Computer Aided Drug Design

——Molecular Simulations I

Qin Xu

http://cbb.sjtu.edu.cn/~qinxu/CADD.htm

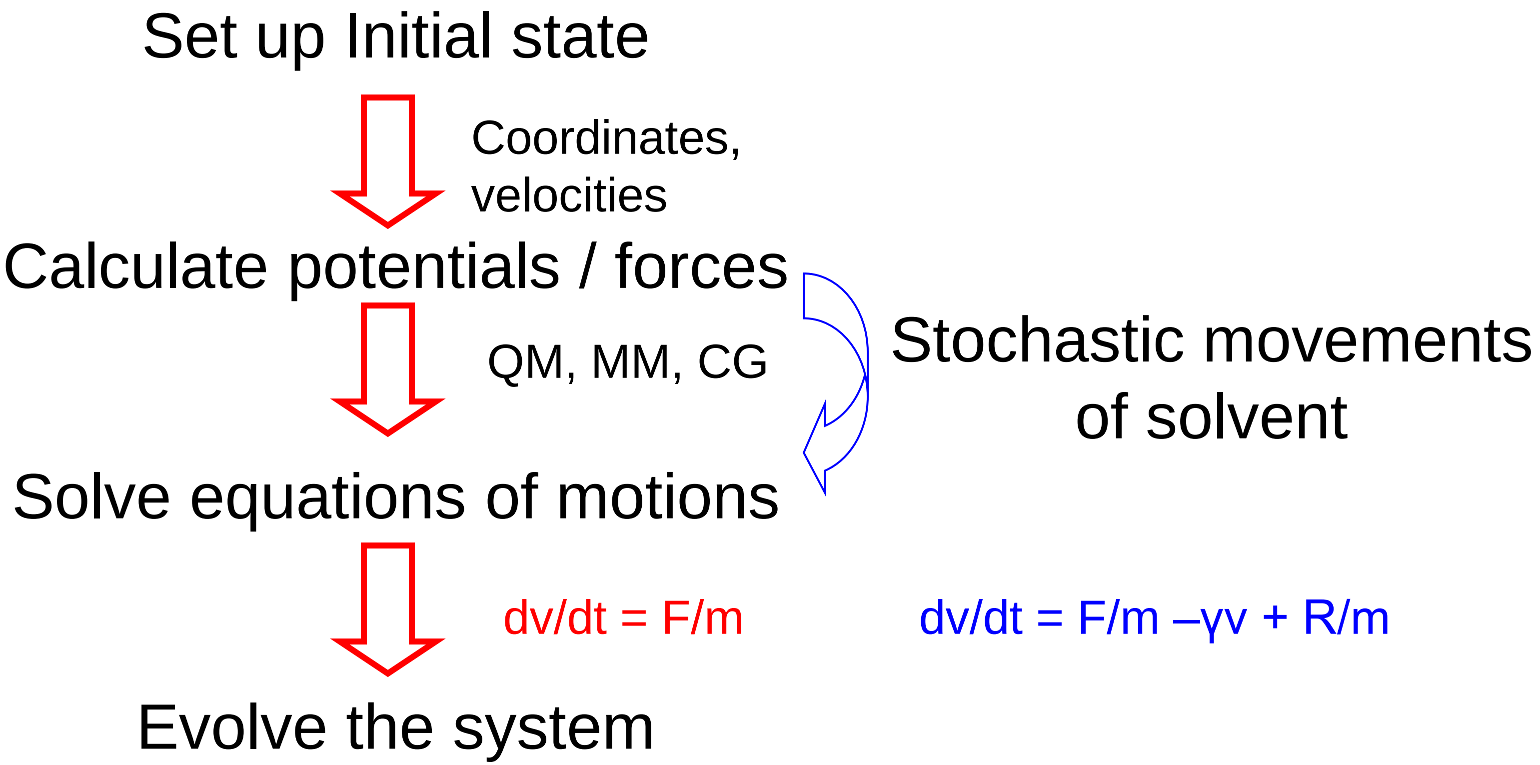
Molecular Simulations

- Molecular Dynamics
  - $dv/dt = F/m$
- Langevin Dynamics
  - $dv/dt = F/m - \gamma v + R/m$
- Monte-Carlo
  - $r * dv/dt = R/m$
  - Markov chain (MCMC)

Work flow for dynamics simulations

Molecular Dynamics

Langevin Dynamics



Set up Initial state

Coordinates,
velocities

Calculate potentials / forces

QM, MM, CG

Stochastic movements
of solvent

Solve equations of motions

$dv/dt = F/m$

$dv/dt = F/m - \gamma v + R/m$

Evolve the system

Statistical Mechanics(统计力学)

Microscopic

Statistical Mechanics

Macroscopic

- Computer simulation at the microscopic level
  - atomic and molecular positions
  - velocities
  - Effective pair potential energies
- Experimental results on macroscopic properties
  - volume
  - pressure
  - Temperature, internal energy

Phase space (相空间)

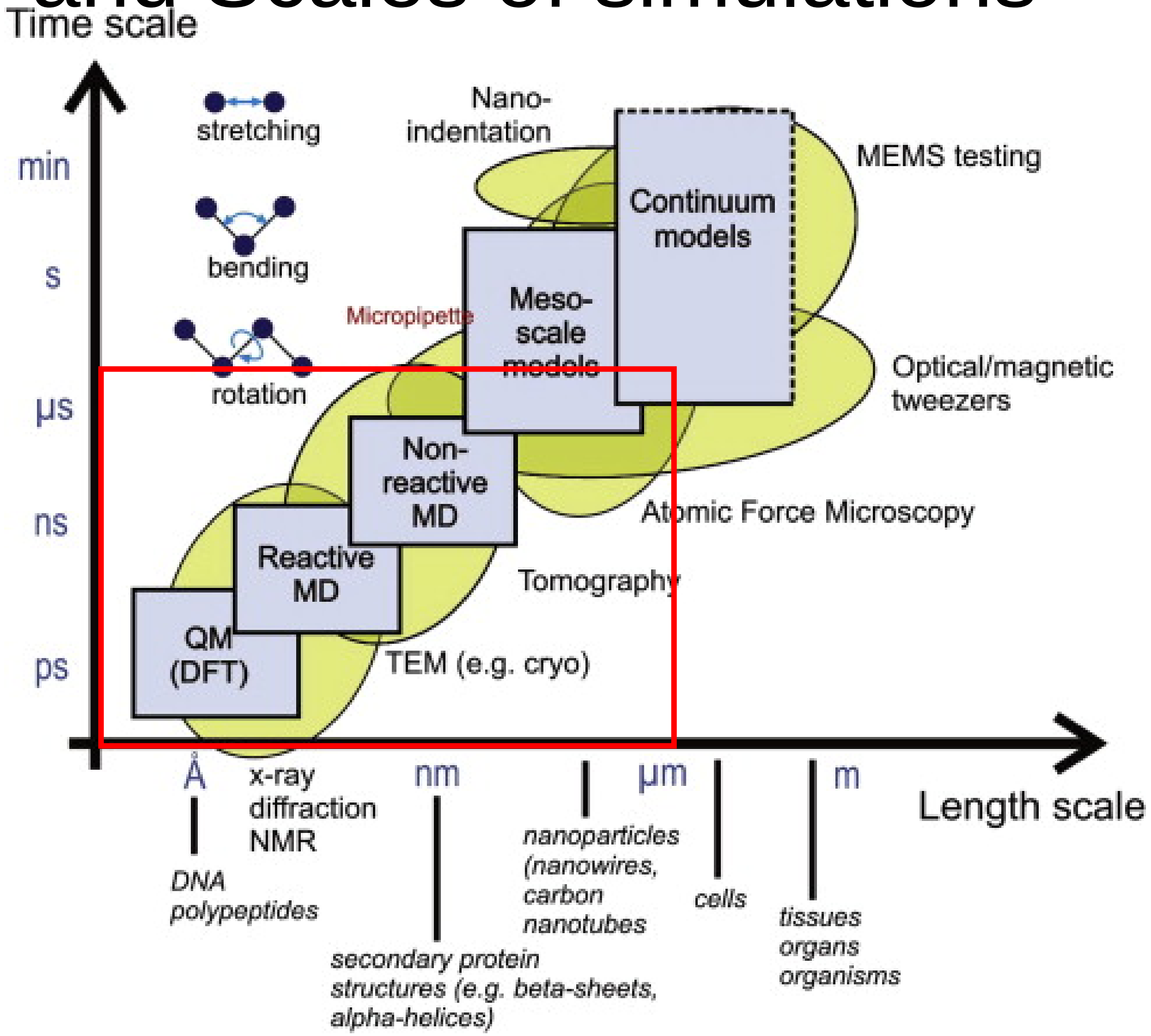
- *N* Particles in three dimensional space
- 3*N* of degree of freedom
  - r(x, y, z)
  - $v(v_x, v_y, v_z)$
- One state has 3*N* for positions and 3*N* for momenta, defines a point in the 6*N*-dimensional phase space
  - All possible state= phase space
  - One state = one point in phase space

Ensembles (系综)

An ensemble can thus be considered to be a collection of the points in phase space

	Micro-canonical (微正则系综)	Canonical (正则系综)	Isothermal-isobaric (等温等压系综)	Grand canonical (巨正则系综)
Fixed thermodynamic variables	N, V, E	N, V, T	N, P, T	μ, V, T
Systems	isolated	closed	closed	opened

Forces calculation and Scales of simulations



http://www.sciencedirect.com/science/article/pii/S0079642509000565

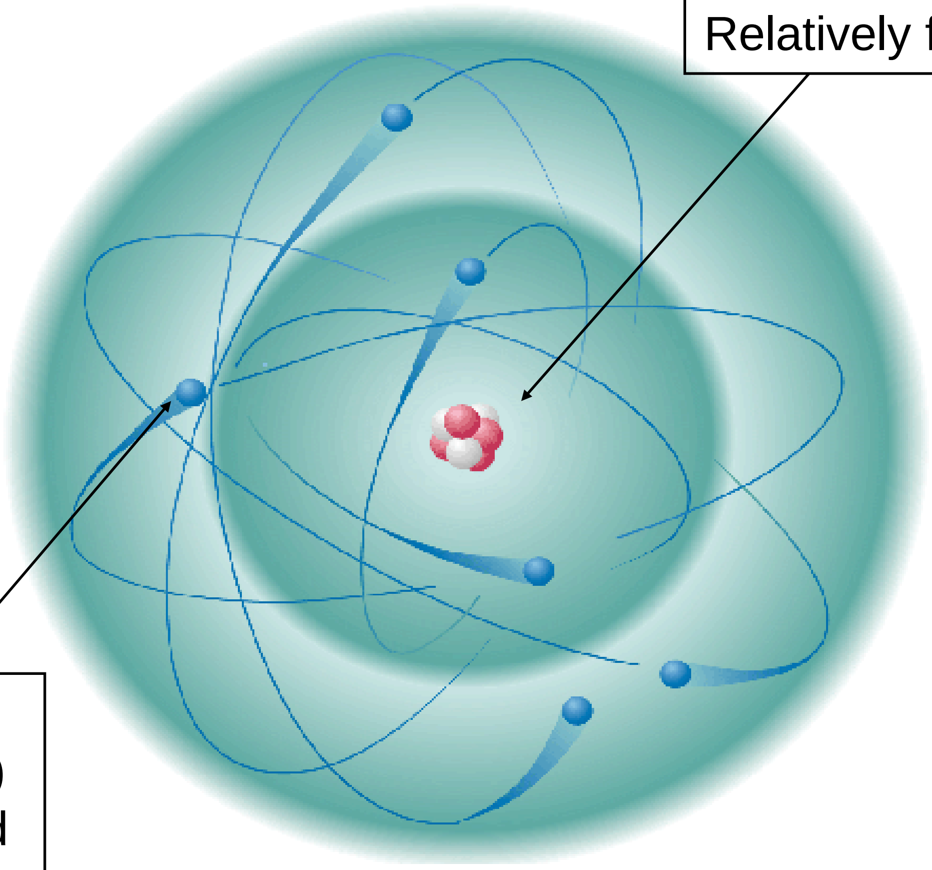
Quantum Mechanical

Ab initio calculations

- Born-Oppenheimer approximation
- Single electron approximation
- Hatree-Forck-Roothaan equation

- Separate movements of Nucleus and electrons
- Atomic orbitals
- LCAO-MO (Linear Combination of Atomic Orbital Molecular Orbital method)

Atoms model



Protons+ Neutrons= Nucleus
Relatively fixed

Electrons
(much smaller)
orbiting around
the nucleus

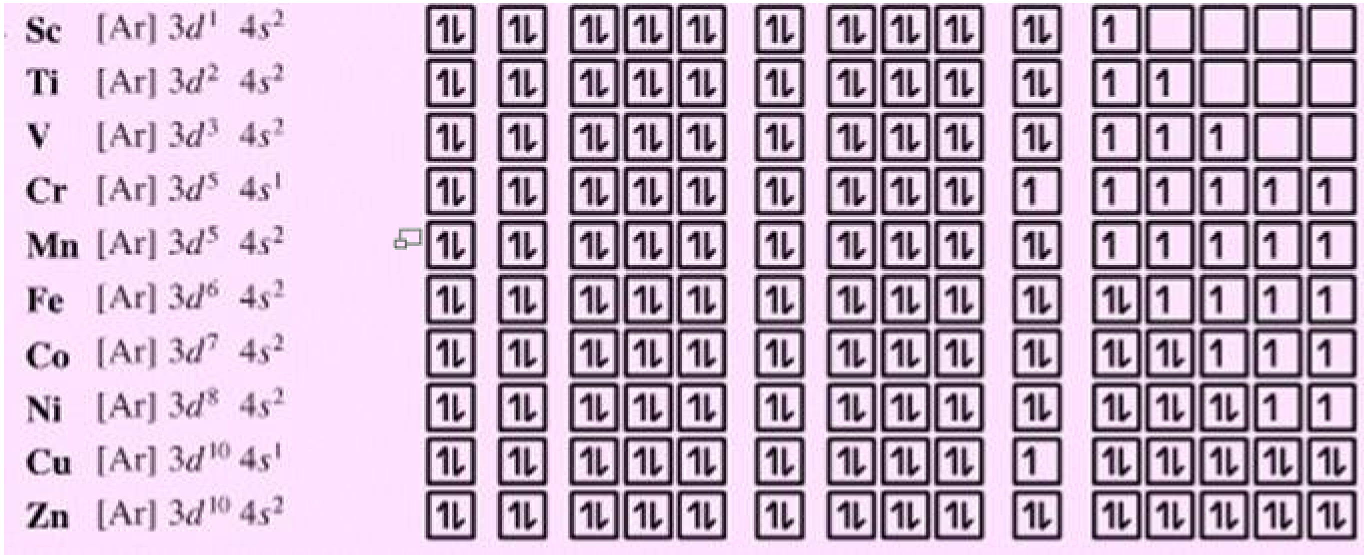
More QM calculations

- Ab initio calculations

- Semi-emprical method
  - MINDO, MNDO, AM1, PM3

- Density Functional Theory (DFT)
  - PW91, B3LYP

Relativistic effects (相对论效应)



Sc	[Ar] $3d^1$ $4s^2$	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑				
Ti	[Ar] $3d^2$ $4s^2$	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑	↑			
V	[Ar] $3d^3$ $4s^2$	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑	↑	↑		
Cr	[Ar] $3d^5$ $4s^1$	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑	↑	↑	↑	↑	↑
Mn	[Ar] $3d^5$ $4s^2$	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑	↑	↑	↑	↑
Fe	[Ar] $3d^6$ $4s^2$	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑	↑	↑	↑
Co	[Ar] $3d^7$ $4s^2$	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑	↑	↑
Ni	[Ar] $3d^8$ $4s^2$	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑	↑
Cu	[Ar] $3d^{10}$ $4s^1$	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑	↑↓	↑↓	↑↓	↑↓	↑↓
Zn	[Ar] $3d^{10}$ $4s^2$	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓

铬: [Cr] 3d5 4s1 and not: [Cr] 3d4 4s2
铜: [Ar] 3d10 4s1 and not: [Ar] 3d9 4s2

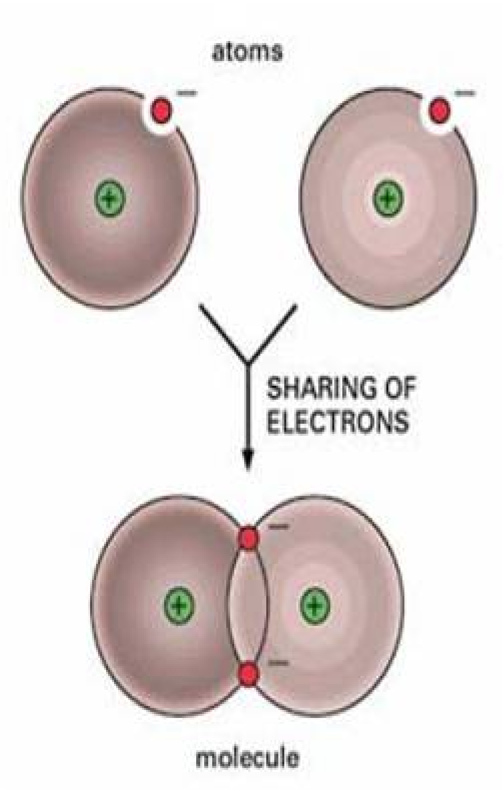
金：4f14 5d10 6s1

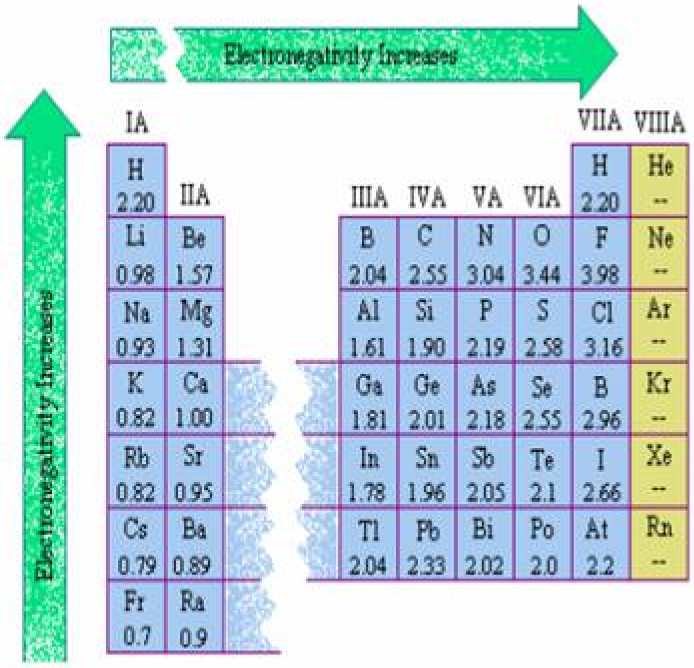
汞：4f14 5d10 6s2

“Pair” of Atoms

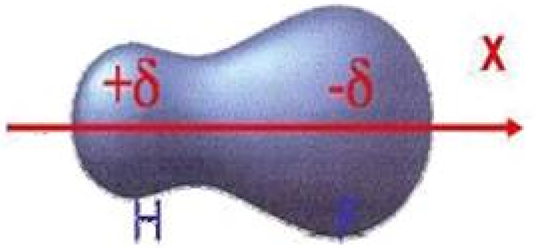
Types of bonds in protein:

Covalent bond:





IA	IIA	IIIA	IVA	VA	VIA	VIIA	VIIIA
H 2.20						H 2.20	He --
Li 0.98	Be 1.57	B 2.04	C 2.55	N 3.04	O 3.44	F 3.98	Ne --
Na 0.93	Mg 1.31	Al 1.61	Si 1.90	P 2.19	S 2.58	Cl 3.16	Ar --
K 0.82	Ca 1.00	Ga 1.81	Ge 2.01	As 2.18	Se 2.55	B 2.96	Kr --
Rb 0.82	Sr 0.95	In 1.78	Sn 1.96	Sb 2.05	Te 2.1	I 2.66	Xe --
Cs 0.79	Ba 0.89	Tl 2.04	Pb 2.33	Bi 2.02	Po 2.0	At 2.2	Rn --
Fr 0.7	Ra 0.9						



Origin of Force Fields for Molecular Mechanics

Quantum Mechanics

The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble. It therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed, which can lead to an explanation of the main features of complex atomic systems without too much computation.

