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 wigglings 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)

actual probability depends on temperature

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 3*N* 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

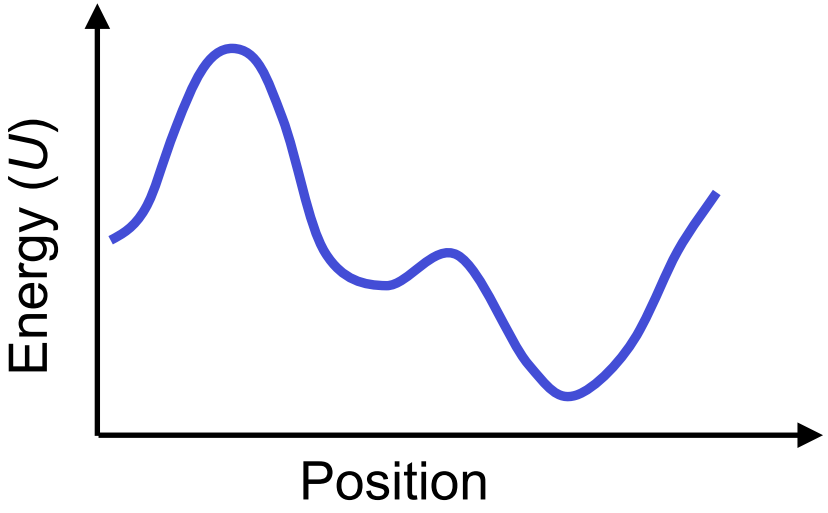
Specifying atom positions

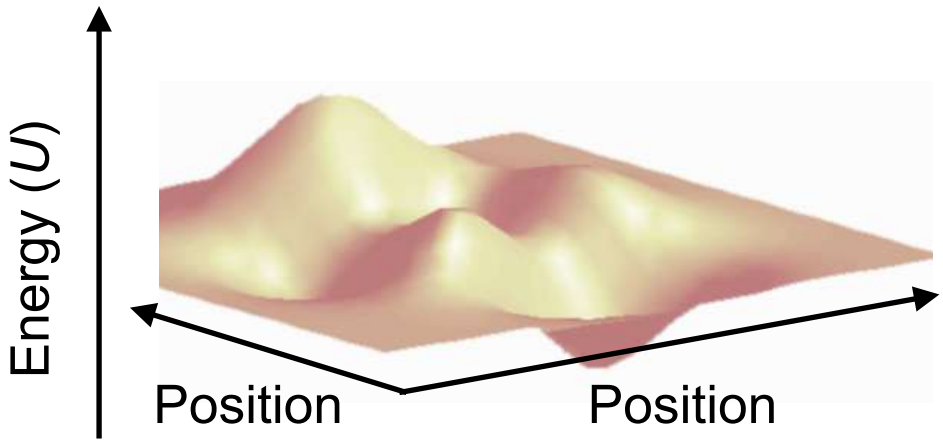
- For a molecular system with *N* atoms, we can specify the position of all atoms by a single vector ***x*** of length 3*N*
  - This vector contains the *x*, *y*, and *z* coordinates of every atom

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

Energy function

- A potential energy function $U(\boldsymbol{x})$ specifies the total potential energy of a system of atoms as a function of all their positions ($\boldsymbol{x}$)
  - 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

