

# Energy functions and their relationship to molecular conformation

CS/BioE/Biophys/BMI/CME 279

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# Outline

- Overview
  - The big questions
  - Demo
- Energy functions for biomolecular systems
  - Definition and properties
  - Molecular mechanics force fields
- What does the energy function tell us about biomolecular structure/conformation?
  - The Boltzmann distribution
  - Conformations and conformational states
  - Free energy

# Overview

# A biomolecule adopts many shapes

- The atoms in biomolecules are constantly jiggling around
  - “Everything that living things do can be understood in terms of the jigglings and wiggings of atoms.” — Richard Feynman, 1963 (Nobel Prize, 1965)
- A biomolecule adopts many geometries/shapes!
- We refer to each geometry of a molecule (i.e., precise arrangement of atoms, specified by 3D coordinates) as a **conformation**
  - “Conformation” is similar to “structure,” except that “structure” is often used to describe an average structure, which is what one typically gets when determining a structure experimentally

# The big questions

- **Given a biomolecule (e.g., protein), which conformations will it adopt? How frequently will it adopt each conformation?**
  - Note that this depends on the other molecules surrounding it, so we typically consider a “molecular system” consisting of multiple molecules
  - It also depends on temperature
  - We can ask these questions either for individual conformations or for sets of similar conformations (referred to as “conformational states”)

# Demo

- Take-aways:
  - The system adopts many conformations
  - It adopts low-energy conformations more frequently than high-energy conformations
  - **If we can define the energy associated with each conformation, we can determine how often the system will adopt each conformation**
- We'll thus discuss how to calculate energies for conformations of biomolecules (and biomolecular systems)

# Key difference between demo and molecular systems

- To specify the “conformation” (horizontal position) of the cheerio or ball, I need only two numbers
- To specify the conformation of a molecular system (or a single biomolecule), I need to specify the  $x$ ,  $y$ , and  $z$  coordinates of each atom.
  - For  $N$  atoms, that’s  $3N$  coordinates.
  - Energy depends on all of these coordinates!
- All the take-aways still apply to molecular systems!

# Energy functions for biomolecular systems



# Energy functions for biomolecular systems

**Definition and properties**

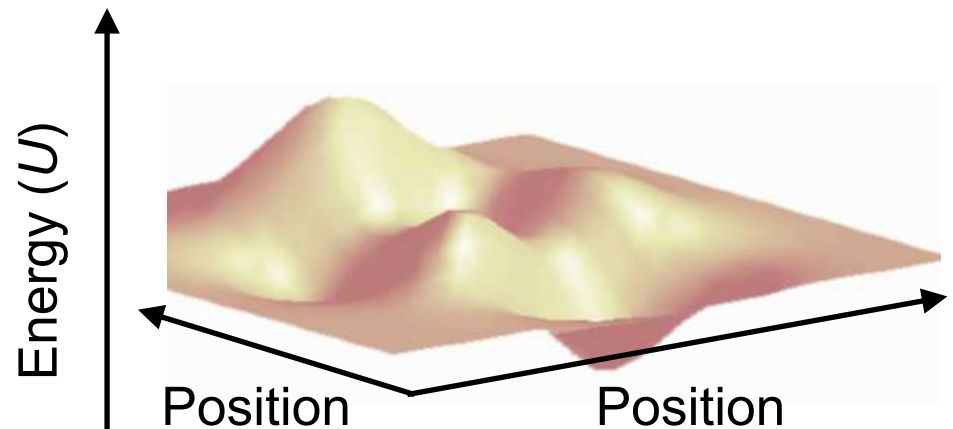
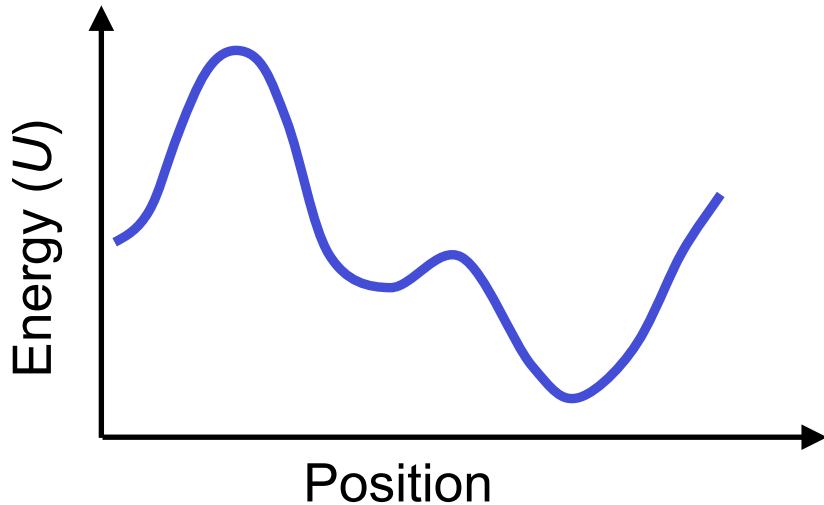
# Specifying atom positions

- For a molecular system with  $N$  atoms, we can specify the position of all atoms by a single vector  $\mathbf{x}$  of length  $3N$ 
  - This vector contains the  $x$ ,  $y$ , and  $z$  coordinates of every atom

$$\mathbf{x} = \begin{pmatrix} x_1 \\ y_1 \\ z_1 \\ x_2 \\ y_2 \\ z_2 \\ \vdots \\ x_N \\ y_N \\ z_N \end{pmatrix}$$

# Energy function

- A potential energy function  $U(\mathbf{x})$  specifies the total potential energy of a system of atoms as a function of all their positions ( $\mathbf{x}$ )
  - In the general case, include not only atoms in the protein but also surrounding atoms (e.g., water)
- The potential energy function  $U$  is also called a *force field*, because one can use it to compute forces on atoms



# Types of force fields (energy functions)

- A wide variety of force fields are used in atomic-level modeling of macromolecules
- Physics-based vs. knowledge-based
  - Physics-based force fields attempt to model actual physical forces
  - Knowledge-based force fields are based on statistics about, for example, known protein structures
  - Most real force fields are somewhere in between
- Atoms represented
  - Most realistic choice is to model all atoms
  - Some force fields omit waters and other surrounding molecules. Some omit certain atoms within the protein.

