

# Molecular Dynamics Simulations Force-Field

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# The Nobel Prize in Chemistry 2013

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Mahmoud

**Martin Karplus**

Prize share: 1/3



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**Michael Levitt**

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**Arieh Warshel**

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Chemists used to create models of molecules using plastic balls and sticks. Today, the modelling is carried out in computers. In the 1970s, **Martin Karplus, Michael Levitt** and **Arieh Warshel** laid the foundation for the powerful programs that are used to understand and predict chemical processes. Computer models mirroring real life have become crucial for most advances made in chemistry today

# To Compute Forces, Take the Derivative of the Potential Energy

$$\mathbf{f}_i = m_i \mathbf{a}_i = -\nabla_{\mathbf{r}_i} U,$$

where  $\mathbf{f}_i$  is the force experienced by the particle (or atom)  $i$  due to the presence of the potential energy  $U$ .  $m_i$  and  $\mathbf{a}_i$  are the respective mass and acceleration of particle  $i$ .  $\nabla_{\mathbf{r}_i}$  designates the gradient operator, that is, partial derivatives of  $U$ , such as  $\partial U / \partial x_i$ , with respect to the  $x$ -,  $y$ -, and  $z$ -components of the position  $\mathbf{r}_i$  of the particle  $i$ . So, the  $x$ -,  $y$ -, and  $z$ -components of  $\mathbf{f}_i$  are found from the partial derivatives of  $U$  as

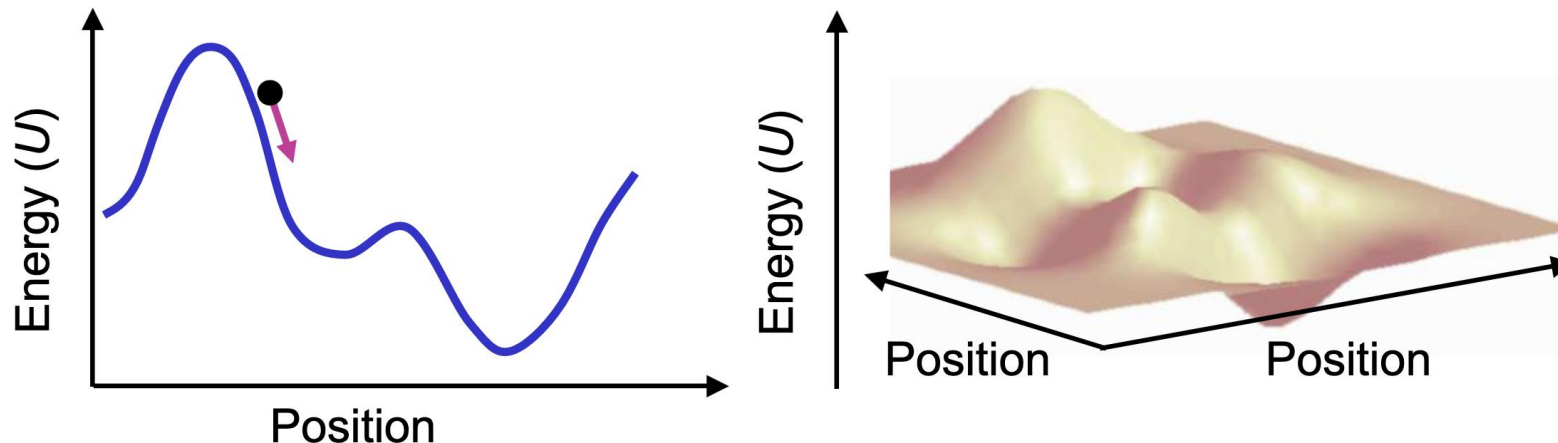
$$\mathbf{f}_i = \begin{bmatrix} f_{ix} \\ f_{iy} \\ f_{iz} \end{bmatrix} = \begin{bmatrix} -\partial U / \partial x_i \\ -\partial U / \partial y_i \\ -\partial U / \partial z_i \end{bmatrix}.$$