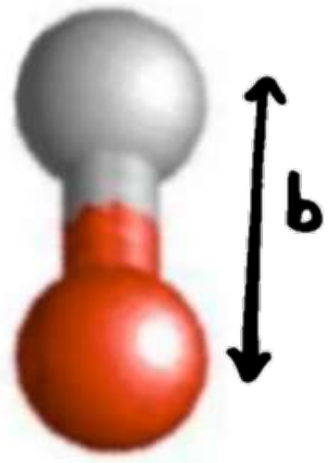
Molecular mechanics force fields

a *class* of 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

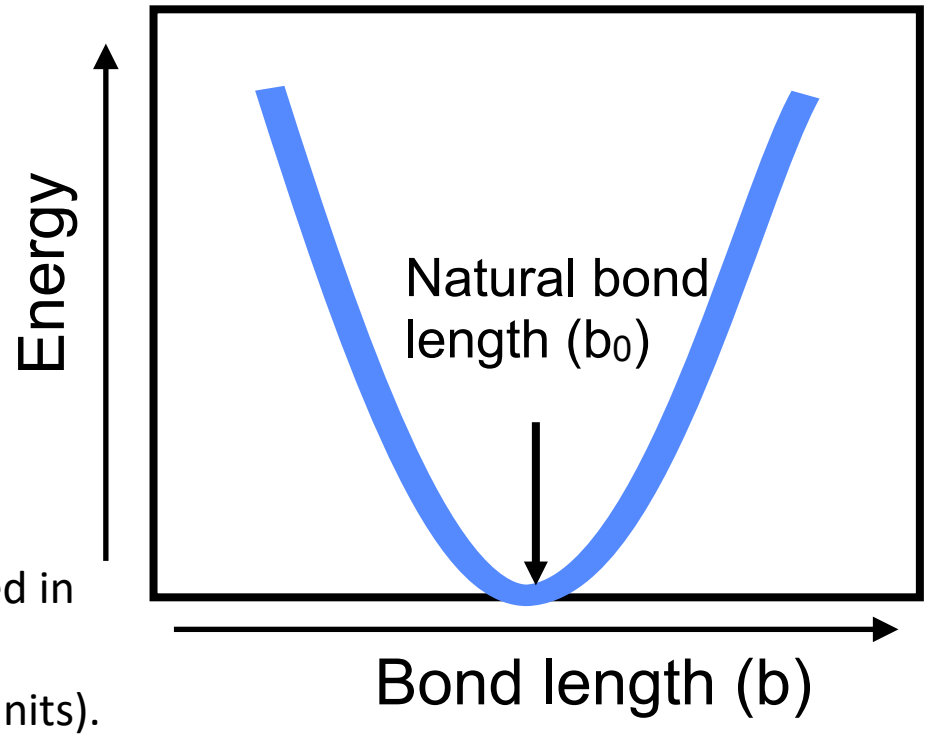
Bond length stretching

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



clarification: kb is a parameter for a particular bond representing rate of change of energy as we move away from the bond's natural length

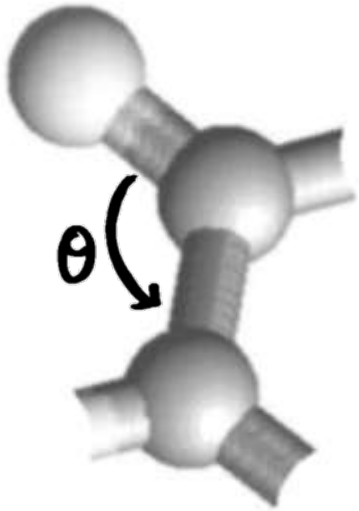
$$U(b) = k_b\left(b - b_0\right)^2$$

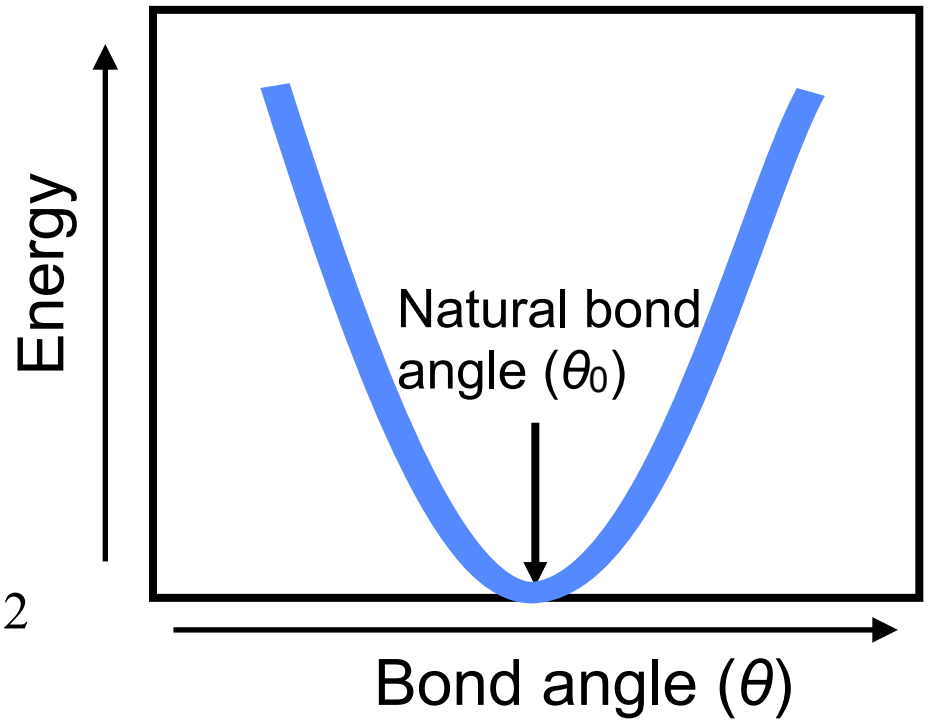


Note: A factor of 1/2 is sometimes included in this equation. I'm ignoring such constant factors (they can be folded into k_b or the units).