-- Dirac, 1929

Nobel Prize in Physics
for 1933

Paul Dirac
Erwin Schrödinger

Various Types of Force Fields

- Lattice models
- Off-lattice models
- United-atom force fields (OPLS, MM, AMBER, CHARMM19)
- All-atom force fields (OPLSAA, AMBER94, CHARMM22)
- Next generation force fields: Polarizable Force Fields (Polarizable OPLSAA, AMBER2002, TINKER PFF)

Source of Parameters

- Experimental data
  - Spectra (bond stretching, angle bending ...)
  - X-ray crystal structures (geometry)
- High-level QM calculations
  - Solvent simulation to match physical properties
  - Ab initio calculations (partial charges, geometry ...)
  - Free energy perturbation in comparison to experimental data

Force Fields: Typical Energy Functions

$$U = \sum_{bonds} \frac{1}{2} k_r (r - r_0)^2$$

Bond stretches

$$+ \sum_{angles} \frac{1}{2} k_\theta (\theta - \theta_0)^2$$

Angle bending

$$+ \sum_{torsions} \frac{V_n}{2} [1 + \cos(n\phi - \delta)]$$

Torsion rotation

$$+ \sum_{improper} V(improper\ torsion)$$

Improper torsion (sp2)

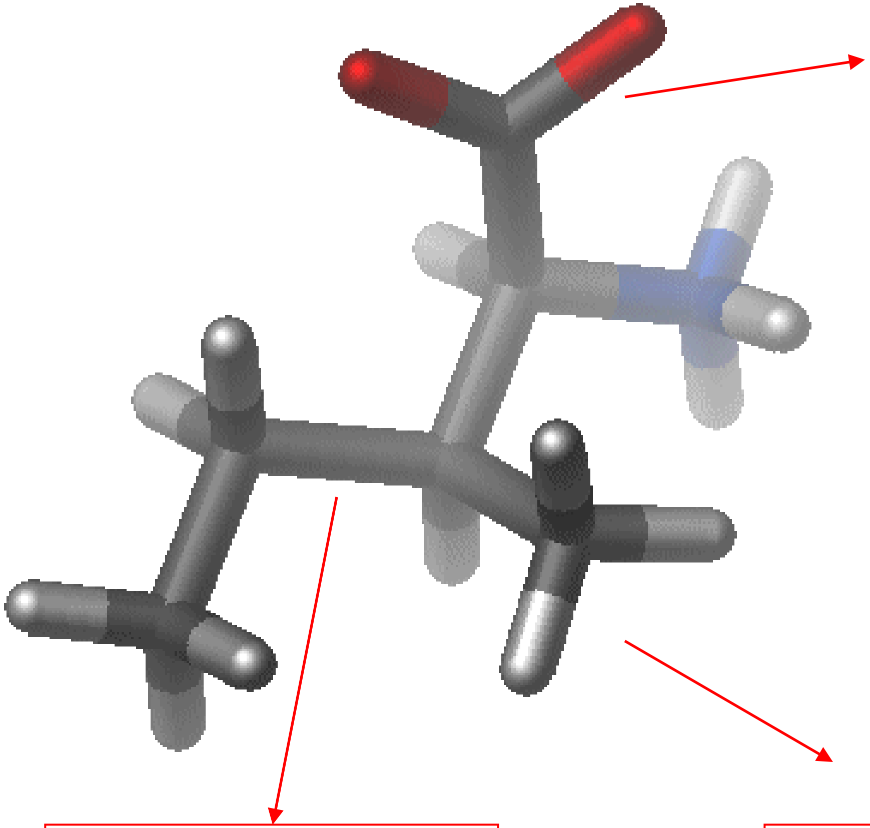
$$+ \sum_{elec} \frac{q_i q_j}{r_{ij}}$$

Electrostatic interaction

$$+ \sum_{LJ} [\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}]$$

Lennard-Jones interaction

Bonded potentials

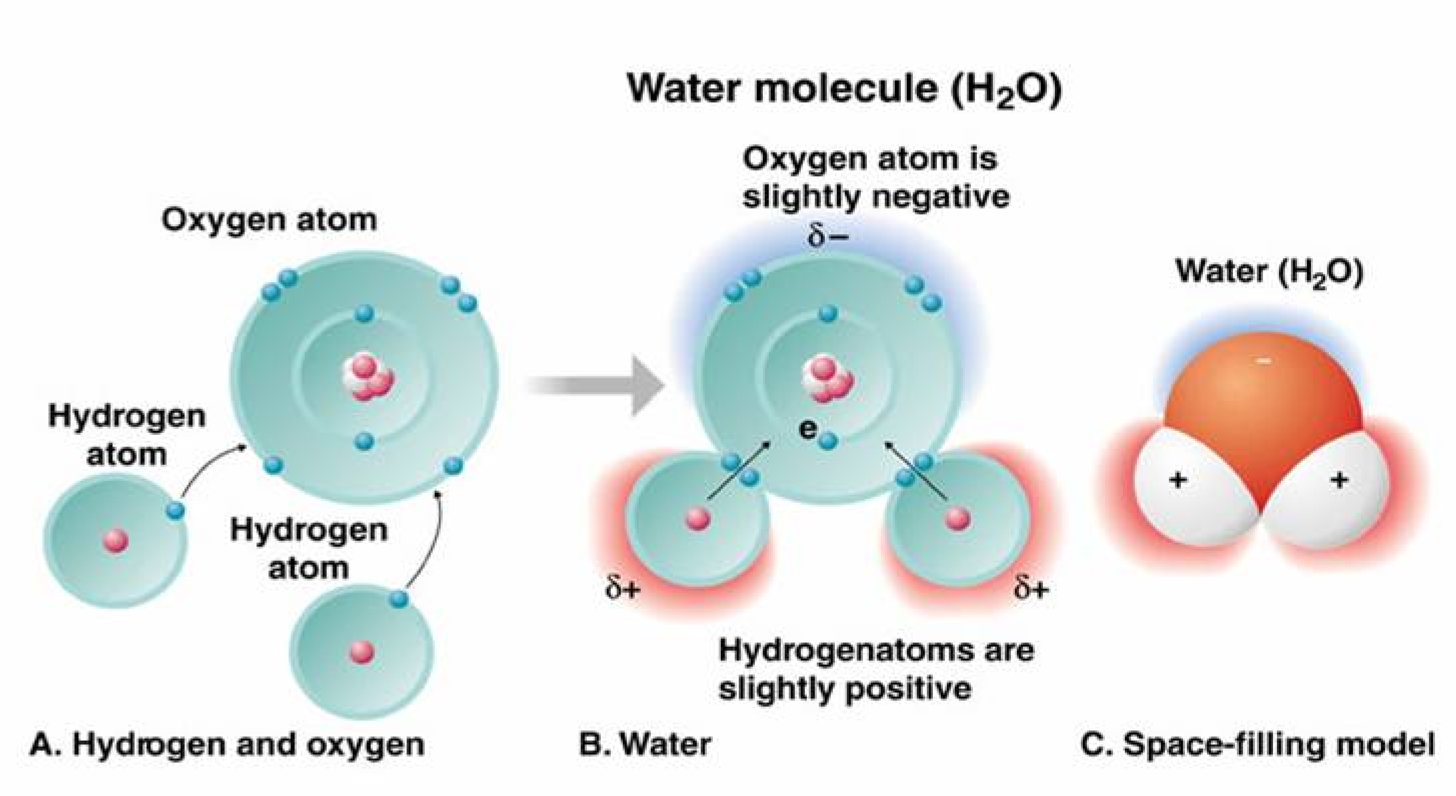


Bond angle-bending

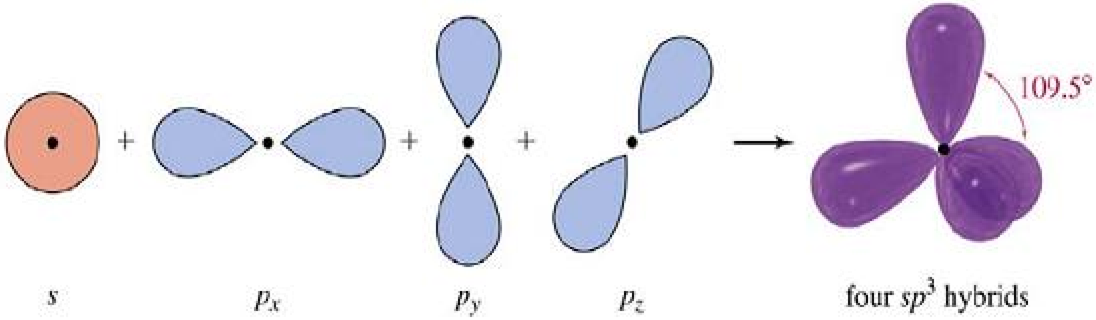
Bond-stretching

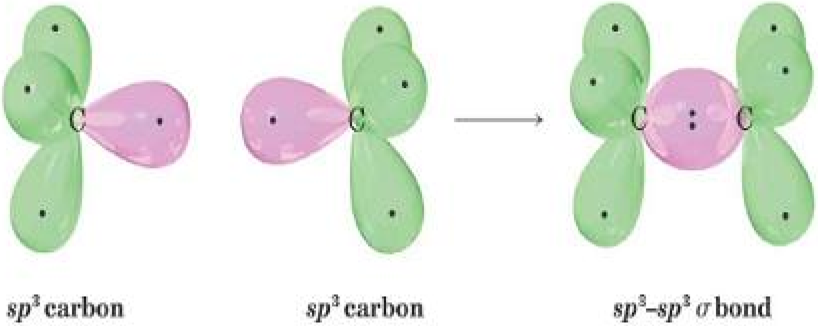
Torsion(rotate-along-bond)

Water molecule, H_2O

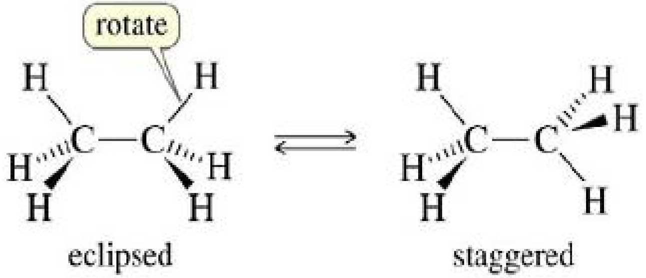


Sp3 hybridization:
(tetrahedral structures)

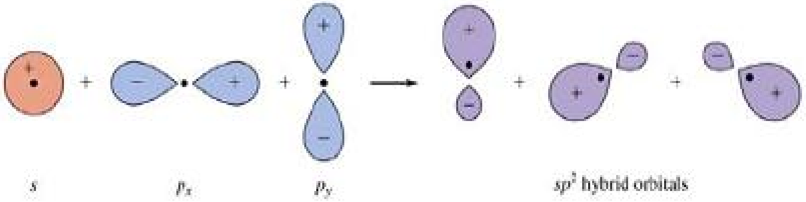


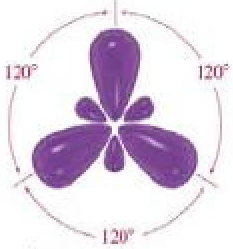


"easy" rotation around the bond!.

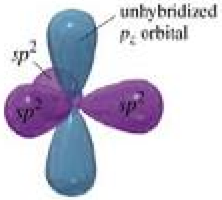


Sp2 hybridization:
(planar structures)

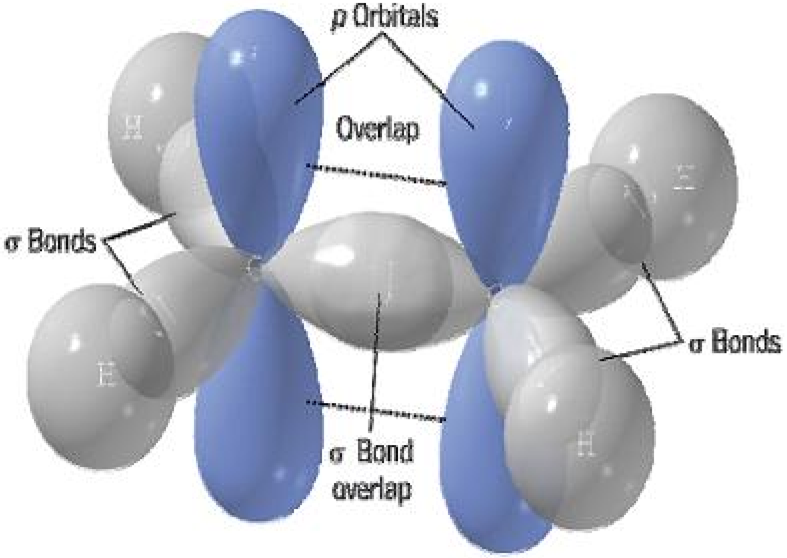


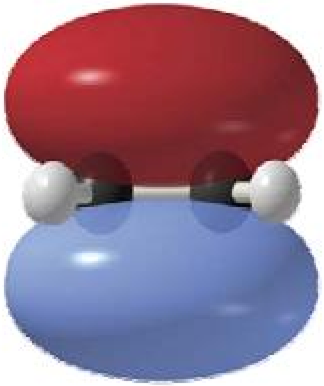


three sp^2 hybrid orbitals superimposed



sp^2 hybrid carbon atom (viewed from the side)



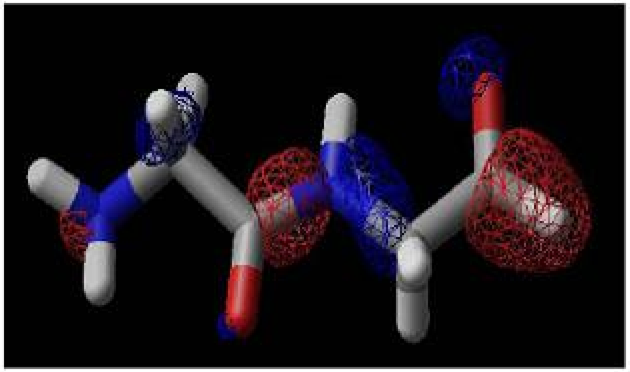


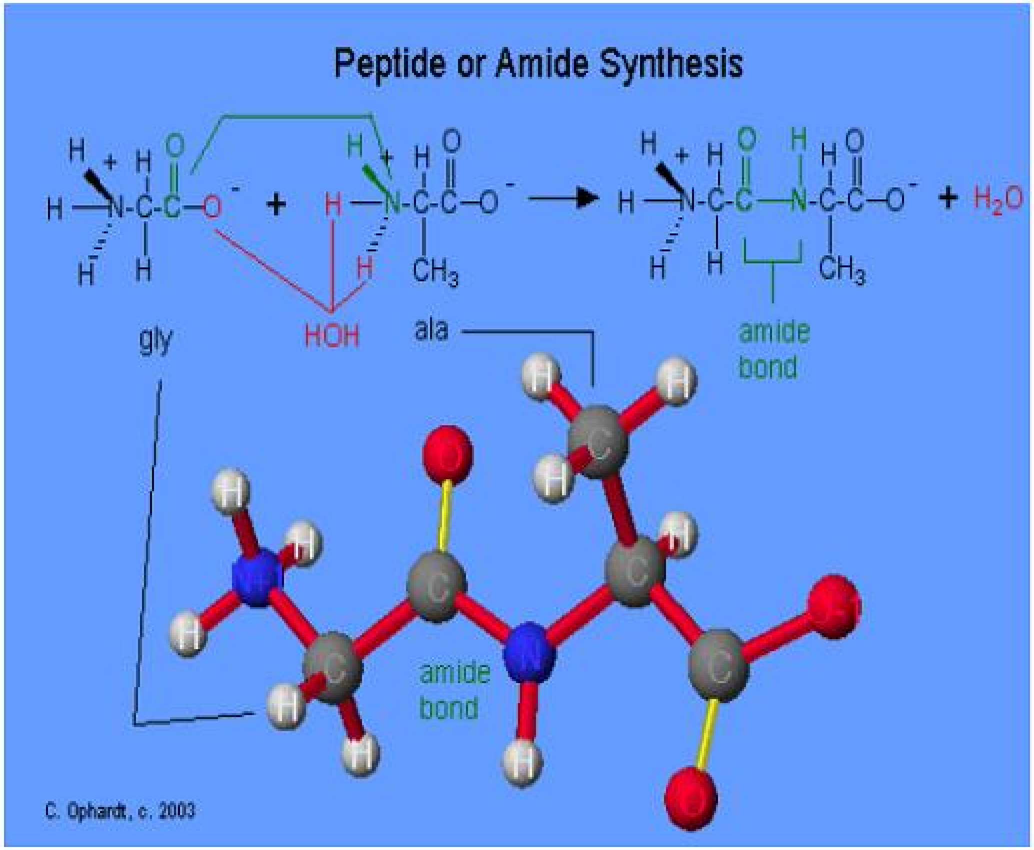
π bond

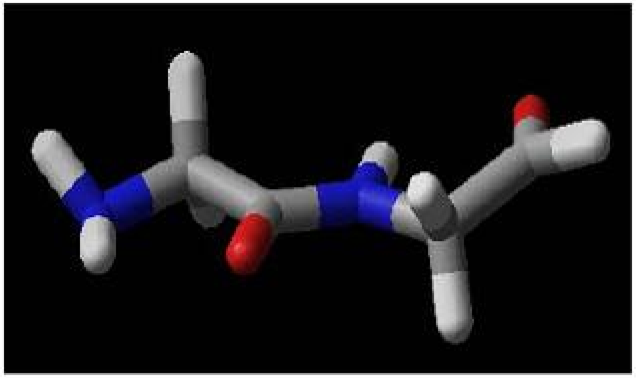
“difficult” rotation around the bond!.

