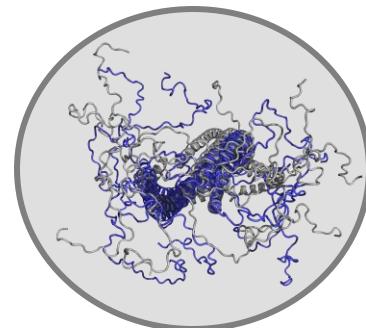


# Molecular simulations for biological problems

Monika Fuxreiter

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Department of Biomedicine  
University of Padova, Italy*

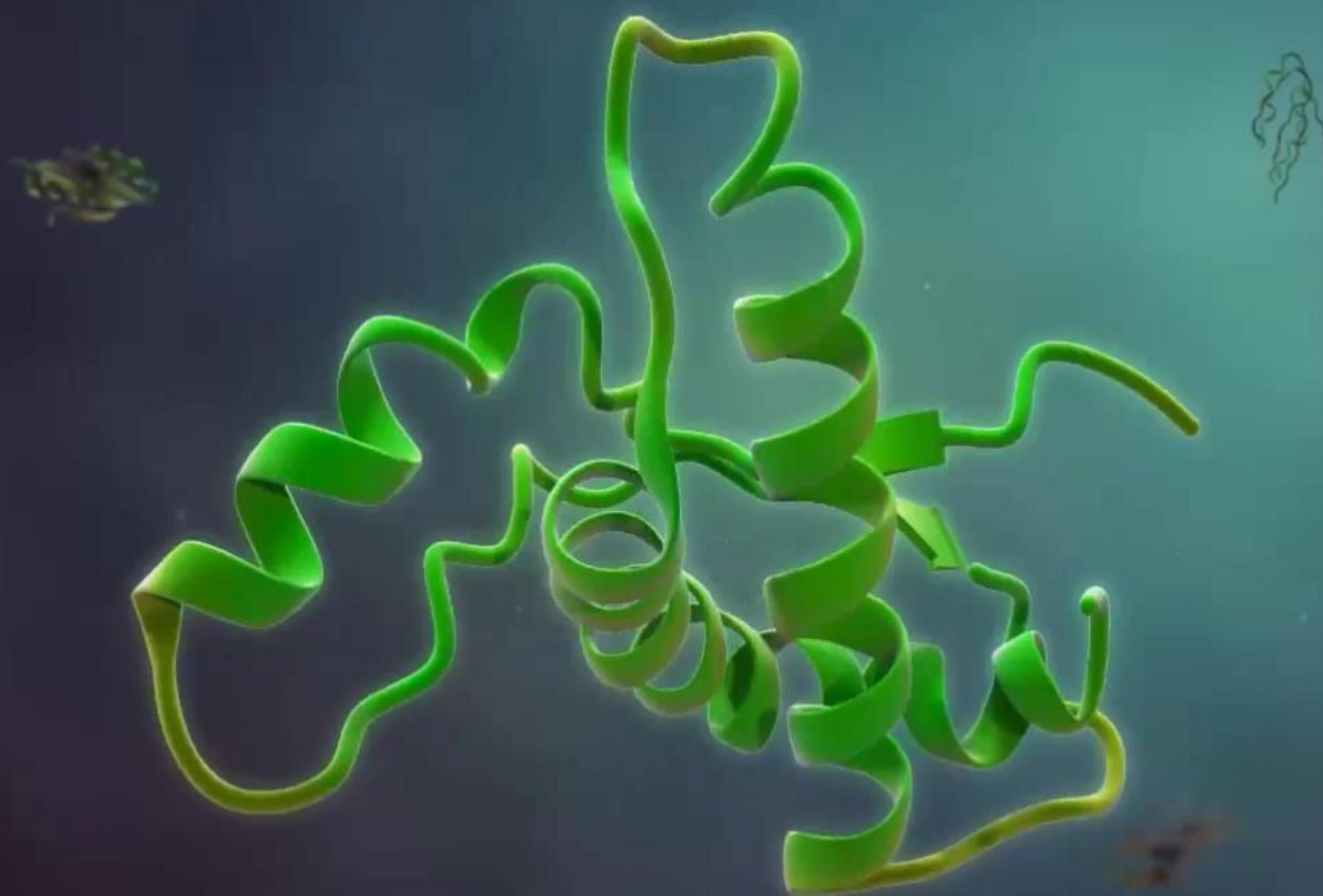


# Molecular simulations for biological problems

## Lecture 6

### Force field