Bond angle bending

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



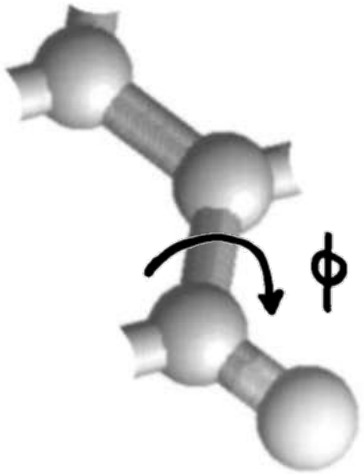


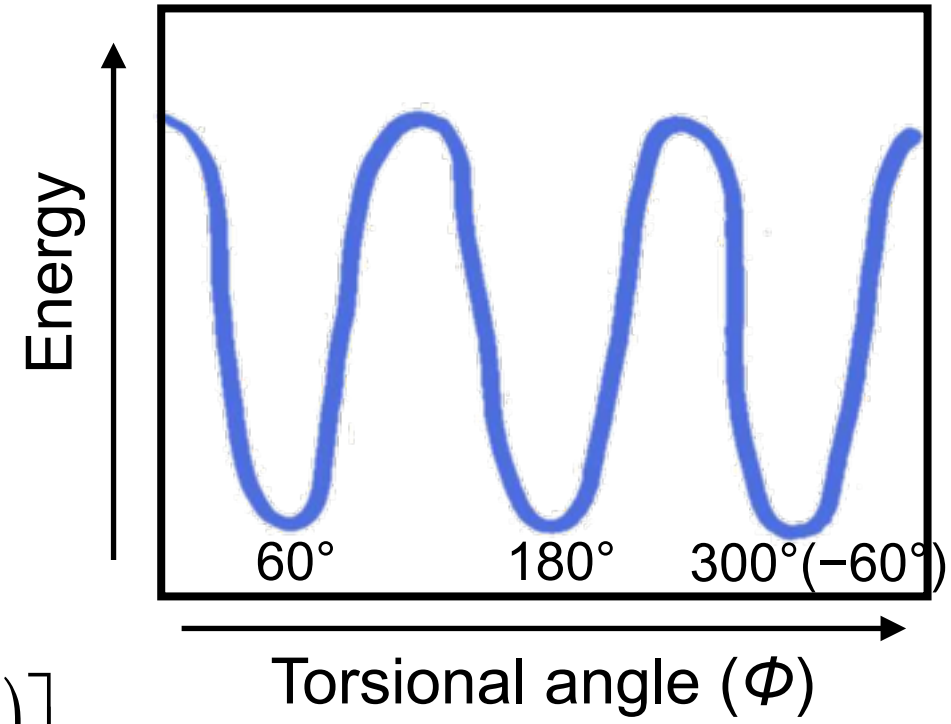
$$U(\theta) = k_\theta \left(\theta - \theta_0\right)^2$$

Torsional angle twisting

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

torsional angle: angle between atoms 1 and 4 when looking down bond between atoms 2 and 3



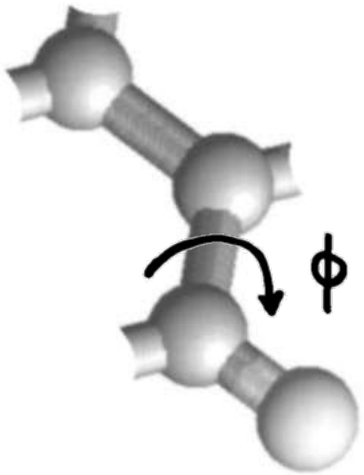


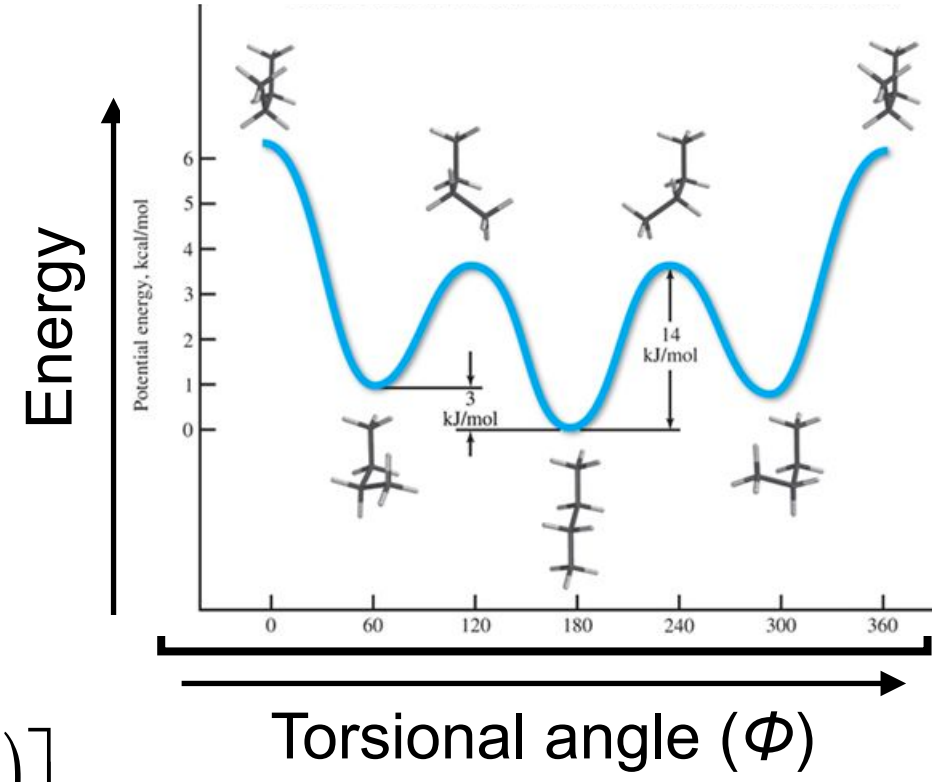
$$U(\phi) = \sum_n k_{\phi,n}\left[1 + \cos\left(n\phi - \phi_n\right)\right]$$