Energy functions for biomolecular  
systems

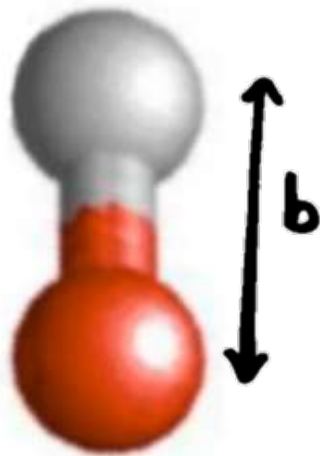
**Molecular mechanics force fields**

# Molecular mechanics force fields

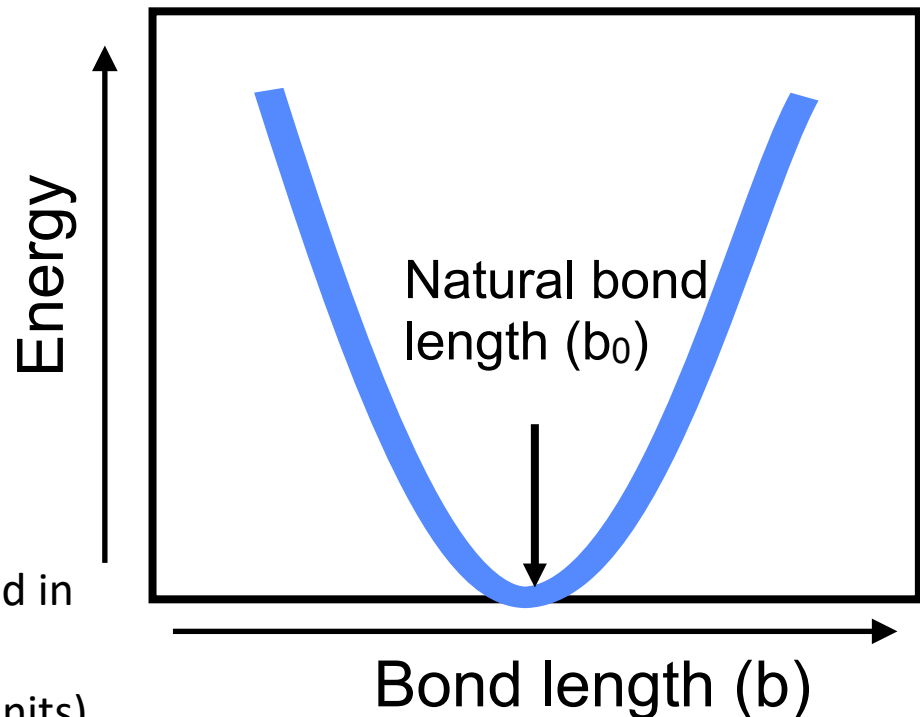
- Today, we'll focus on *molecular mechanics force fields*, which are often used for molecular simulations
- These are more toward the physics-based, all-atom end (i.e., the more “realistic” force fields)
  - Represent physical forces explicitly
  - Typically represent solvent molecules (e.g., water) explicitly
- We'll revisit the forces acting between atoms and write down the functional forms typically used to approximate them

# Bond length stretching

- A bonded pair of atoms is effectively connected by a spring with some preferred (natural) length. Stretching or compressing it requires energy.



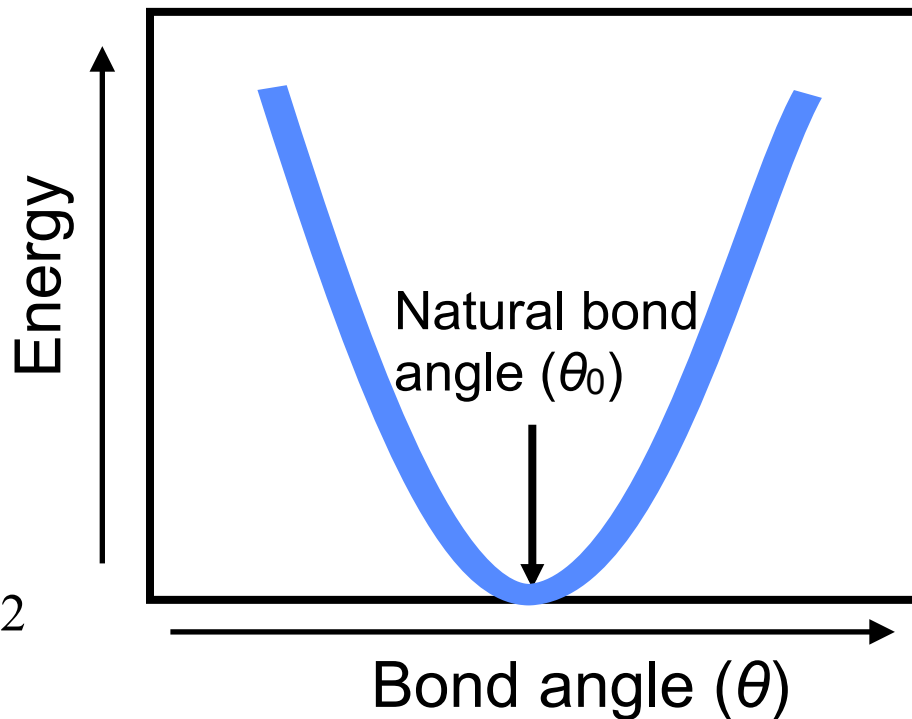
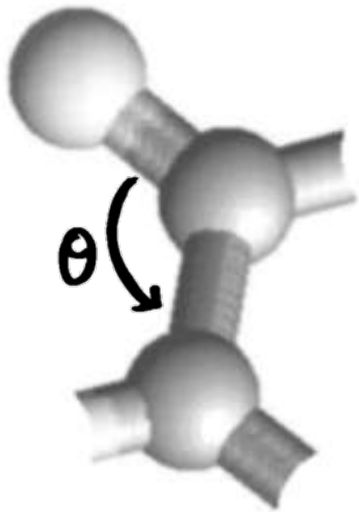
$$U(b) = k_b (b - b_0)^2$$



Note: A factor of 1/2 is sometimes included in this equation. I'm ignoring such constant factors (they can be folded into  $k_b$  or the units).

