Potential energy surfaces in Biomolecules

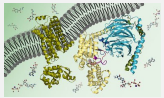
Adolfo Bastida

Universidad de Murcia (Spain)

Máster Universitario en Bioinformática

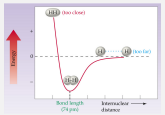
Modelado Molecular

Index

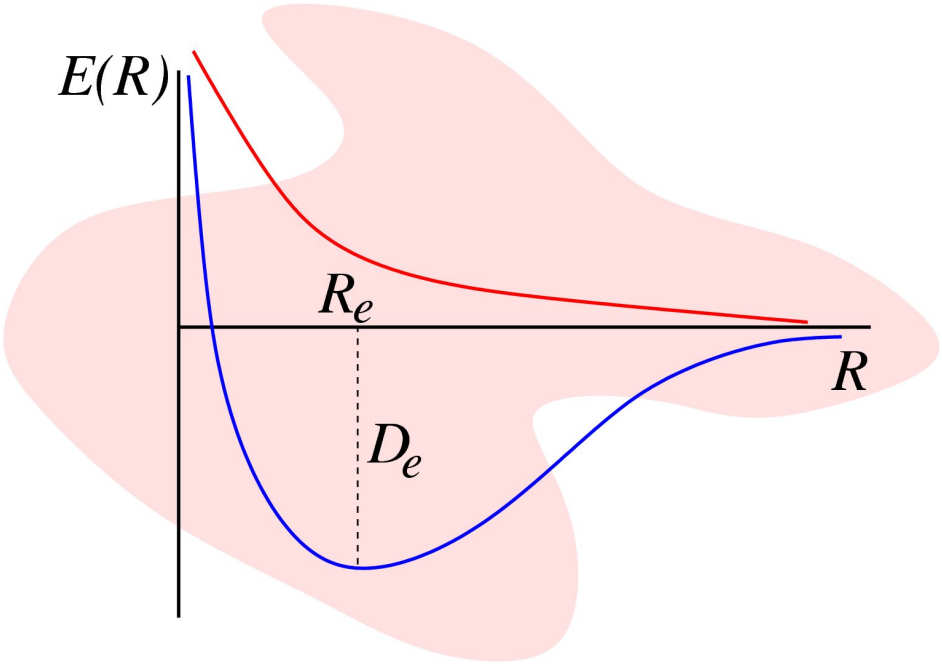


Biomolecules

- Electronic Schrödinger equation
  - QM methods
    - QM description the whole system $\Rightarrow$ computationally forbidden
    - QM treatment depends on the particular case
    - QM restricted to reactivity or quantum effects (proton transfer,...)
  - Molecular Mechanics potentials
    - Proteins and nucleic acids are made with the same units
    - Self-assembly potential energy functions
    - Fixed functional form with parameters fitted to experiments or QM data
- Nuclear Schrödinger equation
  - Time-dependent evolution $\Rightarrow$ Molecular Dynamics (classical)
  - Monte-Carlo,...
- Solvent
  - Atomistic MM models
  - Continuum models



Potential energy curve

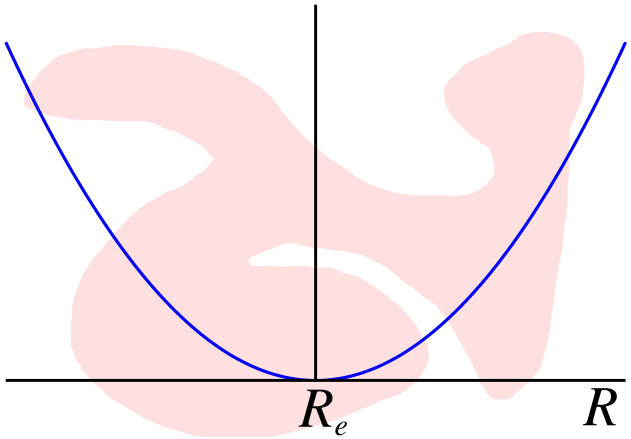


- Unbound states.
- Bound states.
  - Dissociation energy $\Rightarrow D_e$
  - Internuclear equilibrium distance $\Rightarrow R_e$ (bond length)

- Potential energy curve

$$V(R) = \underbrace{\cancel{V(R_e)}}_{\text{energy origin}} + \underbrace{\cancel{\left(\frac{\partial V}{\partial R}\right)_{R_e}}}_{\text{minimun}}(R-R_e) + \frac{1}{2}\left(\frac{\partial^2 V}{\partial R^2}\right)_{R_e}(R-R_e)^2 + \frac{1}{6}\left(\frac{\partial^3 V}{\partial R^3}\right)_{R_e}(R-R_e)^3 + \text{higher order terms}$$

Harmonic oscillator

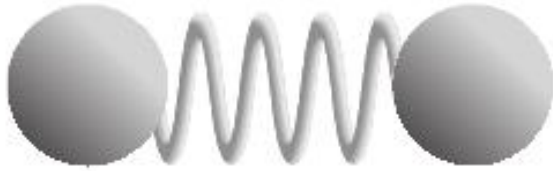


- $\lim_{R\to\infty} V_h(R) = \infty \neq D_e$
- Minimun at $R = R_e$
- $\lim_{R\to 0} V_h(R) = \frac{1}{2} k R_e^2 < \infty$

- Harmonic potential

$$V_h(R) = \frac{1}{2} \underbrace{\left(\frac{\partial^2 V}{\partial R^2}\right)_{R_e}}_{k} \underbrace{(R - R_e)^2}_{q}$$

$k \rightarrow$ force constant



Hooke's law

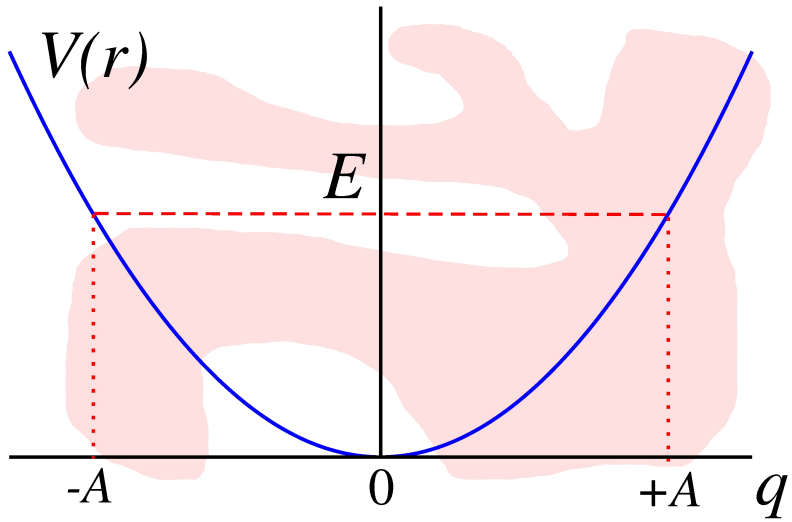
$$F = -\frac{dV_h}{dq} = -k\, q_h$$

Harmonic oscillator (HO)

