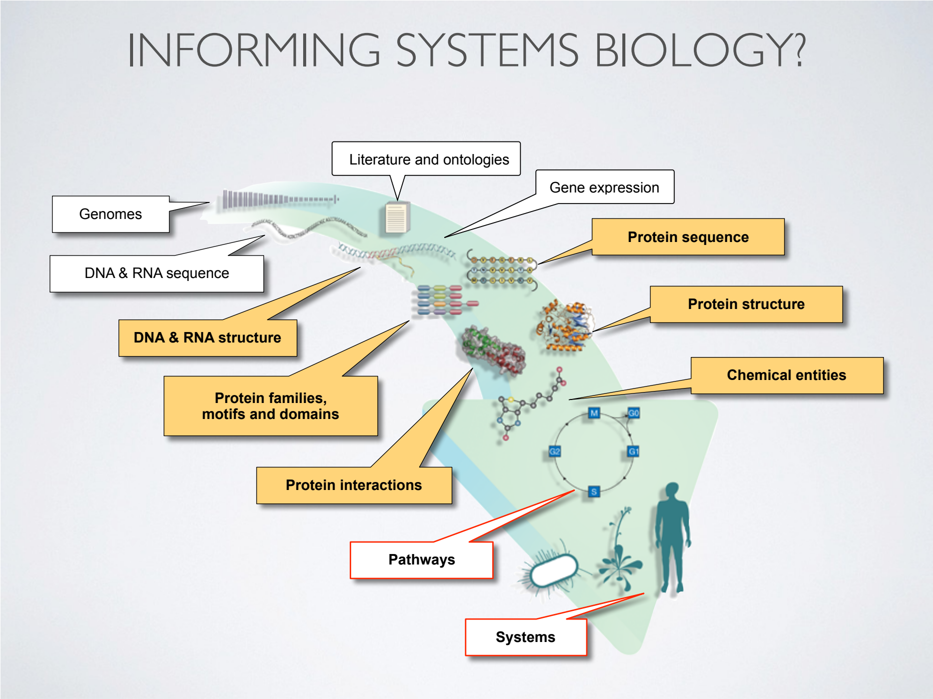
- MD is still time-consuming for large systems
- Elastic network model NMA (ENM-NMA) is an example of a lower resolution approach that finishes in seconds even for large systems.



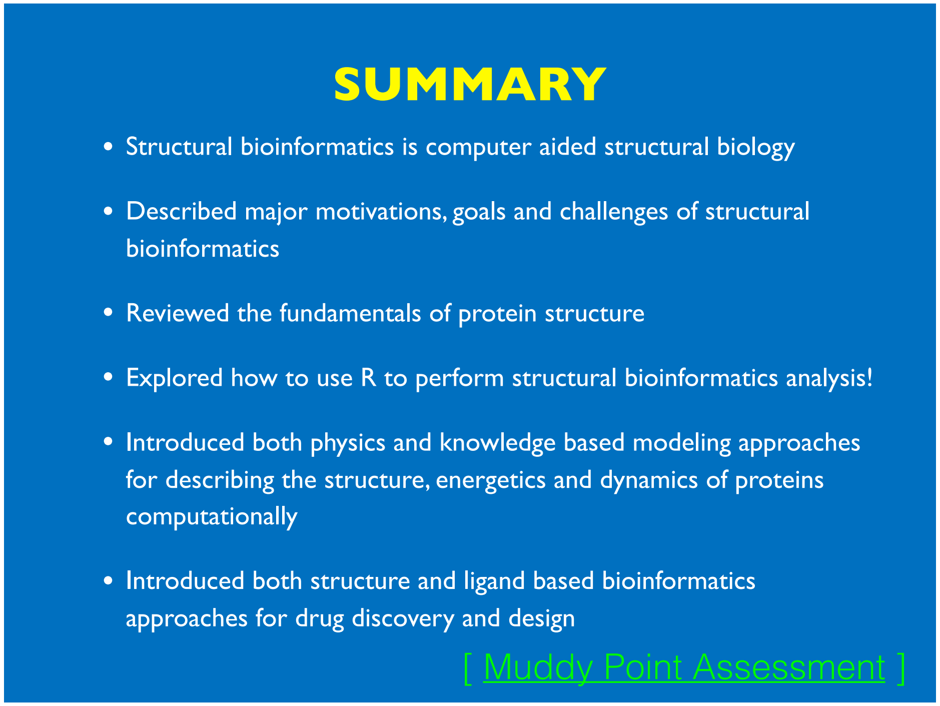
- 1 bead / 1 amino acid
- Connected by springs


ACHIEVEMENTS
CHALLENGES
Computational power
Data coverage and community resources
Open Data
Chemical systems biology and small-molecule docking simulations
Objective method assessment
Energy
Correlated mutations
Modeling protein structure
Accessibility and integration of data and methods
OPEN ACCESS
Protein engineering and synthetic biology
Modeling 3D RNA structures
Modeling multi-domain proteins and large assemblies
Small differences may have drastic effects
Protein folding
Biomolecules as dynamic objects
Origins and evolution of protein structure
Integration with systems biology

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



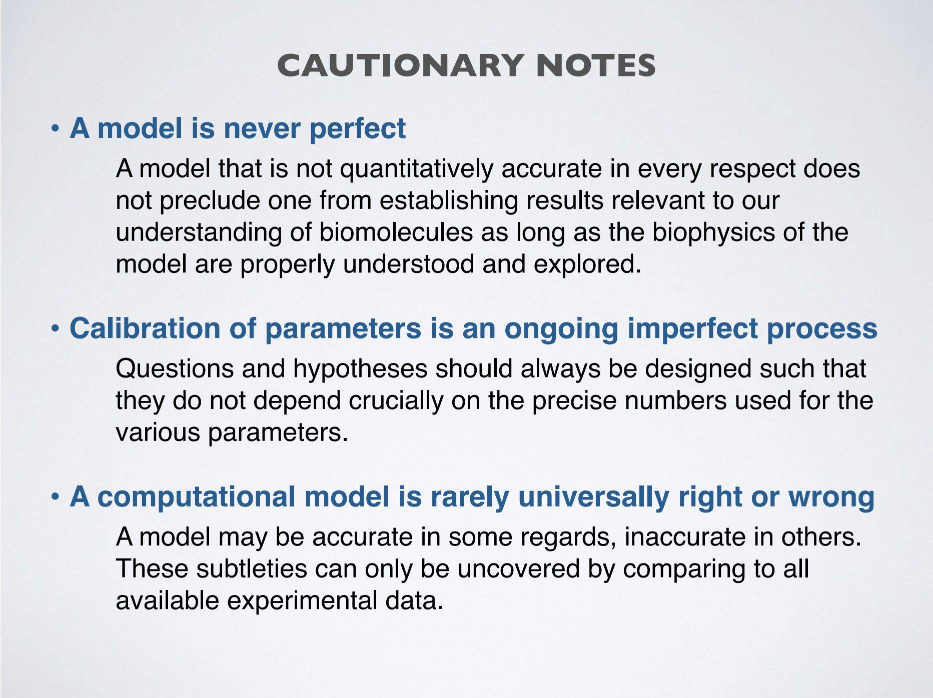
INFORMING SYSTEMS BIOLOGY?



SUMMARY

- Structural bioinformatics is computer aided structural biology
- Described major motivations, goals and challenges of structural bioinformatics
- Reviewed the fundamentals of protein structure
- Explored how to use R to perform structural bioinformatics analysis!
- 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

[Muddy Point Assessment]



CAUTIONARY NOTES

- **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 parameters is an ongoing 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.