# Relationship between energy and force

- Force on atom  $i$  is given by derivatives of  $U$  with respect to the atom's coordinates  $x_i$ ,  $y_i$ , and  $z_i$

$$\mathbf{F}(\mathbf{x}) = -\nabla U(\mathbf{x})$$

- At local minima of the energy  $U$ , all forces are zero



# Force vector

- A single vector  $\mathbf{F}$  specifies the force acting on every atom in the system
- For a system with  $N$  atoms,  $\mathbf{F}$  is a vector of length  $3N$ 
  - This vector lists the force on each atom in the x-, y-, and z- directions
- Notation:
  - Force on atom 1 in the x-direction:  $F_{1,x}$
  - Rate of change of  $U$  as  $x_1$  increases:  $\frac{\partial U}{\partial x_1}$

$$\mathbf{X} = \begin{pmatrix} x_1 \\ y_1 \\ z_1 \\ x_2 \\ y_2 \\ z_2 \\ \vdots \\ x_N \\ y_N \\ z_N \end{pmatrix} \quad \mathbf{F} = \begin{pmatrix} F_{1,x} \\ F_{1,y} \\ F_{1,z} \\ F_{2,x} \\ F_{2,y} \\ F_{2,z} \\ \vdots \\ F_{N,x} \\ F_{N,y} \\ F_{N,z} \end{pmatrix} = - \begin{pmatrix} \frac{\partial U}{\partial x_1} \\ \frac{\partial U}{\partial y_1} \\ \frac{\partial U}{\partial z_1} \\ \frac{\partial U}{\partial x_2} \\ \frac{\partial U}{\partial y_2} \\ \frac{\partial U}{\partial z_2} \\ \vdots \\ \frac{\partial U}{\partial x_N} \\ \frac{\partial U}{\partial y_N} \\ \frac{\partial U}{\partial z_N} \end{pmatrix}$$

Note that  $U$  depends on which atoms are present in the system and the covalent bonds between them. Two different molecular systems with the same number of atoms will have different potential energy functions.

How can we formulate the potential energy  
defining forces acting on a protein ?

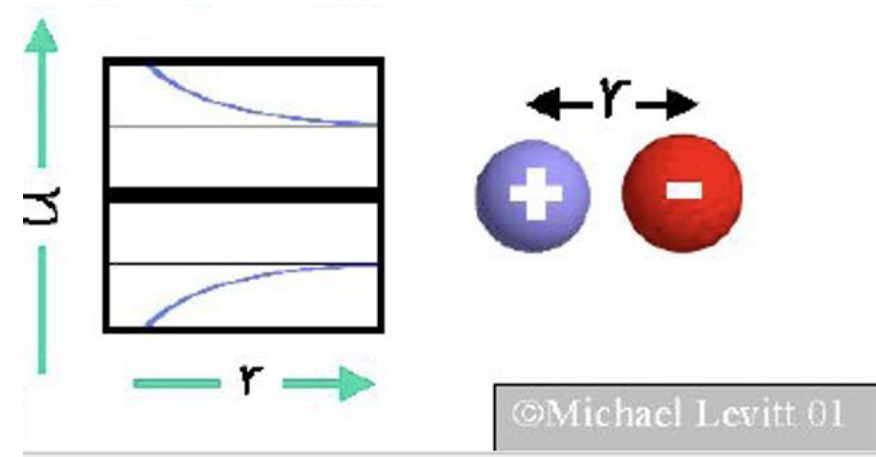
# Non-Bonded Interactions

# Coulomb Law

- Note: a negative force is attractive, and a positive force is repulsive.

$$F = k \frac{q_1 q_2}{r^2}$$

$$k = 8.99 \times 10^9 \text{ N M}^2/\text{C}^2$$

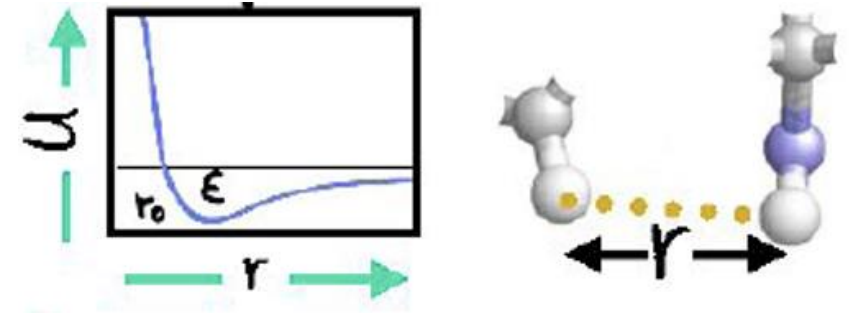


The force between two electrically charged particles is proportional to the product of their charges and inversely proportional to the square of the distance between the particles.