# Bond angle bending

- Likewise, each bond angle has some natural value. Increasing or decreasing it requires energy.

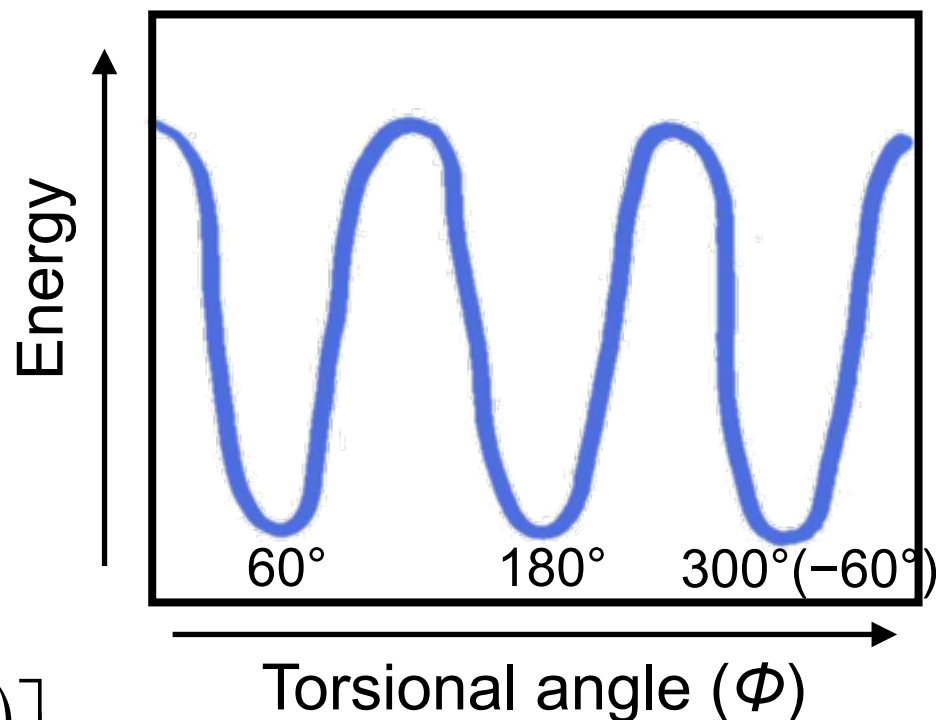
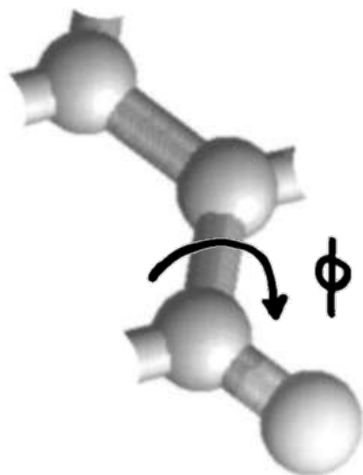


$$U(\theta) = k_{\theta} (\theta - \theta_0)^2$$



# Torsional angle twisting

- Certain values of each torsional angle are preferred over others.

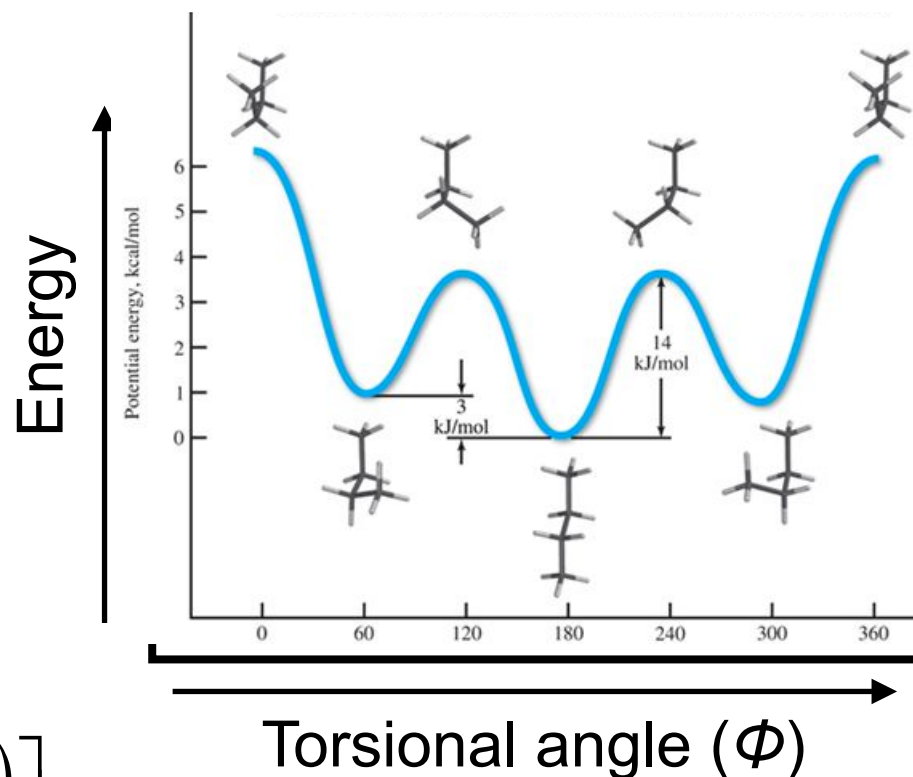
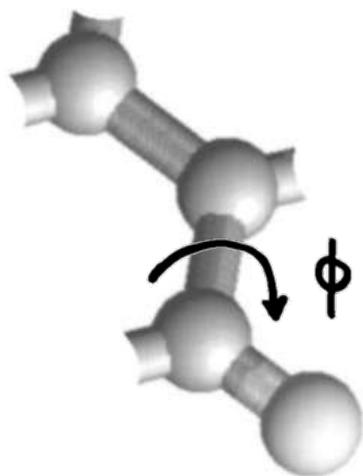