- Classical HO

$$E = \frac{p_{\mathrm{h}}^2}{2\mu} + \frac{1}{2} k q_{\mathrm{h}}^2 = \frac{1}{2} k A^2$$

$$\mu = \frac{m_A m_b}{m_A + m_B}$$

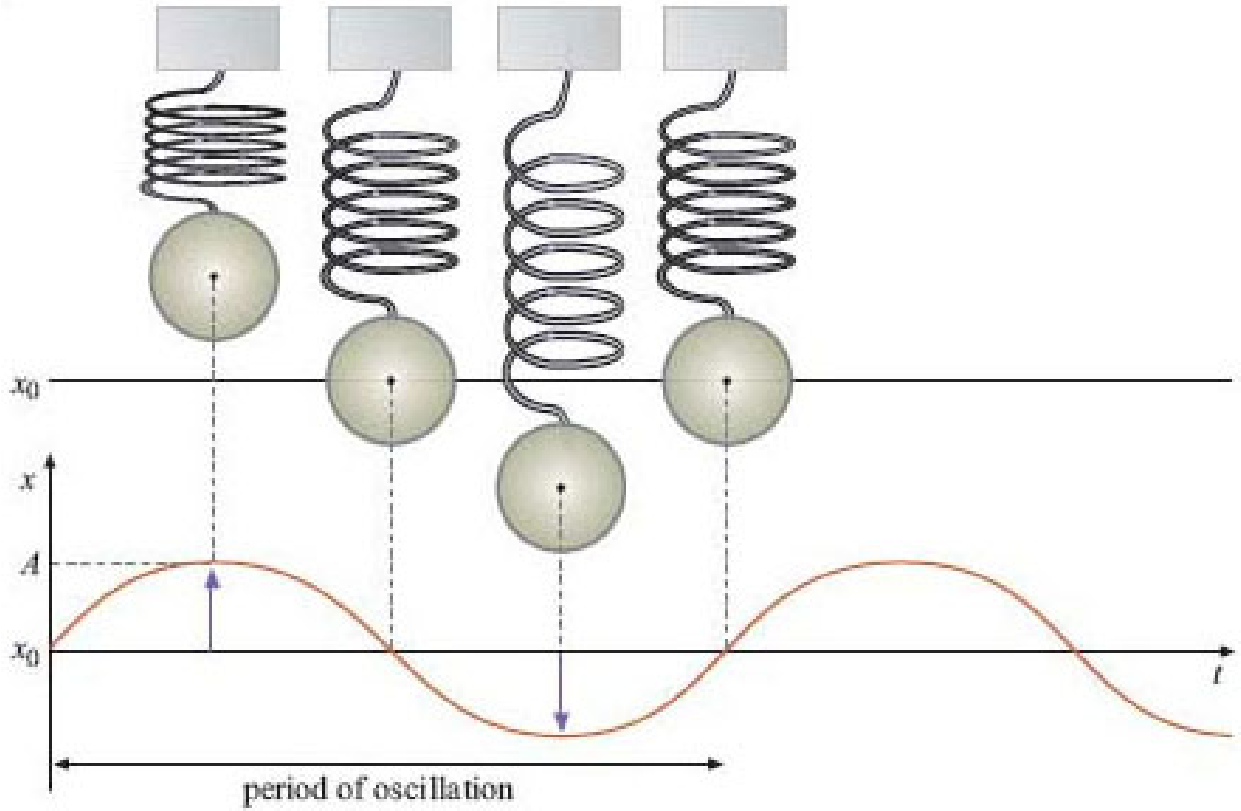


$$F = -k\, q_{\mathrm{h}} = \mu\, a \rightarrow -k\, q_{\mathrm{h}} = \mu \frac{d^2 q_{\mathrm{h}}}{dt^2}$$

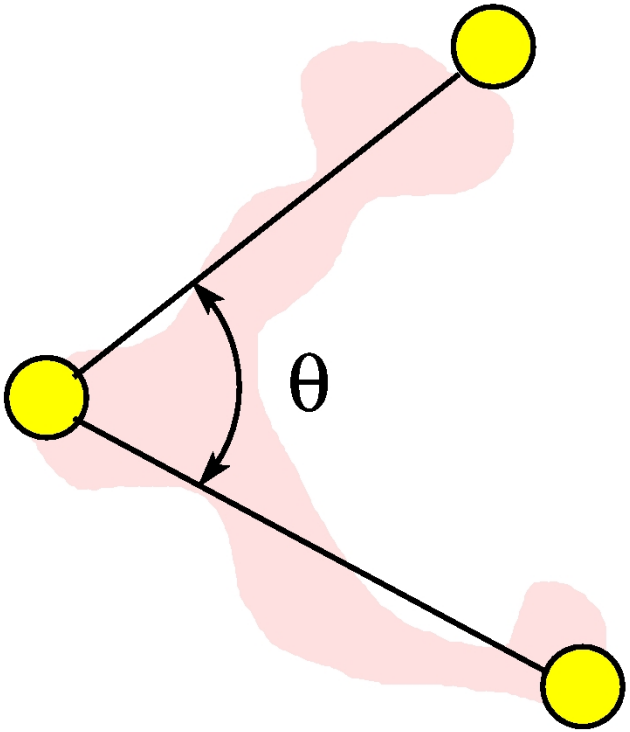
$$\downarrow \quad q_{\mathrm{h}}(0)=0$$

$$q_{\mathrm{h}}(t) = A \sin(\omega t) \rightarrow \omega = 2\pi\nu = \sqrt{k/\mu}$$

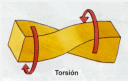
Harmonic oscillator (HO)