Note: a negative force is attractive, and a positive force is repulsive.



# Lennard Jones Potential



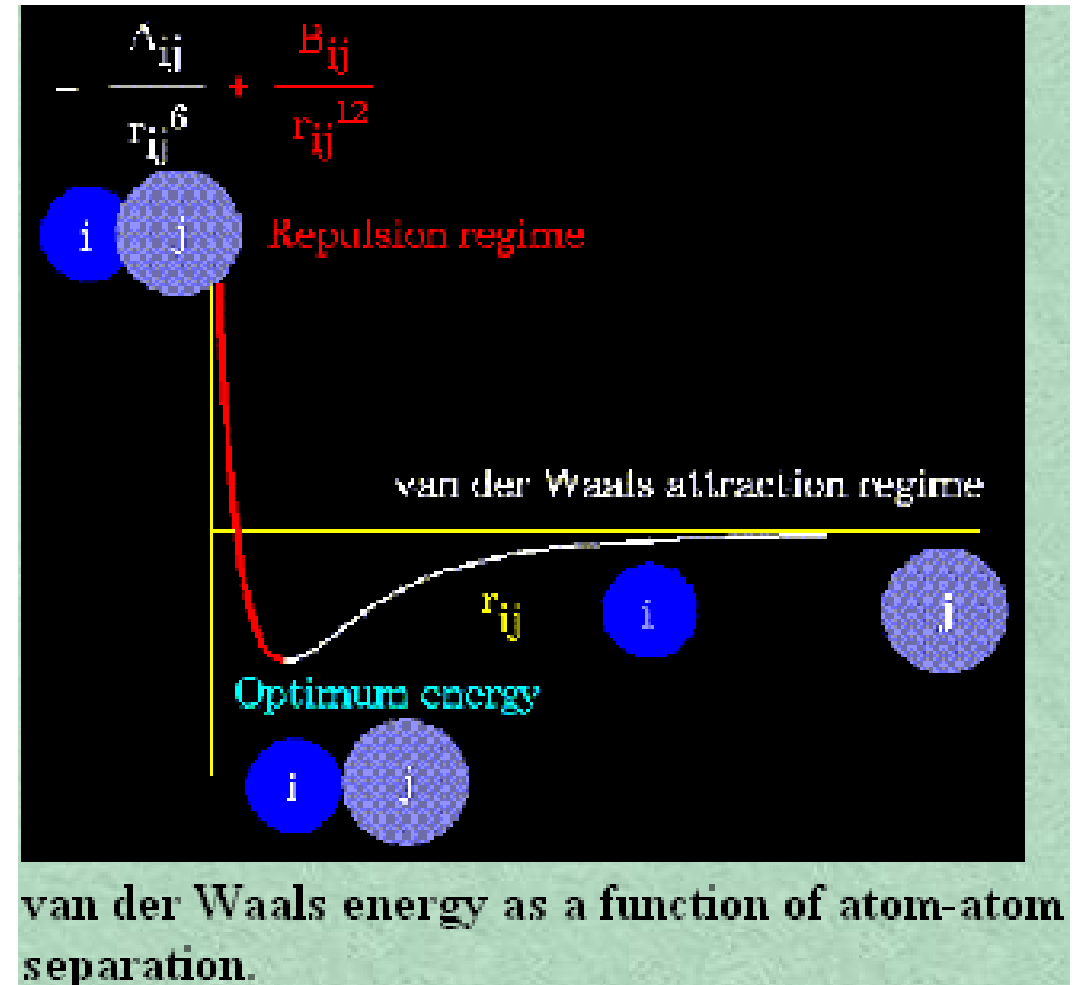
$$V_{LJ} = 4\epsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^6 \right]$$

Accounts for Pauli exclusion, but not in a rigorous way. The 12th power is used simply for computational convenience. In simple terms, this term reflects the fact that atoms take up space and have “size”.