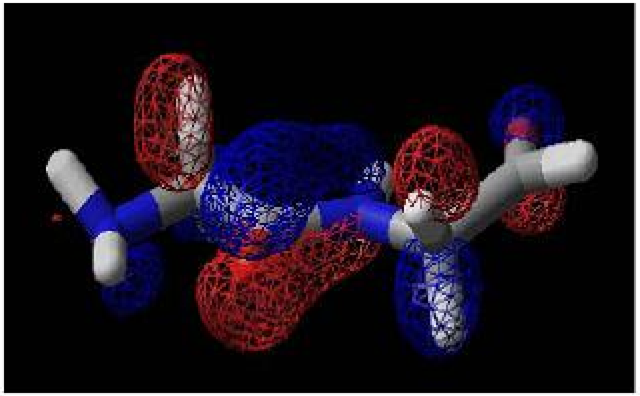
RESIDUES

Lets look at the protein backbone



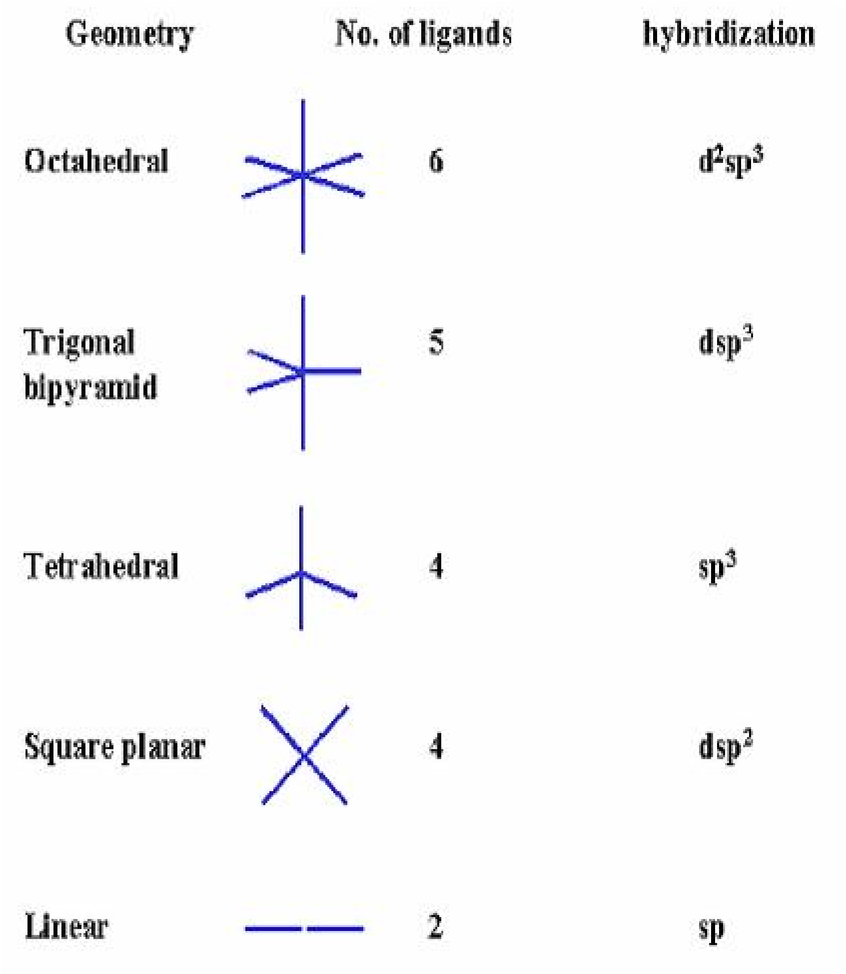




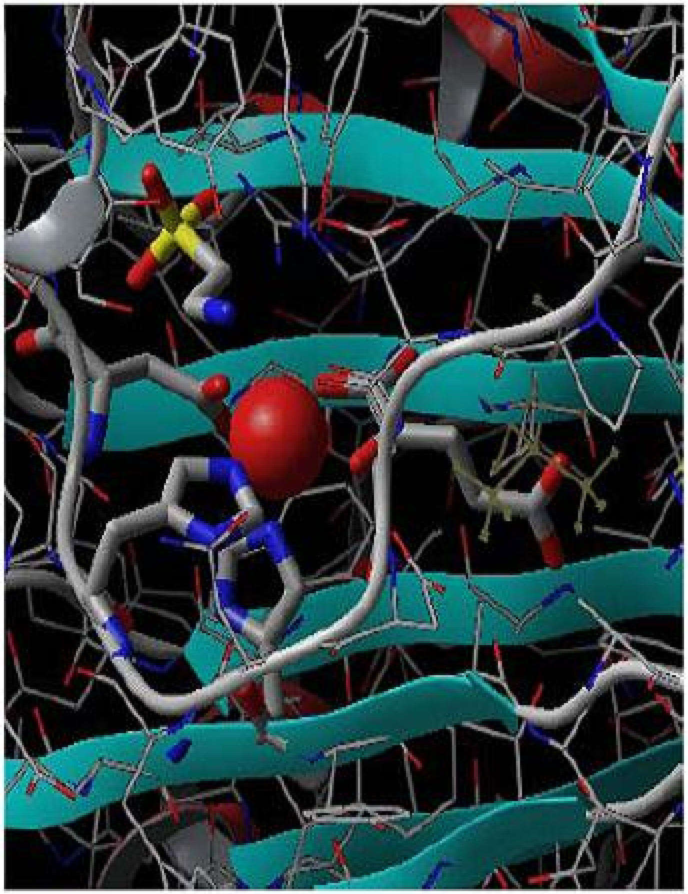


Coordination (Metal) bond:

配位键

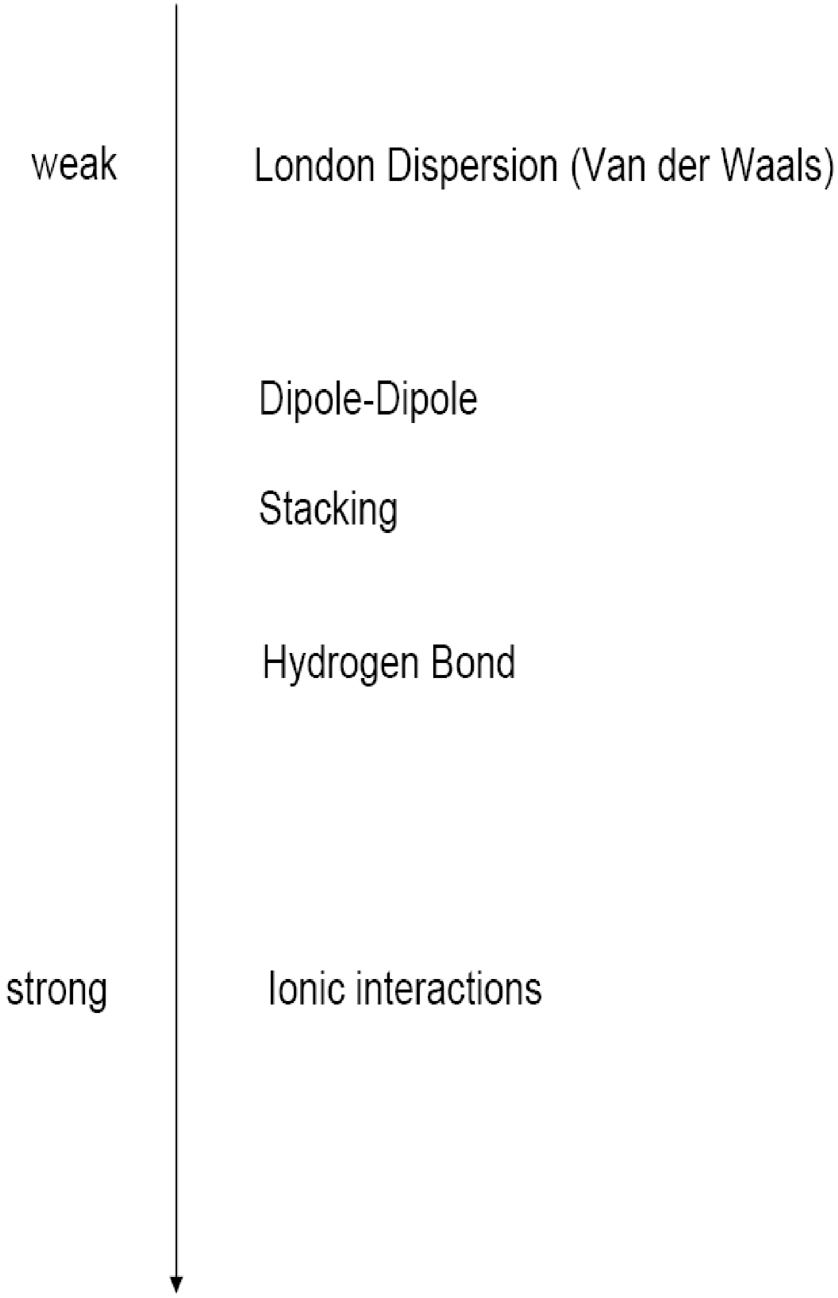


Geometry		No. of ligands	hybridization
Octahedral		6	d^2sp^3
Trigonal bipyramid		5	dsp^3
Tetrahedral		4	sp^3
Square planar		4	dsp^2
Linear		2	sp



Non-bonded interactions

Intermolecular interactions:



weak

London Dispersion (Van der Waals)

Dipole-Dipole

Stacking

Hydrogen Bond

strong

Ionic interactions

This energy order (highly) depends on local environment and specific interactions

Intermolecular interactions:

weak

London Dispersion (Van der Waals)

Dipole-Dipole

Stacking

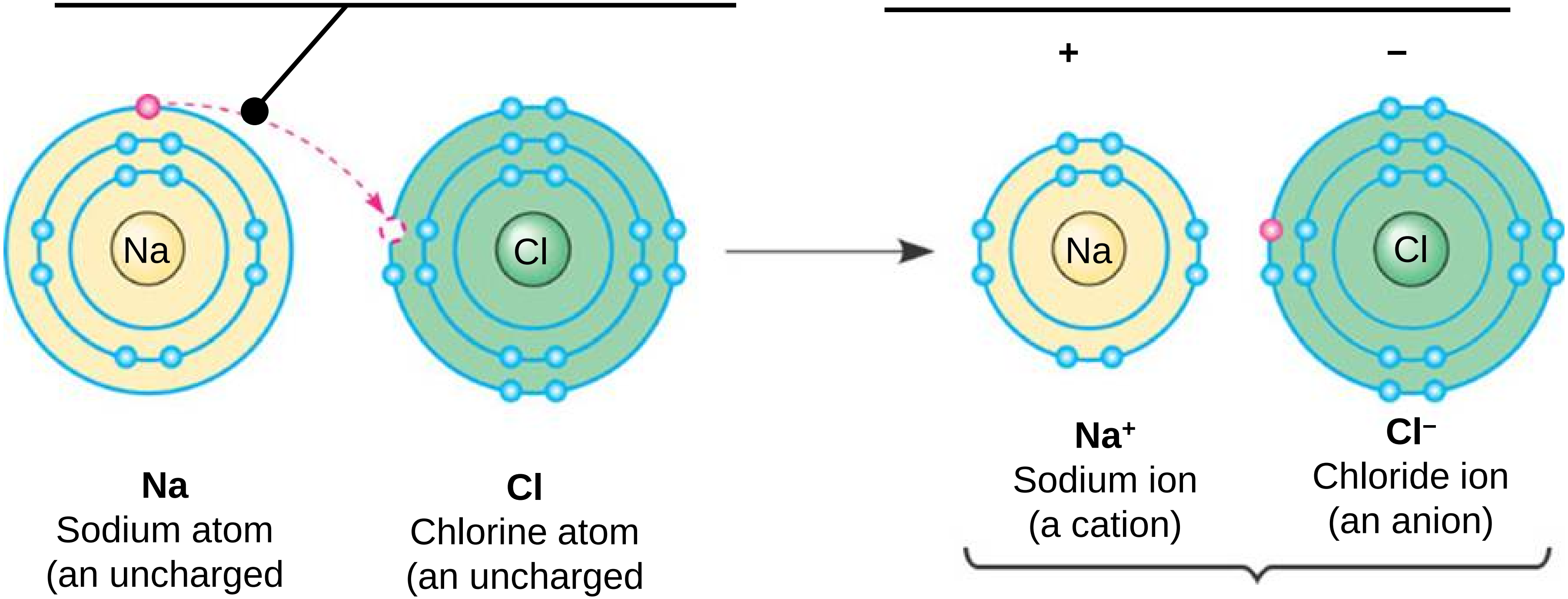
Hydrogen Bond

strong

Ionic interactions

This energy order (highly) depends on local environment and specific interactions

Electron transfer and ionic bonding



① The lone valence electron of a sodium atom is transferred to join the 7 valence electrons of a chlorine atom.

② Each resulting ion has a completed valence shell. An ionic bond can form between the oppositely charged ions.

Na
Sodium atom
(an uncharged atom)

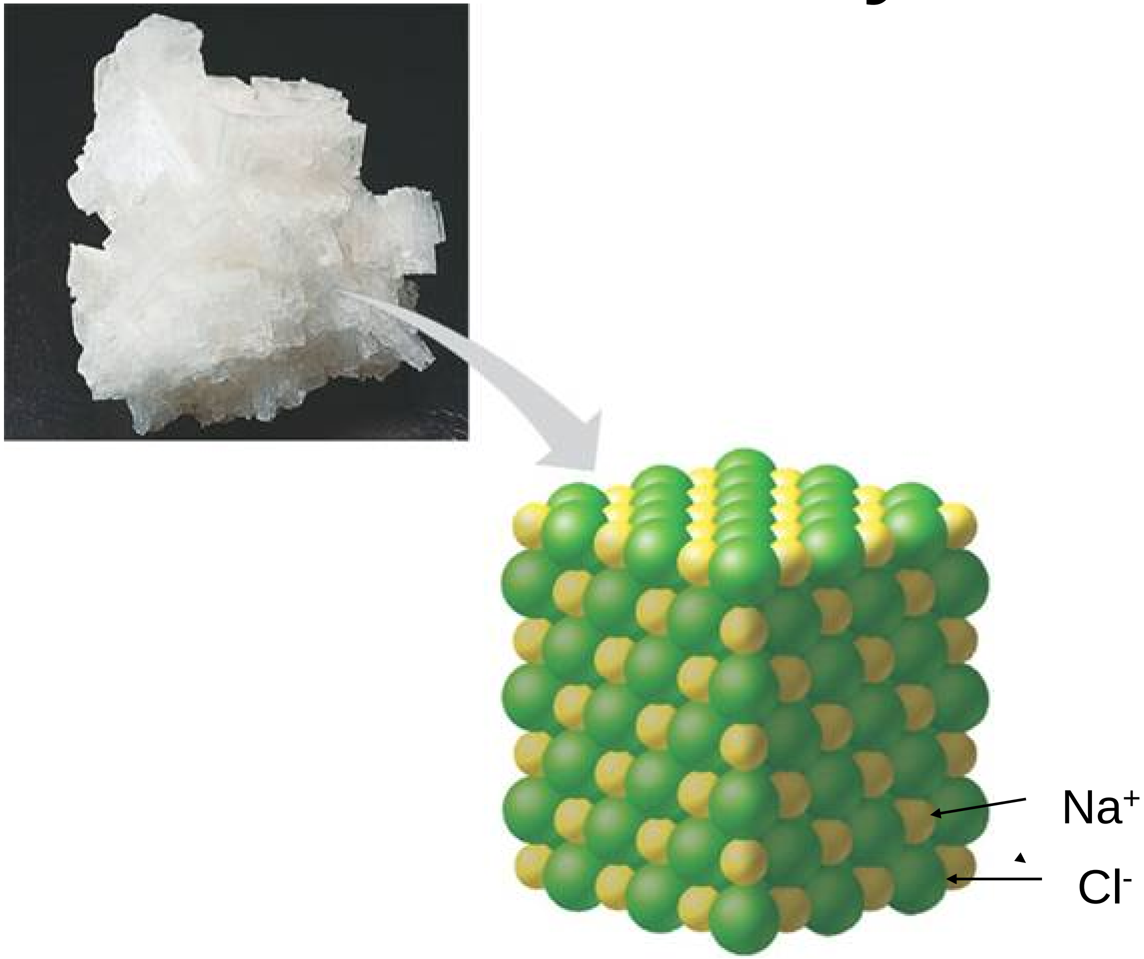
Cl
Chlorine atom
(an uncharged atom)

Na^+
Sodium ion
(a cation)

Cl^-
Chloride ion
(an anion)

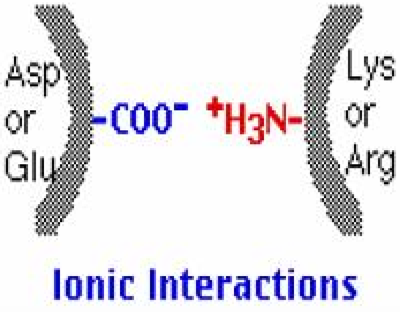
Sodium chloride (NaCl)

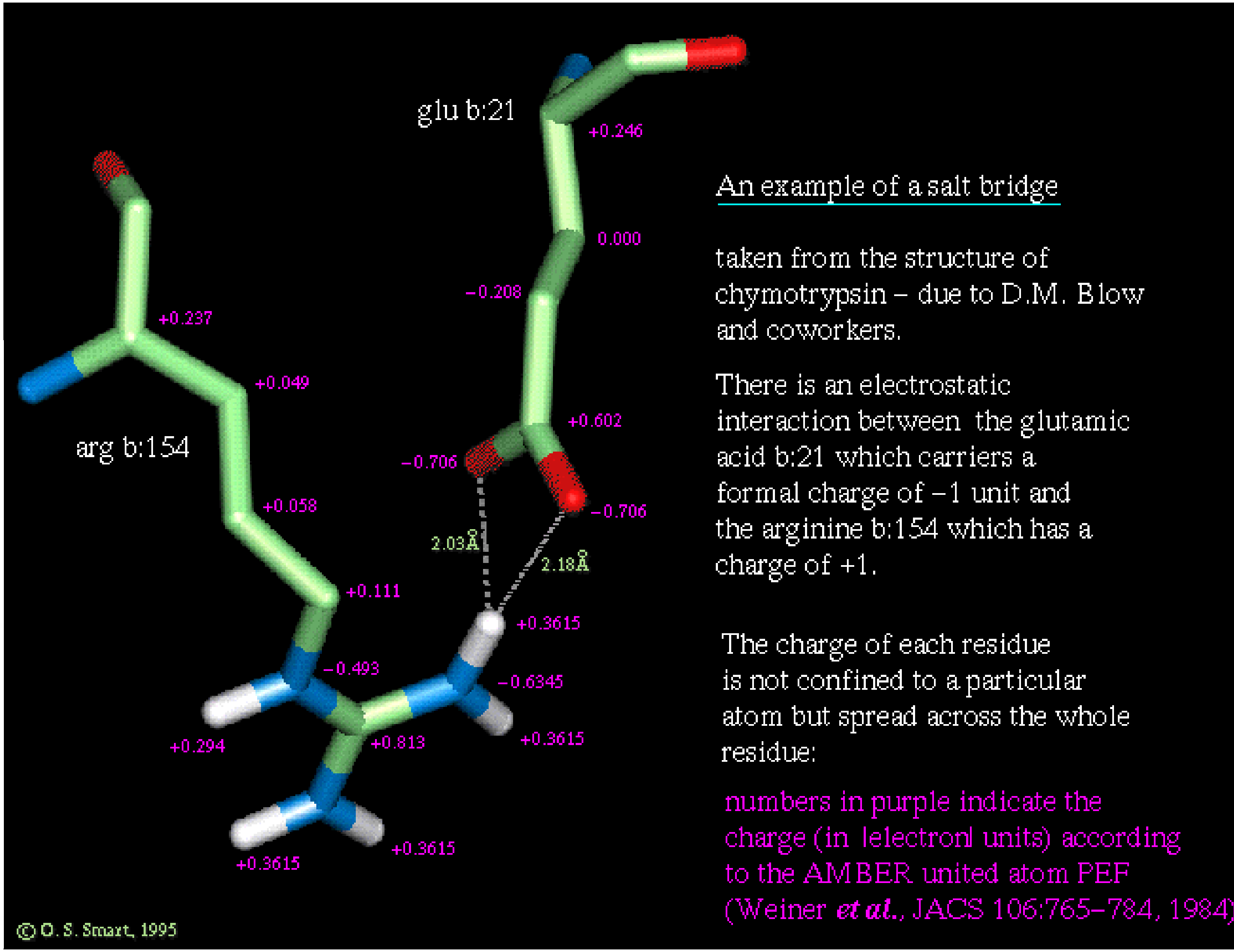
Sodium chloride crystal



Salt Bridge

A relatively weak ionic bond between positively and negatively charged side-chains of proteins.





An example of a salt bridge

taken from the structure of chymotrypsin – due to D.M. Blow and coworkers.

There is an electrostatic interaction between the glutamic acid b:21 which carriers a formal charge of −1 unit and the arginine b:154 which has a charge of +1.