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

Torsional angle twisting

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





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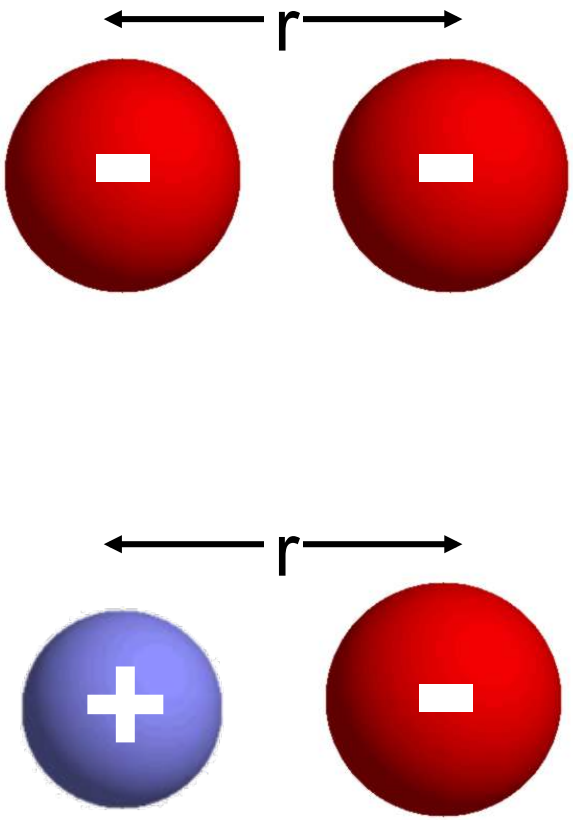
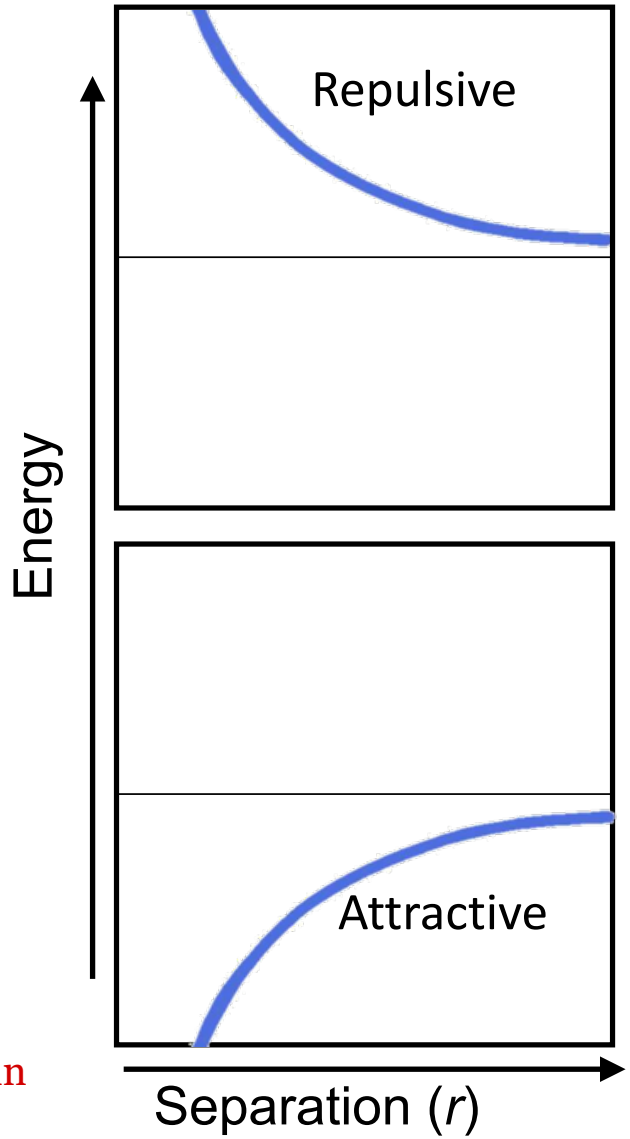
Electrostatics interaction



Note: U(r) represents *energy*;