Bending vibrations

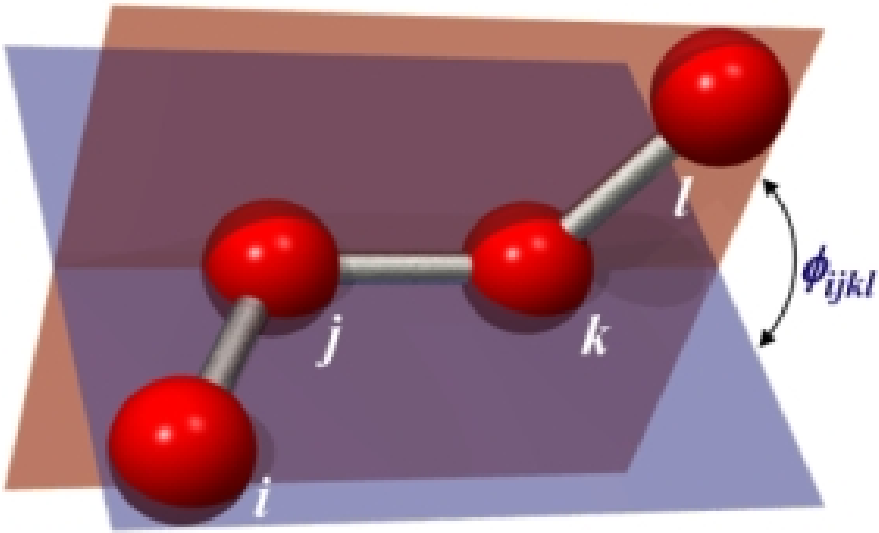


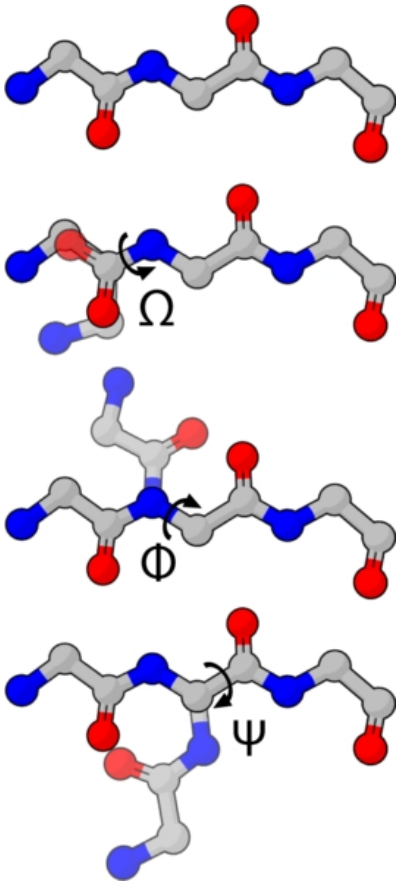
- Harmonic bending vibrations
  - $V(\theta) = \frac{1}{2}\, k\, (\theta - \theta_e)^2$
  - $F_\theta = -k\, (\theta - \theta_e)$
- Anharmonic terms
  $\Rightarrow k_3\, (\theta - \theta_e)^3 + \ldots$