$$U(\phi) = \sum_n k_{\phi,n} \left[ 1 + \cos(n\phi - \phi_n) \right]$$

Typically  $n$  takes on one or a few values between 1 and 6

# Torsional angle twisting

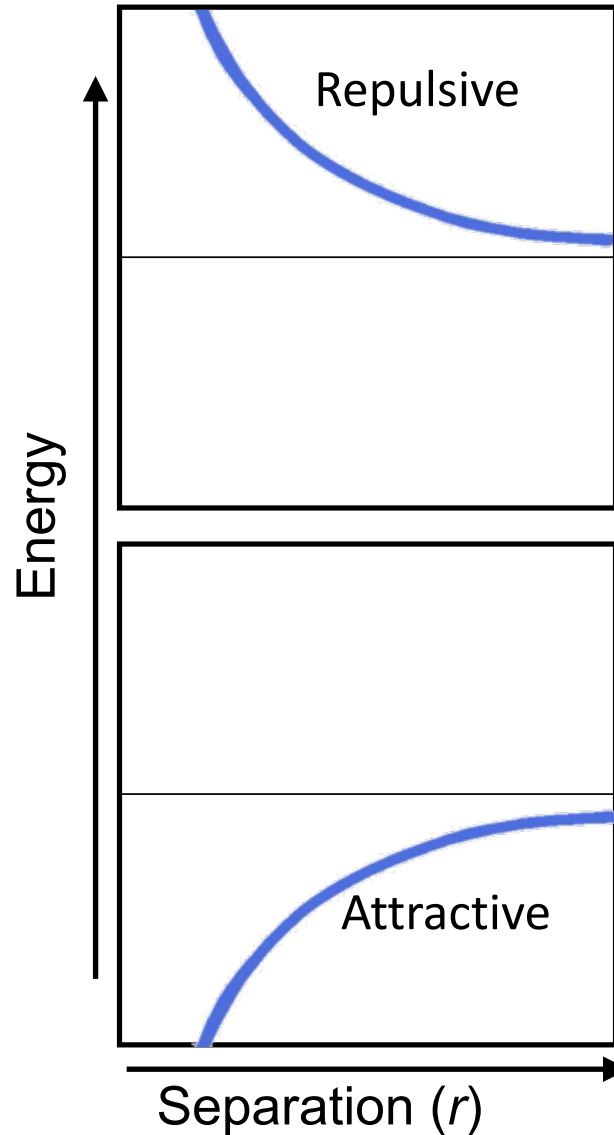
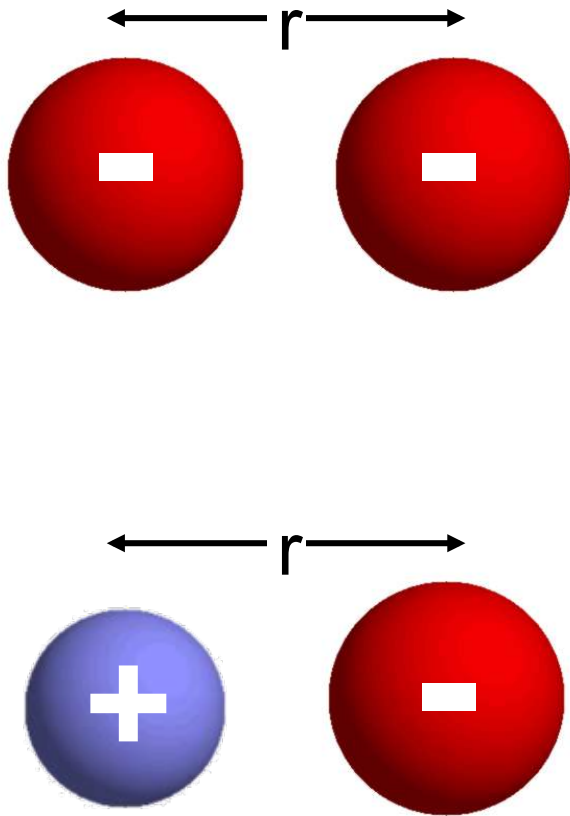
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Typically  $n$  takes on one or a few values between 1 and 6

# Electrostatics interaction

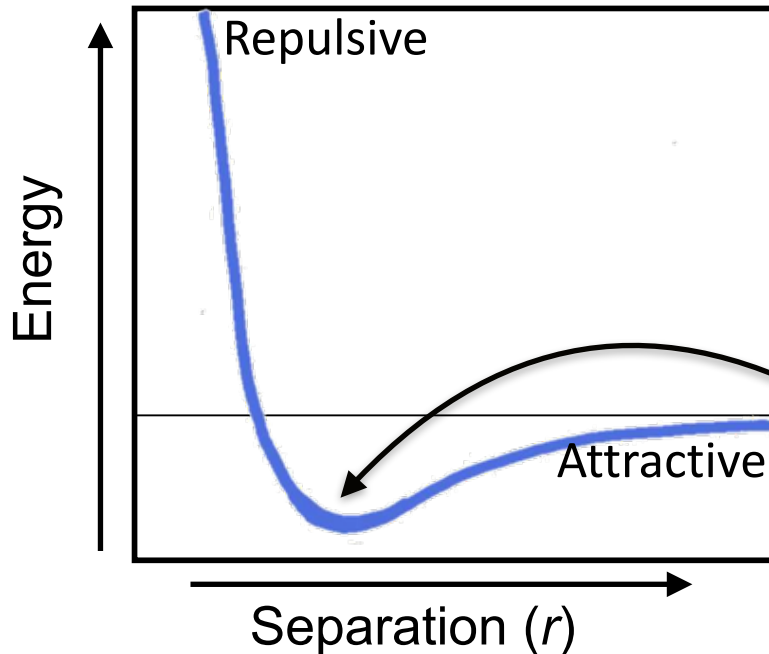
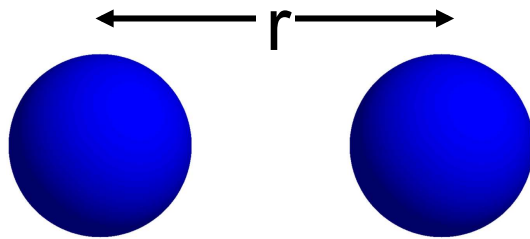