The equation for force has r^2 in the denominator

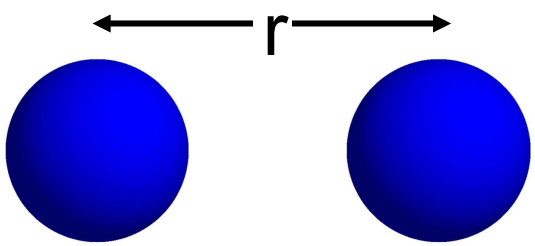


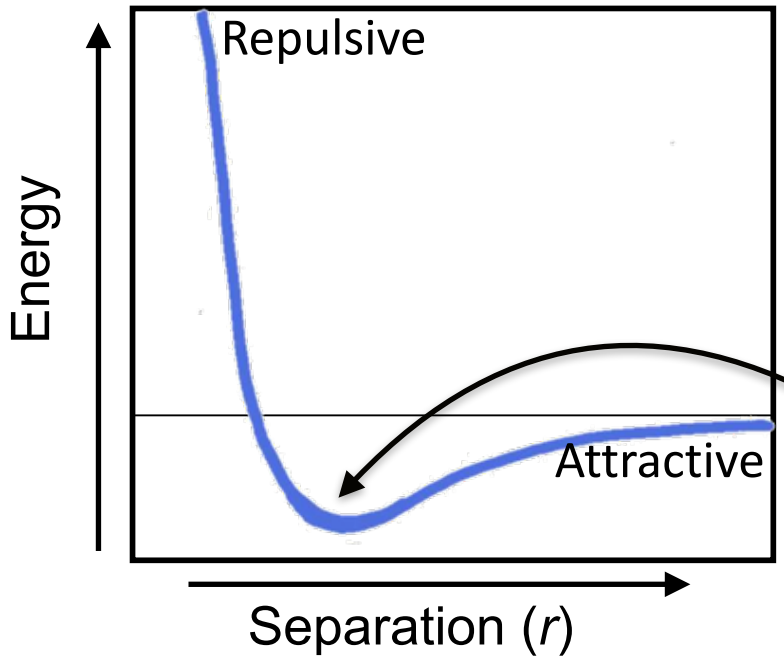
- Like charges repel. Opposite charges attract.
- Acts between all pairs of atoms, including those in different molecules.
- Each atom carries some "partial charge" (may be a fraction of an elementary charge), which depends on which atoms it's connected to

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

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

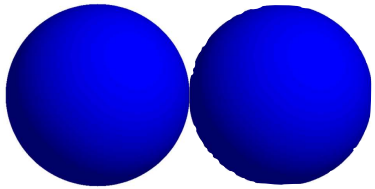
van der Waals interaction





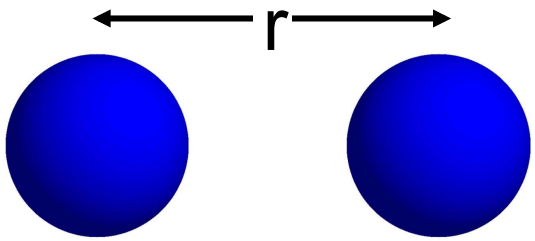
- van der Waals forces act between all pairs of atoms and do not depend on charge.
- When two atoms are too close together, they repel strongly.
- When two atoms are a bit further apart, they attract one another weakly.

Energy is minimal when atoms are "just touching" one another



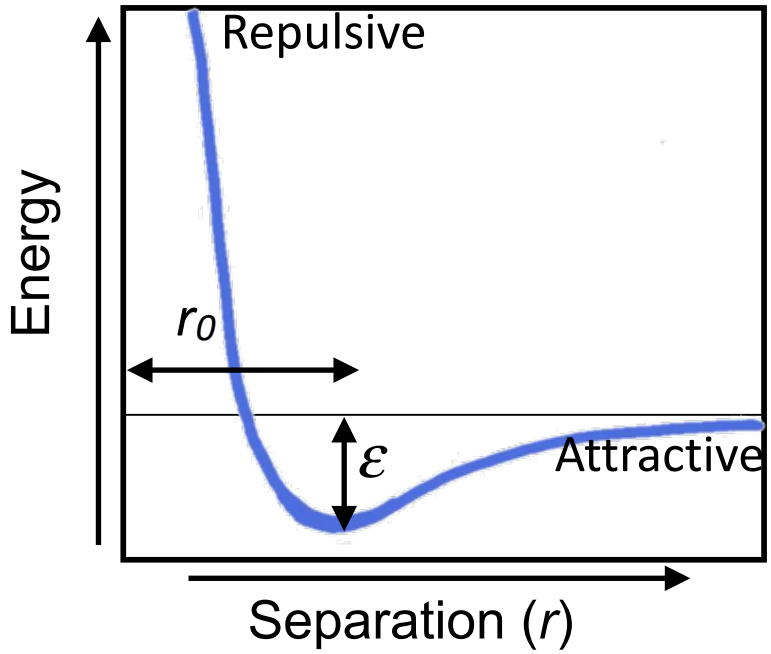
van der Waals interaction

A_ij and B_ij are parameters specific to a pair of atoms (i, j)



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

We can also write this as:



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

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

A typical molecular mechanics force field

note: values of k_b and b_0 are specific to each bond in the summation

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

Bond lengths ("Stretch")

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

Bond angles ("Bend")

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

Torsional/dihedral angles

Bonded terms

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

Electrostatics

summing over all pairs of atoms in the system

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

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)

$$U(b) = K_b\left(b - b_0\right)^2$$

- 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

Neural networks require fitting far more parameters but provide more flexibility

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

At a high level: conformation has a higher potential energy -> less likely to see that 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 adapt 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).

recall: **x** is a vector of x, y, z coordinates of all atoms in a molecule for a particular conformation