The charge of each residue is not confined to a particular atom but spread across the whole residue:

numbers in purple indicate the charge (in |electron| units) according to the AMBER united atom PEF (Weiner *et al.*, JACS 106:765–784, 1984)

© O. S. Smart, 1995

Intermolecular interactions:

weak

London Dispersion (Van der Waals)

Dipole-Dipole

Stacking

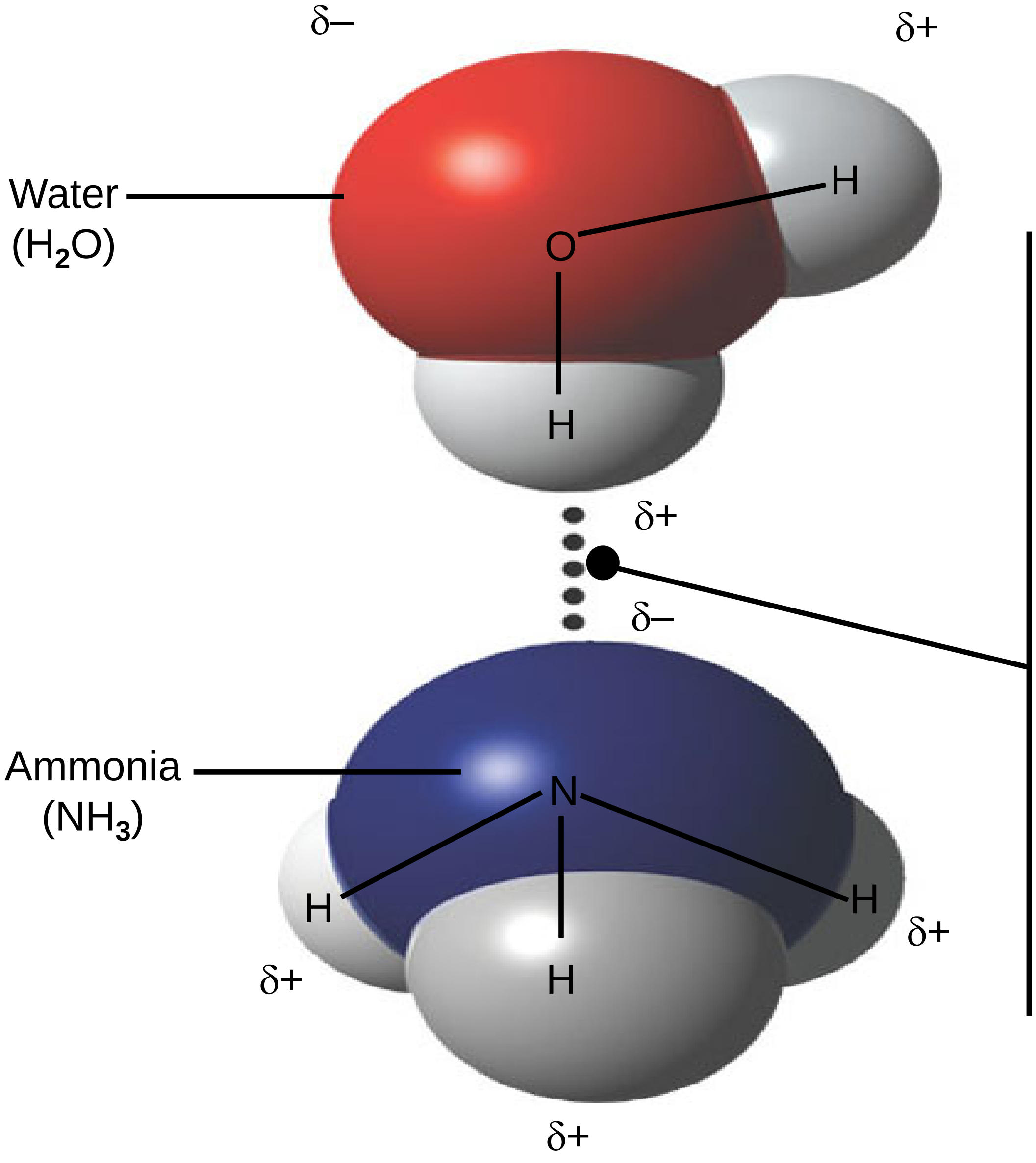
Hydrogen Bond

strong

Ionic interactions

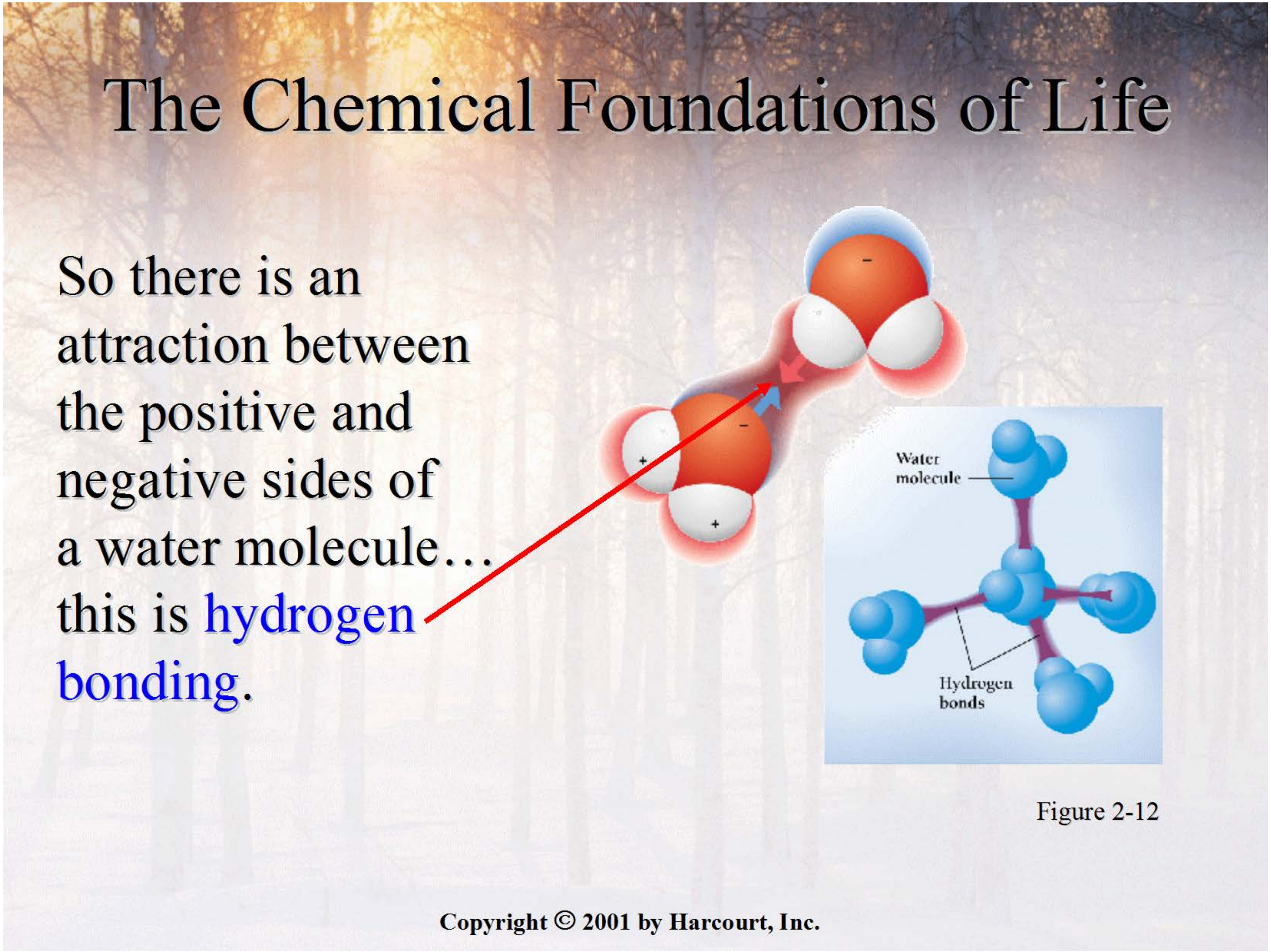
This energy order (highly) depends on local environment and specific interactions

Hydrogen bond



A hydrogen bond results from the attraction between the partial positive charge on the hydrogen atom of water and the partial negative charge on the nitrogen atom of ammonia.

Hydrogen bond

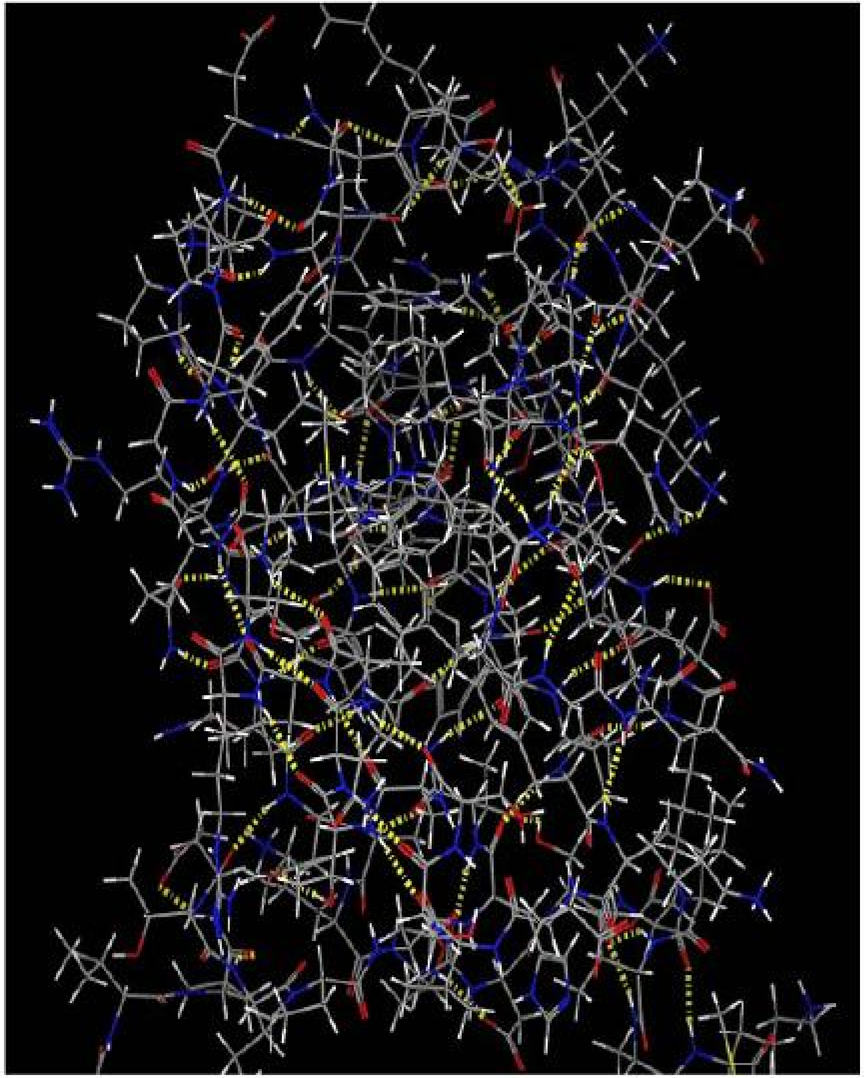


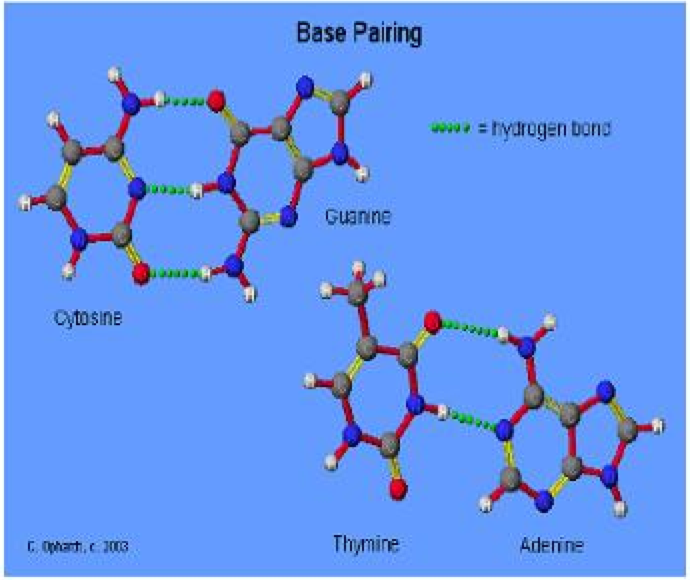
The Chemical Foundations of Life

So there is an attraction between the positive and negative sides of a water molecule… this is hydrogen bonding.

Figure 2-12

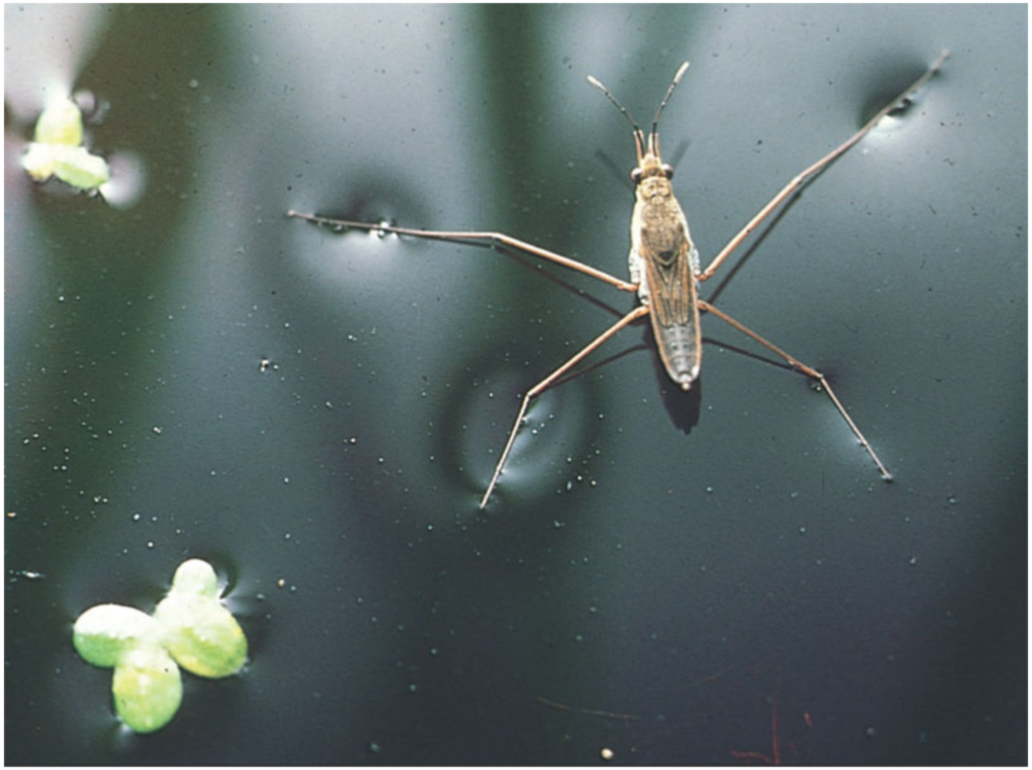
Hydrogen Bond H “shared by two more electronegative groups




Base Pairing

C. Ophardt, c. 2003

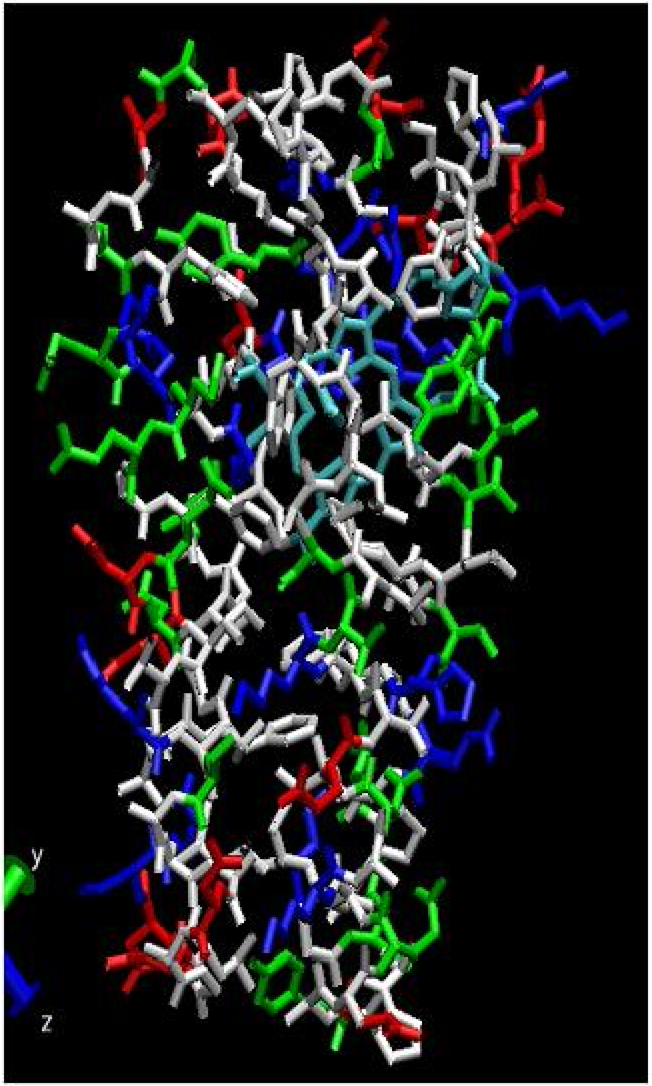
Walking on water

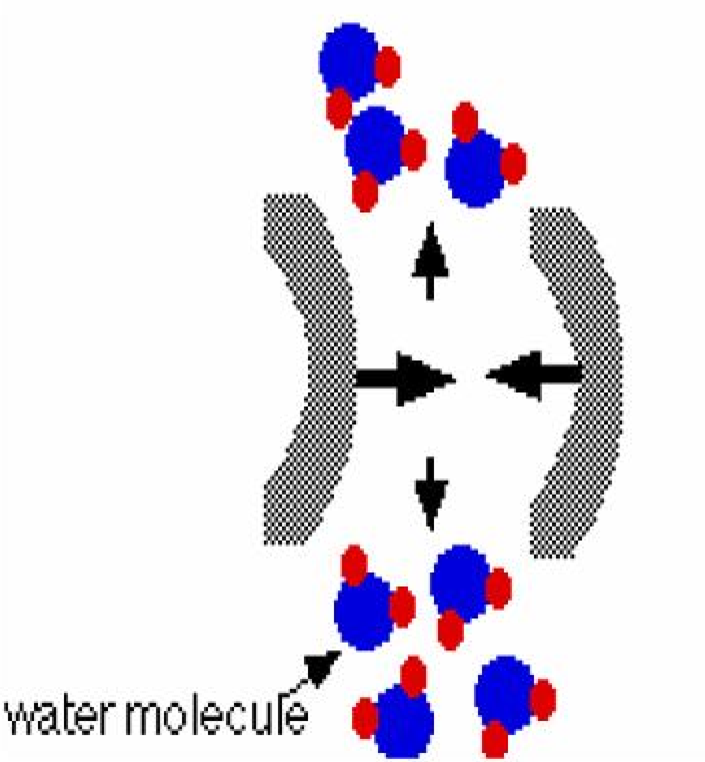


Hydrophobic Effect

A droplet of water forms a spherical shape to minimize contact with the hydrophobic leaf.

Hydrophobic effects (entropic).

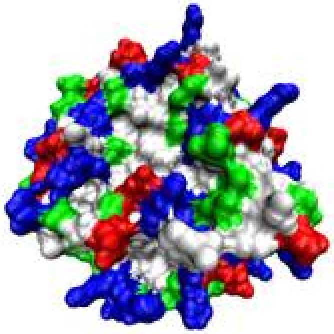


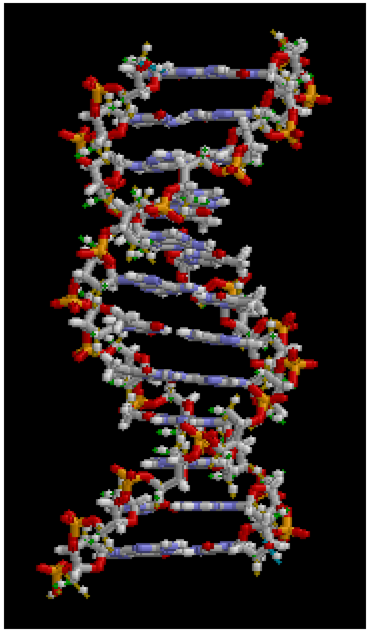


Water molecules and molecules
Consist of carbon and hydrogen
Would try to avoid each other!