development, molecular mechanics

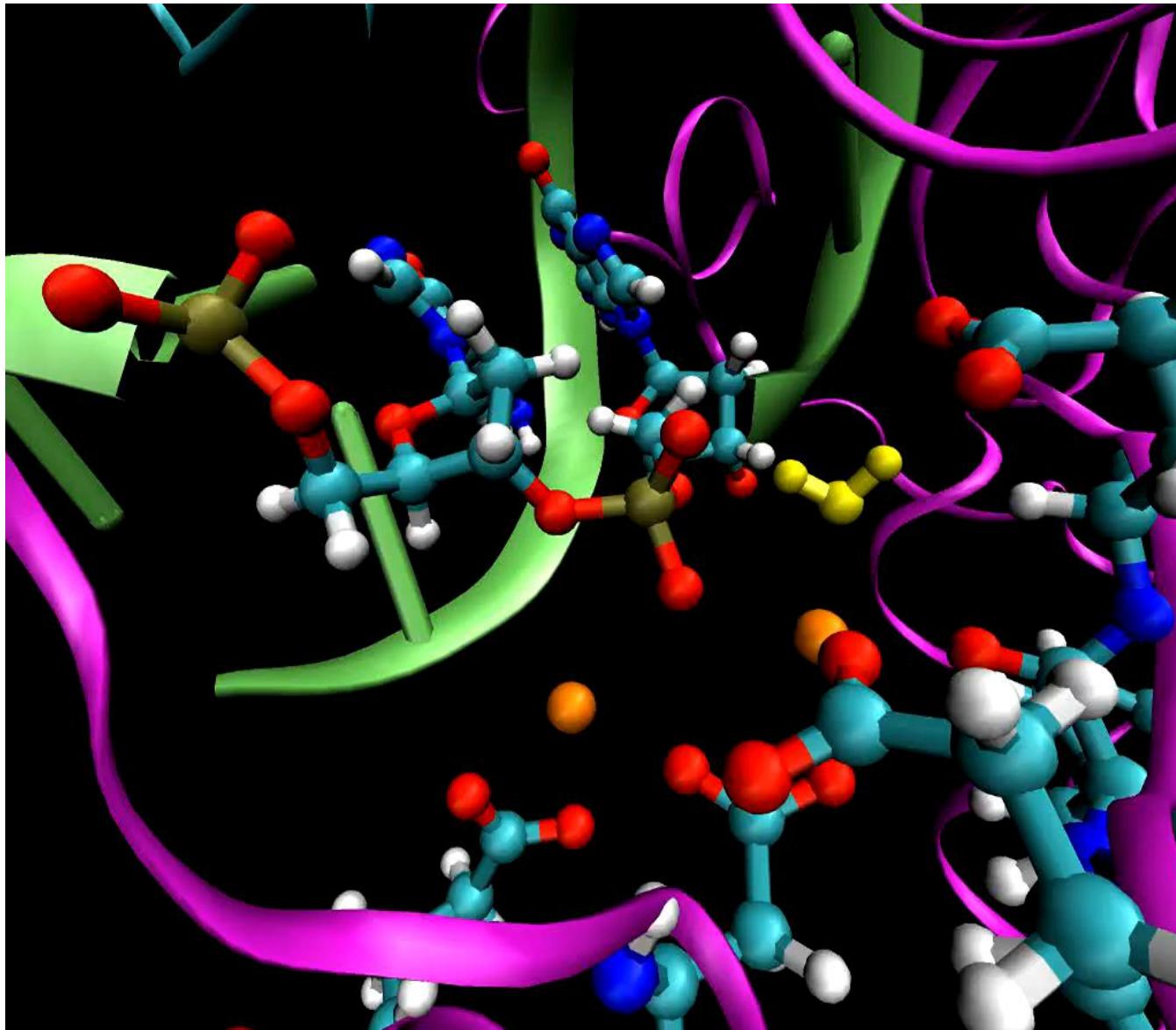
# protein misfolding, aggregation



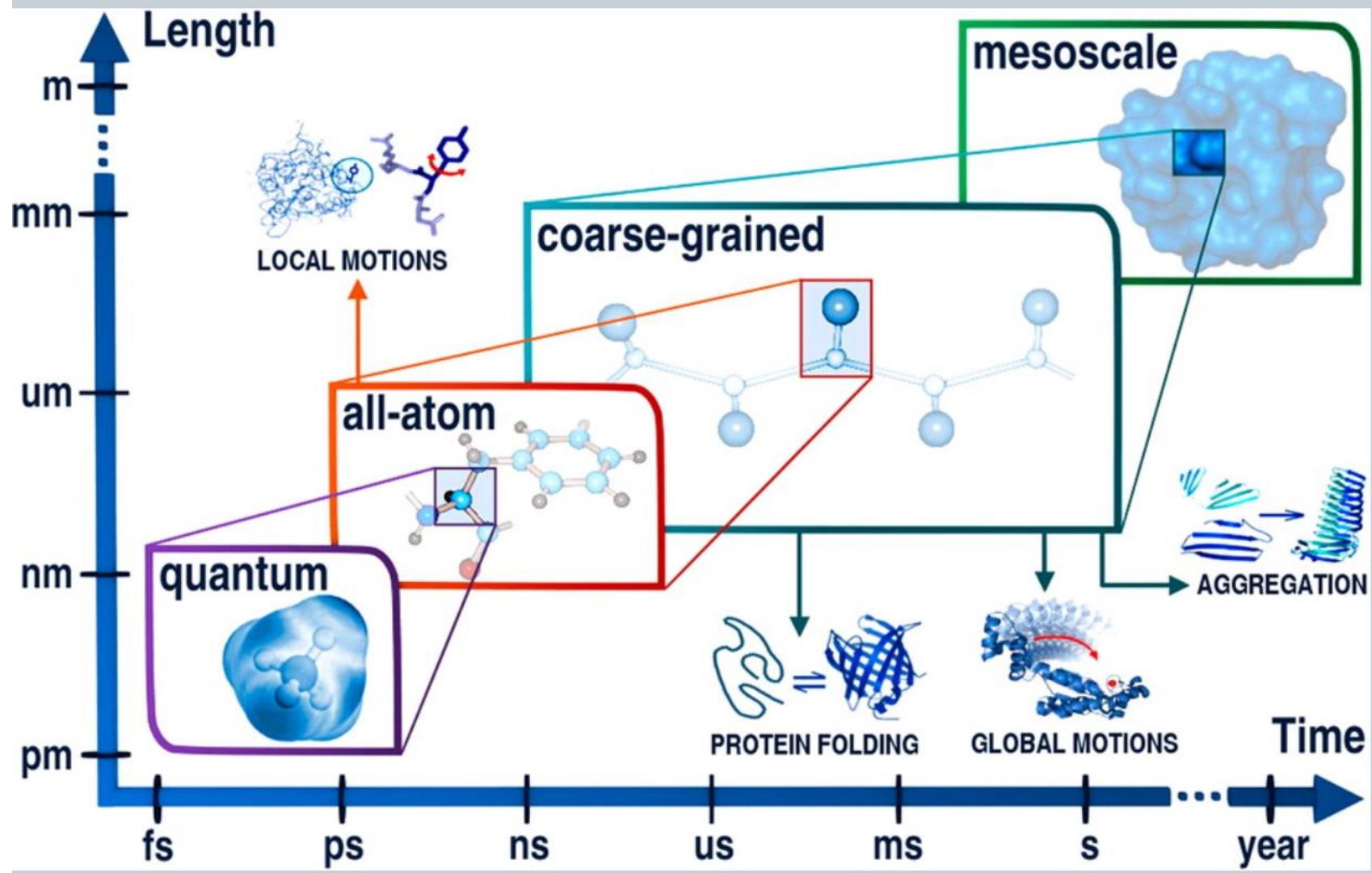
Healthy: $\alpha$ -helical structure



