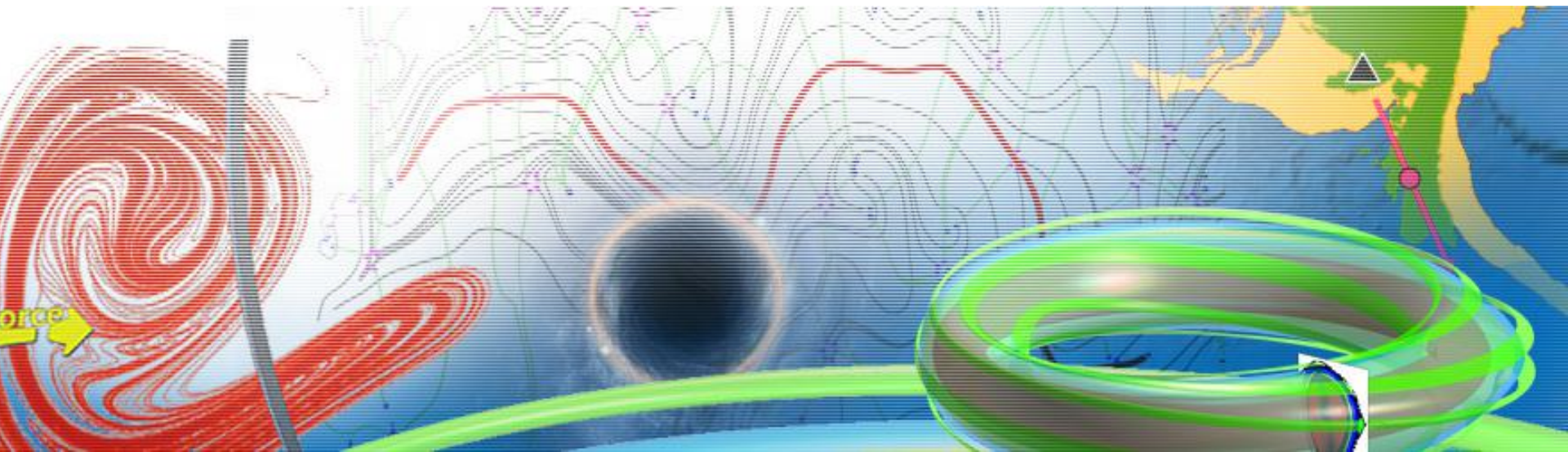


# 生物动力系统模拟



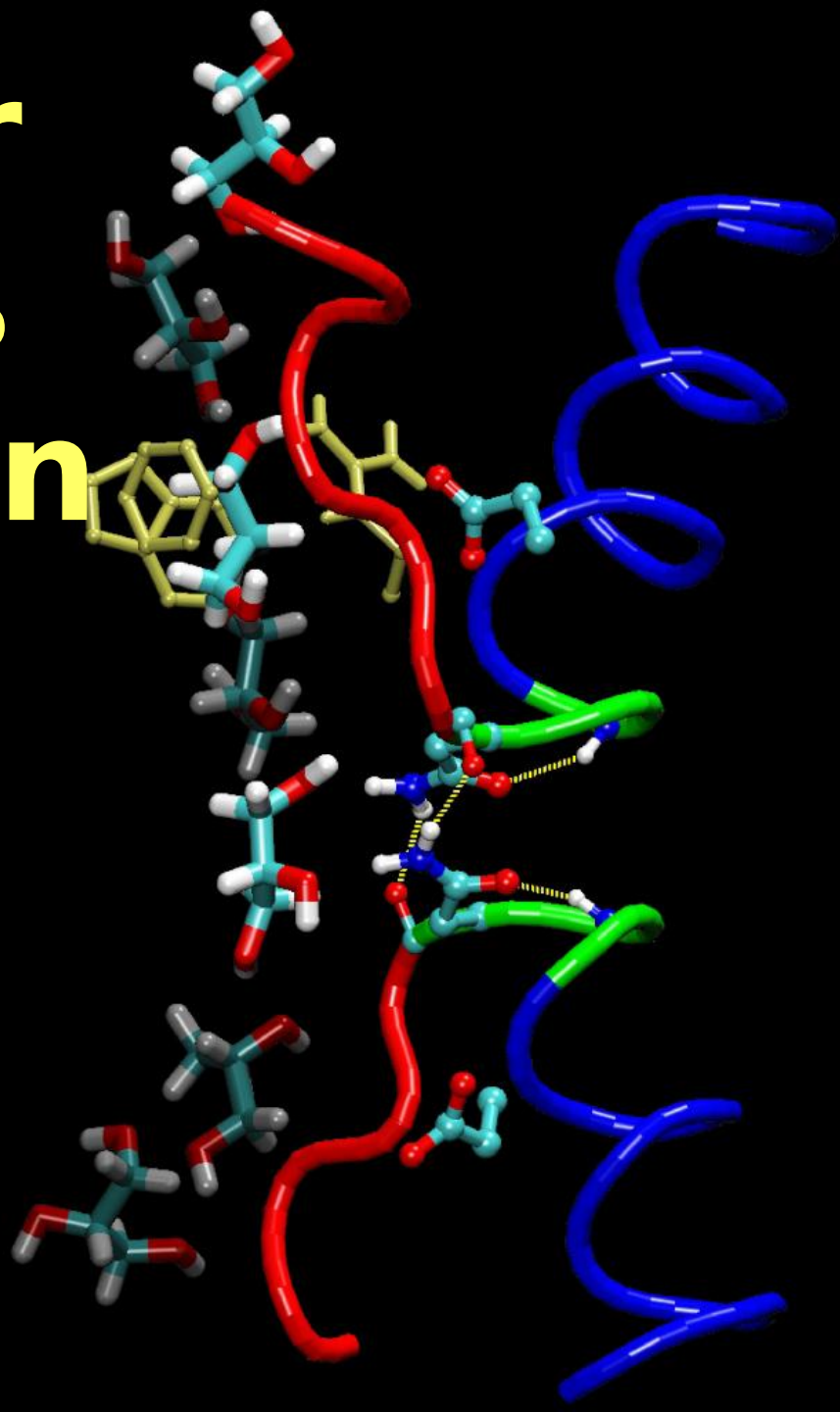
王冠宇 18665955633  
[wanggy@sustc.edu.cn](mailto:wanggy@sustc.edu.cn)

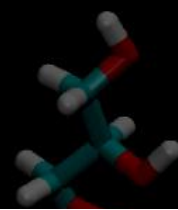
韦添元（助教）  
15811823840  
11849117@mail.sustc.edu.  
cn



# Molecular Dynamics Simulation

*(a brief introduction)*





Experiment



Insight into  
atomic scale processes  
Predictions of  
experimental results

Theory and Computation



**Experimental –  
Theoretical Collaboration**

Observations  
needing explanation  
Verification of  
approximations



Amount of Physical Detail ↑

One calculation for 2-3 atoms

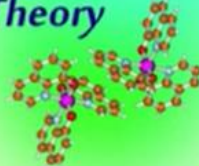
$$H\Psi = E\Psi$$



100 fs, 30 atoms:  
photochemistry

*Correlated methods*  
(MP2, CCSD, CI)

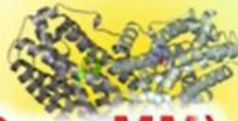
*Density Functional Theory*



10 ps, 100 atoms: fast chemical reactions

*Hartree-Fock*

1 μs-1 ms, 100k atoms: protein dynamics, drug binding



**(OpenMM)**

*Atomistic MM*

1 ms+, 1 million atoms: folding of large proteins, virus capsids

*Coarse-grained simulations*

*Continuum mechanics*

Cost of Calculation →

- More detailed theories can describe complex phenomena and offer higher accuracy

- Less detailed theories allow for simulation of larger systems / longer timescales

# Why Not Quantum Mechanics?

- Modeling the motion of a complex molecule by solving the wave functions of the various subatomic particles would be accurate...

$$\frac{\hbar^2}{2m} \nabla^2 \psi(x, y, z) + U(x, y, z) \psi(x, y, z) = E \psi(x, y, z)$$

- But it would also be **very** hard to program and take more computing power than anyone has!