Basis for globular proteins

Hydrophobic Effect in Biology





- Protein folding, the hydrophobic
  - Hydrophobic amino acids, such as Ala, Val, Leu, Ile, Phe, Met grouped together within the protein
  - Charged or polar side chains on the solvent-exposed surface where they interact with surrounding water molecules.
- The DNA Double Helices structure
  - backbones of sugars and phosphate groups outside
  - the aromatic base pairs inside

Intermolecular interactions:

weak

London Dispersion (Van der Waals)

Dipole-Dipole

Stacking

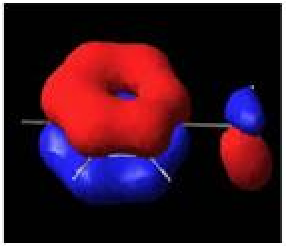
Hydrogen Bond

strong

Ionic interactions

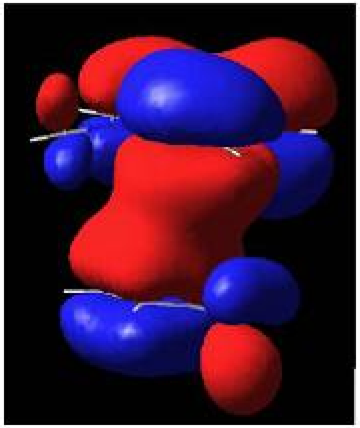
This energy order (highly) depends on local environment and specific interactions

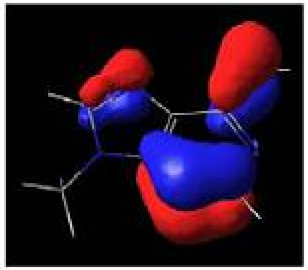
1) “Classical” view of stacking.



PHE56

E=-0.485

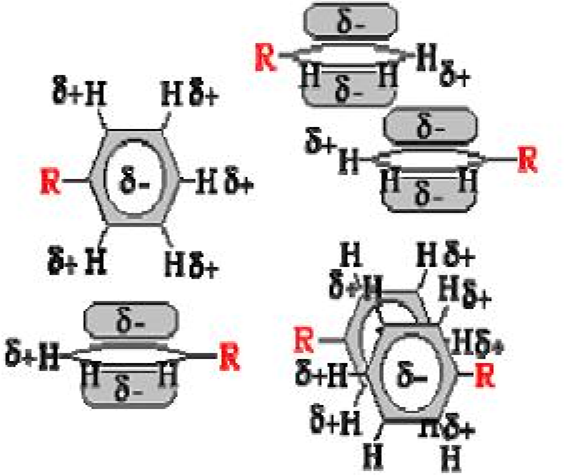




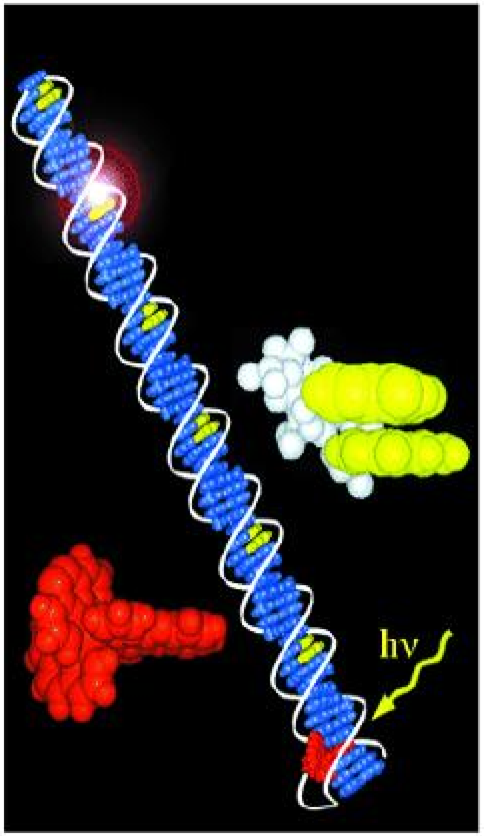
A11

E=-0.489

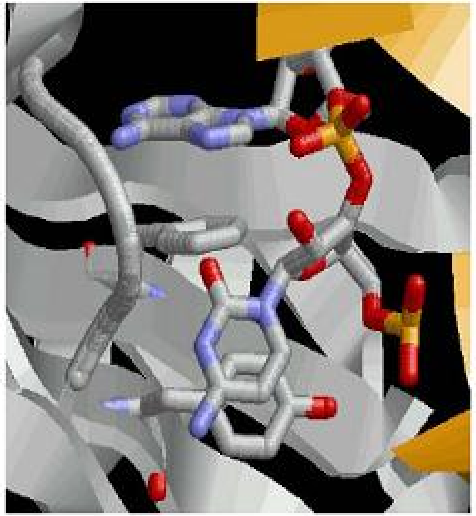
1) “Modern” view of stacking.

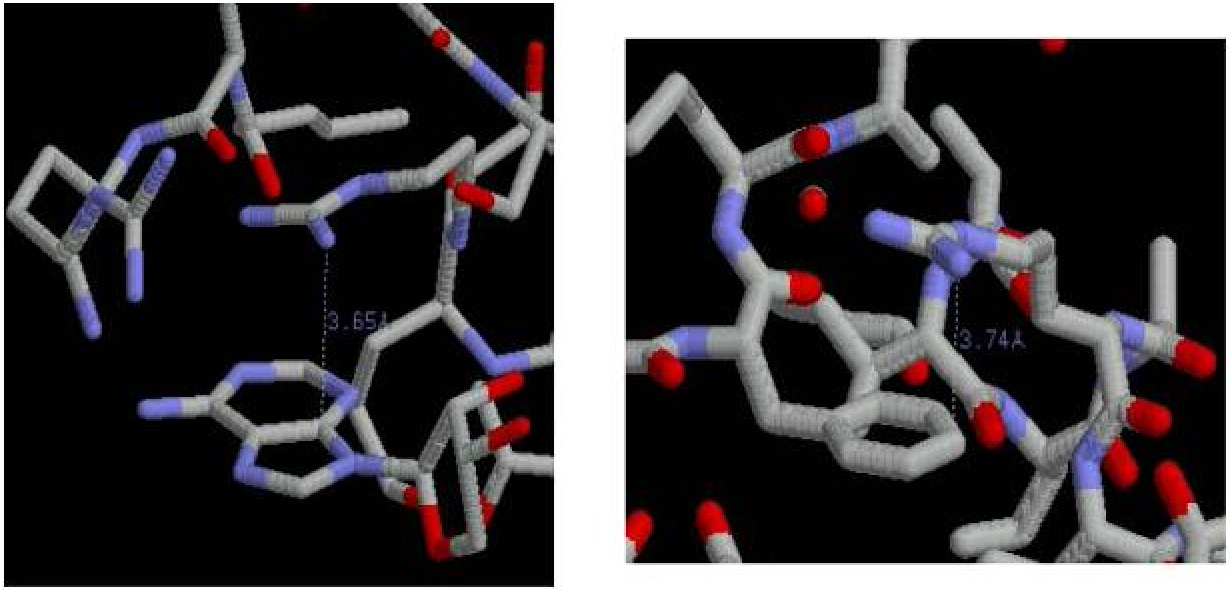


Dna-mediated electron transfer

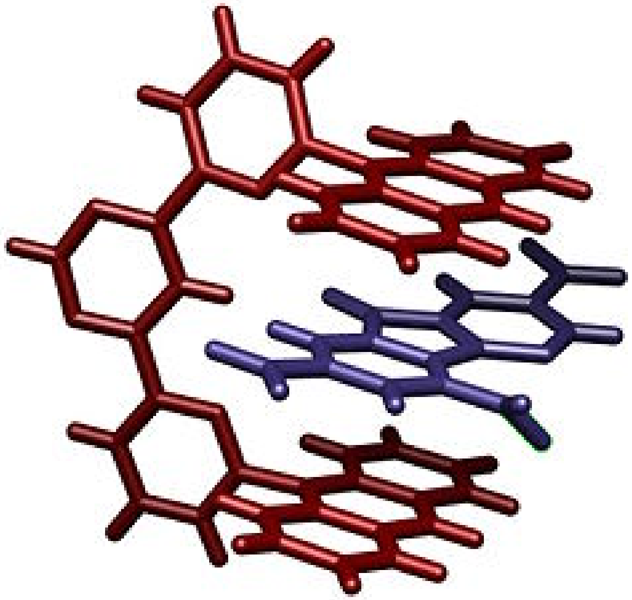


Stacking examples

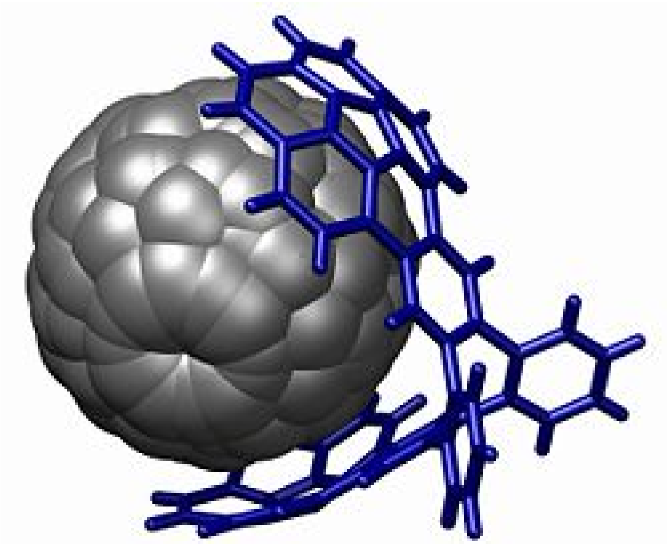




Arginine stacking

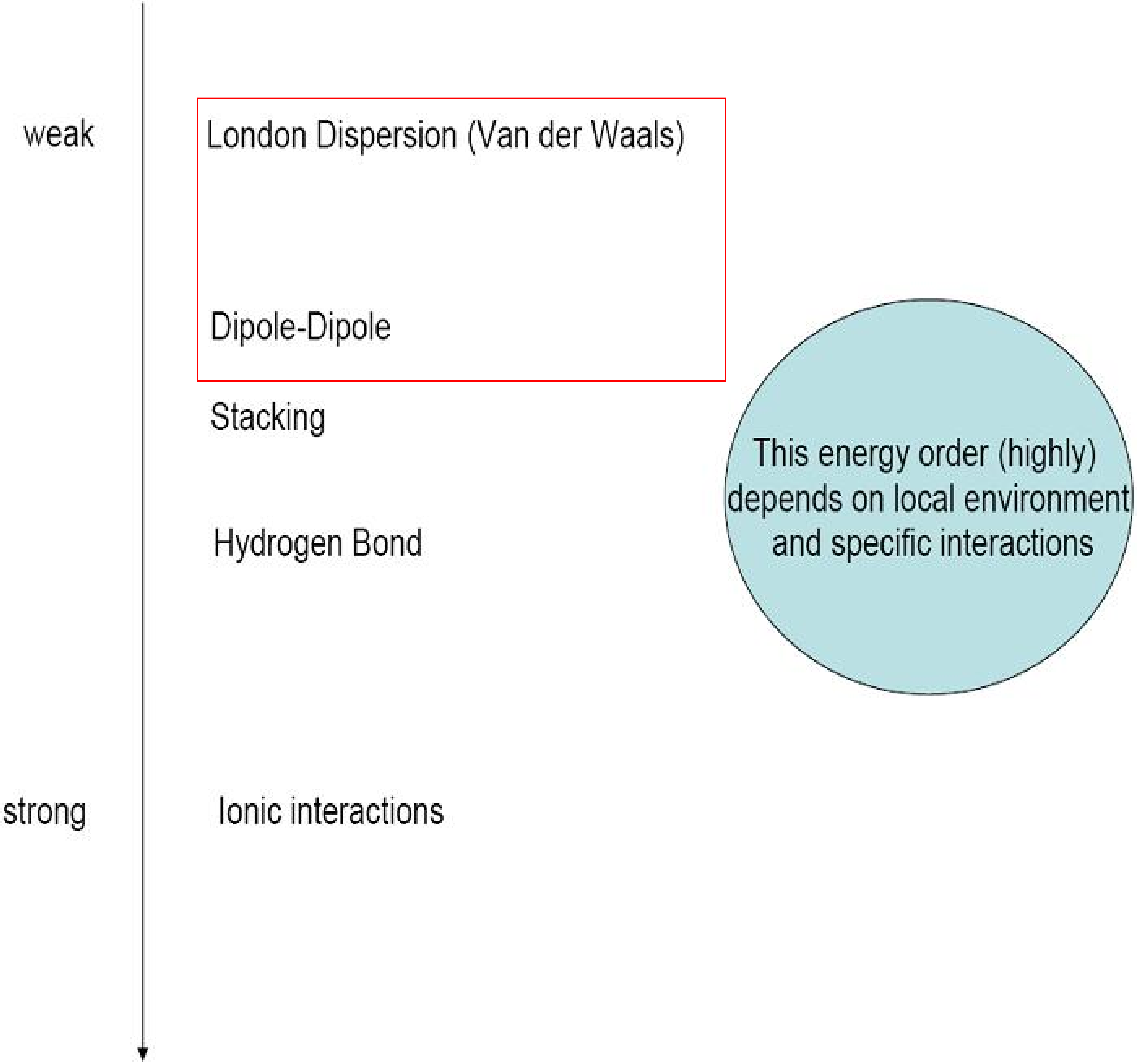


Crystal structure of a trinitrofluorene bound in molecular tweezers through aromatic stacking interactions. Reported by Lehn and coworkers.[1]



Crystal structure of a fullerene bound in a buckycatcher through aromatic stacking interactions. Reported by Sygula and coworkers.[2]

Intermolecular interactions:



weak

London Dispersion (Van der Waals)

Dipole-Dipole

Stacking

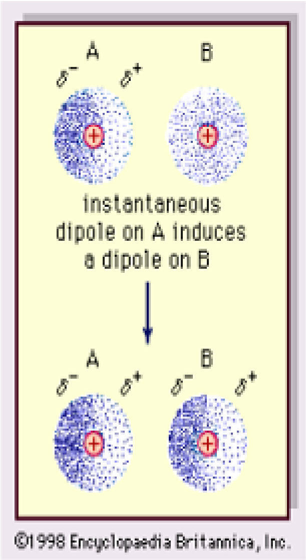
Hydrogen Bond

strong

Ionic interactions

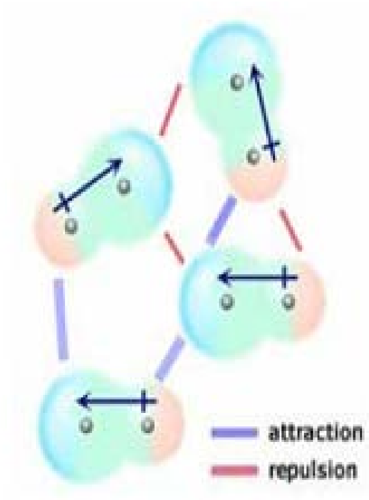
This energy order (highly) depends on local environment and specific interactions

Dispersion forces (Van der waals): induced/instantaneous dipoles



©1998 Encyclopaedia Britannica, Inc.

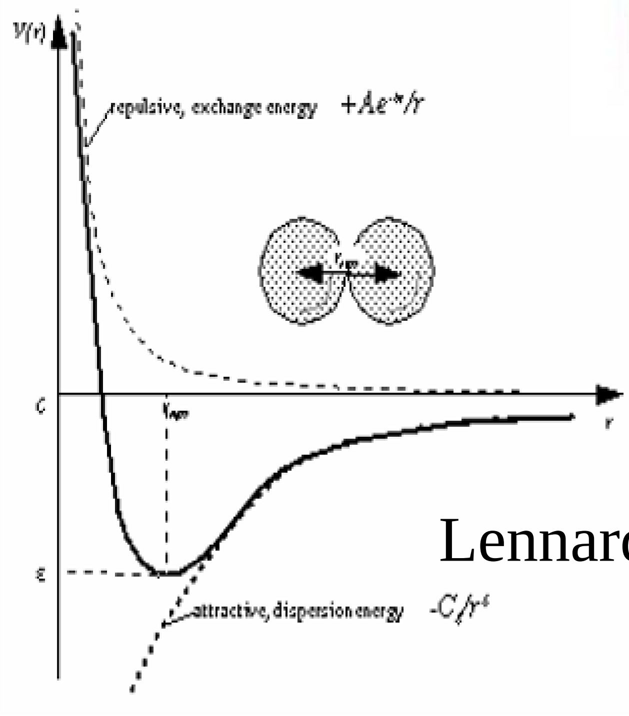
Permanent Dipole-Dipole



取向力

诱导力

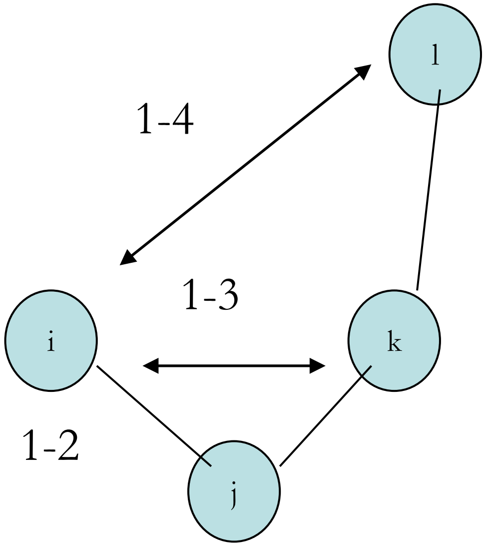
色散力



Lennard-Jones potential

1-4 Non-bonded Interactions

- Non-bonded exclusions
  - 1-2 and 1-3 interactions excluded
  - 1-4 interactions partially excluded
- Partly?
  - included in bonded terms already
  - If included, they would be huge to cause stability problem
- 1-4 interaction scalings
  - OPLSAA scales by 0.5 for both electrostatic and LJ
  - AMBER94 scales 0.5 for LJ and 1/1.2 for electrostatic interaction
  - CHARMM22 has special 1,4-terms
- 1-4 terms vs torsion terms



Even though they are non-bonded interactions, 1-4 terms are often calculated along with bonded terms.