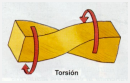


Torsional motions

- Dihedral angles

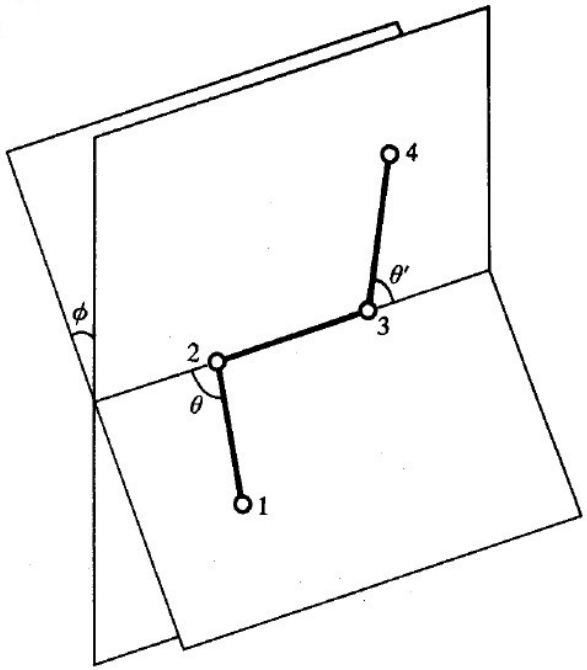


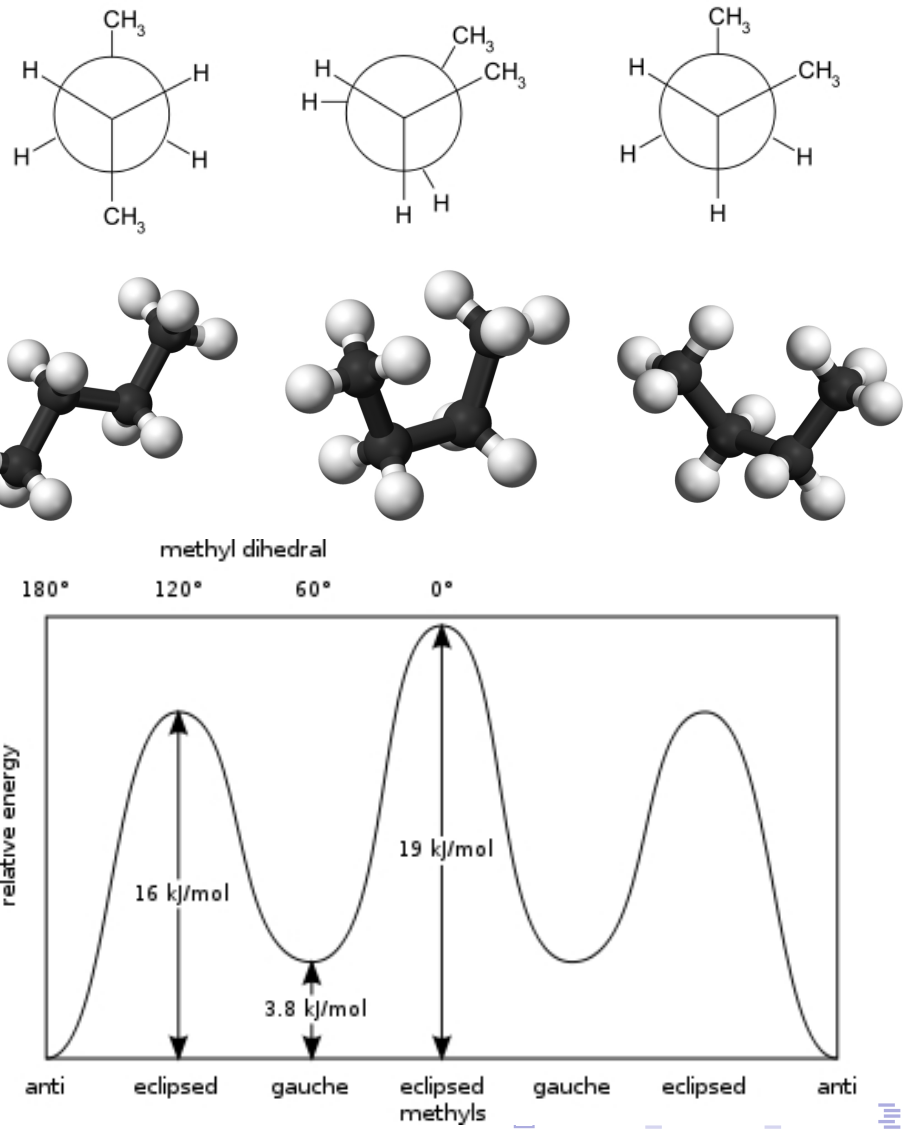


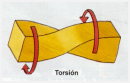


Torsional motions

- Torsional motions

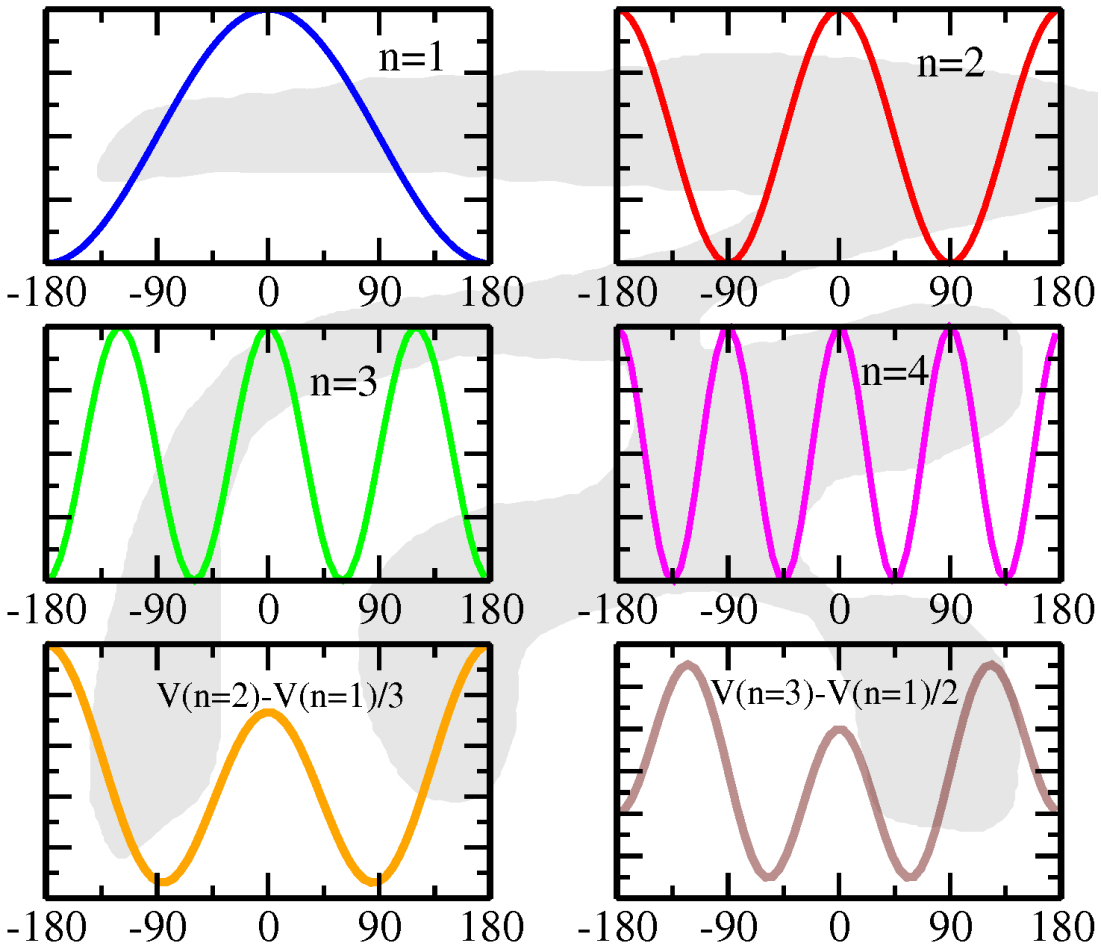




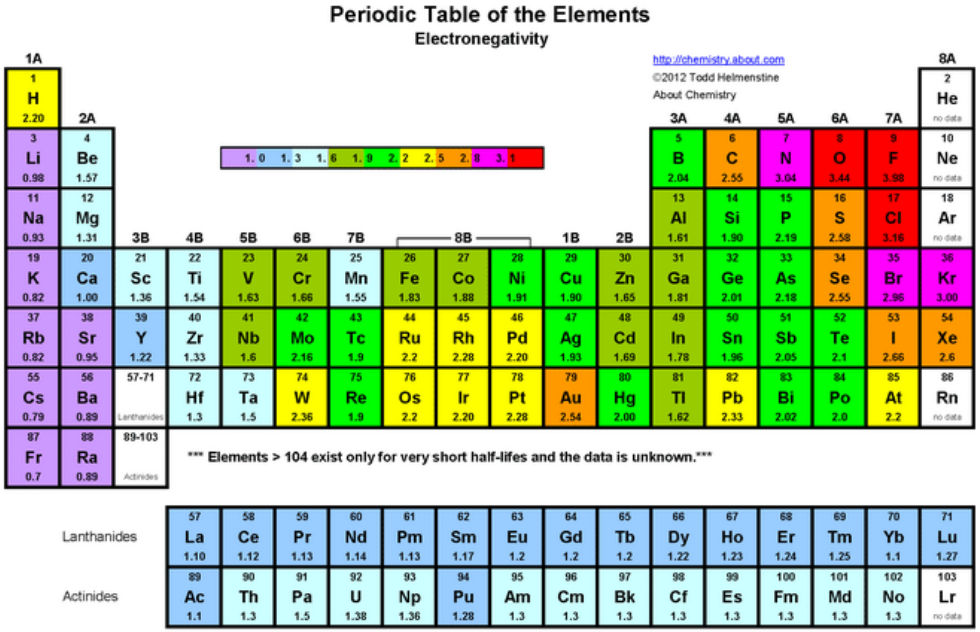


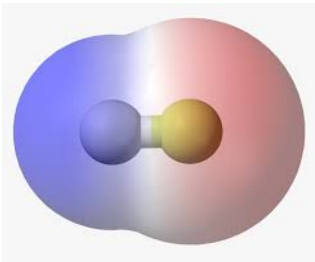
Torsional motions

$$V(\phi) = \frac{1}{2}\, k\, (1 + \cos(n\,\phi + \gamma))$$



Coulomb forces

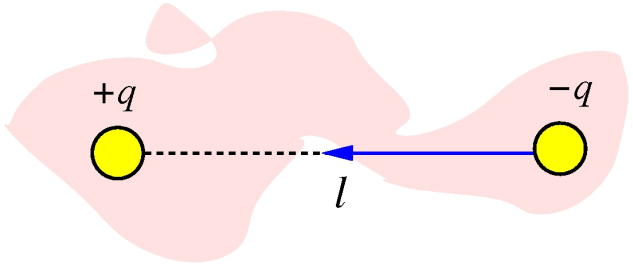




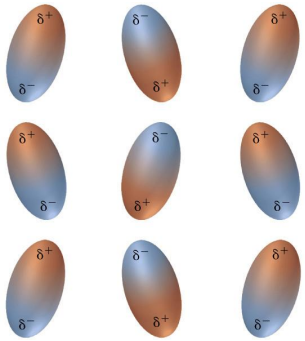
- $V(r_{ij}) = \frac{1}{4\pi\epsilon_0} \frac{q_i\, q_j}{r_{ij}}$