Accounts for “Dispersion” forces. Dispersion forces are short-ranged attractions that result from the fact that the electrons move in the atom so that the atom is polarizable.

# Lennard Jones Potential

- van der Waals attraction occurs at short range, and rapidly dies off as the interacting atoms move apart.
- Repulsion occurs when the distance between interacting atoms becomes even slightly less than the sum of their contact distance.
- Electrostatic energy dies out slowly and it can affect atoms quite far apart.



# Lennard Jones Potential

$$V_{LJ} = 4\epsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^6 \right]$$

$\sigma$  is called the “Lennard-Jones diameter”.

$\epsilon$  is called the “well depth”.

For what value of  $r$  does the Lennard-Jones energy equal zero?

# Lennard Jones Potential

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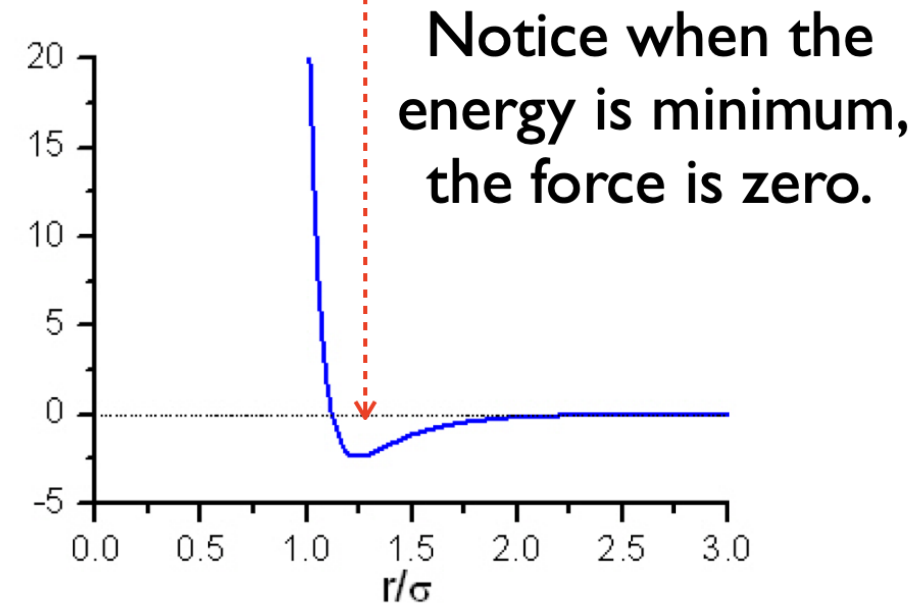
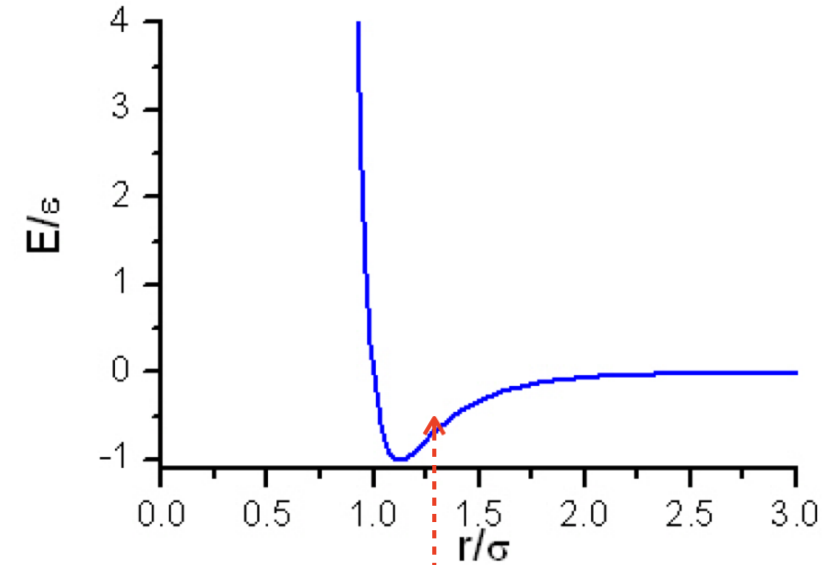
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# Lennard-Jones Forces

$$V_{LJ} = 4\epsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^6 \right]$$

$$F_{LJ} = \frac{4\epsilon}{\sigma} \left[ 12 \left( \frac{\sigma}{r} \right)^{13} - 6 \left( \frac{\sigma}{r} \right)^7 \right]$$