Model construction

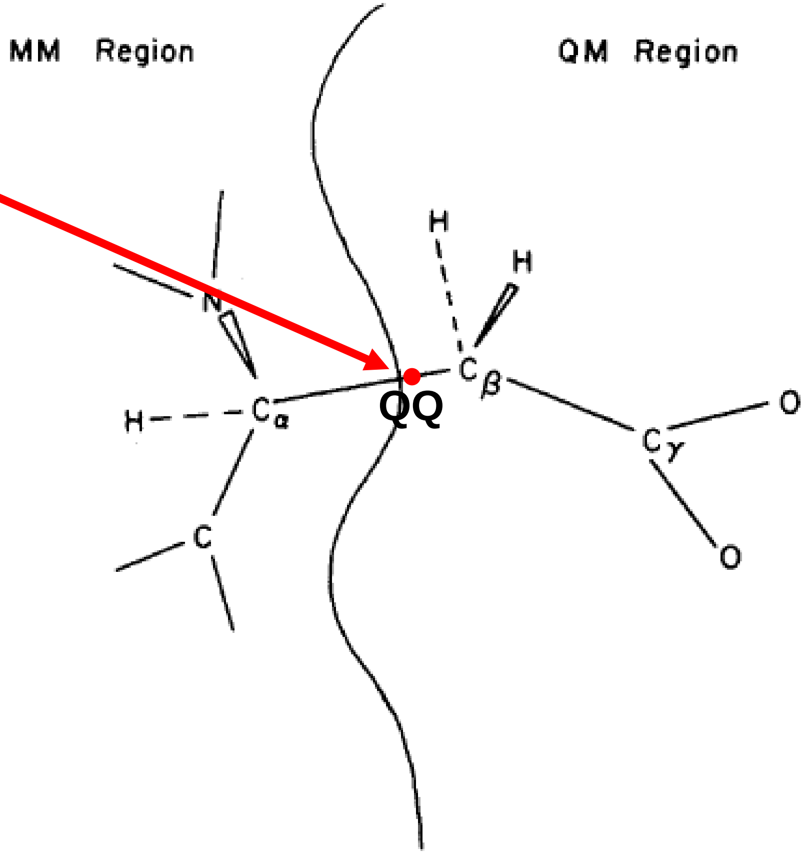
- Read in parameters
  - Force field parameters
  - Topology definitions
- Read in sequences
  - *Protein structure file* (PSF)
  - segments
- Read in coordinates
  - .pdb, crd, etc
  - From RCSB PDB, unpublished data
  - X-ray, NMR, homology modeling

Revision on models

- Revision on solvated model
  - Mutation
  - Construction of S-S bond
  - Protonation/deprotonation
  - Deletion of unnecessary/unreasonable solvents
  - Modification on coordinates
  - Change origin of coordinates
- Add link-atoms in QM/MM simulations

Bonds on QM/MM interface
Link-atom method

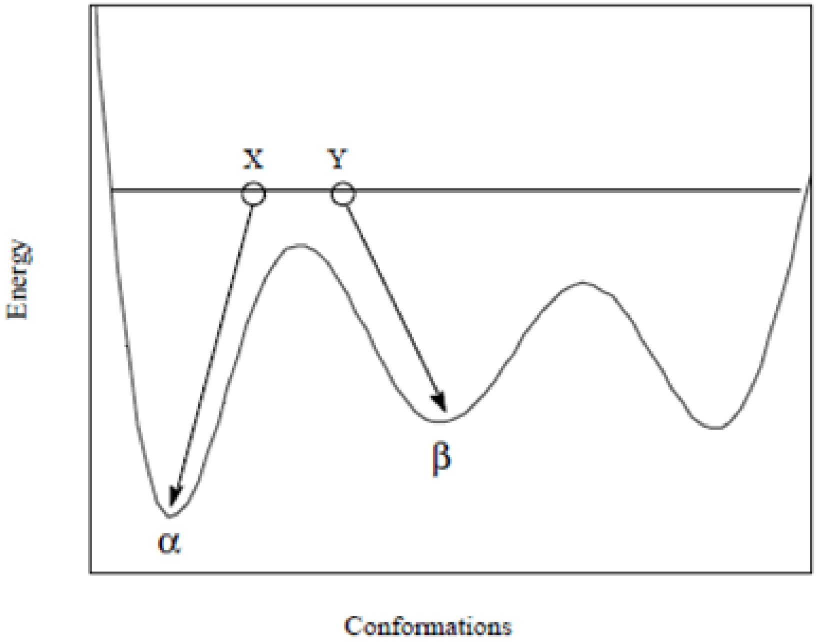
- A virtual "link-atom" is added along the covalent bond
- Initially 1Å from the QM atom
- Generally a dummy hydrogen atom
- Satisfy bonding in MM and the valency of the QM atom



Field et al., *J. Comput. Chem.* 1990

Model optimization

- Original structure under different conditions
  - Temperature
  - Solvent conditions
  - No hydrogens
- Revision on structure
  - hydrogens added
  - substrate or ligand ad
  - mutations on residues



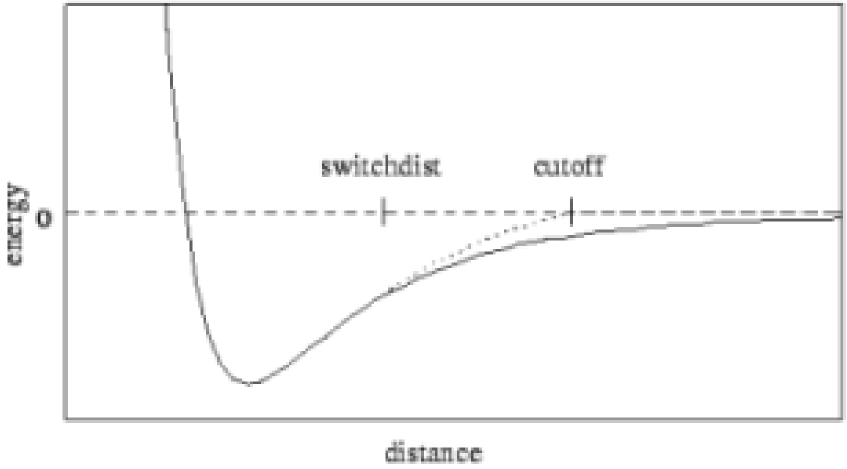
Minimization algorithms

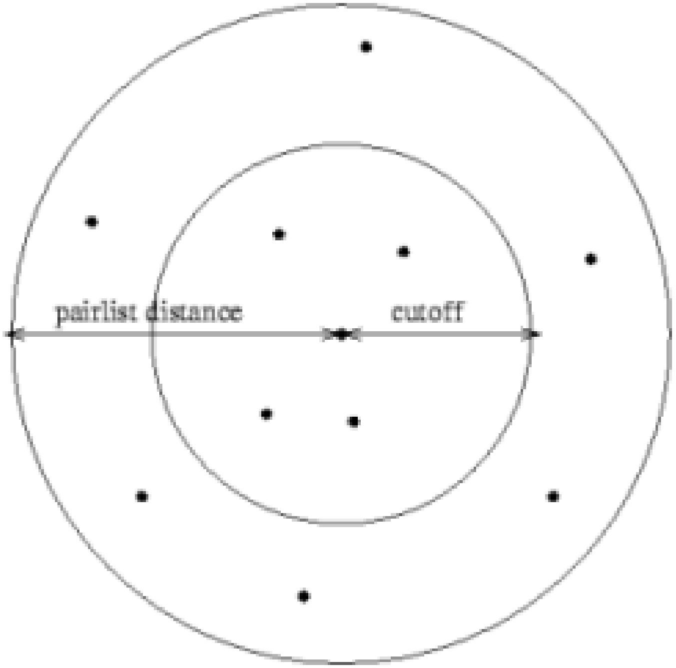
- Steepest-descent (SD)
  - Simplest, first derivative method
  - Poor convergence and accuracy
  - initial steps to relieve bad contacts
- Newton-Raphson (NR)
  - Expensive, second derivative method
  - Good convergence and accuracy
- Adopted-Basis Newton-Raphson (ABNR) and Conjugated Gradients (CONJ)
  - Intermediate first derivative method
  - Very useful for large systems

Minimization on Energies

- E_{QM}
  - QM methods
  - Possible for bond breaking-making
  - Expensive, time-consuming
- E_{MM}
  - Force field
  - Impossible for bond breaking-making
  - Empirical parameters, quick and cheap
- Complicated energy
  - $E_{total}=E_{QM}+E_{MM}+E_{QM/MM}$
  - ONION, SMBP, GSBP

Potential truncation



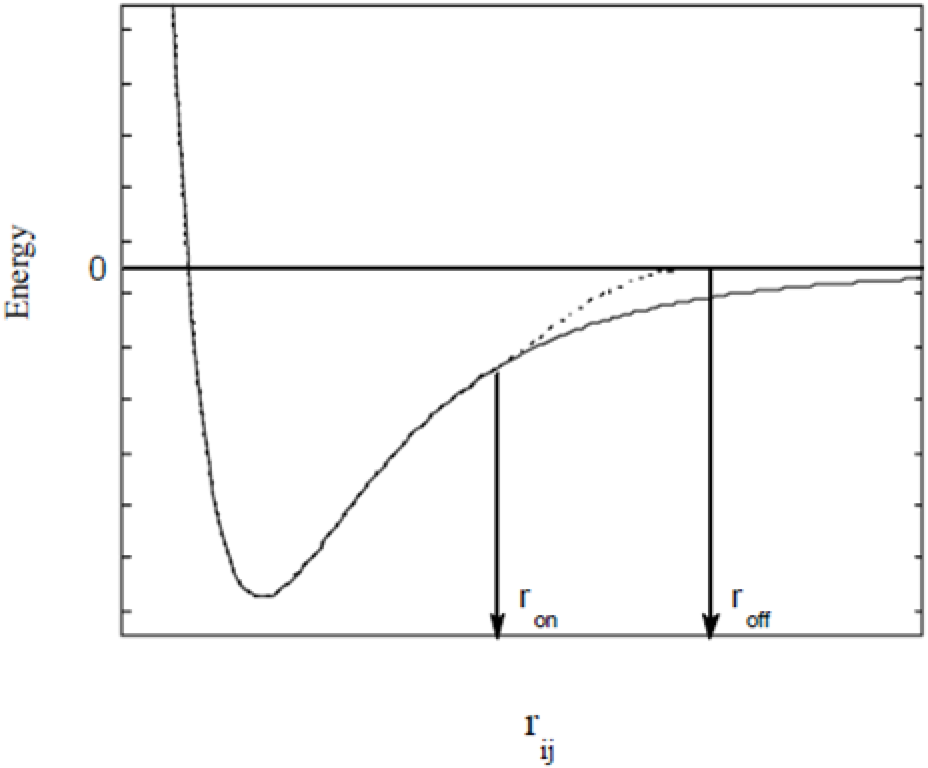


In the MD or MC, in order to save time, we introduce a spherical cutoff. The cutoff distance should be sufficient large to ensure that it is a small perturbation, but it must be no greater than BOXL/2 for the consistency with minimum image convention.

Truncation for non-bonded interactions

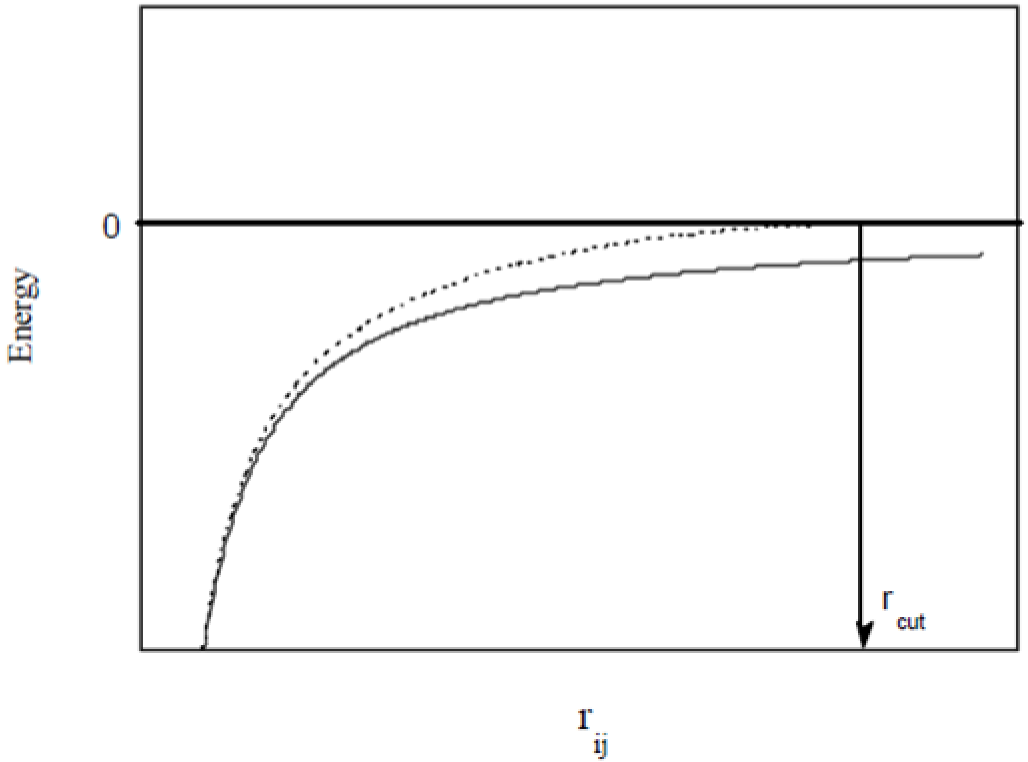
- Assuming the overall contribution from atoms farther than certain CUTOFF distance is quite small
- A gradual truncation in energy leads to E=0 when $r > r_{cutoff}$
  - SWITCH
    - Limit trunction in a small range $[r_{on}, r_{off}]$
    - Generally applied to van der waals potential
  - SHIFT
    - Applied to whole range of distances
    - Generally applied to electrostatic potential

Switch truncation function



$$sw\left(r, r_{\text{on}}, r_{\text{off}}\right) = \left\{ \begin{array}{cc} 1 & r < r_{\text{on}} \\ \dfrac{\left(r_{\text{off}} - r\right)^2 \left(r_{\text{off}} + 2r - 3r_{\text{on}}\right)}{\left(r_{\text{off}} - r_{\text{on}}\right)^2} & r_{\text{on}} < r < r_{\text{off}} \\ 0 & r > r_{\text{off}} \end{array} \right\}$$

Shift truncation function



$$sh(r, r_{\text{cut}}) = \begin{cases} \left[1 - \dfrac{2r^2}{r_{\text{cut}}^2} + \dfrac{r^4}{r_{\text{cut}}^4}\right] & r < r_{\text{cut}} \\ 0 & r > r_{\text{cut}} \end{cases}$$

Constraints

- An extra energy term
  - Removed when calculating real energy
- Force the molecules into a desired conformation
  - Prohibit dramatic movements
  - Simulate specific interactions
  - Limit the system into desired conformation
  - Umbrella sampling

Typical constraints

$$E_{Cr} = \Sigma K_i (r_i - r_{io})^2$$

$$E_{C\phi} = \Sigma K_i (\phi_i - \phi_{io})^2$$

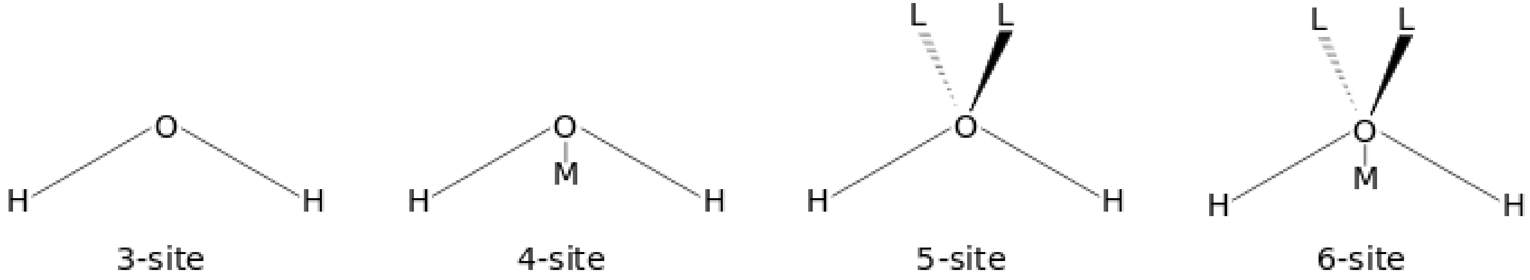
- Harmonic function
  - Distance or dihedral constraints
  - On boundary condition
  - On specific positions (restraints)
- SHAKE algorithm $s_{ij} = (r_{ij}^2 - d_{ij}^2)/d_{ij}^2 < \varepsilon$
  - More rigid than harmonic function
  - Useful to increase time step of molecular dynamics from 0.5 to 1 or 2 fs

Solvation

- Implicit condition: continuum
  - Empirical equations and functionals
  - Poisson-Boltzmann, Generalized Born, GBSA
- Explicit condition: particles
  - Add ions or other solvent molecules
  - Programs
    - Preconstructed water droplets or water boxes
    - VMD, packmol, etc
    - Online generator: http://charmm-gui.org/
  - Boundary condition
    - Periodic boundary condition
    - Harmonic boundary condition

Explicit water models

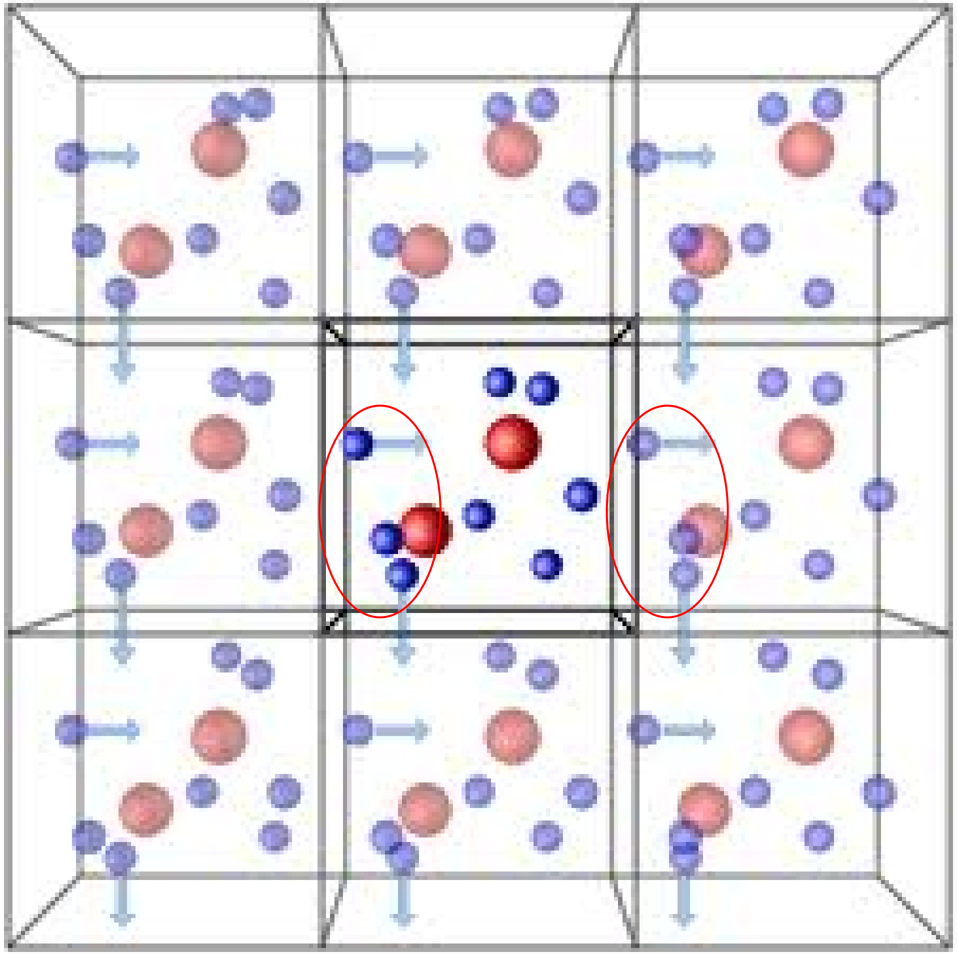
- Simple water models



  - TIP3P TIP4P TIP5P
- Other models
  - SPC, SPC/E, Flexible SPC
  - BF, BNS, ST2, GG, MG

Period boundary condition

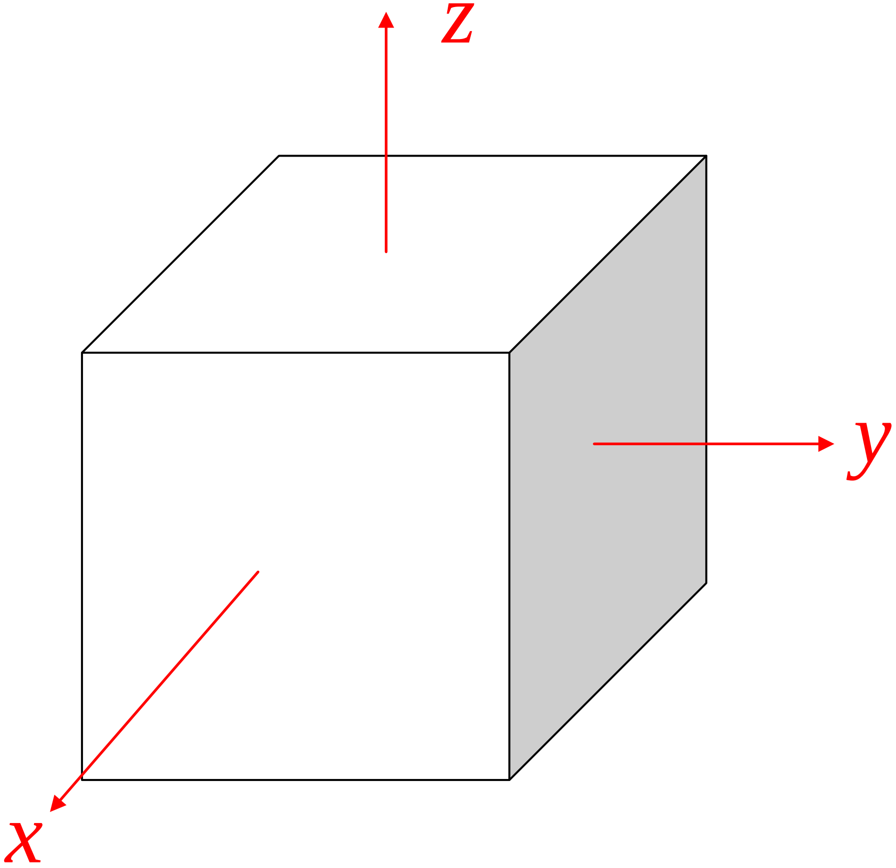
- Images
  - Around the unit cell (simulation box)
  - Only particles in unit cell are recorded and propagated