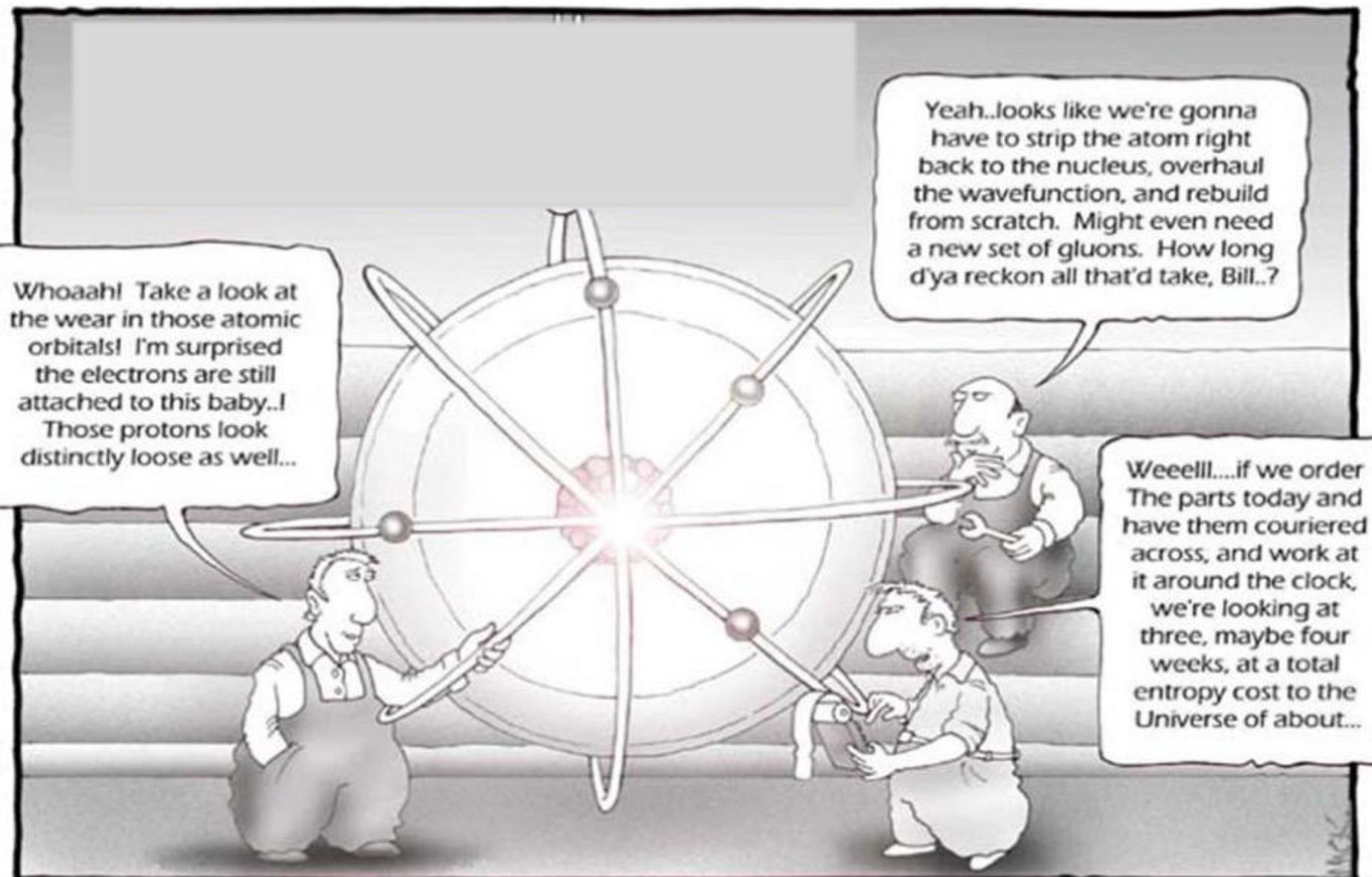
# protein action, catalysis



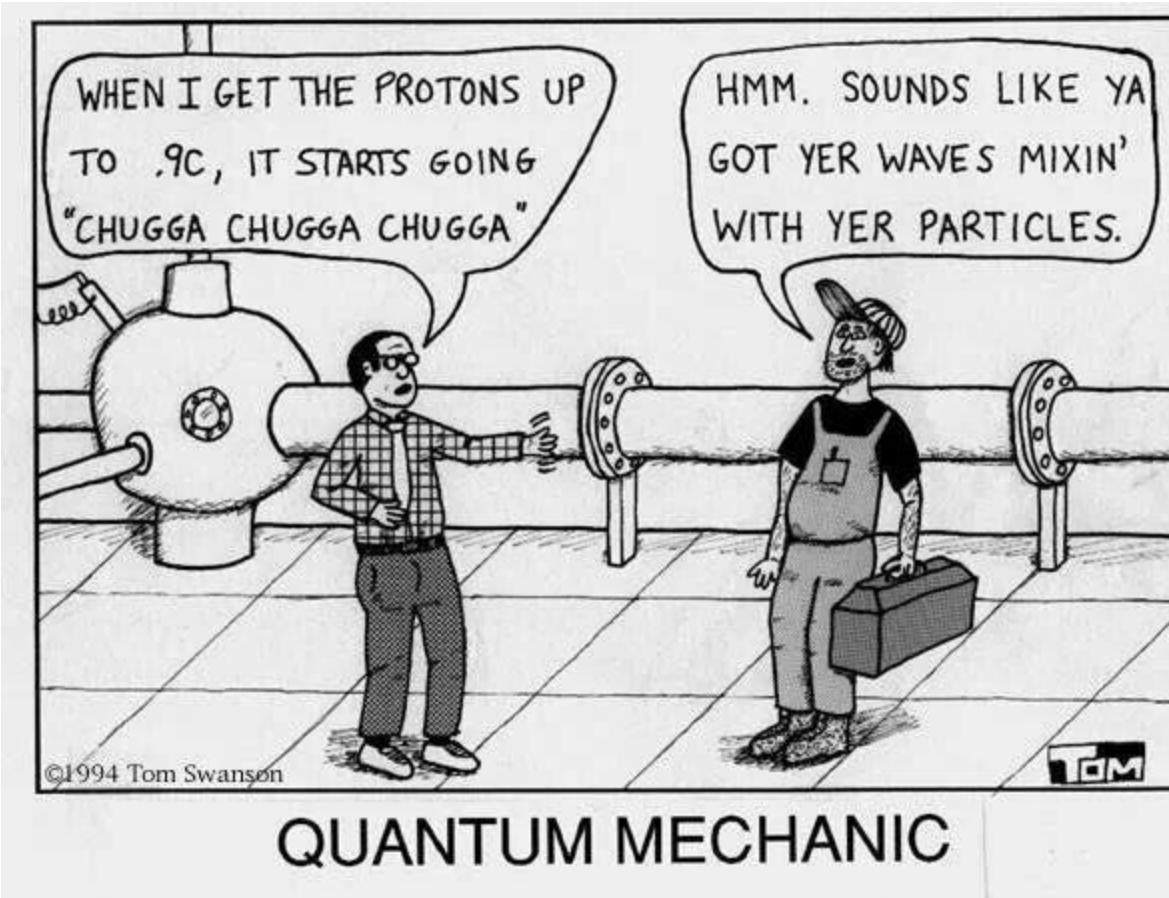
## II.3. Simulations at different scales