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):

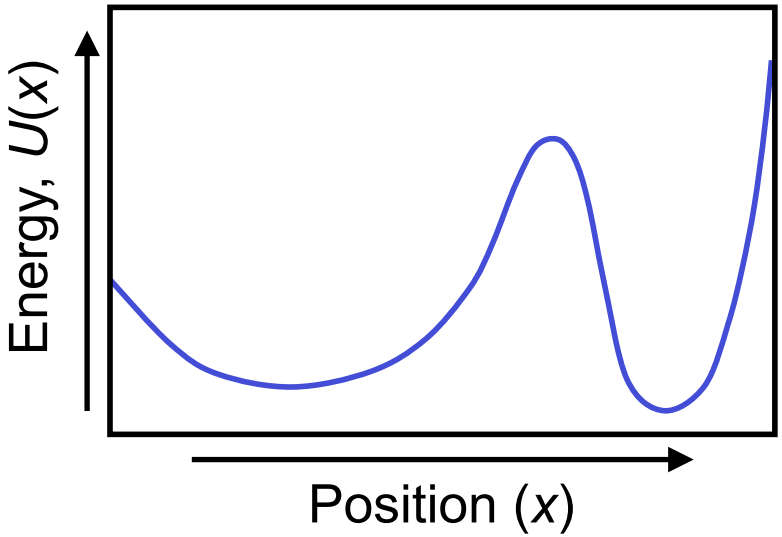
$$p(\boldsymbol{x}) \propto \exp\left(-U(\boldsymbol{x}) \Big/ k_B T\right)$$

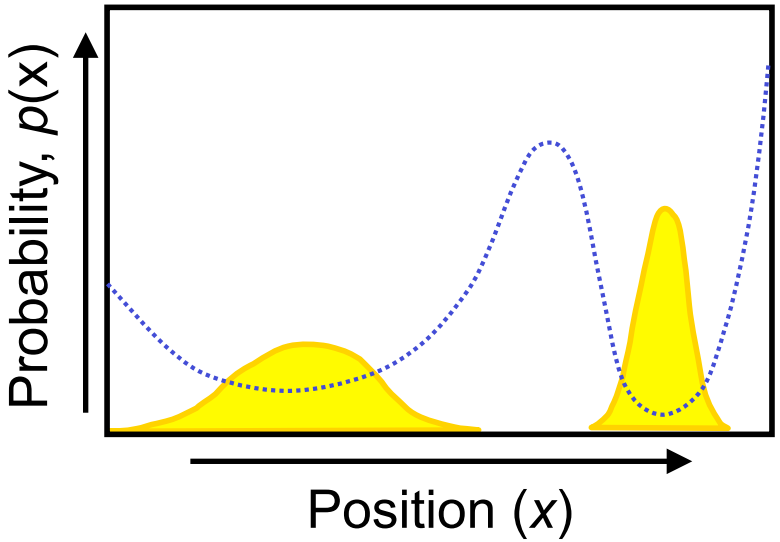
Equivalently,

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

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 **x**.