# Classical Mechanics

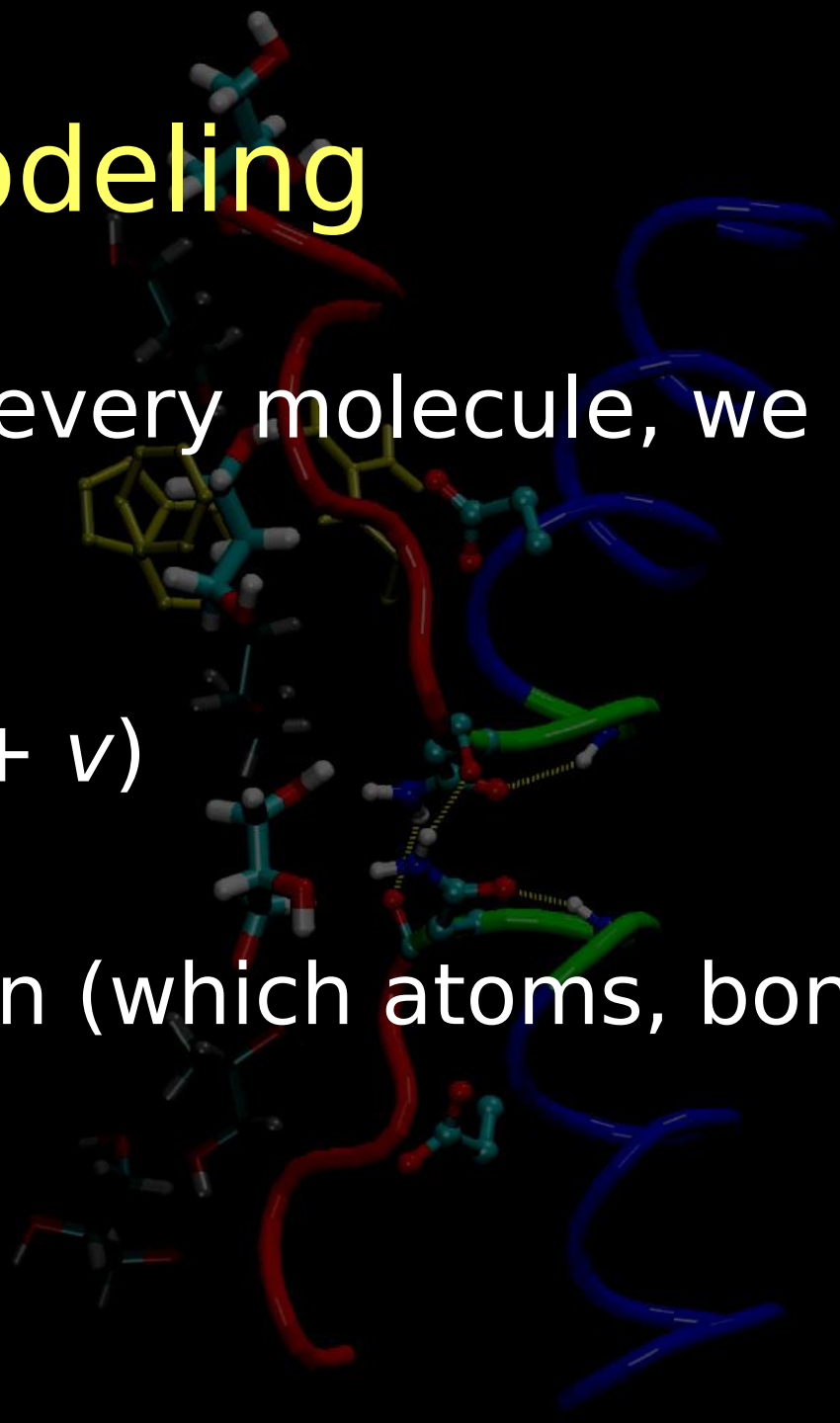


- Instead of using Quantum mechanics, we can use classical Newtonian mechanics to model our system.
- This is a simplification of what is actually going on, and is therefore less accurate.
- To alleviate this problem, we use numbers derived from QM for the constants in our classical equations.

# Molecular Modeling

For each atom in every molecule, we need:

- Position ( $r$ )
- Momentum ( $m + v$ )
- Charge ( $q$ )
- Bond information (which atoms, bond angles, etc.)



# Interactions

## Covalent Interactions

The ***macromolecules*** that participate in the structural and functional matrix of life are immense structures held together by strong, ***covalent bonds***.

bond motions describe vibrations about equilibrium states.

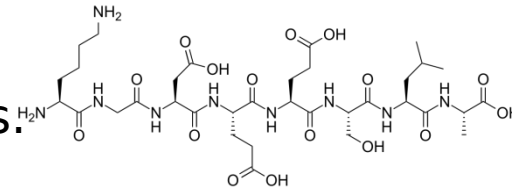
## Noncovalent Interactions

Noncovalent interactions are critically important determinants of biomolecular structure, stability, and function.

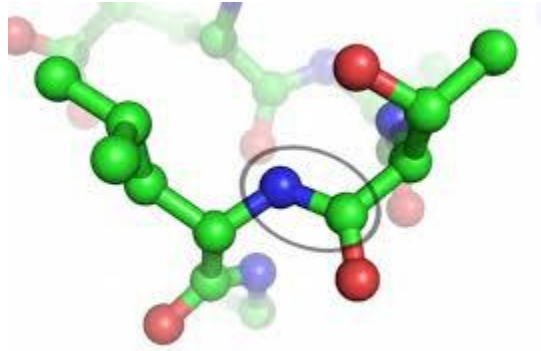


## Consider proteins:

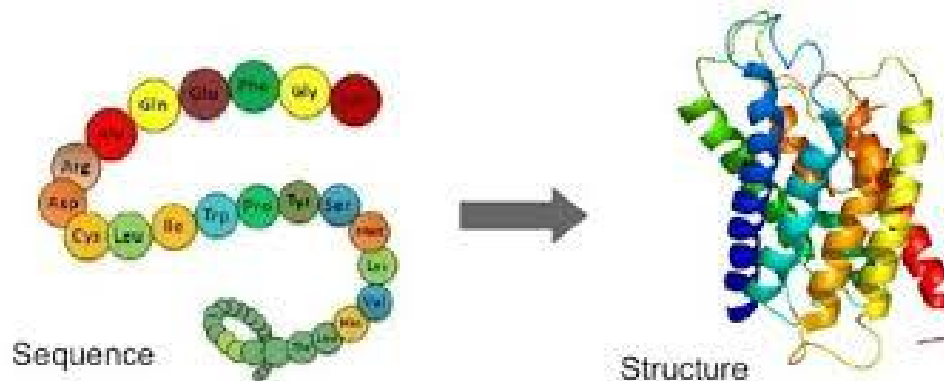
- Proteins are polymers of amino acids.