# Problems

- 1. Neon atoms can be approximated as Lennard-Jones atoms with  $\sigma = 0.26$  nm and  $\varepsilon = 306$  kJ/mol. What is LJ potential energy between the atoms when they are separated by 0.28 nm?
- Hint: You can write your answer in kJ/mol. What do you think “per mole” means in this case? Now, see if you can convert this to Joules! You’ll get a tiny number.
- 2. At what distance of separation is the force between two Lennard-Jones atoms zero? Write your answer in terms of  $\sigma$ .
- Get some help on working with powers if you need it!

# Molecular Mechanics Force Fields: Functional Forms

The basic functional form of a force field encapsulates both bonded terms relating to atoms that are linked by covalent bonds, and nonbonded (also called "noncovalent") terms describing the long-range electrostatic and van der Waals forces. The specific decomposition of the terms depends on the force field, but a general form for the total energy can be written as

$$E_{total} = E_{covalent} + E_{noncovalent}$$

$$E_{covalent} = E_{bond} + E_{angle} + E_{dihedral}$$

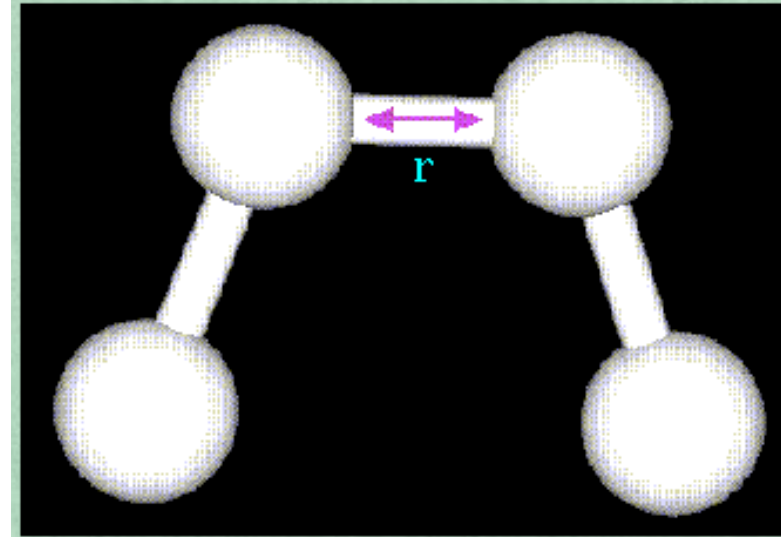
$$E_{noncovalent} = E_{electrostatic} + E_{vanderWaals}$$

# Bonded Interactions

- The stretching energy equation is based on Hooke's law. The "kb" parameter controls the stiffness of the bond spring, while "ro" defines its equilibrium length.

## Stretching Energy:

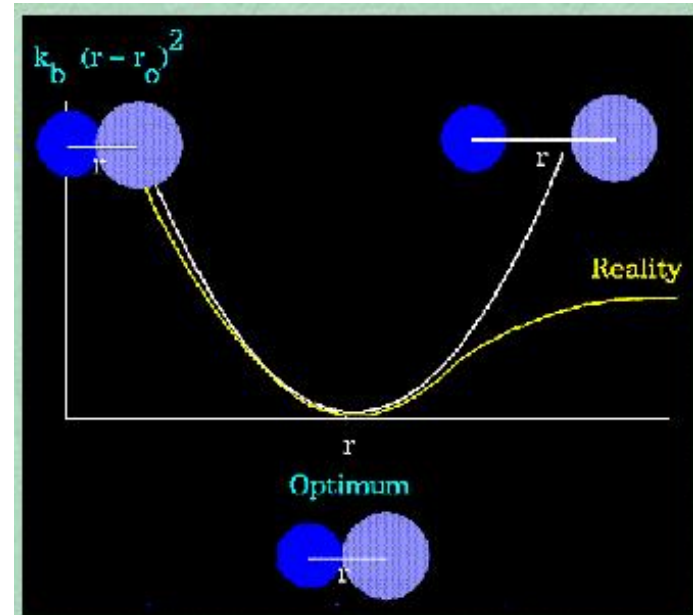
$$E = \sum_{\text{bonds}} k_b (r - r_o)^2$$