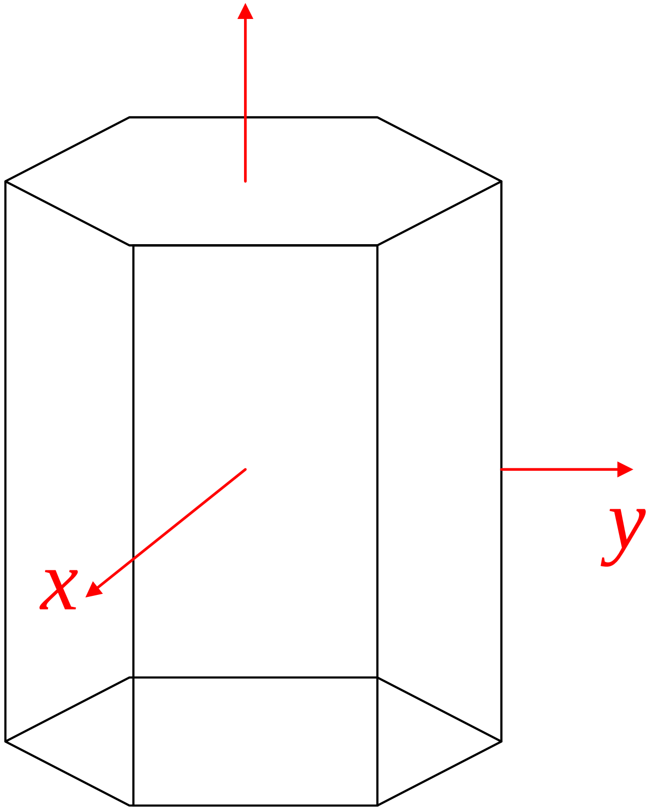
- Conserved
  - The number of particles
  - Linear momentum of the system

isaacs.sourceforge.net/phys/pbc.html

Simulation box

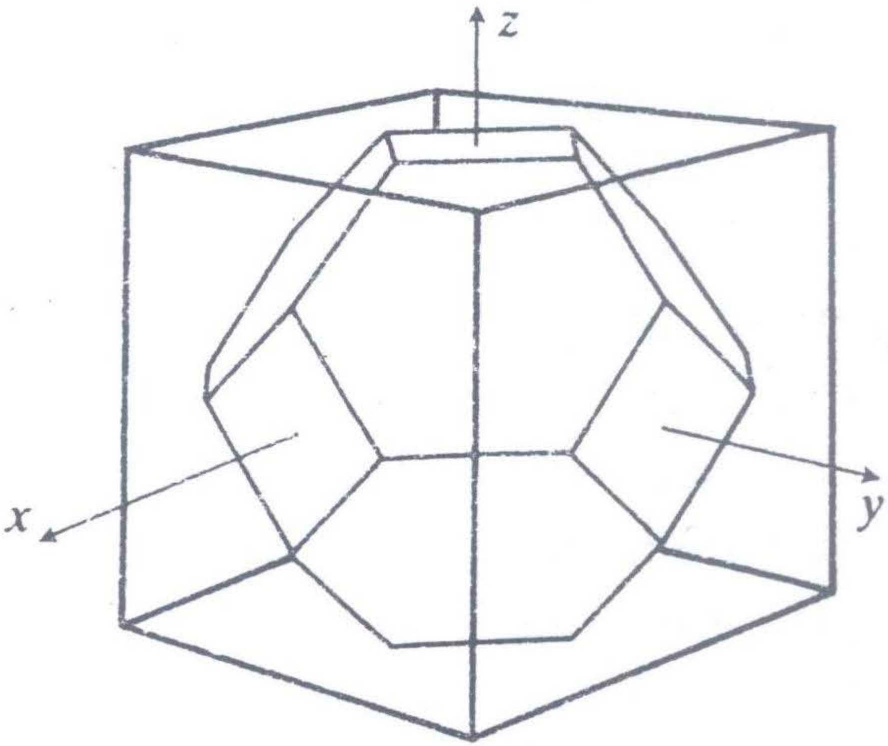


Cube or cuboid



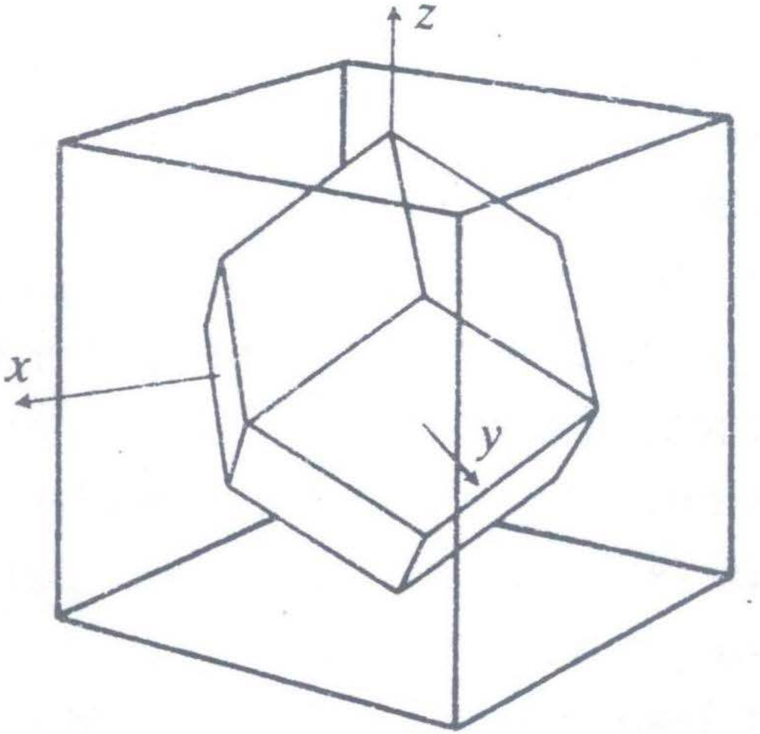
Hexagonal prism

Simulation box



(a)

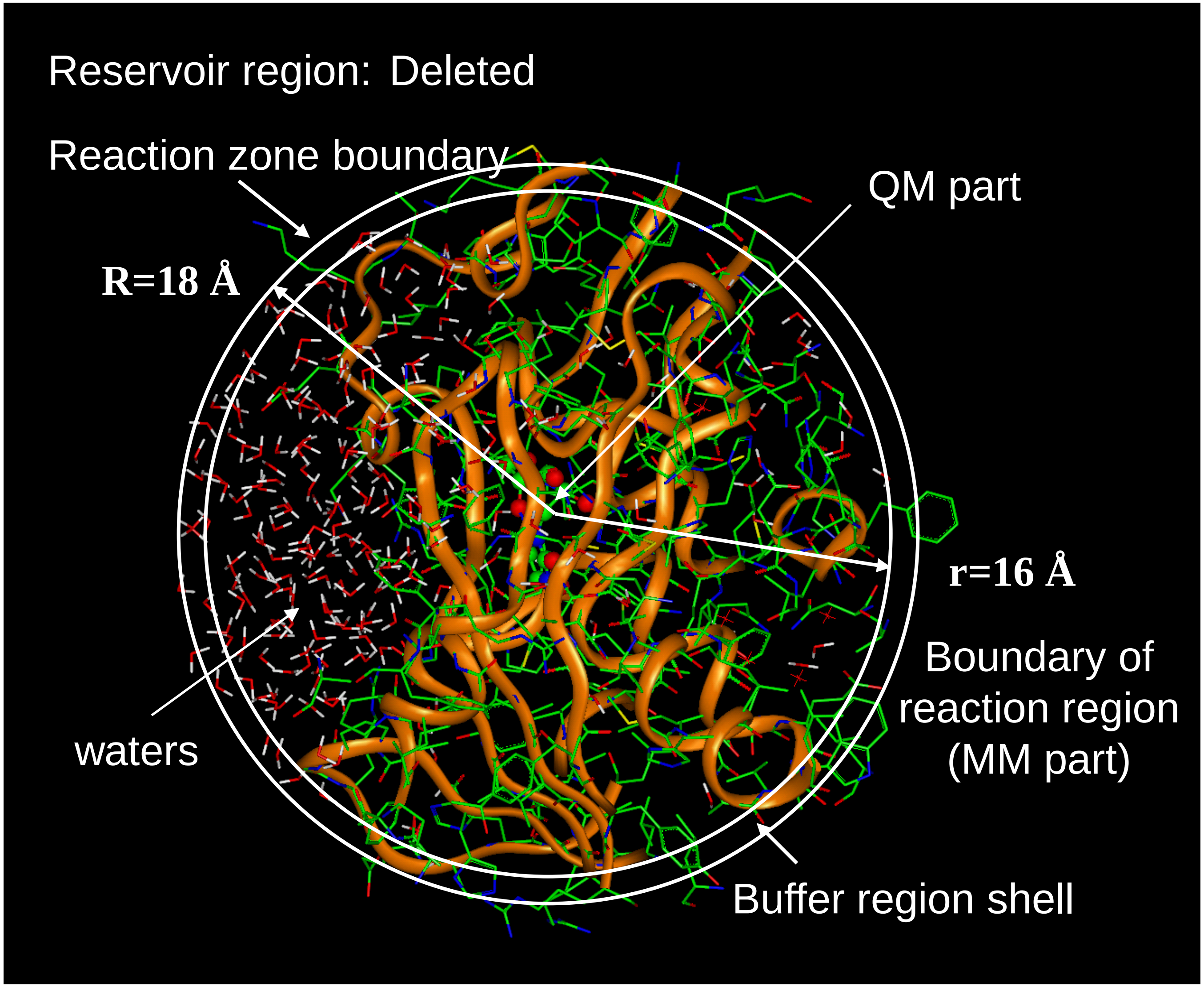
Truncated octahedron



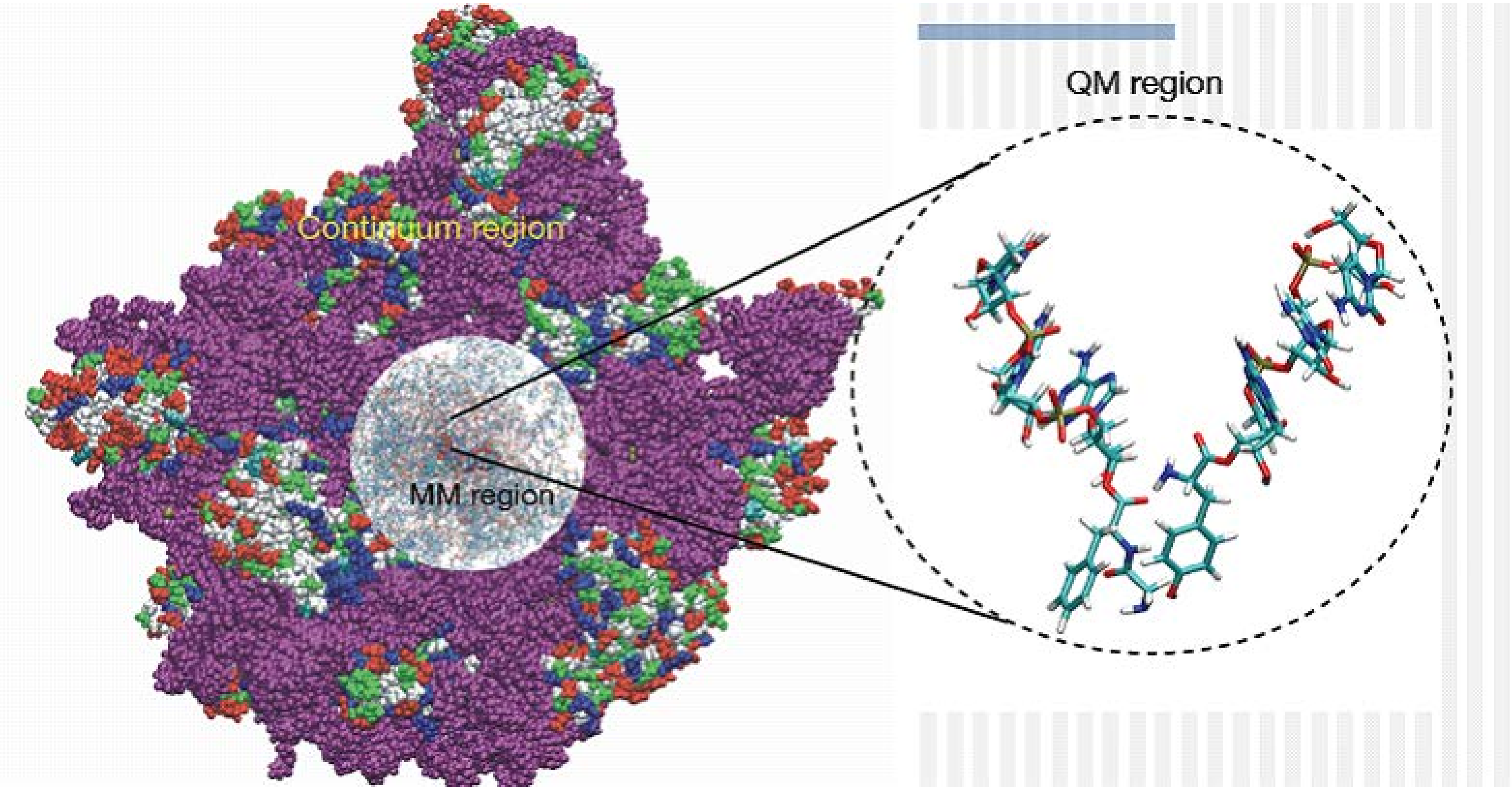
(b)

Rhombic dodecahedron

Stochastic Boundary System



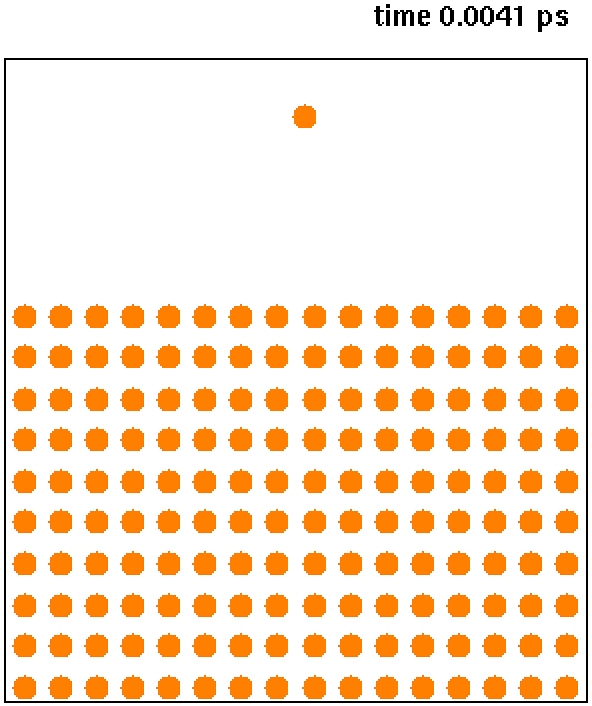
GSBP (Generalized Solvent Boundary Potential)



Combine explicit and implicit solvent condition

Molecular dynamics (MD) simulation

- A computational simulation
  - Atoms and Molecules (model)
  - Within a given time (time step)
  - Physical movements
  - Based on interactions
  - By numerically solving the Newton's equations of motion



$F = m \bullet a$

(Force = mass • acceleration)

or $-\nabla_i E = m_i \, d^2 r_i / dt^2$, $i = 1, \ldots, N$

Flow of Molecular Dynamics Simulations

- Initial structure
  - Model construction and revision
  - Minimization
- Initialization on velocities
- Heating
- Equilibration
- Production run
- Analyze data from trajectories

Initialization

- Initial velocities
  - a random number distributed uniformly in the [–0.5,0.5]
  - from a Maxwell-Boltzmann distribution
- Purpose
  - Generate the previous positions before t=0

Integrating the Equations of Motion in molecular dynamics

Algorithms for solving Newton's equations of motion in given time step (Δt)

Verlet algorithm

$$r_i(t + \Delta t) = 2r_i(t) - r_i(t - \Delta t) + (\Delta t)^2 F_i(t)/m_i$$

$$v_i(t) = \tfrac{1}{2}[r_i(t + \Delta t) - r_i(t - \Delta t)]/\Delta t$$

Leap-frog algorithm

$$r_i(t + \Delta t) = r_i(t) + v(t + \tfrac{1}{2}\Delta t)\Delta t$$

$$v(t + \tfrac{1}{2}\Delta t) = v(t - \tfrac{1}{2}\Delta t) + \Delta t F_i(t)/m_i$$

Velocity Verlet algorithm

$$r_i(t + \Delta t) = r_i(t) + v(t)\Delta t + \tfrac{1}{2}(\Delta t)^2 F_i(t)/m_i$$

$$v_i(t + \Delta t) = v_i(t) + \tfrac{1}{2}\Delta t[F_i(t)/m_i + F_i(t + \Delta t)/m_i]$$

Verlet algorithm

- To derive it, we start with a Taylor expansion of the coordinate of a particle, around time *t*,

$$\boxed{\mathbf{r}(t+\Delta t)=\mathbf{r}(t)+\mathbf{v}(t)\Delta t+\frac{\mathbf{f}(t)}{2m}\Delta t^2+\dddot{\mathbf{r}}(t)\frac{\Delta t^3}{3!}+O(\Delta t^4)}$$

$$\boxed{\mathbf{r}(t-\Delta t)=\mathbf{r}(t)-\mathbf{v}(t)\Delta t+\frac{\mathbf{f}(t)}{2m}\Delta t^2-\dddot{\mathbf{r}}(t)\frac{\Delta t^3}{3!}+O(\Delta t^4)}$$