- $-e < q_i, q_j < +e$

van der Waals forces

- van der Waals forces
  - Electric dipole $\Rightarrow \mu = q \cdot l$

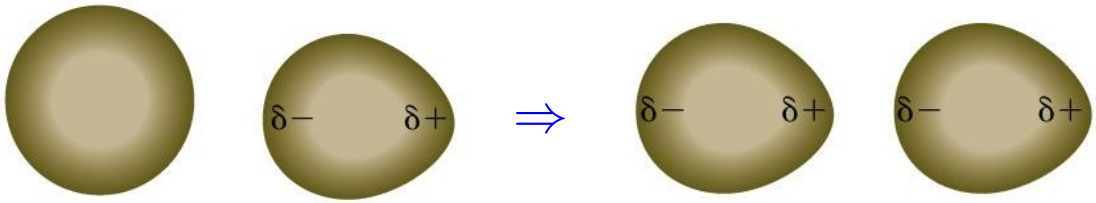


  - Dipole-dipole interactions



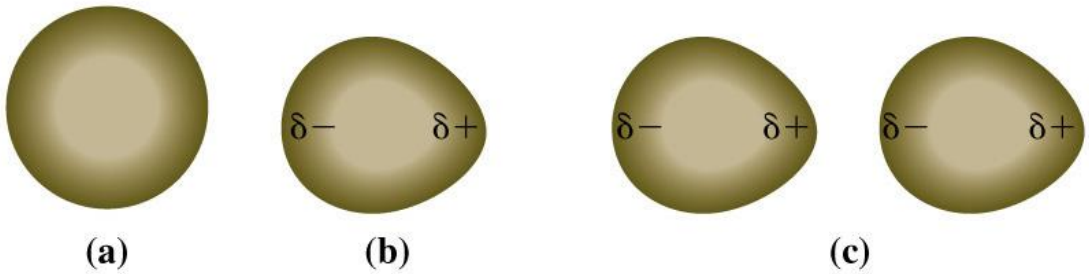
$$V_{\mathrm{dd}} = -\frac{C}{r^6} \rightarrow C \propto \frac{\mu_1 \mu_2}{T}$$

  - Dipole-induced dipole interactions



van der Waals forces

- Instantaneous dipole-induced dipole interactions.
  Ej. $He_{(l)}$, $Ne_{(l)}$, ...

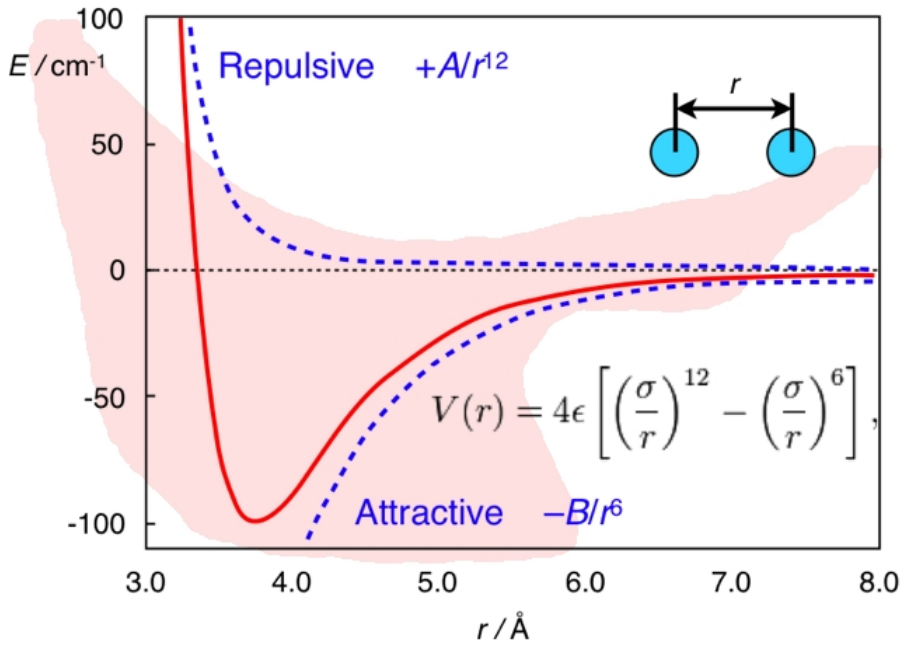


$V_{dd} = -\frac{C}{r^6} \rightarrow C \propto \frac{\alpha_1 \alpha_2}{I} \rightarrow \alpha$ polarizability