# Bonded Interactions

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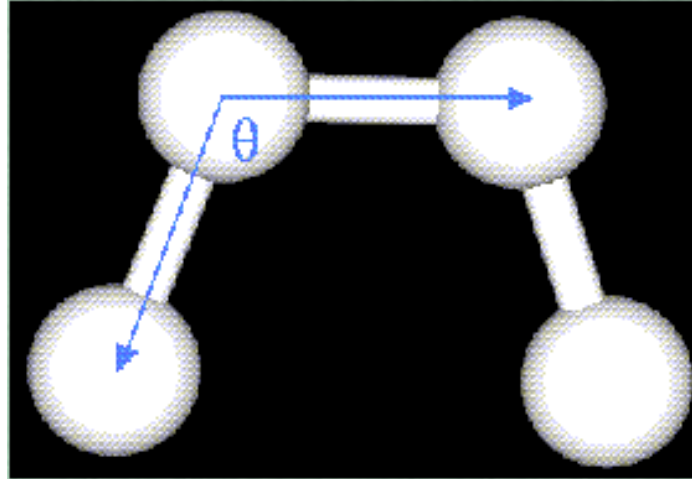
Stretching energy as a function of bond length

## Bonded Interactions

- The bending energy equation is also based on Hooke's law

### Angle Bending Energy:

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



# Harmonic Equation

- **Near Energy Minima, the Forces Are Linear, Acting Like Hooke's-Law Springs**

$$U(r) = \frac{k_s}{2} (r - r_0)^2$$

What is the  $r$  that minimize the force (when force is equal to 0

# Harmonic Equation

- **Near Energy Minima, the Forces Are Linear, Acting Like Hooke's-Law Springs**

$$U(r) = \frac{k_s}{2} (r - r_0)^2$$

What is the  $r$  that minimize the force (when force is equal to 0

$$F(r) = -k_s (r - r_0)$$

The negative sign indicates that the force acting on the particle is in the direction *opposite* to that of the deformation,  $\Delta r = (r - r_0)$ . For bond stretching or bending, the force constants are  $k_s = k_l$  or  $k_\theta$ , and  $(r - r_0)$  is replaced by  $(l - l_0)$  and  $(\theta - \theta_0)$ , respectively. The bond stretching constant  $k_l$  is large, implying stiff springs.

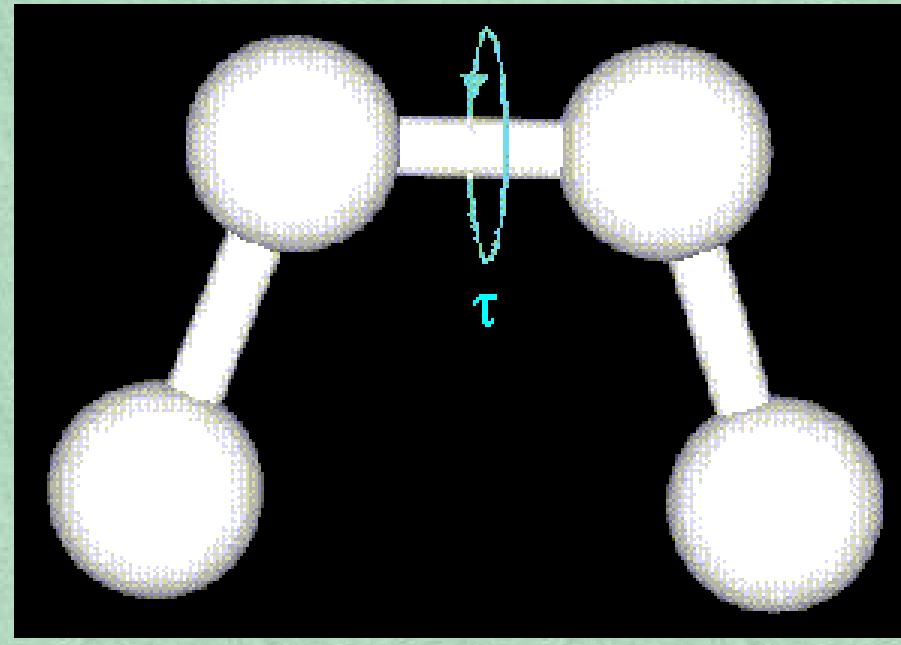
# Bonded Interactions

The torsion energy is modeled by a simple periodic function

Why?