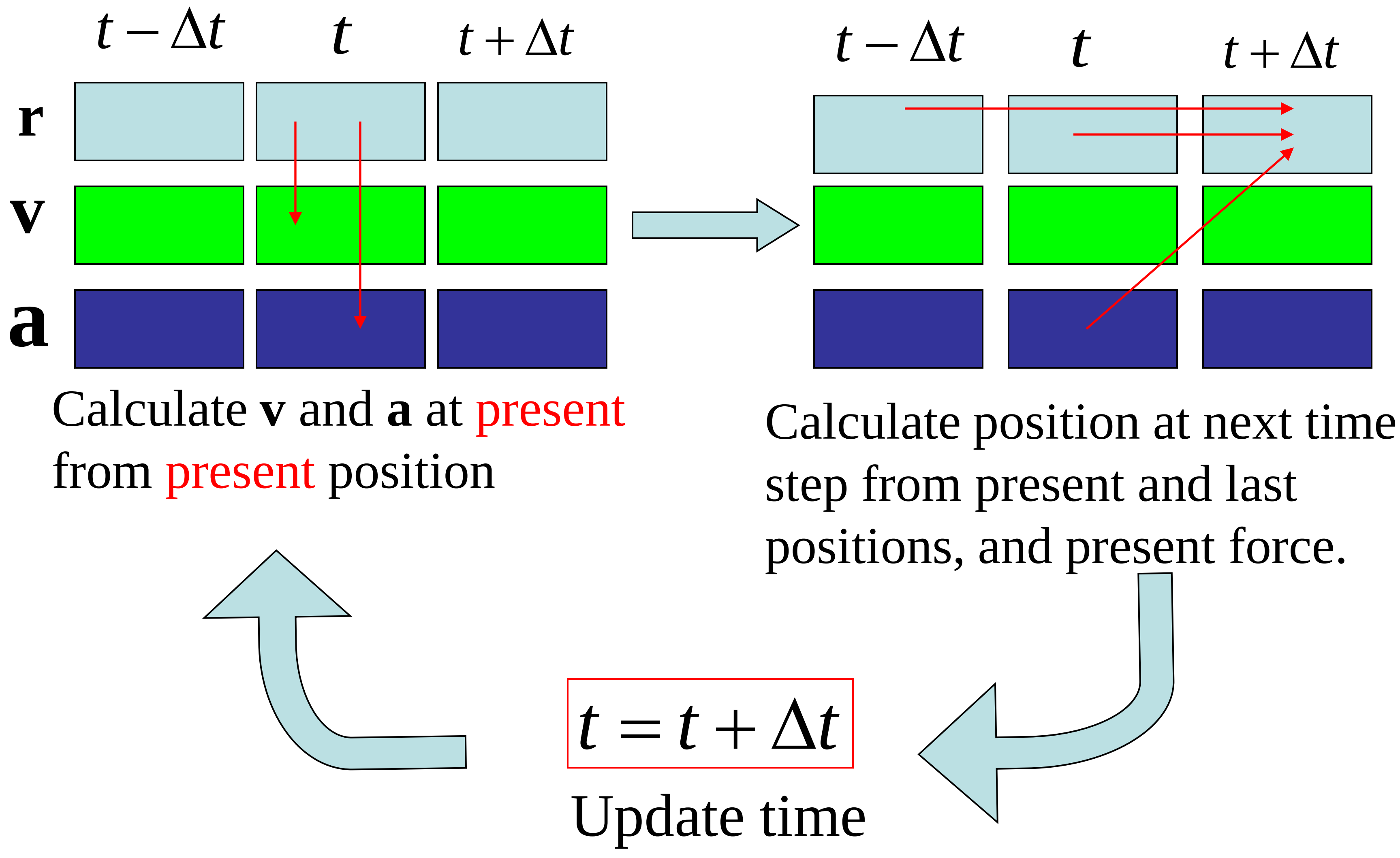
- Summing the two equations in the above slide, we obtain:

$$\boxed{\mathbf{r}(t+\Delta t)\approx 2\mathbf{r}(t)-\mathbf{r}(t-\Delta t)+\frac{\mathbf{f}(t)}{m}\Delta t^2}$$

- Similarly

$$\boxed{\mathbf{v}(t)=\frac{\mathbf{r}(t+\Delta t)-\mathbf{r}(t-\Delta t)}{2\Delta t}+O(\Delta t^2)}$$

Verlet algorithm calculation procedure



Calculate **v** and **a** at present from present position

Calculate position at next time step from present and last positions, and present force.

$$\boxed{t=t+\Delta t}$$

Update time

Advantages of Verlet algorithm

- The Verlet method requires essentially 9N words (3[RXOLD(I), RX(I) & RXNEWI]) of storage, make it very compact, and it is simple to program.
- The algorithm is exactly reversible in time and, given conservative forces, is guaranteed to conserve linear momentum. Have excellent energy-conserving properties even with long time steps.

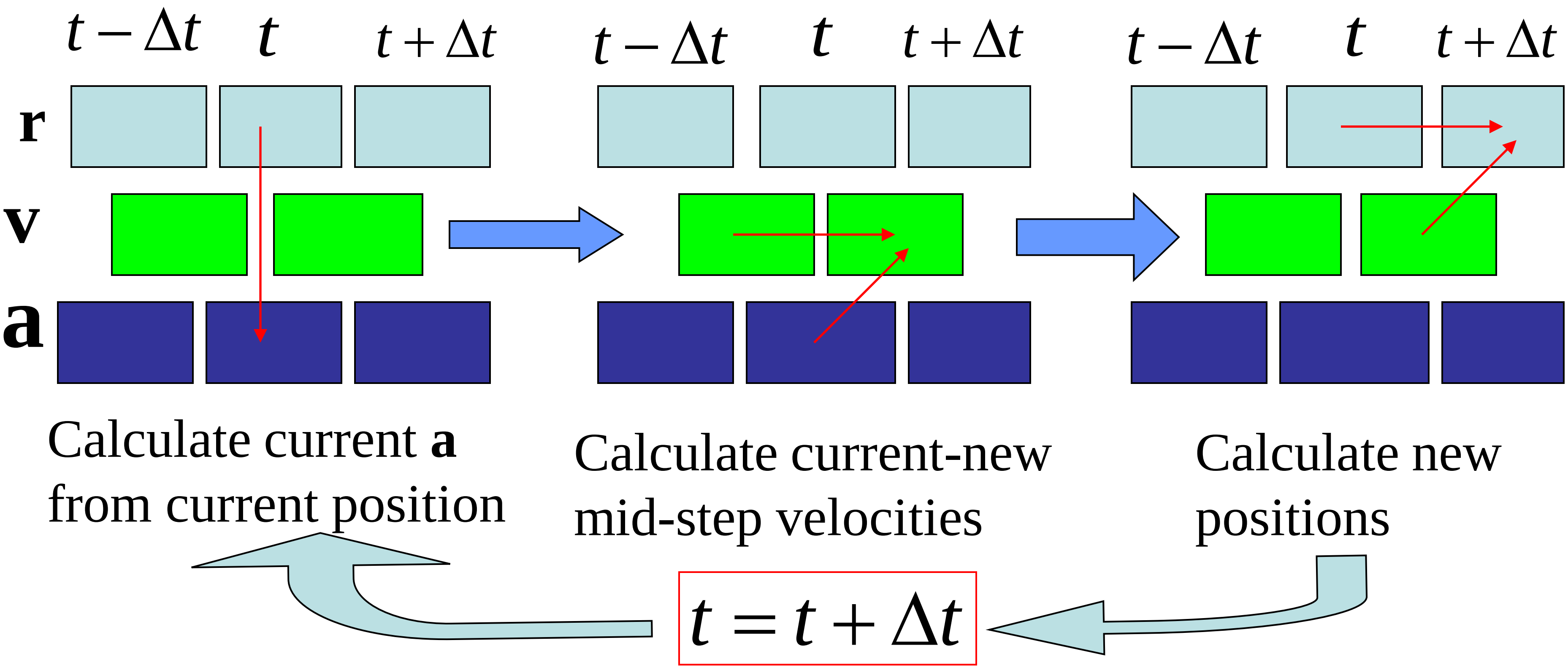
Disadvantages of Verlet algorithm

- The velocities from Verlet algorithm are subject to errors of order Δt^2. More accurate estimates of $\mathbf{v}(t)$ can be made, if more variables are stored, but this adds to the inconvenience, namely $\mathbf{v}(t)$ can only be computed once $\mathbf{r}(t+\Delta t)$ is known.

- The handling of velocities is rather awkward, and that the form of the algorithm may needlessly introduce some numerical imprecision.

- Modifications on basic Verlet scheme
  - half-step leap-frog algorithm
  - velocity Verlet algorithm.

Half-step leap-frog scheme---calculation procedure



Calculate current **a** from current position

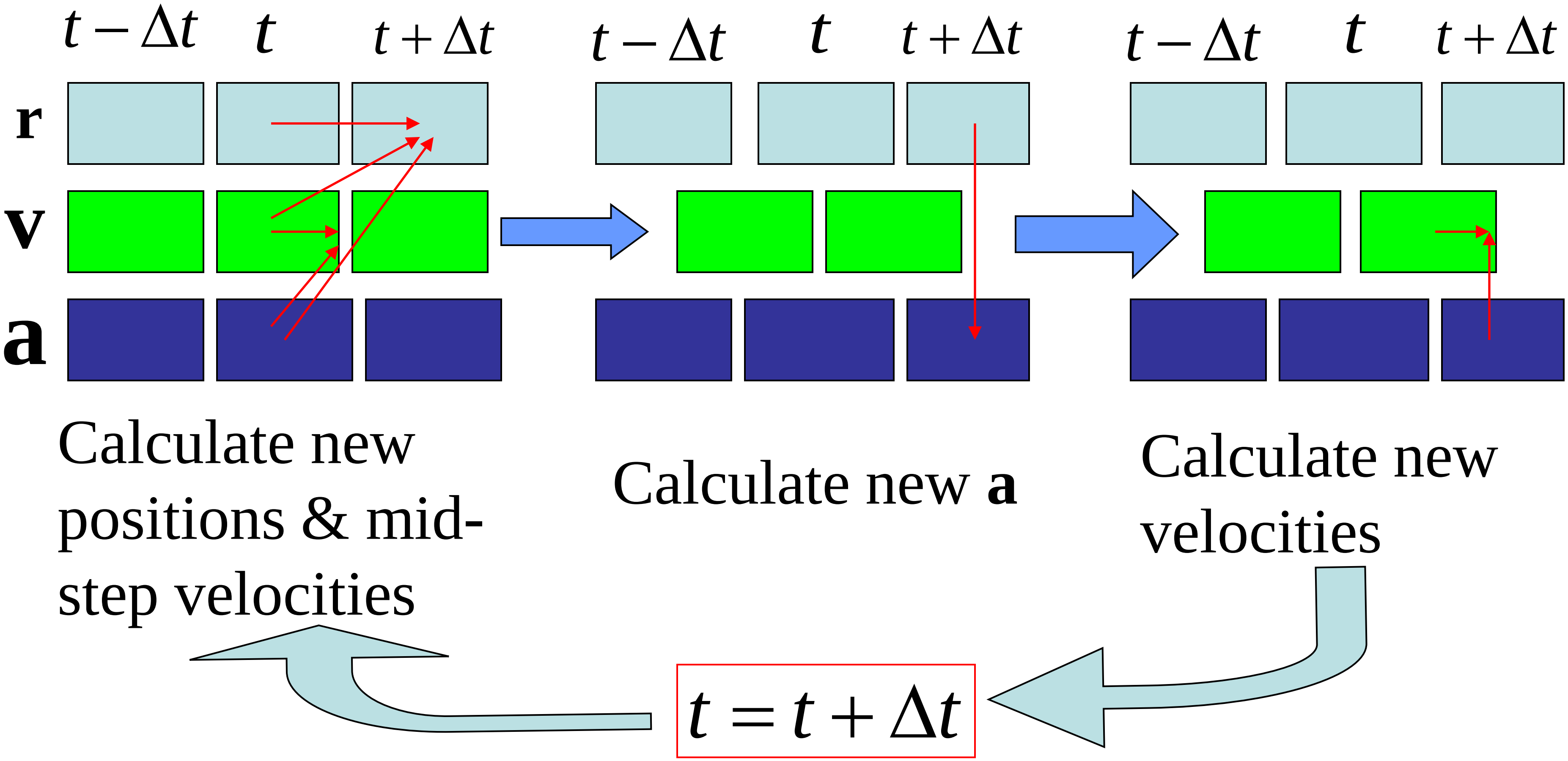
Calculate current-new mid-step velocities

Calculate new positions

$$t = t + \Delta t$$

Update time

Velocity Verlet algorithm---calculation procedure



Calculate new positions & mid-step velocities

Calculate new **a**

Calculate new velocities

$$t = t + \Delta t$$

Update time

A successful MD simulation algorithm

- It should be fast, and require little memory.

- Permit the use of a long time step Δt.

- Duplicate the classical trajectory as closely as possible.

- Satisfy the known conservation laws for energy and momentum, and be time-reversible

- Simple in form and easy to program.

Other methods

- Beeman's method
  - The method stores **r**(*t*), **v**(*t*), **a**(*t*), and **a**(*t*-Δ*t*).

$$\boxed{\mathbf{r}(t+\Delta t)=\mathbf{r}(t)+\mathbf{v}(t)\Delta t+[\tfrac{2}{3}\mathbf{a}(t)-\tfrac{1}{6}\mathbf{a}(t-\Delta t)]\Delta t^2}$$

$$\boxed{\mathbf{v}(t+\Delta t)=\frac{\mathbf{a}(t+\Delta t)\Delta t}{3}+\frac{5\mathbf{a}(t)-\mathbf{a}(t-\Delta t)}{6}\Delta t^2}$$

- Predictor-corrector integration methods

$$\boxed{\mathbf{r}(t+\Delta t)=\mathbf{r}(t)+\mathbf{v}(t)\Delta t+\frac{\mathbf{a}(t)\Delta t^2}{2}+\frac{\mathbf{b}(t)\Delta t^3}{6}+\frac{\mathbf{c}(t)\Delta t^4}{24}+\cdots}$$

$$\boxed{\mathbf{v}(t+\Delta t)=\mathbf{v}(t)+\mathbf{a}(t)\Delta t+\tfrac{1}{2}\mathbf{b}(t)\Delta t^2+\tfrac{1}{6}\mathbf{c}(t)\Delta t^3+\cdots}$$

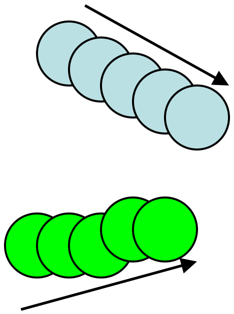
$$\boxed{\mathbf{a}(t+\Delta t)=\mathbf{a}(t)+\mathbf{b}(t)\Delta t+\tfrac{1}{2}\mathbf{c}(t)\Delta t^2+\cdots}$$

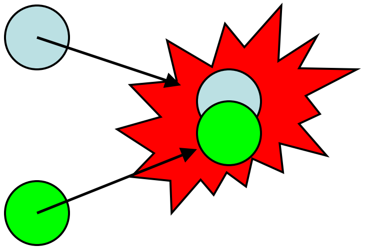
$$\boxed{\mathbf{b}(t+\Delta t)=\mathbf{b}(t)+\mathbf{c}(t)\Delta t+\cdots}$$

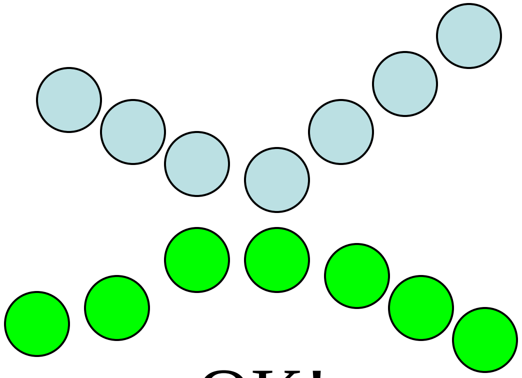
Δt, time step

With an appropriate time step, phase space is covered efficiently and collisions occur smoothly.

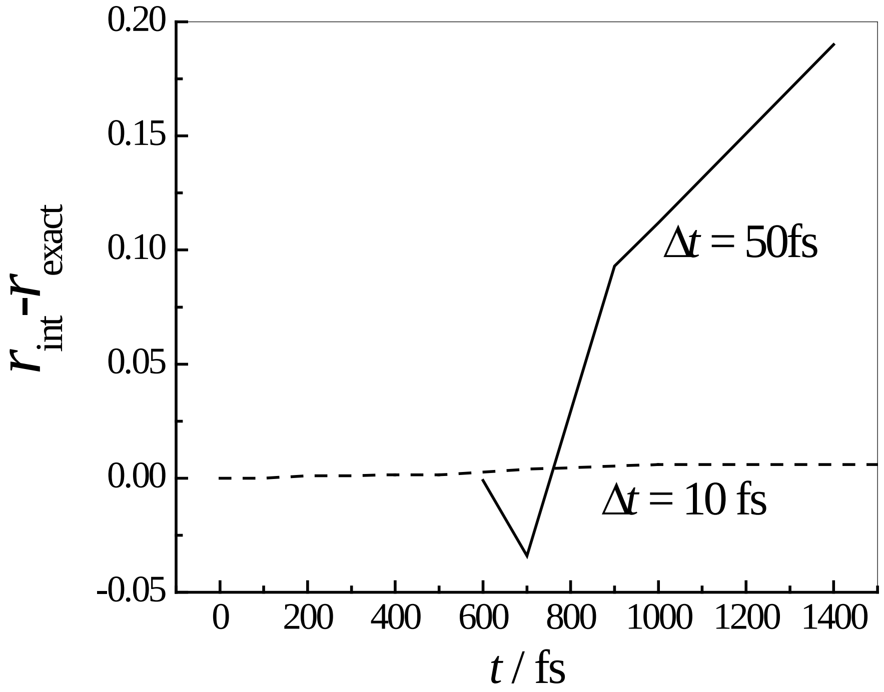
- Too small and the trajectory will cover only a limit proportion of the phase space.
- Too large and instabilities may arise in the integration algorithm due to high overlaps between atoms.

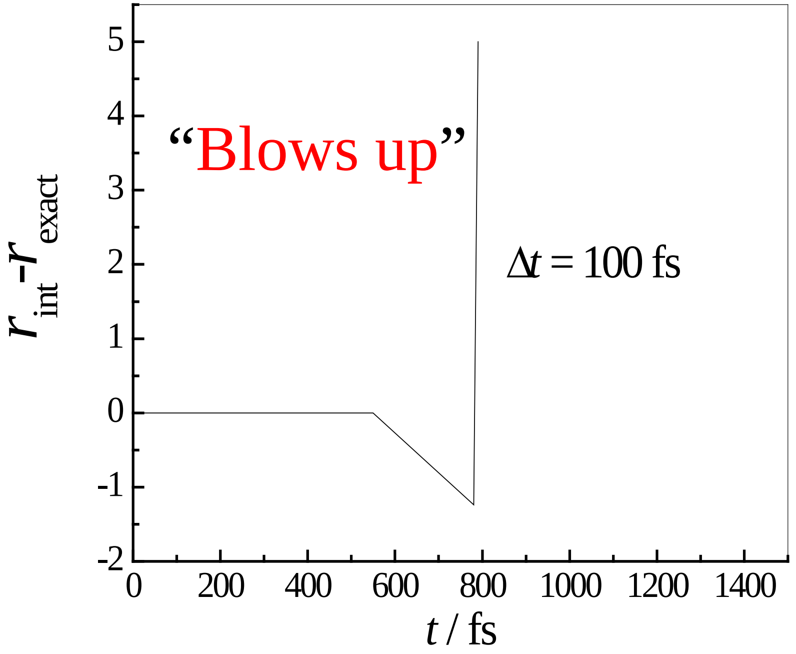

Too small Δt


Too large→instabilities


OK!

Time step





Difference between exact and numerical trajectory for the approach of two argon atoms with different time steps.

Ar atoms are moving towards each other along the *x* axis with initial velocities of 353m/s (corresponds to 300K).

Choosing time step

- When simulating an atomic fluid the time step should be small compared to the mean time between collisions.
- When simulating flexible molecules a useful guide is that the time step should be approximately one tenth the time of the shortest period of motion.
  - A C-H bond vibrates with a repeat period of approximately 10 fs.
  - MD simulations on biological micromolecule, 0.5~2fs

Types of motion present in various systems with suggested time steps

System	Types of motion	Suggested Δt
Atoms	translation	10^{-14}s
Rigid molecules	Translation & rotation	5×10^{-15}s
Flexible molecules with rigid bond	Translation, rotation & torsion	2×10^{-15}s
Flexible molecules with flexible bond	Translation, rotation, torsion, vibration	10^{-15} or 5×10^{-16}s

Advanced method of MD simulations

- Free energy simulations
- Free energy pertubations (FEP)
- Metadynamics
- Steered Molecular Dynamics (SMD)
- Targeted Molecular Dynamics (TMD)
- Accelerated Molecular Dynamics (aMD)
- Collective Variable-based Calculations
- 。。。。。。

Free Energy Simulations

- Potential of Mean Force (PMF)
  - The change of free energy as the function of specific reaction coordinates

- Umbrella Sampling method
- WHAM (Weighted Histogram Analysis Method) program