- Like charges repel. Opposite charges attract.
- Acts between all pairs of atoms, including those in different molecules.
- Each atom carries some “partial charge” (may be a fraction of an elementary charge), which depends on which atoms it's connected to

$$U(r) = \frac{q_i q_j}{r}$$

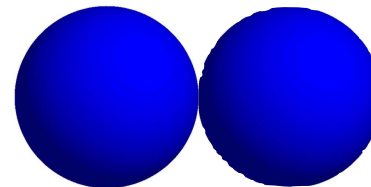
where  $q_i$  and  $q_j$  are partial charges on atoms  $i$  and  $j$

# van der Waals interaction

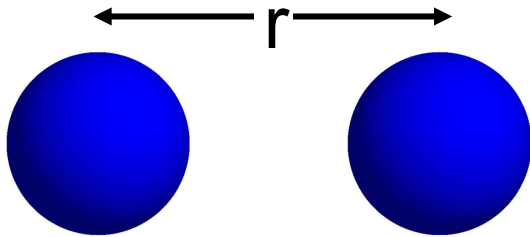


- van der Waals forces act between all pairs of atoms and do not depend on charge.
- When two atoms are too close together, they repel strongly.
- When two atoms are a bit further apart, they attract one another weakly.

Energy is minimal when atoms are “just touching” one another



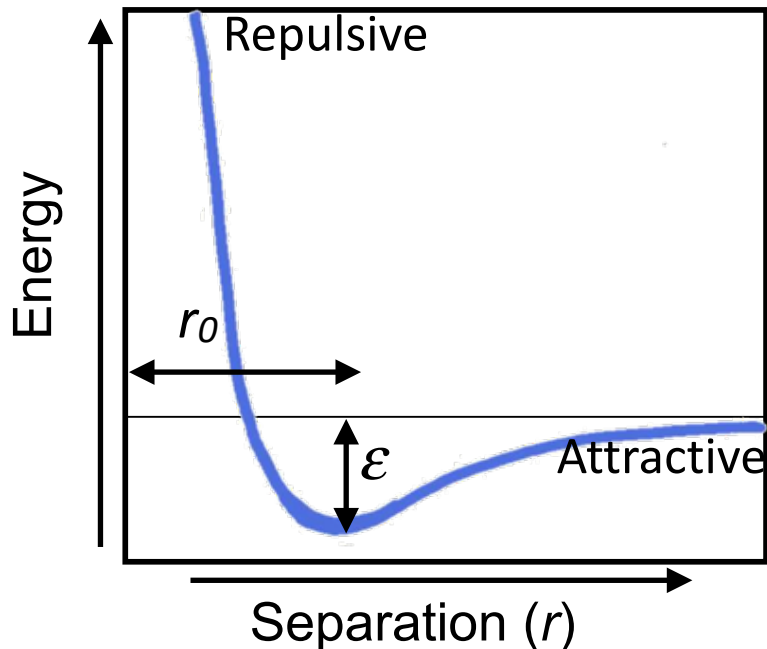
# van der Waals interaction



$$U(r) = \frac{A_{ij}}{r^{12}} - \frac{B_{ij}}{r^6}$$

We can also write this as:

$$U(r) = \epsilon \left[ \left( \frac{r_0}{r} \right)^{12} - 2 \left( \frac{r_0}{r} \right)^6 \right]$$



Note: Historically,  $r^{12}$  term was chosen for computational convenience; other forms are sometimes used

# A typical molecular mechanics force field

$$U = \sum_{\text{bonds}} k_b (b - b_0)^2$$

**Bond lengths (“Stretch”)**

$$+ \sum_{\text{angles}} k_\theta (\theta - \theta_0)^2$$

**Bond angles (“Bend”)**

**Bonded  
terms**

$$+ \sum_{\text{torsions}} \sum_n k_{\phi,n} \left[ 1 + \cos(n\phi - \phi_n) \right]$$

**Torsional/dihedral angles**

$$+ \sum_i \sum_{j>i} \frac{q_i q_j}{r_{ij}}$$

**Electrostatics**

$$+ \sum_i \sum_{j>i} \frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6}$$

**Van der Waals**

**Non-  
bonded  
terms**

# How are the parameters fit?

- Combination of:
  - Quantum mechanical calculations
  - Experimental data
    - For example:  $b_0$  can be estimated from x-ray crystallography, and  $K_b$  from spectroscopy (infrared absorption)

$$U(b) = K_b (b - b_0)^2$$

- The torsional parameters are usually fit last. They absorb the “slop.” Fidelity to physics is debatable.
- *These force fields are approximations!*

# Neural network–based force fields

- Researchers are now developing force fields by training neural networks to predict results of quantum mechanical calculations
  - These are not yet in widespread use, but I think this is a promising research direction
  - See optional reading on course website



What does the energy function tell us about biomolecular structure/conformation?

What does the energy function tell us about biomolecular conformation?

**The Boltzmann distribution**

# Relating energy to probability

- Given the potential energy associated with a particular conformation (i.e., arrangement of atoms, or set of atomic coordinates), what is the probability that the molecular system will adopt that conformation at a given point in time?
- Assumptions:
  - System is at constant temperature (so atoms are constantly jiggling around).
  - We watch the system for a really long time (allowing it to fully equilibrate).