# Quantum mechanics



# Quantum mechanics



# Quantum mechanics

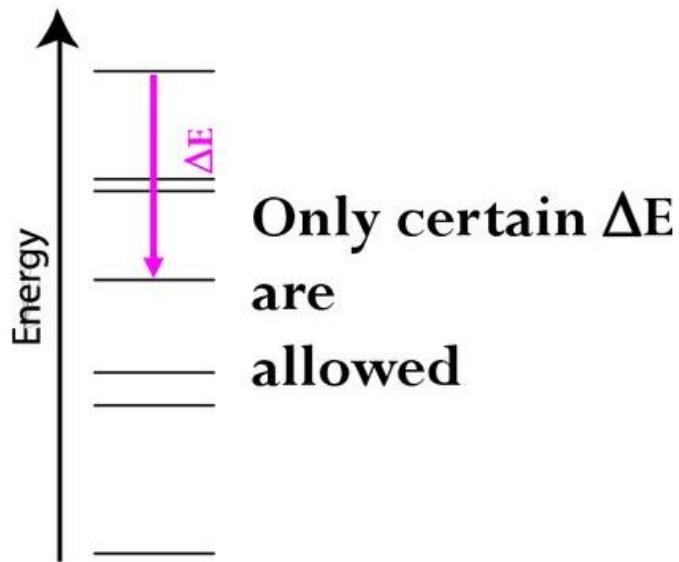
uncertainty relation

$$\Delta x \Delta p \geq \hbar$$

$$\Psi(\vec{r}, t)$$

$$\Psi^*(\vec{r}, t)^* \Psi(\vec{r}, t)$$

quantized energy spectrum

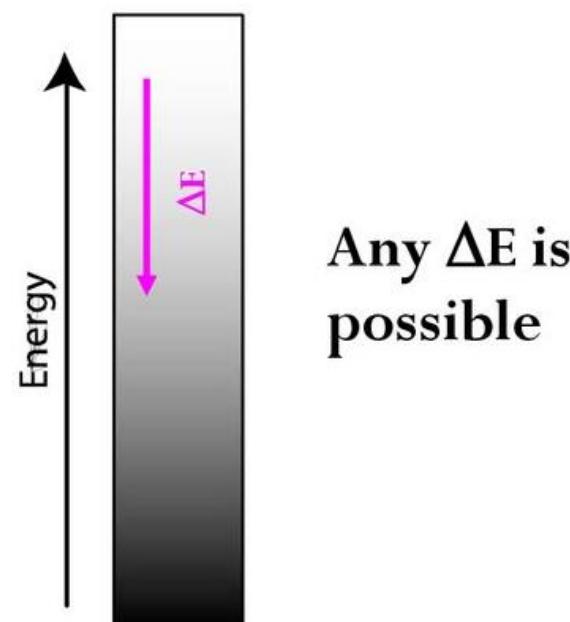


# Classical mechanics

position, momenta sharply defined

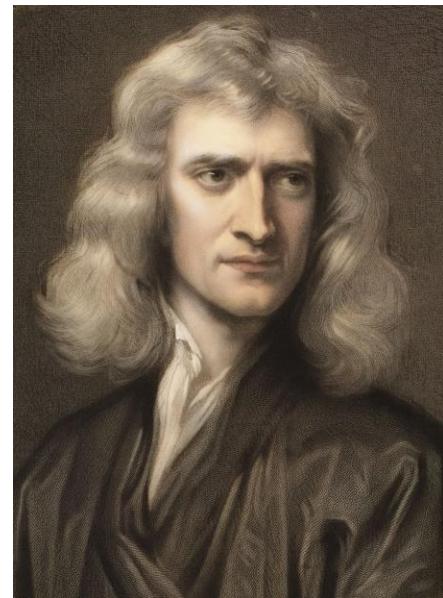
$$\vec{r}, \vec{v}$$

continuous energy spectrum



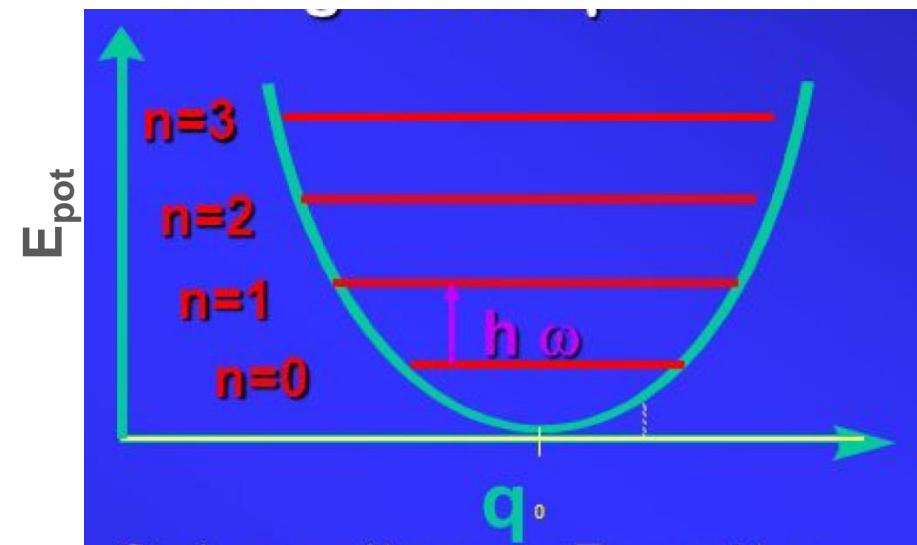


*Erwin Schrödinger*

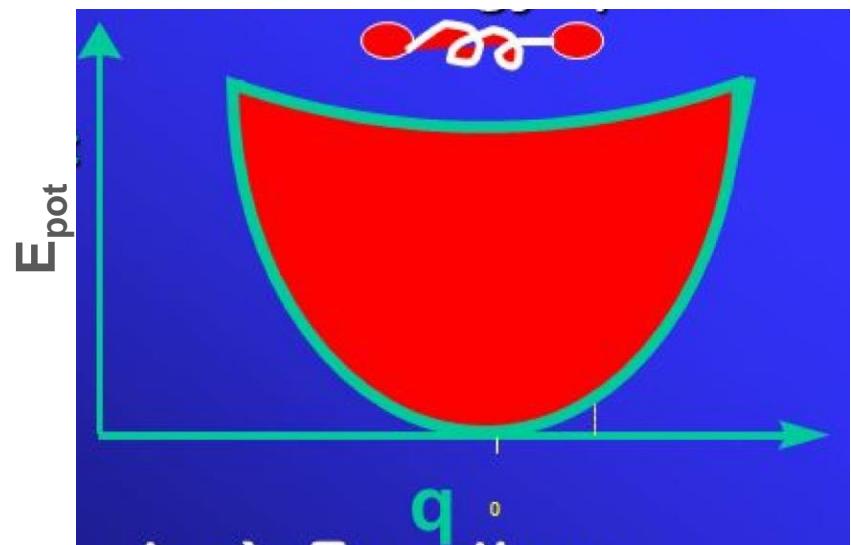


*Isaac Newton*

## quantized energy spectrum



## continuous energy spectrum



# Describing molecular motions:

continuous energy

$$E_{kin} = \frac{1}{2}mv^2$$

$$\mathbf{r}_o, \mathbf{v}_o \Rightarrow \mathbf{r}(t), \mathbf{v}(t)$$

position and velocity  $\vec{\mathbf{r}}, \vec{\mathbf{v}}$   
to be computed at any time t

$$\mathbf{F} = m\mathbf{a}$$

$$\vec{\mathbf{r}}(t) = \vec{\mathbf{r}}_o + \vec{\mathbf{v}}_o t + \frac{1}{2} \mathbf{a} t^2$$

$$\vec{\mathbf{v}}(t) = \vec{\mathbf{v}}_o + \mathbf{a}t$$

# Molecular simulations

computational method to describe the microscopic properties  
of complex systems

**problem:**

for N nuclei and n electrons time-dependent Schrödinger equation is  
not available

$$-i\hbar \frac{\delta}{\delta t} \Psi(\vec{R}_1, \vec{R}_2, \vec{R}_3, \dots, \vec{R}_N, \vec{r}_1, \vec{r}_2, \vec{r}_3, \dots, \vec{r}_n, t) = H\Psi(\vec{R}_1, \vec{R}_2, \vec{R}_3, \dots, \vec{R}_N, \vec{r}_1, \vec{r}_2, \vec{r}_3, \dots, \vec{r}_n, t)$$