- Intensity $\Rightarrow$ dipole-dipole $>$ dipole-ind. dipole $>$ inst. dipole-ind. dipole
- Short range repulsive forces $\Rightarrow V_{rep} \propto \frac{1}{r^{12}}$

van der Waals forces

- Lennard-Jones potential



- $V_{\mathrm{LJ}}(r) = 4\epsilon\left(\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right) = \epsilon\left(\left(\frac{r_{\mathrm{min}}}{r}\right)^{12} - 2\left(\frac{r_{\mathrm{min}}}{r}\right)^{6}\right)$
- $r_{\mathrm{min}} = 2^{1/6}\,\sigma \Rightarrow V_{\mathrm{LJ}}(r_{\mathrm{min}}) = -\epsilon$
- $V_{\mathrm{LJ}}(\sigma) = 0 \Rightarrow$ effective atomic radius

van der Waals forces

- Homoatomic interactions

Table 1.1. *Atom–atom interaction parameters*

Atom	Source	ε/k_B(K)	σ(nm)
H	[Murad and Gubbins 1978]	8.6	0.281
He	[Maitland *et al.* 1981]	10.2	0.228
C	[Tildesley and Madden 1981]	51.2	0.335
N	[Cheung and Powles 1975]	37.3	0.331
O	[English and Venables 1974]	61.6	0.295
F	[Singer *et al.* 1977]	52.8	0.283
Ne	[Maitland *et al.* 1981]	47.0	0.272
S	[Tildesley and Madden, 1981]	183.0	0.352
Cl	[Singer *et al.* 1977]	173.5	0.335
Ar	[Maitland *et al.* 1981]	119.8	0.341
Br	[Singer *et al.* 1977]	257.2	0.354
Kr	[Maitland *et al.* 1981]	164.0	0.383

- Heteroatomic interactions

$$\sigma_{AB} = \frac{1}{2}(\sigma_A + \sigma_b) \qquad \epsilon_{AB} = \sqrt{\epsilon_A \cdot \epsilon_B}$$

Molecular Mechanics potentials

$$V = \sum_{\text{bonds}} \frac{1}{2} k_b (l - l_0)^2 + \sum_{\text{angles}} \frac{1}{2} k_a (\theta - \theta_0)^2 + \sum_{\text{torsions}} \frac{1}{2} V_n [1 + \cos(n\omega - \gamma)]$$

$$+ \sum_{j=1}^{N-1} \sum_{i=j+1}^{N} \left\{ \epsilon_{i,j} \left[\left(\frac{r_{0ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{r_{0ij}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \right\}$$

- Biomolecules (proteins, ADN,...)
- Very general
- Accuracy

Molecular Mechanics potentials

- AMBER ⇒ Assisted Model Building with Energy Refinement
  W.D. Cornell *et al. A second generation force field for the simulation of proteins, nucleic acids and organic molecules*. J. Am. Chem. Soc. **117**, 5179-5197 (1995).
- CHARMM ⇒ CHemistry At HaRvard Molecular Mechanics
  small M. Karplus *et al. All-atom empirical potential for molecular modeling and dynamics studies of proteins*. J. Phys. Chem. **102**, 3586-3616 (1998).
- GROMOS ⇒ GROningen MOlecular Simulation
  van Gunsteren *et al. A biomolecular force field based on the free enthalpy of hydratation and solvation: The GROMOS force field parameter sets 53A5 and 53A6*. J. Comput. Chem. **25**, 1656-1676 (2004).
- OPLS ⇒ Optimized Potential for Liquid Simulations
  W.L. Jorgensen *et al. Development and testing of the OPLS all-atom force field on conformational energetics and properties of organic liquids*. J. Am. Chem. Soc. **118**, 11225-11236 (1996).

Molecular Mechanics potentials

The Nobel Prize in Chemistry 2013
Martin Karplus, Michael Levitt, Arieh Warshel

Share this: 889

The Nobel Prize in Chemistry 2013

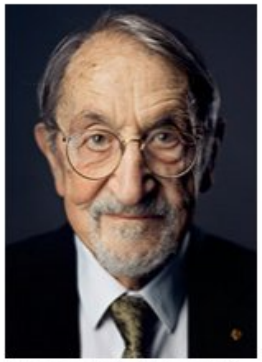


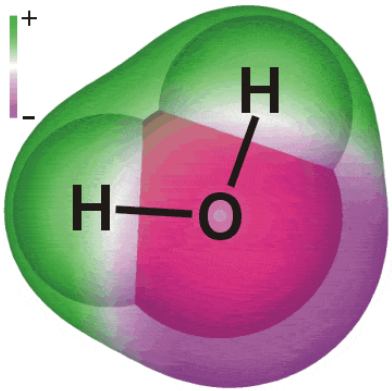
Photo: A. Mahmoud
Martin Karplus
Prize share: 1/3

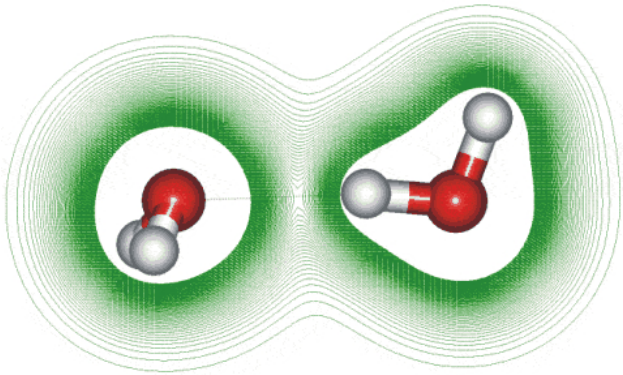
Photo: A. Mahmoud
Michael Levitt
Prize share: 1/3

Photo: A. Mahmoud
Arieh Warshel
Prize share: 1/3

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel *"for the development of multiscale models for complex chemical systems"*.