# The Boltzmann Distribution

- The Boltzmann distribution relates the potential energy of a particular arrangement of atoms to the probability of observing that arrangement of atoms (at equilibrium):

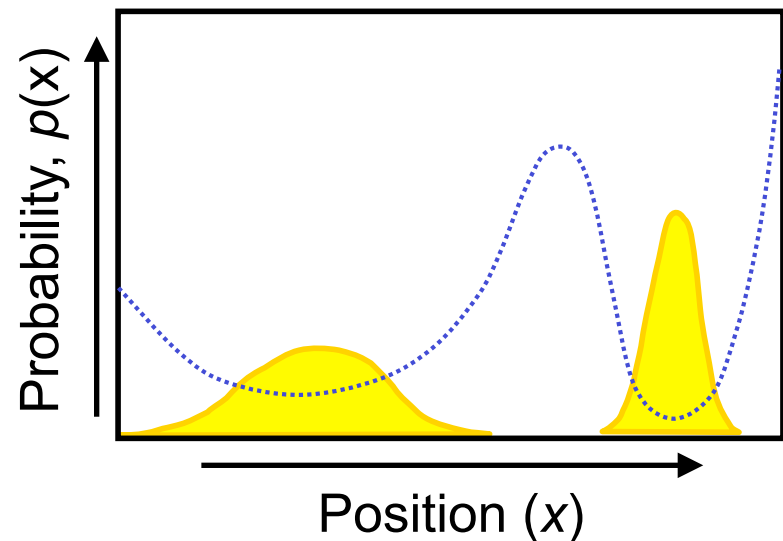
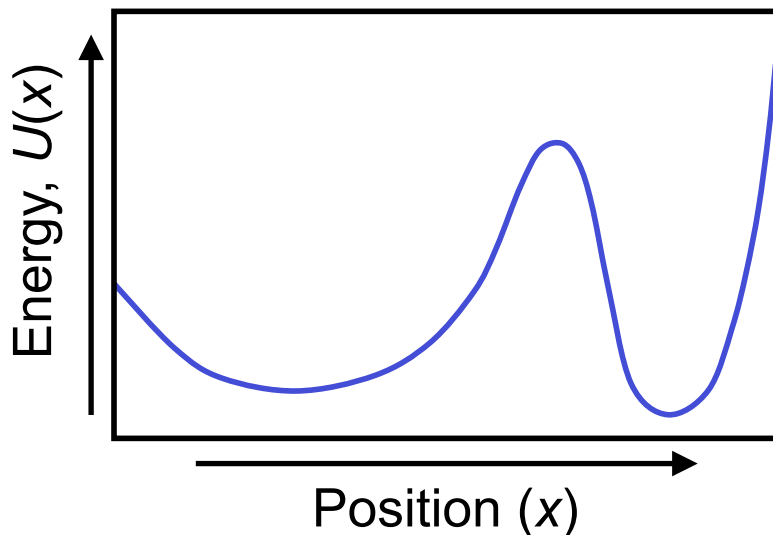
$$p(\mathbf{x}) \propto \exp\left(\frac{-U(\mathbf{x})}{k_B T}\right)$$

Equivalently,

$$p(\mathbf{x}) = \frac{1}{Z} \exp\left(\frac{-U(\mathbf{x})}{k_B T}\right)$$

where  $T$  is temperature and  $k_B$  is the Boltzmann constant

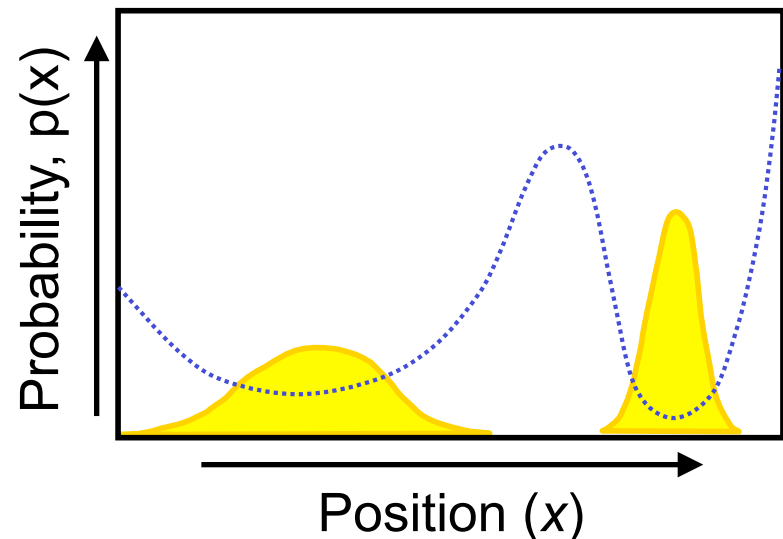
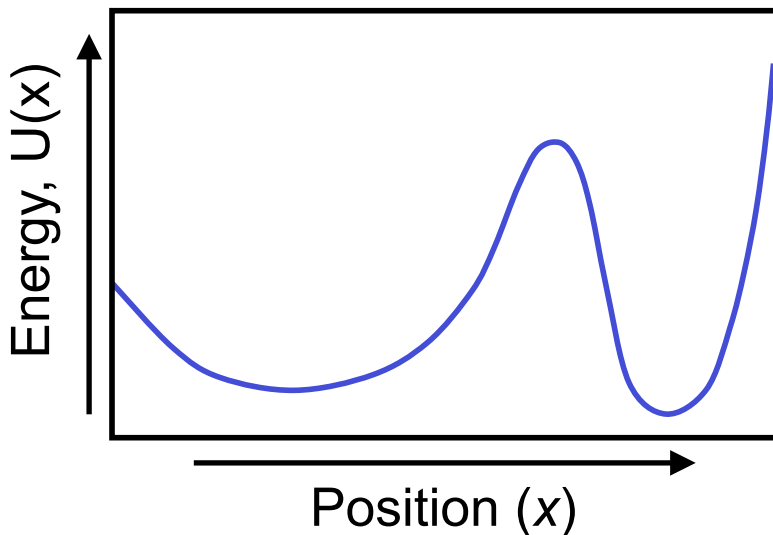
- Note:  $Z$  is chosen such that the probabilities sum to 1 across all arrangements of atoms. It depends on  $U$  and  $T$  but not on  $\mathbf{x}$ .