# Molecular simulations

Born-Oppenheimer approximation  
separating electron and nuclei motions ( $m_{el} < m_p$ )

**total wavefunction**

$$\Psi(\vec{R}_1, \vec{R}_2, \vec{R}_3 \dots \vec{R}_N, \vec{r}_1, \vec{r}_2, \vec{r}_3, \dots \vec{r}_n) = \Psi_{nu}(\vec{R}_1, \vec{R}_2, \vec{R}_3 \dots \vec{R}_N) \Psi_{el}(\vec{r}_1, \vec{r}_2, \vec{r}_3, \dots \vec{r}_n)$$

**electronic Schrödinger equation**

$$H_{el} \Psi_{el}(\vec{r}_1, \vec{r}_2, \vec{r}_3, \dots \vec{r}_n, R) = E \Psi_{el}(\vec{r}_1, \vec{r}_2, \vec{r}_3, \dots \vec{r}_n, R)$$

**electronic Hamilton operator**

$$H_{el} = -\frac{1}{2} \sum_i \nabla_i^2 - \sum_{I,i} \frac{Z_I}{R_I r_i} + \sum_{i>j} \frac{1}{r_{ij}}$$

# Molecular simulations

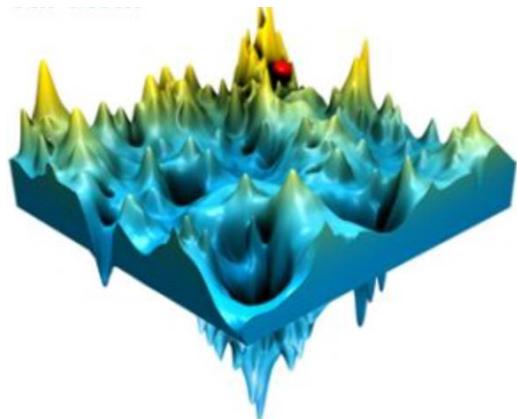
## Born-Oppenheimer approximation

nuclear Schrödinger equation

$$H_{nu} \Psi_{nu}(\vec{R}_1, \vec{R}_2, \vec{R}_3, \dots, \vec{R}_N) = E_{tot} \Psi_{nu}(\vec{R}_1, \vec{R}_2, \vec{R}_3, \dots, \vec{R}_N)$$

nuclear Hamilton operator

$$H_{nu} = -\sum_I \frac{1}{2M_I} \nabla_I^2 + E(R) + \sum_{I,J} \frac{Z_I Z_J}{R_{IJ}}$$



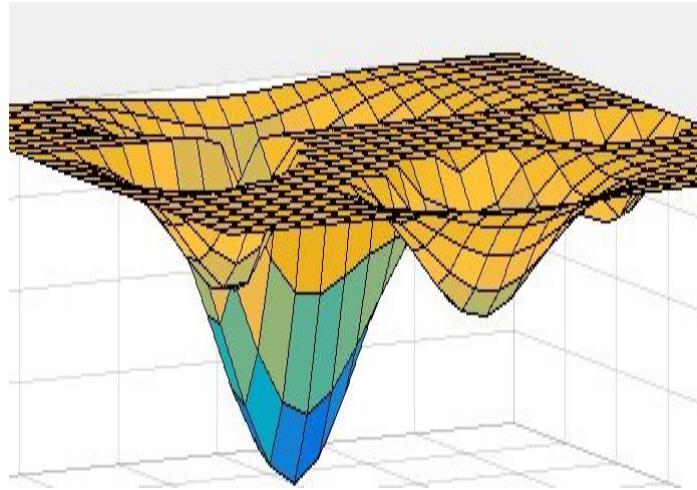
potential energy surface (PES)