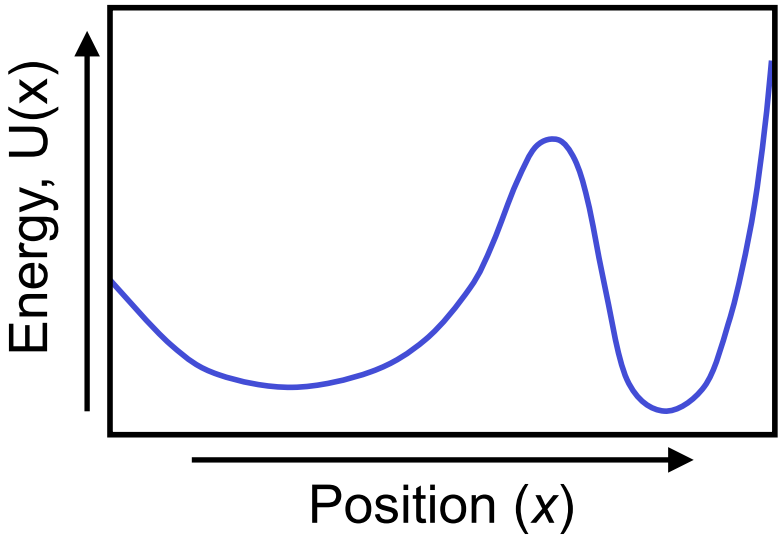


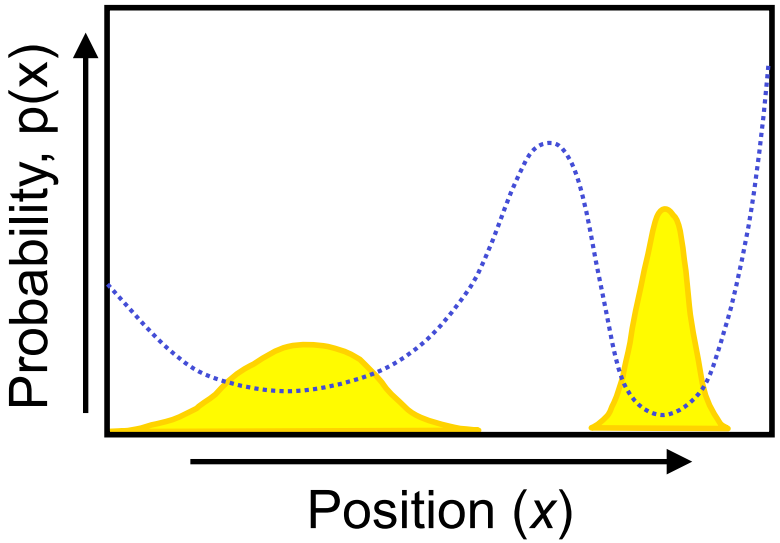


The Boltzmann Distribution

- 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

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





What does the energy function tell us about biomolecular conformation?

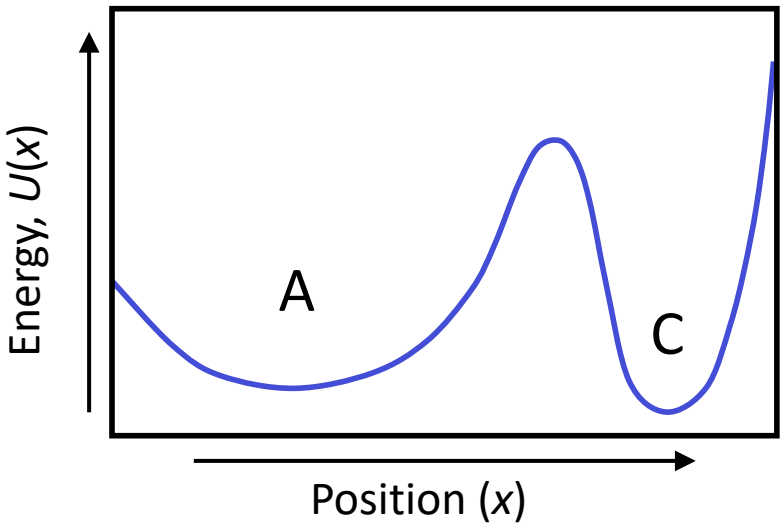
Conformations and conformational states

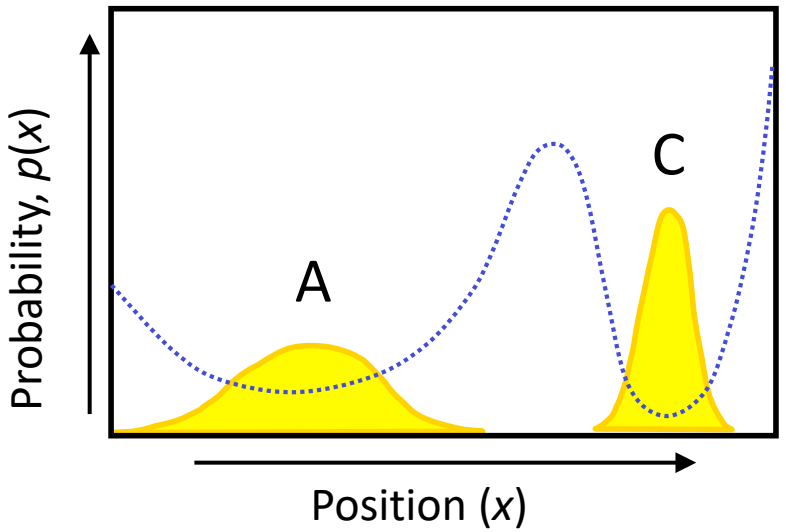
Protein (or other biomolecular) structure: what we care about

- 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

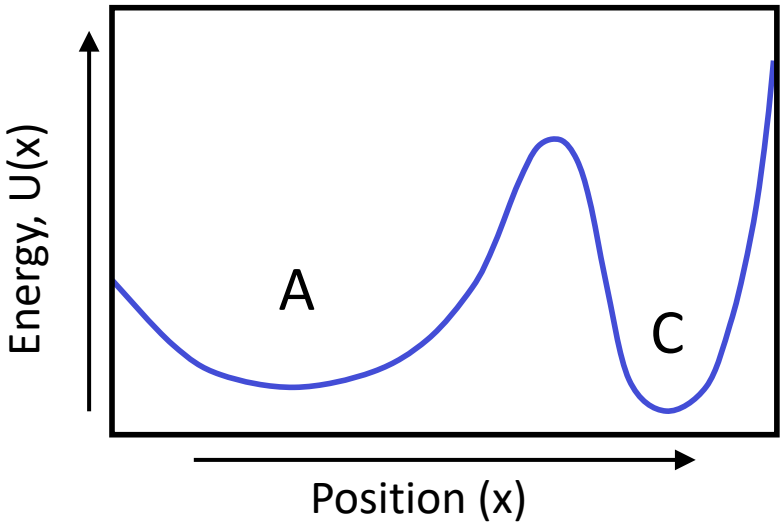
- In other words, we wish to compare probabilities of different sets (neighborhoods) of atomic arrangements
- We define each of these sets as a *conformational state*. Each *conformational state* includes many *conformations*, or specific atom arrangements ***x***.
  - In the example below, conformational 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"