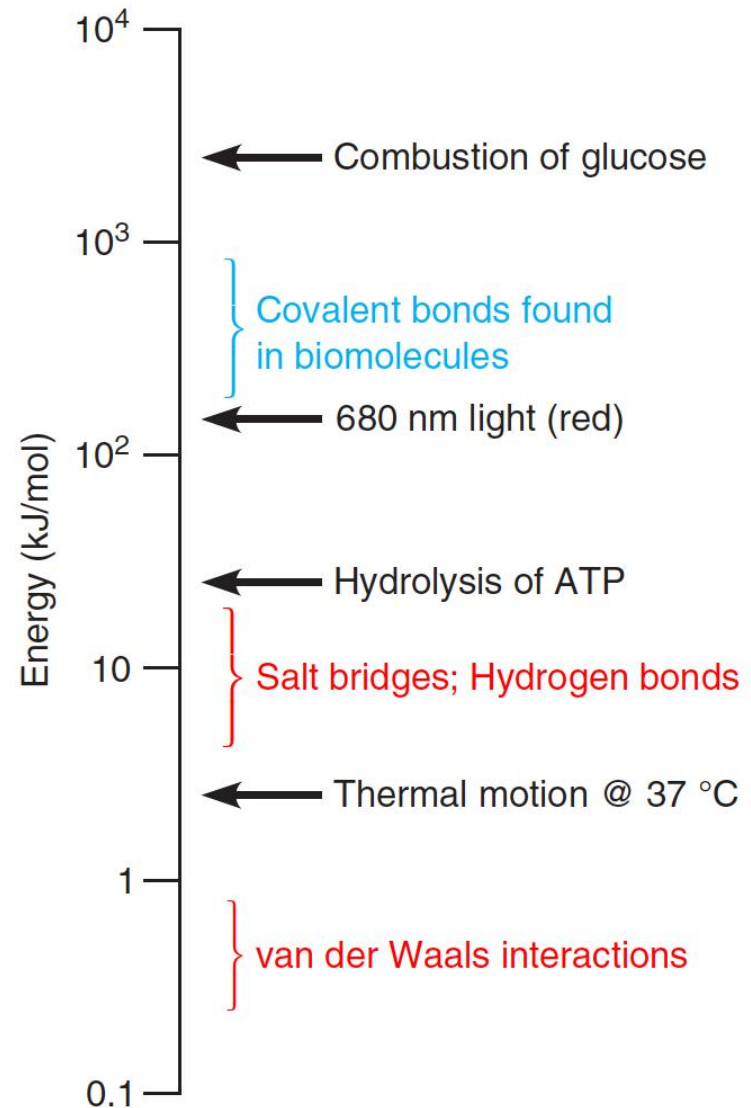
- The amino acids are held together by strong covalent amide (peptide) bonds.



- The 3-D structure, and hence function of proteins are determined by a large number of noncovalent interactions.



**Covalent and noncovalent bond energies.** Energies typical of noncovalent bonds (0.5–20 kJ/mol; red text) are about one to two orders of magnitude weaker than energies of the covalent bonds commonly found in biochemical compounds (150–600 kJ/mol; blue text). The energies available from thermal motion, ATP hydrolysis, red light, and aerobic glucose metabolism are also shown as reference points

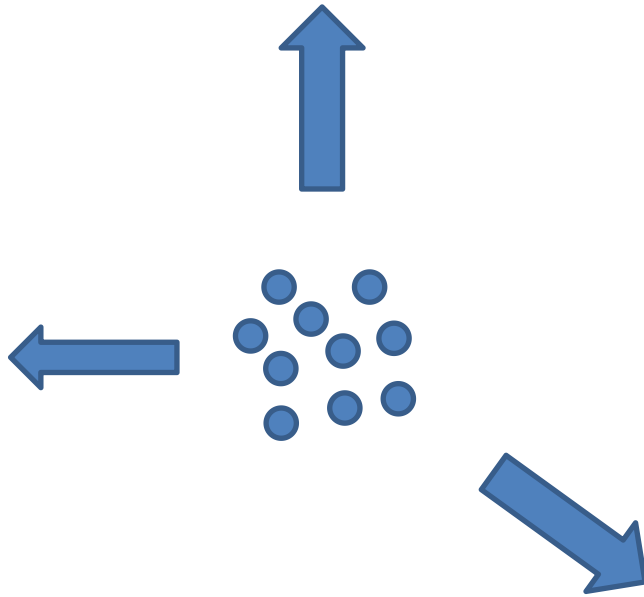


# Covalent Interactions

Each molecule of  $N$  atoms has  $3N - 6$  normal modes:

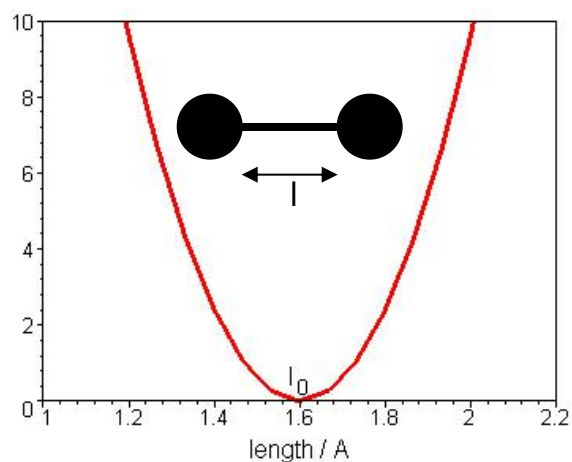
3 degrees of freedom per atom (giving  $3N$ )

minus 3 translational and 3 rotational degrees of freedom  
for the molecule as a whole.



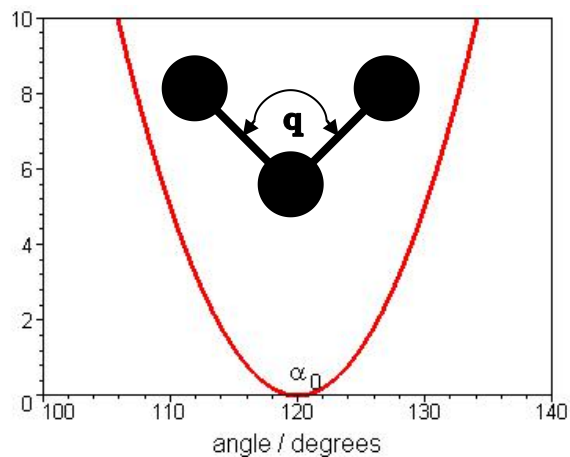
# Covalent Interactions

**Bond stretching**



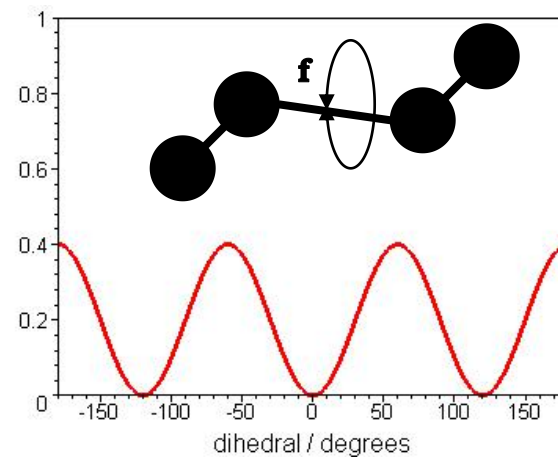
$$\sum_{\text{bonds}} k_b (l - l_0)^2$$

**Angle bending**



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

**torsion**



$$\sum_{\text{dihedrals}} k_\phi (1 - \cos(n\phi - \delta))$$

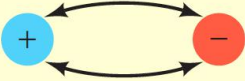
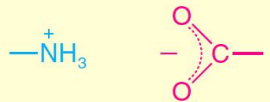