Water



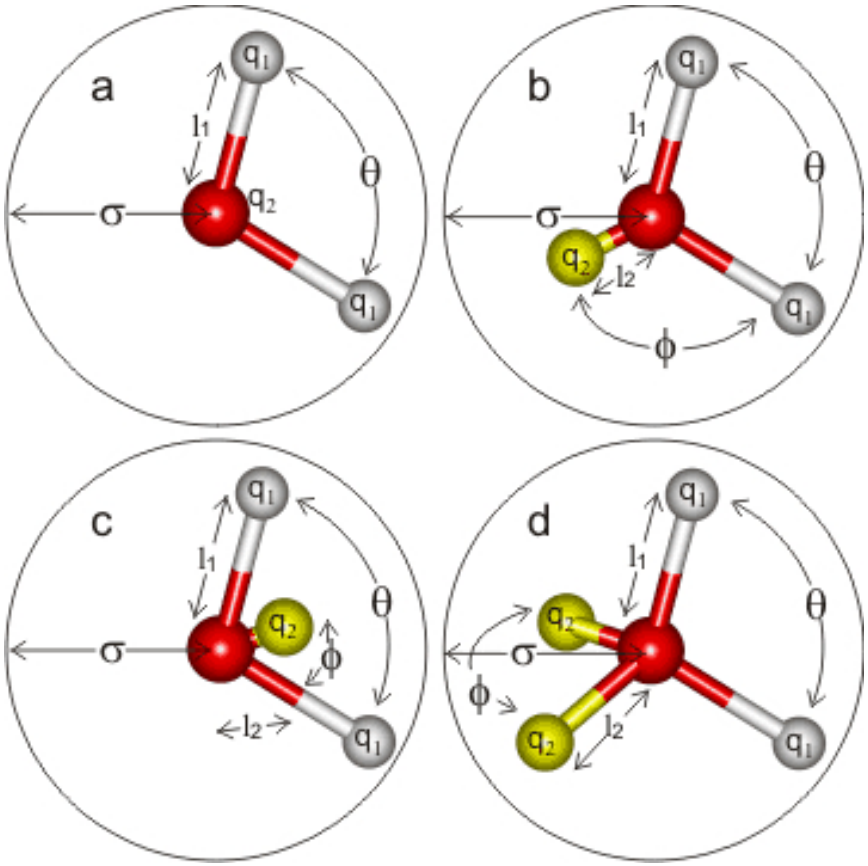


- Most studied molecule
  $\Rightarrow$ H-bond
- 69 anomalous properties of water

https://water.lsbu.ac.uk/water/water_anomalies.html

Water

- Models



Parameters for some water molecular models

Model	Type	σ Å [6]	ε kJ mol^{-1} [6]	l_1 Å	l_2 Å	q_1 (e)	q_2 (e)	θ°	φ°
SSD [511]	-[8]	3.016	15.319	-	-	-	-	109.47	109.47
SPC [94]	a	3.166	0.650	1.0000	-	+0.410	-0.8200	109.47	-
SPC/E [3]	a	3.166	0.650	1.0000	-	+0.4238	-0.8476	109.47	-
SPC/HW (D_2O) [220]	a	3.166	0.650	1.0000	-	+0.4350	-0.8700	109.47	-
SPC/Fw [2] [994]	a	3.166	0.650	1.0120	-	+0.410	-0.8200	113.24	-
TIP3P [180]	a	3.15061	0.6364	0.9572	-	+0.4170	-0.8340	104.52	-
TIP3P/Fw [2] [994]	a	3.1506	0.6368	0.9600	-	+0.4170	-0.8340	104.5	-
PPC [1, 2] [3]	b	3.23400	0.6000	0.9430	0.06	+0.5170	-1.0340	106.00	127.00
TIP4P [180]	c	3.15365	0.6480	0.9572	0.15	+0.5200	-1.0400	104.52	52.26
TIP4P-Ew [649]	c	3.16435	0.680946	0.9572	0.125	+0.52422	-1.04844	104.52	52.26
TIP4P-FQ [197]	c	3.15365	0.6480	0.9572	0.15	+0.63[1]	-1.26[1]	104.52	52.26
TIP4P/Ice [838]	c	3.1668	0.8822	0.9572	0.1577	+0.5897	-1.1794	104.52	52.26
TIP4P/2005 [984]	c	3.1589	0.7749	0.9572	0.1546	+0.5564	-1.1128	104.52	52.26
TIP4P/2005f [1765]	c	3.1644	0.7749	0.9664	0.15555	+0.5564	-1.1128	104.75	52.375
SWFLEX-AI [2] [201]	c	four terms used		0.968[1]	0.14[1,3]	+0.6213	-1.2459	102.7[1]	51.35[1]
COS/G3 [704] [9]	c	3.17459	0.9445	1.0000	0.15	+0.450672	-0.901344	109.47	-
COS/D [1617] [9] [16]	c	3.4365	0.5119	0.9572	0.257	+0.5863	-1.1726	104.52	-
GCPM [2] [859] [10]	c	3.69 [4,11]	0.9146 [4]	0.9572	0.27	+0.6113	-1.2226	104.52	52.26
SWM4-NDP [2] [13] [933]	c	3.18395	0.88257	0.9572	0.24034	0.55733	-1.11466	104.52	52.26
ST2 [872] [12]	d	3.10000	0.31694	1.0000	0.80	+0.24357	-0.24357	109.47	109.47
TIP5P [180]	d	3.12000	0.6694	0.9572	0.70	+0.2410	-0.2410	104.52	109.47
TIP5P-Ew [619]	d	3.097	0.7448	0.9572	0.70	+0.2410	-0.2410	104.52	109.47
TTM2-F [1027] [14]	c	five parameters used		0.9572	0.70	+0.574	-1.148	104.52	52.26
POL5/TZ [2] [256]	d	2.9837 [4]	4	0.9572	0.5	varies [5]	-0.42188	104.52	109.47
Six-site [491]	c/d[7]	3.115_{OO} 0.673_{HH}	0.715_{OO} 0.115_{HH}	0.980	0.8892_{L} 0.230_{M}	+0.477	-0.044_{L} -0.866_{M}	108.00	111.00
QCT [1251]	a[15]	3.140	0.753	0.9614	-	+0.6064	-1.2128	104.067	-

Water

- Best model? ⇒ B. Guillot. *A reappraisal of what we have learnt during three decades of computer simulations of water.* J.Mol. Liquids **101**, 219 (2002)

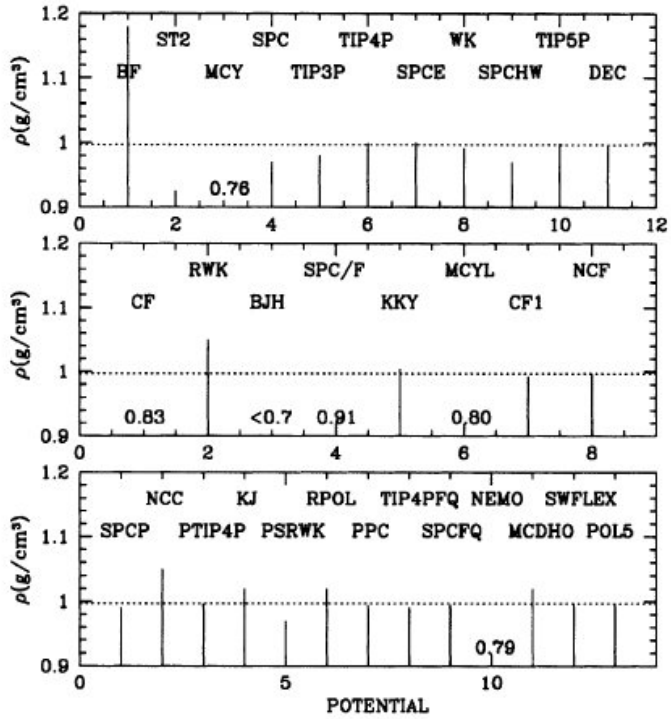


Figure 1. Density of simulated water at 298K and 1bar for different model potentials (see Table):top panel (rigid models), middle panel (flexible models) and bottom panel (polarizable models). The dotted line indicates the experimental value for H_2O (0.997g/cm3).