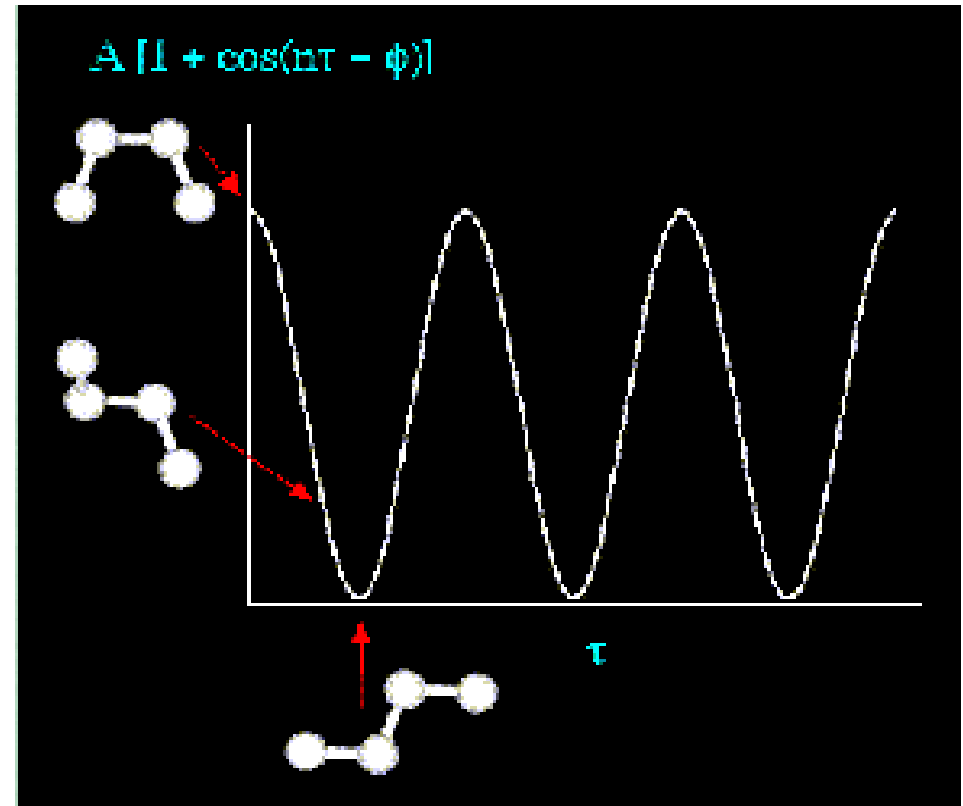
## Torsion Energy:

$$E = \sum_{\text{torsions}} A [1 + \cos(n\tau - \phi)]$$

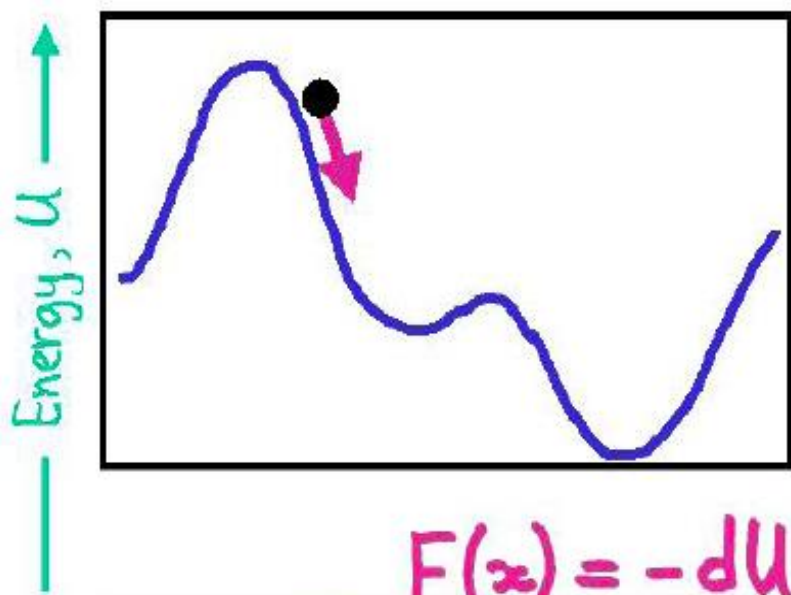


# Bonded (Covalent Interaction)

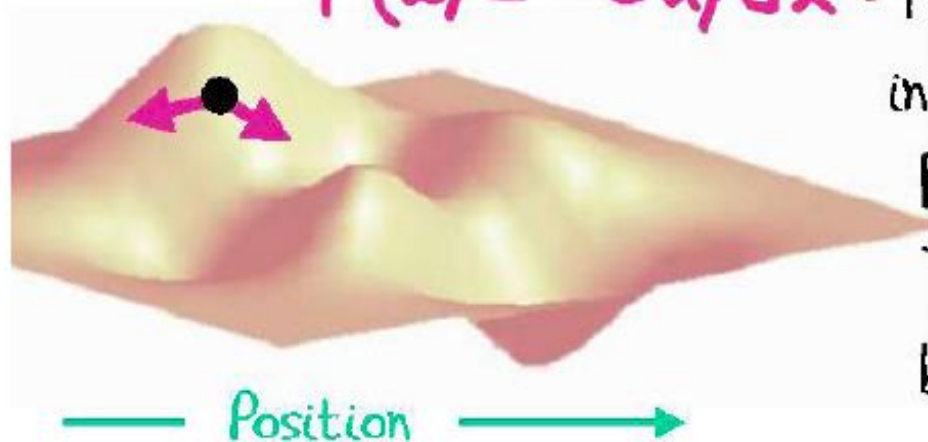
Torsion energy as a function of bond rotation angle.



# We can use Classical Mechanics to sample conformations on the energy-landscape

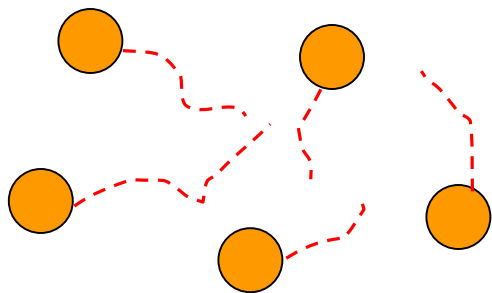


$$F(x) = -dU/dx$$



- The total potential energy or enthalpy fully defines the system,  $U$ .
- The forces are the gradients of the energy.
- The energy is a sum of independent terms for:  
Bonds, Bond angles,  
Torsion angles and non-bonded atom pairs.

# Molecular Dynamics Theory



- Force =  $-dU/dx$  (slope of potential,  $U$ ); acceleration,  $m a(t) = \text{Force}$ .
- All atoms move together so force between atoms change with time.
- Analytical solution for  $x(t)$  and  $v(t)$  is impossible; numerical solution is trivial.

$$\underset{\text{New position}}{x(t+\Delta t)} = \underset{\text{Old position}}{x(t)} + \underset{\text{Old velocity}}{v(t)\Delta t} + \underset{\text{Acceleration}}{[4a(t) - a(t-\Delta t)]\Delta t^2/6}$$

$$\underset{\text{New velocity}}{v(t+\Delta t)} = \underset{\text{Old velocity}}{v(t)} + \underset{\text{Acceleration}}{[2a(t+\Delta t) + 5a(t) - a(t-\Delta t)]\Delta t/6}$$

$$\underset{\text{Kinetic energy}}{U_{\text{kinetic}}} = \frac{1}{2} \sum \underset{\text{Atomic masses, velocities}}{m_i v_i(t)^2} = \frac{1}{2} \underset{\text{Boltzmann's Constant}}{n} \underset{\text{Temperature}}{k_B T}$$

Number of coordinates (not atoms)

Total energy ( $U_{\text{potential}} + U_{\text{kinetic}}$ ) must not change with time

Time step,  $\Delta t$ , must be very small at  $10^{-15}$  seconds or 0.001 ps.