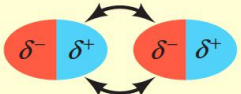
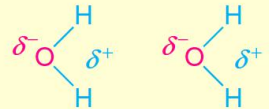
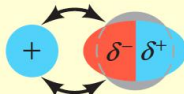

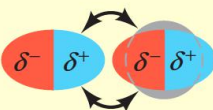
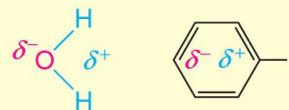
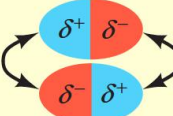
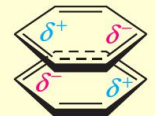
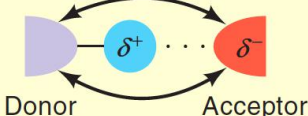
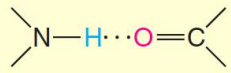
# Noncovalent Interactions

- All noncovalent interactions are **electrostatic** in nature.
- The simplest electrostatic interactions are those between a pair of charged particles, called a **salt bridge**.
- The attraction of the oppositely charged ions is governed by  $F = k \frac{q_1 q_2}{r^2}$  **Law:**



**TABLE 2.1** Energies of noncovalent interactions in biomolecules

Type of interaction	Approximate energy (kJ/mol)
Charge–charge	–13 to –17
Charge–dipole (H–bond)	–13 to –21
Dipole–dipole (H–bond)	–2 to –8
van der Waals	–0.4 to –0.8

Type of Interaction	Model	Example	Dependence of Energy on Distance
<b>(a) Charge–charge</b> Longest-range force; nondirectional			$1/r$
<b>(b) Charge–dipole</b> Depends on orientation of dipole			$1/r^2$
<b>(c) Dipole–dipole</b> Depends on mutual orientation of dipoles			$1/r^3$
<b>(d) Charge–induced dipole</b> Depends on polarizability of molecule in which dipole is induced			$1/r^4$
<b>(e) Dipole–induced dipole</b> Depends on polarizability of molecule in which dipole is induced			$1/r^5$
<b>(f) Dispersion (van der Waals)</b> Involves mutual synchronization of fluctuating charges			$1/r^6$
<b>(g) Hydrogen bond</b> Charge attraction + partial covalent bond			Length of bond fixed

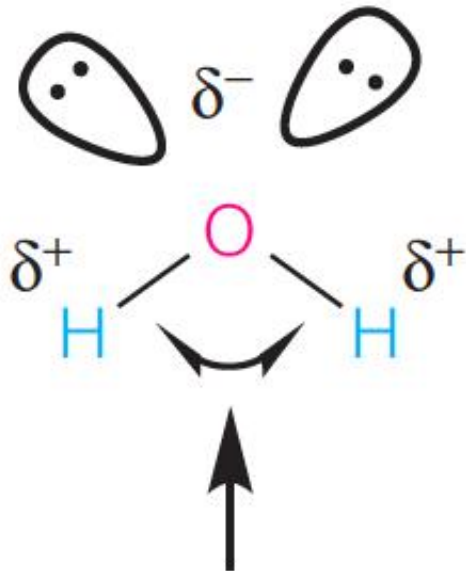
# The Role of Water in Biological Processes

## Hydrogen-bond donors and acceptors in water.

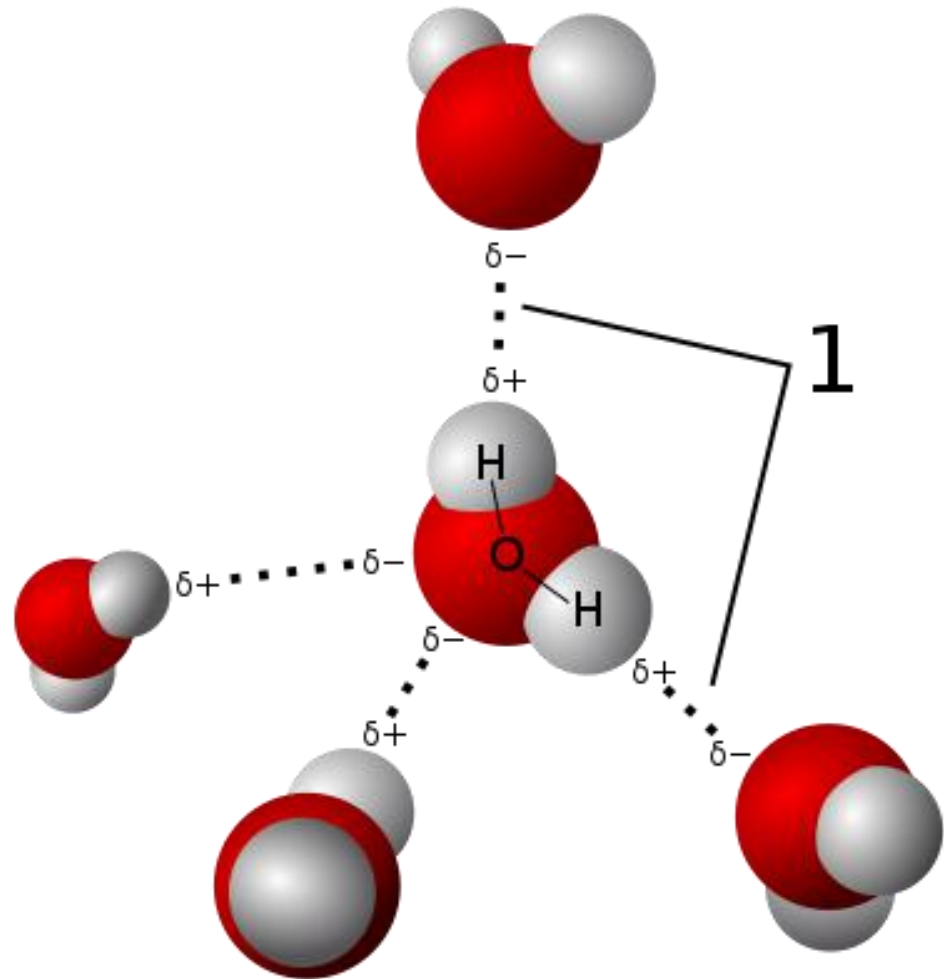
The two nonbonded electron pairs on O act as H-bond acceptors and the two O-H bonds act as H-bond donors.