# The Boltzmann Distribution

- Key properties:
  - Higher energy gives lower probability
  - Exponential relationship: as energy increases, probability goes down quickly
  - Temperature dependence: increasing temperature decreases differences in probability between high-energy and low-energy conformations

$$p(\mathbf{x}) \propto \exp\left(\frac{-U(\mathbf{x})}{k_B T}\right)$$



What does the energy function tell us about biomolecular conformation?

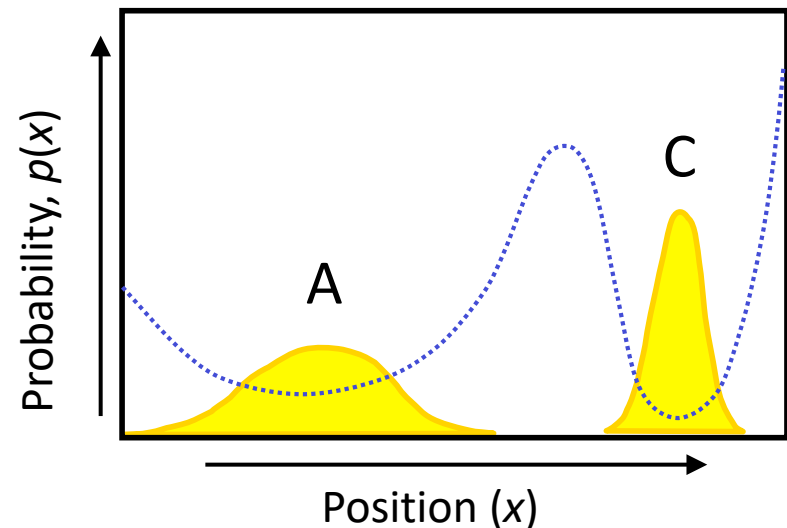
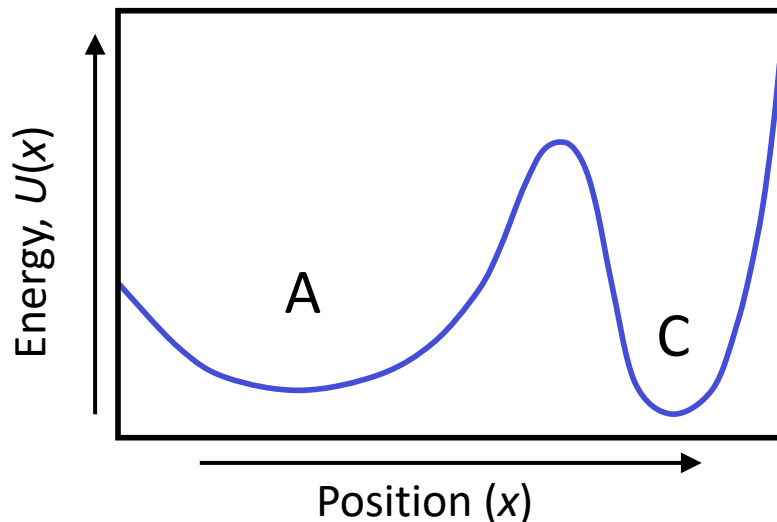
**Conformations and  
conformational states**

# Protein (or other biomolecular) structure: what we care about

- We **don't** really care about the probability that all the atoms of the protein and all the surrounding water atoms will be in one precise arrangement
- Instead, we care about the probability that protein atoms will be in some *approximate* arrangement, with *any* arrangement of surrounding water

# Protein (or other biomolecular) structure: what we care about

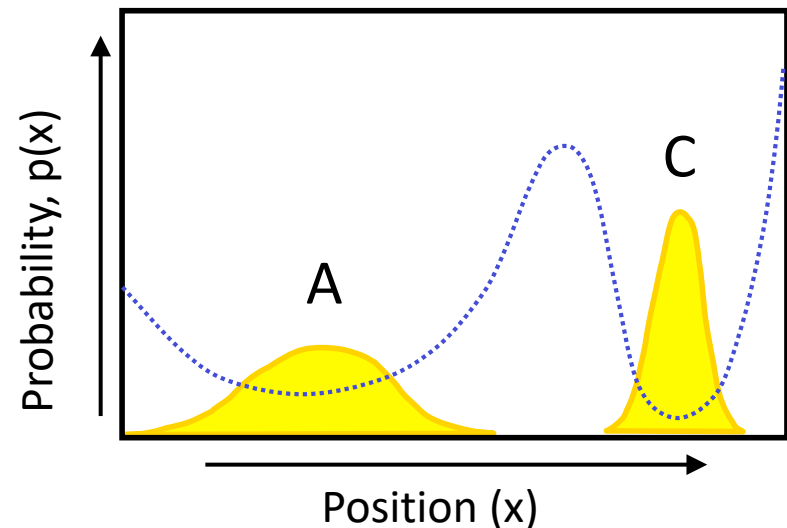
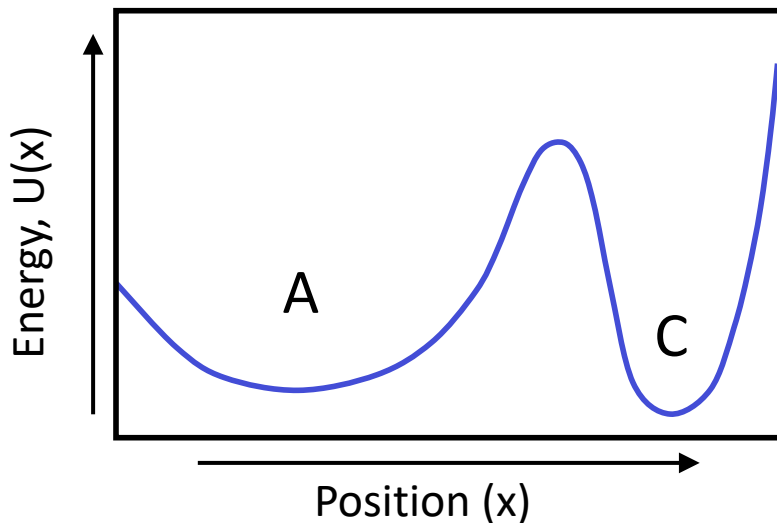
- In other words, we wish to compare probabilities of different sets (neighborhoods) of atomic arrangements
- We define each of these sets as a *conformational state*. Each *conformational state* includes many *conformations*, or specific atom arrangements  $\mathbf{x}$ .
  - In the example below, conformational states A and C correspond to wells in the energy landscape
  - A more general term for “conformational state” is “macrostate,” and a more general term for “conformation” is “microstate”