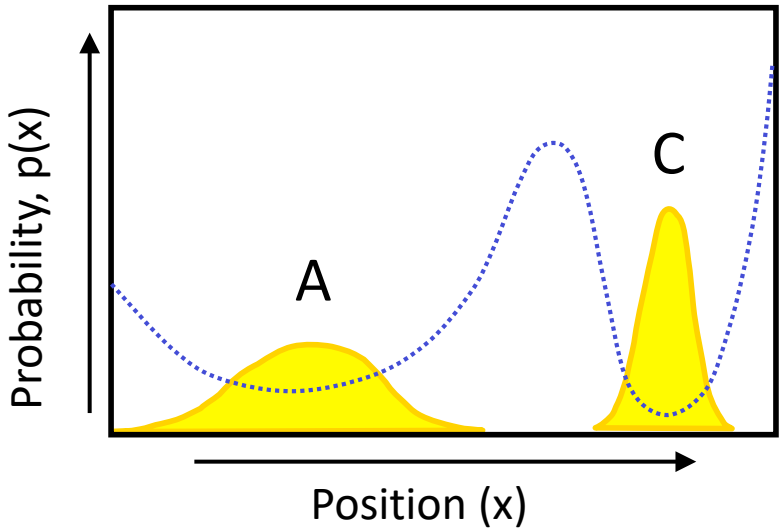




Probabilities of conformational states

- 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)



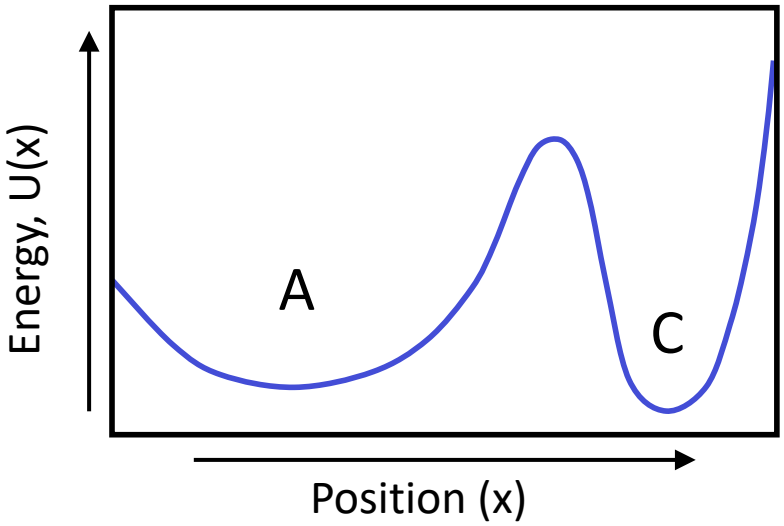


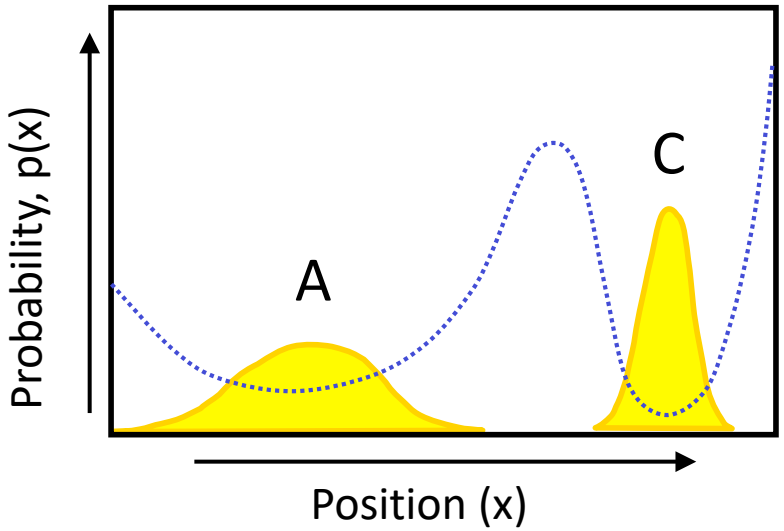
Probabilities of conformational states

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

$$P(A) = \int_{x \in A} P(\boldsymbol{x}) \propto \int_{x \in A} \exp\left({}^{-U(\boldsymbol{x})}\!/_{k_B T} \right) d\boldsymbol{x}$$

- 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

AKA Gibbs 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:

$$P(A) = \exp\left(-G_A \Big/ k_B T\right)$$

- This is analogous to Boltzmann distribution formula:

$$p(\boldsymbol{x}) \propto \exp\left(-U(\boldsymbol{x}) \Big/ k_B T\right)$$

- **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

note: potential energy doesn't depend on temperature - only depends on the atomic coordinates of the molecule

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, $\boldsymbol{x}$ gives the coordinates for one structure, and $\boldsymbol{w}$ 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**