The angle between the two O-H bonds is  $104.5^\circ$ ; thus, water has a **net dipole**

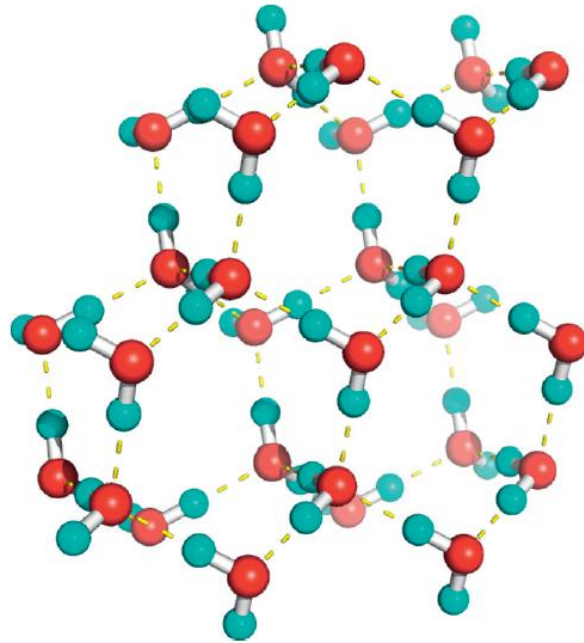
**r**



bond angle =  $104.5^\circ$



# The Role of Water in Biological Processes



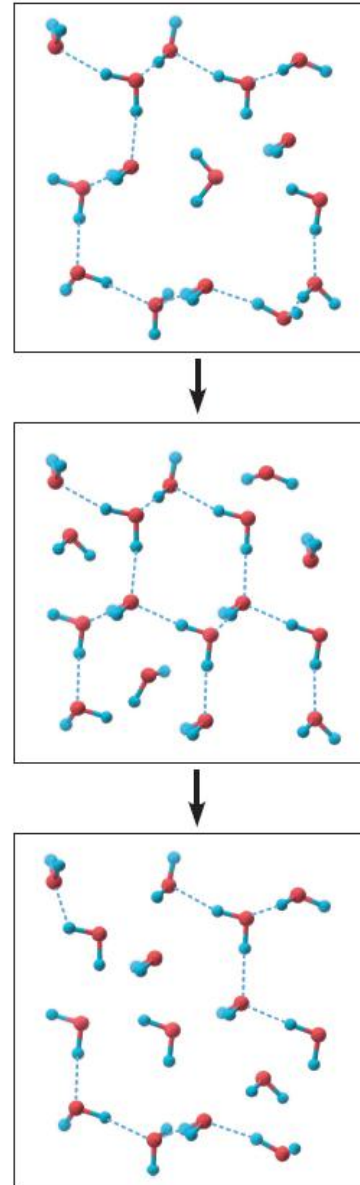
**A skeletal model of the ice lattice.**

## The structure of liquid water.

When ice melts, the regular tetrahedral lattice is broken, but substantial portions of it remain, especially at low temperatures.

In liquid water, flickering clusters of molecules are held together by hydrogen bonds that continually break and re-form.

In this schematic “motion picture,” successive frames represent changes occurring in picoseconds ( $10^{-12}$  s).





# The Role of Water in Biological Processes

Water serves as the universal intracellular and extracellular medium, thanks primarily to two properties:

- ability to form ***hydrogen bonds***
- ***polar*** character

Substances that can take advantage of these properties so as to readily dissolve in water are called ***hydrophilic***, or “water loving.”

# The Role of Water in Biological Processes

**Water is an excellent solvent for ionic compounds.**

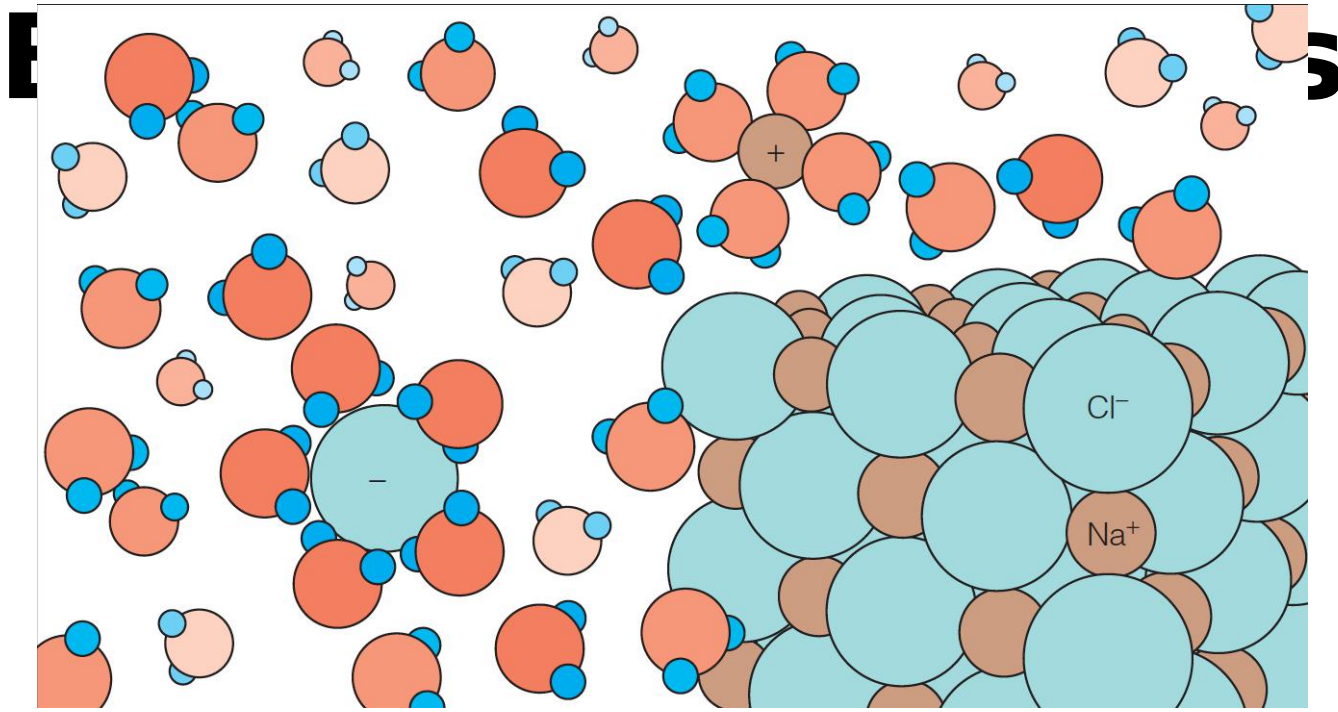
- The interactions of the negative ends of the water dipoles with cations and the positive ends with anions in aqueous solution cause the ions to become **hydrated, that is, surrounded** by shells of water molecules called **hydration shells**.

- The dissolution of ionic compounds like NaCl in water can be

accounted for largely by two factors.

- o The formation of hydration shells is energetically favorable.
- o The high dielectric constant of water screens and decreases the electrostatic force between oppositely charged ions that would otherwise pull them back together.

# The Role of Water in



**Hydration of ions in solution.** A salt crystal is shown dissolving in water. As sodium and chloride ions leave the crystal, the noncovalent interaction between these ions and the dipolar water molecules produces a hydration shell around each ion. The energy released in this interaction helps overcome the charge-charge interactions stabilizing the crystal.