# Probabilities of conformational states

- Which has greater probability, A or C?
  - C is a deeper well, so the individual atomic arrangements (conformations) within it are more likely
  - A is a broader well, so it includes more distinct individual arrangements (conformations)

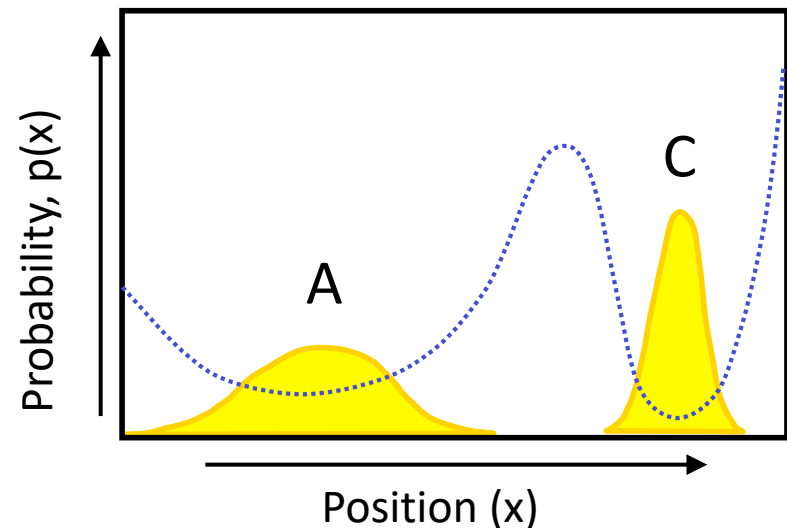
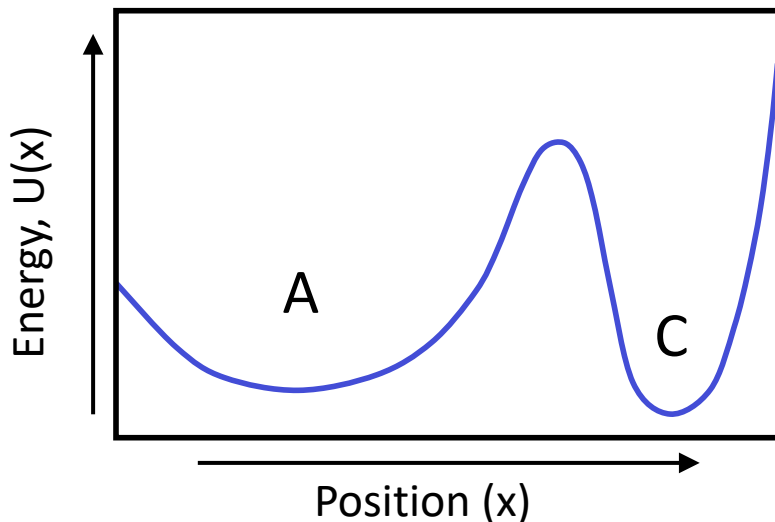


# Probabilities of conformational states

- Which has greater probability, A or C?
- To get probability of a conformational state, sum/integrate over all conformations within it

$$P(A) = \int_{x \in A} P(\mathbf{x}) \propto \int_{x \in A} \exp\left(\frac{-U(\mathbf{x})}{k_B T}\right) d\mathbf{x}$$

- At low temperature,  $P(C) > P(A)$
- At high temperature,  $P(A) > P(C)$



What does the energy function tell us about biomolecular conformation?

**Free energy**

# Free energy of a conformational state

- So far we have assigned energies only to individual conformations, but it's useful to assign them to conformational states as well.
- Define the *free energy*  $G_A$  of a conformational state  $A$  such that:

$$P(A) = \exp\left(\frac{-G_A}{k_B T}\right)$$

- This is analogous to Boltzmann distribution formula:

$$p(\mathbf{x}) \propto \exp\left(\frac{-U(\mathbf{x})}{k_B T}\right)$$

- **Key takeaway: Free energy is for a conformational state (i.e., set of conformations) what potential energy is for an individual conformation**

# Entropy and enthalpy

- One can also express free energy in terms of enthalpy (mean potential energy,  $H$ ) and entropy (“disorder”,  $S$ , a measure of the energy well’s breadth)

$$G_A = H_A - TS_A$$

- This slide is optional material for this class. If you remember one thing, it should be that the entropy of a conformational state is the number of conformations in that state (roughly speaking).

# So which conformational state will a biomolecule (e.g., protein) adopt?

- The one with the *minimum free energy*
  - Wide, shallow wells often win out over narrow, deep ones
- This depends on temperature
- At room or body temperature, the conformational state (macrostate) of minimum free energy is usually very different from the conformation with minimum potential energy

# Comparing structures (conformations) of a biomolecule

- The most common measure of the similarity/difference between two structures of the same molecule is *root mean squared deviation (RMSD)*, defined as

$$\sqrt{\frac{1}{N} \sum_{i=1}^{3N} (\mathbf{x}_i - \mathbf{w}_i)^2}$$

where  $N$  is the number of atoms,  $\mathbf{x}$  gives the coordinates for one structure, and  $\mathbf{w}$  gives the coordinates for the other structure.

- We generally want to align the structures, which can be done by finding the rigid-body rotation and translation of one structure that will minimize its RMSD from the other
  - **The relevant measure of similarity is RMSD *after* alignment**