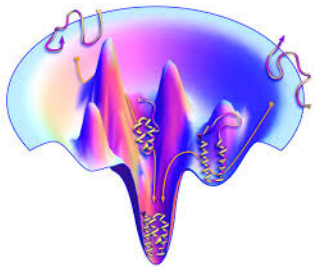
PES minima

- Gradient descent or stepest descent

$$\boldsymbol{x}_{n+1} = \boldsymbol{x}_n - \gamma \boldsymbol{\nabla} V(\boldsymbol{x}_n)$$

$$V(\boldsymbol{x}_0) \geq V(\boldsymbol{x}_1) \geq V(\boldsymbol{x}_2) \geq \ldots$$

- Local minima and absolute minimum



- Simulated annealing $\Rightarrow$ probabilistic technique
- Minimun energy does not necessarily means minimun free energy

Monte Carlo methods

- d dimensions $\rightarrow M^d$ grid $\left\{ \begin{array}{l} N{=}10 \rightarrow d{=}30 \\ M{=}100 \text{ grid points} \end{array} \right\}$ $100^{30} = 10^{60}$ grid points
- Most of the grid points $\Rightarrow V \gg k_{\mathrm{B}} T \Rightarrow N(\boldsymbol{r}^N) \simeq 0$
- How to generate points in configuration space with relative probabilities proportional to the Boltzmann factor?

  $\rightarrow$ o (old) configuration with Boltzmann factor $e^{-\beta V(o)}$

  $\rightarrow$ small random displacement

  $\rightarrow$ n (new) configuration with Boltzmann factor $e^{-\beta V(n)}$

  $\rightarrow$ Accept or reject n?

The Metropolis method

- Detailed balance $\Rightarrow$ Equilibrium

$$N(o)\,\pi(o \to n) = N(n)\,\pi(n \to o)$$

$$\frac{\pi(o \to n)}{\pi(n \to o)} = \frac{N(n)}{N(o)} = \frac{e^{-\beta\,V(n)}/Z}{e^{-\beta\,V(o)}/Z} = e^{-\beta\,(V(n)-V(o))} \qquad (1)$$

- The Metropolis method [Metropolis *et al* (1953)]

$$\pi(o \to n) = \begin{cases} e^{-\beta\,(V(n)-V(o))} & V(n) > V(o) \\ 1 & V(n) \leq V(o) \end{cases}$$

$$V(n) > V(o) \Downarrow \left\{ \begin{array}{l} \pi(o \to n) = e^{-\beta\,(V(n)-V(o))} \\ \pi(n \to o) = 1 \end{array} \right\} \rightarrow (1) \leftarrow \left\{ \begin{array}{l} \pi(o \to n) = 1 \\ \pi(n \to o) = e^{-\beta\,(V(o)-V(n))} \end{array} \right\} \Downarrow V(n) \leq V(o)$$

The Metropolis method

1. Select a particle at random, and calculate its energy $\mathcal{U}(\mathbf{r}^N)$.
2. Give the particle a random displacement, $\mathbf{r}' = \mathbf{r} + \Delta$, and calculate its new energy $\mathcal{U}(\mathbf{r}'^N)$.
3. Accept the move from $\mathbf{r}^N$ to $\mathbf{r}'^N$ with probability

$$\mathrm{acc}(o \to n) = \min\left(1, \exp\{-\beta[\mathcal{U}(\mathbf{r}'^N) - \mathcal{U}(\mathbf{r}^N)]\}\right). \qquad (3.2.1)$$

Algorithm 1 (Basic Metropolis Algorithm)

```
PROGRAM mc                          basic Metropolis algorithm

do icycl=1,ncycl                    perform ncycl MC cycles
  call mcmove                       displace a particle
  if (mod(icycl,nsamp).eq.0)
+   call sample                     sample averages
enddo
end
```

Comments to this algorithm:

1. *Subroutine* `mcmove` *attempts to displace a randomly selected particle (see Algorithm 2).*
2. *Subroutine* `sample` *samples quantities every* `nsampth` *cycle.*

Algorithm 2 (Attempt to Displace a Particle)

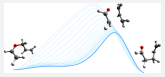
```
SUBROUTINE mcmove                   attempts to displace a particle

o=int(ranf()*npart)+1               select a particle at random
call ener(x(o),eno)                 energy old configuration
xn=x(o)+(ranf()-0.5)*delx           give particle random displacement
call ener(xn,enn)                   energy new configuration
if (ranf().lt.exp(-beta             acceptance rule (3.2.1)
+   *(enn-eno)) x(o)=xn             accepted: replace x(o) by xn
return
end
```

Comments to this algorithm:

1. *Subroutine* `ener` *calculates the energy of a particle at the given position.*
2. *Note that, if a configuration is rejected, the old configuration is retained.*
3. *The* `ranf()` *is a random number uniform in* $[0, 1]$.

The Metropolis method

- N. Metropolis, , A. W. Rosenbluth, M. N. Rosenbluth, A. H. Teller, and E. Teller, *Equation of State Calculations by Fast Computing Machines.* J. Chem. Phys. **21**, 1087 (1953).



Reaction coordinate

- Reaction coordinate $\Rightarrow$ one-dimensional coordinate which represents progress along a reaction pathway.
- Conformational change
- Minimun energy path
  - Locate the transition state (TS)
  - Compute the Hessian at the TS, and diagonalize it to obtain the normal modes
  - Make a displacement in either the backward or the forward direction along the mode with imaginary frequency
  - From the displaced point, continue the path along the direction of the gradient until the minimum is reached