# The Role of Water in Biological Processes

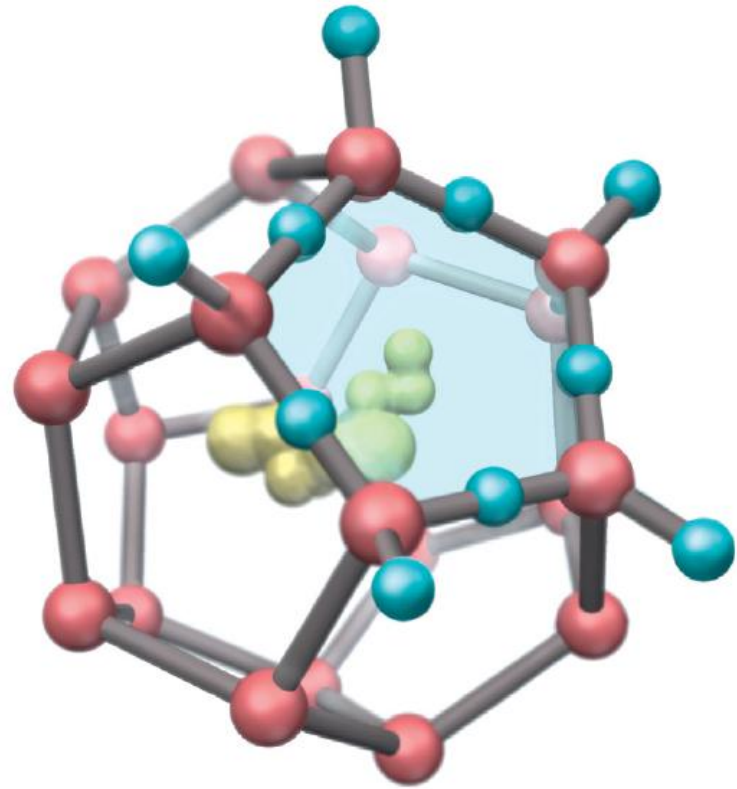
- **Nonpolar** substances like hydrocarbons, are **nonionic** and **cannot form hydrogen bonds**, show only limited solubility in water.
- Such nonpolar molecules are called **hydrophobic**, or “water fearing.”
- We can also call them **lipophilic**, or “fat loving.”
- When hydrophobic molecules do dissolve, they are not surrounded by hydration shells, rather the regular water lattice forms ice-like **clathrate structures**, or “cages,” **about the nonpolar molecules.**

# The Role of Water in Biological Processes

**One unit of clathrate structure surrounding a hydrophobic molecule (yellow).**

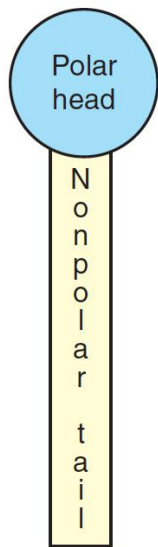
Oxygen atoms are shown in red. Hydrogens are shown for one pentagon of oxygens.

The ordered structure may extend considerably further into the surrounding water.





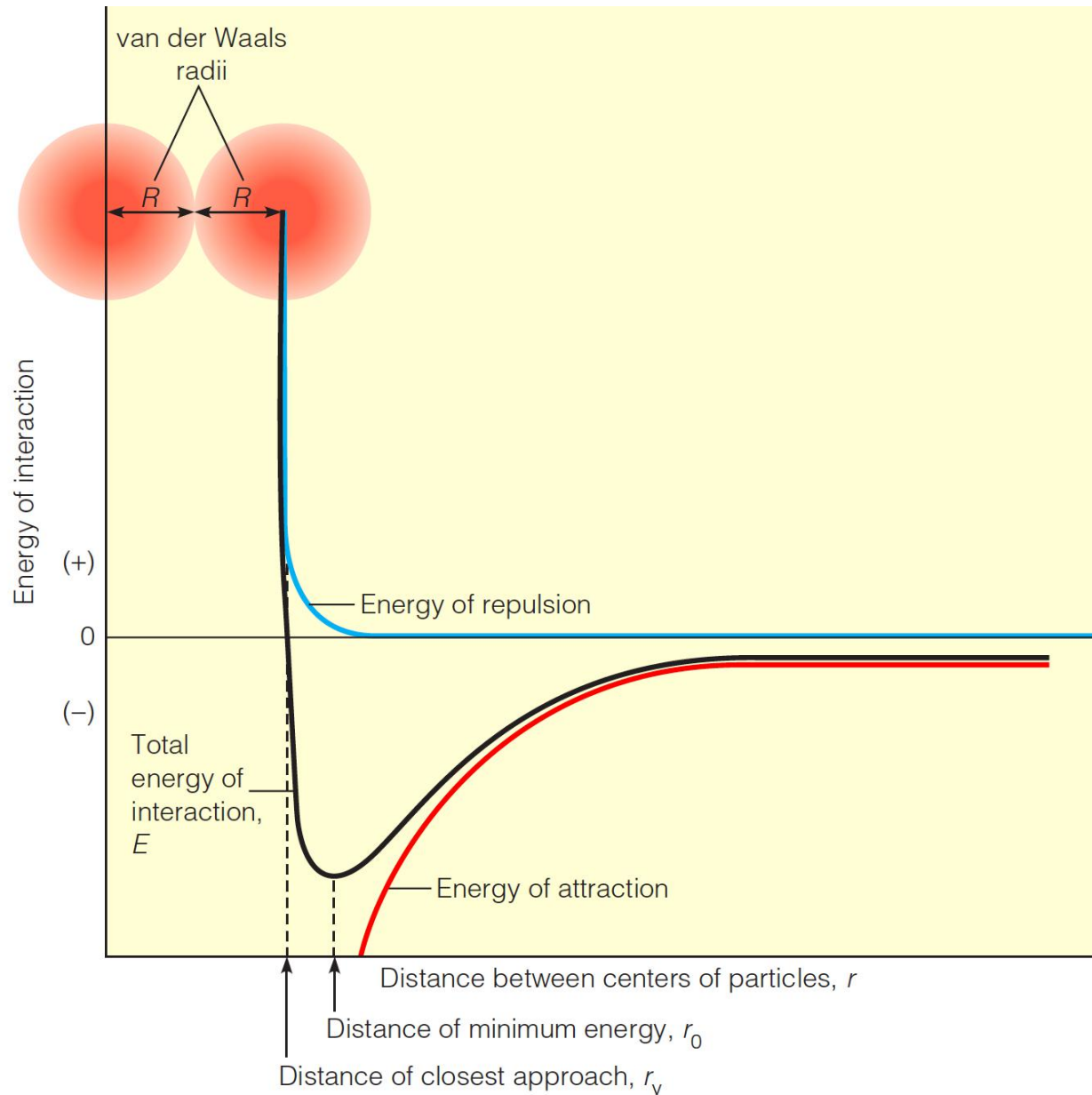
# The Role of Water in Biological Processes



A simplified representation  
of an amphipathic lipid molecule

- An important class of molecules are those that exhibit both hydrophilic and hydrophobic properties simultaneously.
- Such ***amphipathic*** substances include
  - o Fatty acids
  - o Lipids
  - o Detergents
- The amphipathic molecules are characterized by a ***polar “head” group*** coupled to a ***hydrophobic “tail”***—usually a hydrocarbon.

# The van der Waals Potential



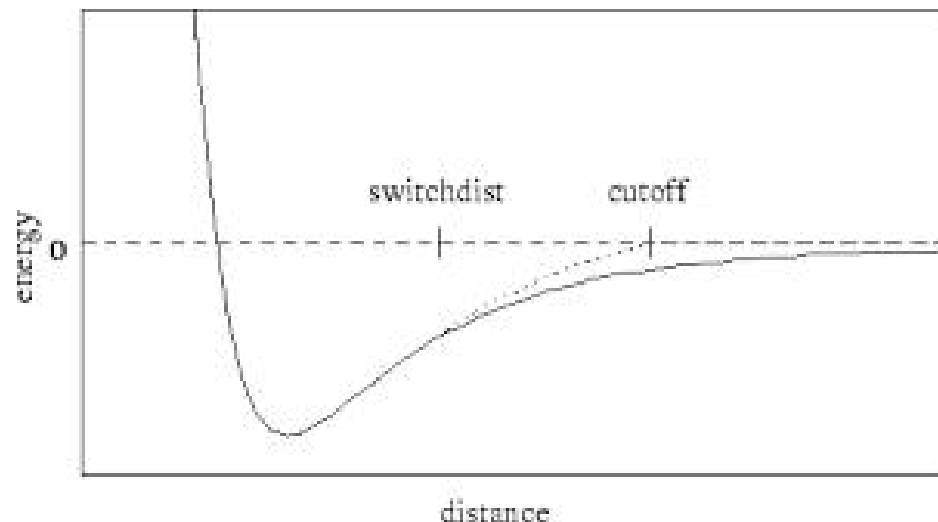
The van der Waals potential for a nonbonded distance  $r_{ij}$  has the common 6/12 Lennard-Jones form in macromolecular force fields:

$$E_{\text{LJ}}(r_{ij}) = \frac{-A_{ij}}{r_{ij}^6} + \frac{B_{ij}}{r_{ij}^{12}}$$

Where

$A$  and  $B$  depend on the type of the two interacting atoms.

Note that as  $r \rightarrow \infty$ ,  $E_{\text{LJ}} \rightarrow 0$  rapidly, so the van der Waals force is short range. For computational convenience, van der Waals energies and forces can be computed for pairs of atoms only within some “cutoff radius”.

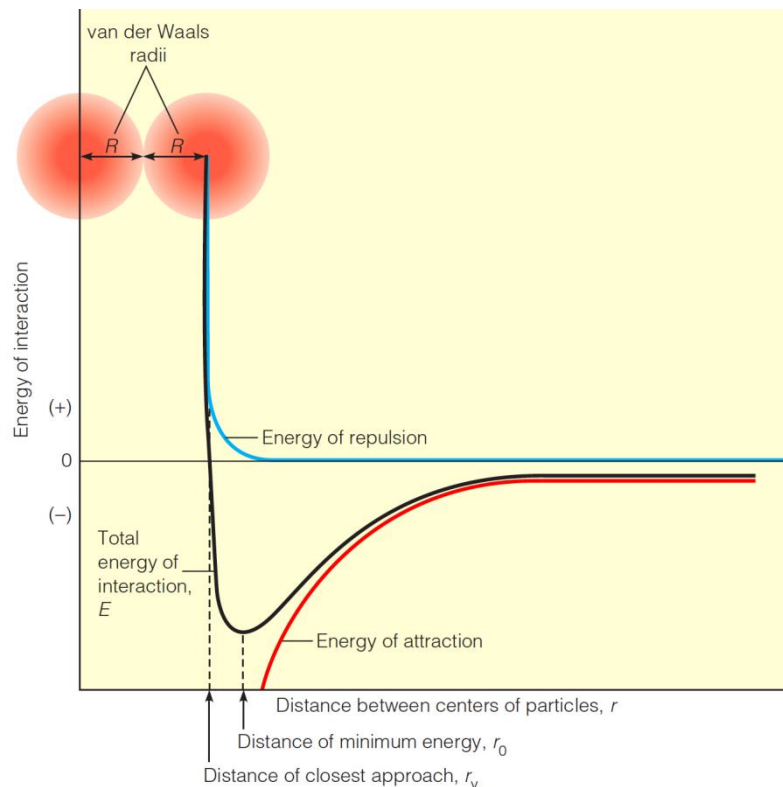


The attractive  $r^{-6}$  term originates from quantum mechanics.

The weak bonding attraction is due to London or dispersion force (in quantum mechanics this corresponds to electron correlation contributions). Namely, the rapid fluctuations of the electron density distribution around a nucleus create a transient dipole moment and induce charge reorientations (dipole-induced dipole interactions), or London forces.

the repulsive  $r^{-12}$  term has been chosen mainly for computational convenience.

The steep repulsion has a quantum origin in the interaction of the electron clouds with each other, as affected by the Pauli-exclusion principle, and this combines with internuclear repulsions.





# The Coulomb Potential

## *Coulomb's Law: Slowly Decaying Potential*

Ionic interactions between fully or partially charged groups can be approximated by Coulomb's law for each atom pair  $\{i, j\}$ :

$$F_{\text{coul}}(r_{ij}) \propto q_i q_j / r_{ij}^2$$

This leads to the Coulomb potential of form

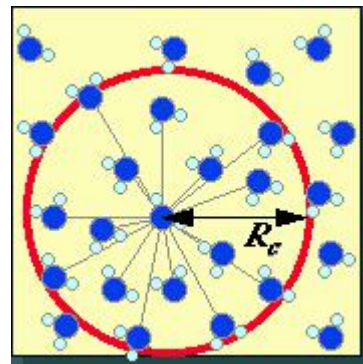
$$E_{\text{coul}} = K_{\text{coul}} \frac{q_i q_j}{\epsilon r_{ij}},$$

where  $\epsilon$  is the dielectric constant and  $K_{\text{coul}}$  is the conversion factor needed to obtain energies in units of kcal/mol with the charge units used

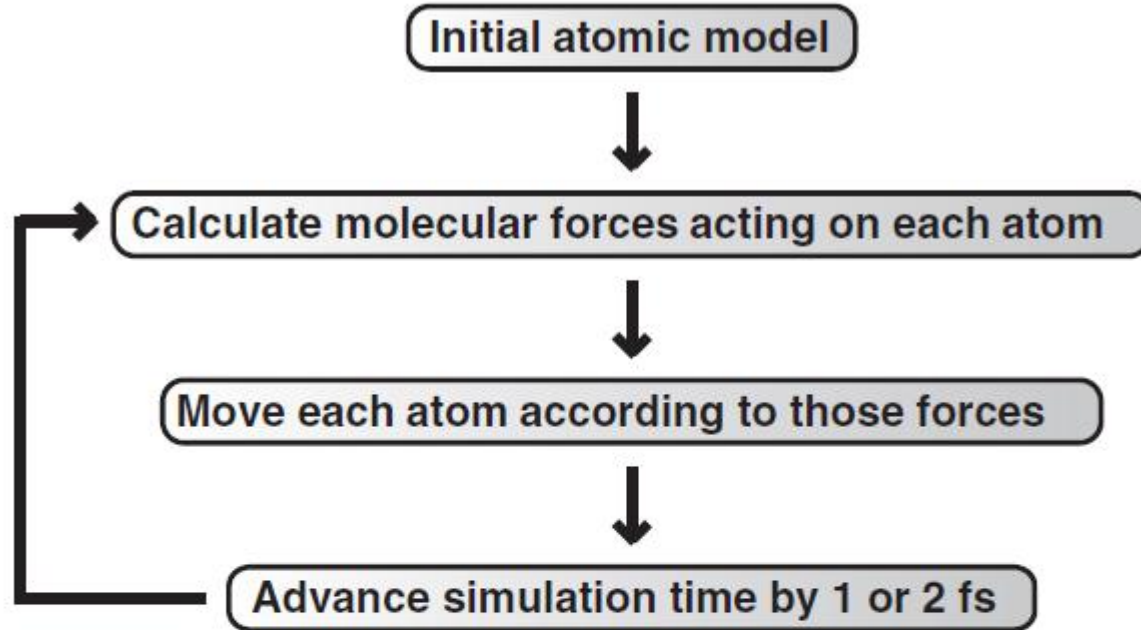
Unlike the van der Waals potential, the Coulomb interactions decay slowly with distance

In fact, electrostatic interactions are important for stabilizing biomolecular conformations in solvent and associating distant residues in the primary sequence closer in the folded structure.

However, because of the  $\mathcal{O}(N^2)$  complexity in evaluating all pairwise terms directly, calculations have often only counted interactions within a cutoff radius (e.g., 10 Å).



# Steps



$$1 \text{ fs} = 10^{-15} \text{ s}$$

**Figure 2. A schematic showing how a molecular dynamics simulation is performed.** First, a computer model of the receptor-ligand system is prepared. An equation like that shown in Figure 3 is used to estimate the forces acting on each of the system atoms. The positions of the atoms are moved according to Newton's laws of motion. The simulation time is advanced, and the process is repeated many times. This figure was adapted from a version originally created by Kai Nordlund.

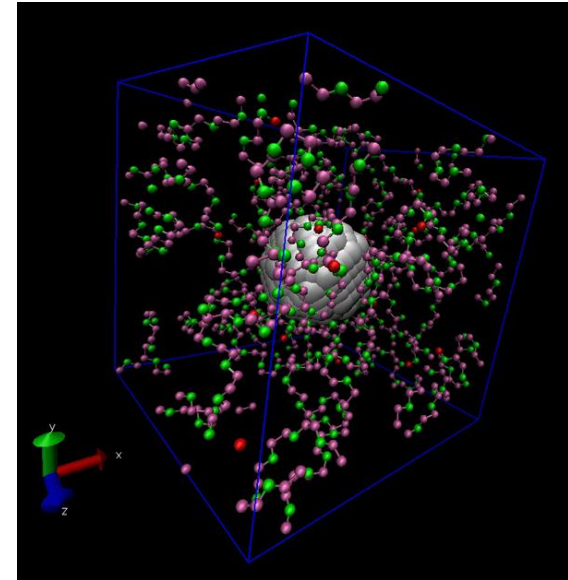
Give atoms initial positions  $\mathbf{r}^{(t=0)}$ , choose short  $\Delta t$

Get forces  $\mathbf{F} = -\nabla V(\mathbf{r}^{(i)})$  and  $\mathbf{a} = \mathbf{F}/m$

Move atoms:  $\mathbf{r}^{(i+1)} = \mathbf{r}^{(i)} + \mathbf{v}^{(i)} \Delta t + \frac{1}{2} \mathbf{a} \Delta t^2 + \dots$

Move time forward:  $t = t + \Delta t$

Repeat as long as you need





# Basic Computation

The classical MD simulations boil down to numerically integrating Newton's equations of motion for the particles (atoms, in the simplest case) which build up the investigated system:

$$m \frac{d^2 \mathbf{r}_i}{dt^2} = \mathbf{F}_i(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N), \quad i = 1, 2, \dots, N.$$

Here  $\mathbf{r}_i$  are the position vectors and  $\mathbf{F}_i$  are the forces acting upon the  $N$  particles in the system.

Quite often forces derive from *potential functions*,  $U(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N)$ , representing the potential energy of the system for the specific geometric arrangement of the particles:

$$\mathbf{F}_i(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N) = -\nabla_{\mathbf{r}_i} U(\mathbf{r}_1, \mathbf{r}_2, \dots, \mathbf{r}_N).$$

This form implies the conservation of the total energy  $E = E_{\text{kin}} + U$ , where  $E_{\text{kin}}$  is the instantaneous kinetic energy.

**In some context, we use ~~in~~ instead of ~~in~~.**

# The fundamental reason is that the system is a Hamiltonian system

In Hamiltonian mechanics, a classical physical system is described by a set of canonical coordinates  $\mathbf{r} = (\mathbf{q}, \mathbf{p})$ , where each component of the coordinate  $q_i, p_i$  is indexed to the frame of reference of the system.

The time evolution of the system is uniquely defined by Hamilton's equations:

$$\begin{aligned}\frac{d\mathbf{p}}{dt} &= -\frac{\partial \mathcal{H}}{\partial \mathbf{q}} \\ \frac{d\mathbf{q}}{dt} &= +\frac{\partial \mathcal{H}}{\partial \mathbf{p}}\end{aligned}$$

where  $\mathcal{H} = \mathcal{H}(\mathbf{q}, \mathbf{p}, t)$  is the Hamiltonian, which often corresponds to the total energy of the system. For a closed system, it is the sum of the kinetic and potential energy in the system.

$$\frac{dp}{dt} = -\frac{\partial V}{\partial q}$$

$$\mathcal{H} = T + V, \quad T = \frac{p^2}{2m}, \quad V = V(q).$$

Note that  $T$  is a function of  $p$  alone, while  $V$  is a function of  $q$  alone

$$\frac{d\mathbf{p}}{dt} = -\frac{\partial V}{\partial \mathbf{q}}$$

$$\mathbf{p} = m\mathbf{v} = m\frac{d\mathbf{q}}{dt}$$

$$m\frac{d^2\mathbf{q}}{dt^2} = -\frac{\partial V}{\partial \mathbf{q}}$$

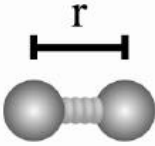
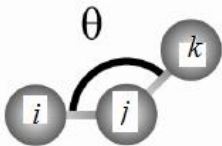
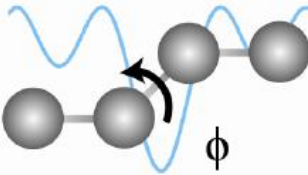
$$\mathbf{F} = -\frac{\partial V}{\partial \mathbf{q}}$$

$$\mathbf{F}_i = -\frac{\partial V}{\partial \mathbf{q}_i}$$



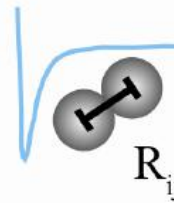
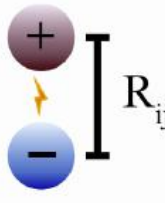
### Bonded

$$\mathbf{V} = \sum_{\text{bonds}} K_r (\mathbf{r} - \mathbf{r}_{eq})^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2} [1 + \cos(n\phi - \gamma)]$$

### Non-bonded

$$+ \sum_{i < j} \left[ \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon R_{ij}} \right]$$

**Figure 3. An example of an equation used to approximate the atomic forces that govern molecular movement.** The atomic forces that govern molecular movement can be divided into those caused by interactions between atoms that are chemically bonded to one another and those caused by interactions between atoms that are not bonded. Chemical bonds and atomic angles are modeled using simple springs, and dihedral angles (that is, rotations about a bond) are modeled using a sinusoidal function that approximates the energy differences between eclipsed and staggered conformations. Non-bonded forces arise due to van der Waals interactions, modeled using the Lennard-Jones potential, and charged (electrostatic) interactions, modeled using Coulomb's law.

$$\theta = \cos^{-1} \frac{(\mathbf{r}_k - \mathbf{r}_j) \cdot (\mathbf{r}_i - \mathbf{r}_j)}{|\mathbf{r}_k - \mathbf{r}_j| |\mathbf{r}_i - \mathbf{r}_j|}$$