$$E(R) \quad R = (\vec{R}_1, \vec{R}_2, \vec{R}_3, \dots, \vec{R}_N)$$

solve the electronic Schrödinger equation  
for each set of nuclear coordinates

# Physics-based approaches

## All-atom methods

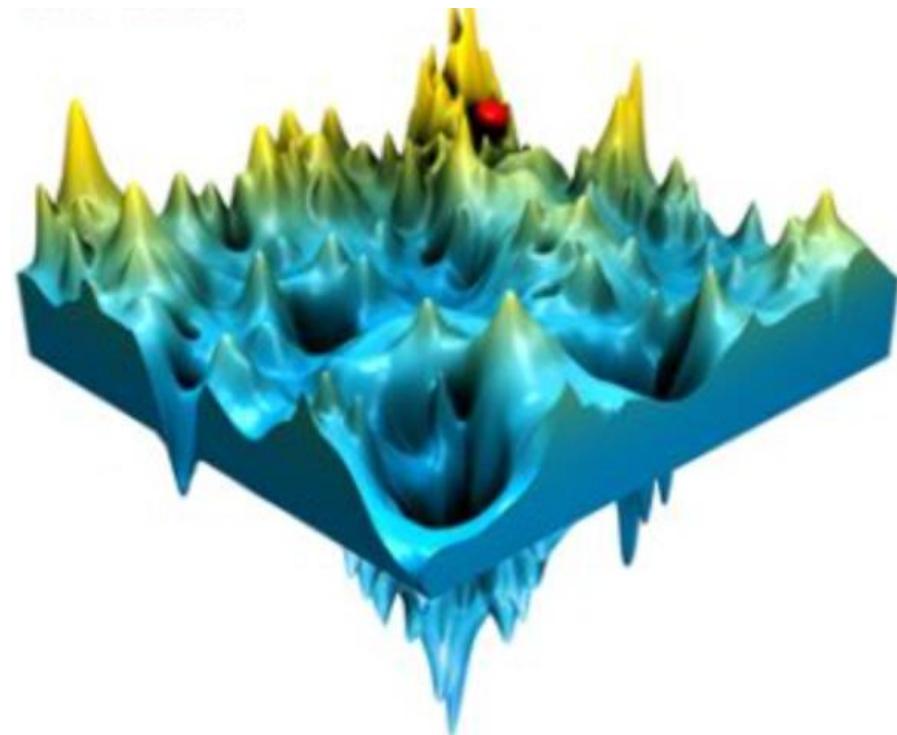


potential energy surface (PES)

*coordinates*

**Task 1:** Define the PES (*force-field*)

**Task 2:** Explore the landscape (*sampling*)



# Molecular mechanics

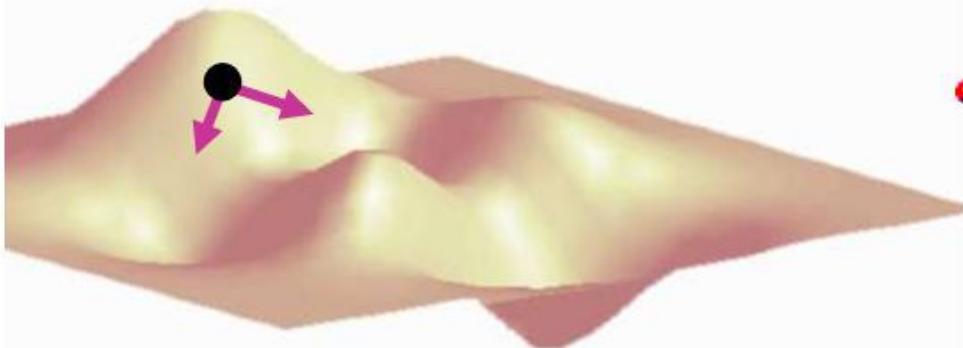
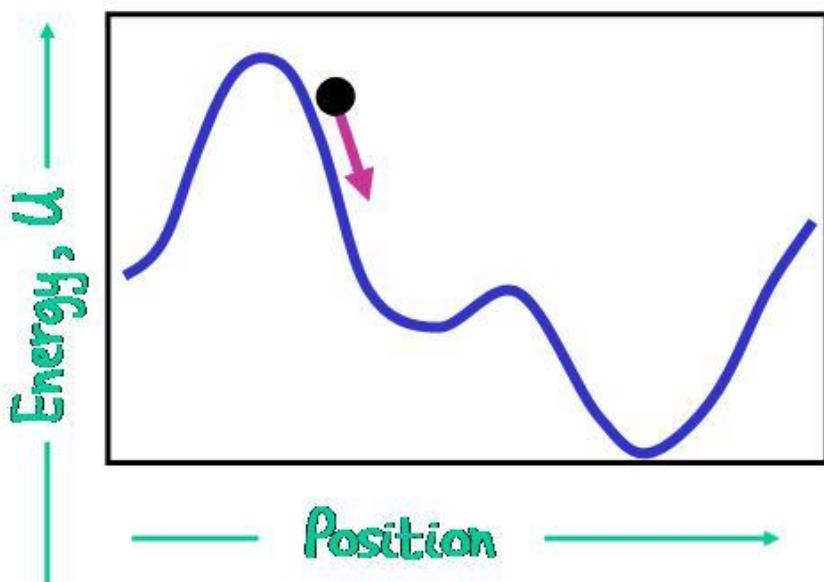
## Force fields

### Approximations

- Born-Oppenheimer approximation ( $\Psi_{\text{mol}} = \Psi_{\text{el}} \Psi_{\text{nucl}}$  ;  $E_{\text{tot}} = E_{\text{el}} + E_{\text{nucl}}$ )
- energy is the sum of pairwise interactions
- separation of conformational energy  
(bond stretch, angle bend, torsion)
- use simple mechanical functions for conformational terms
- atoms are represented by point charges

# Molecular mechanics

## TOTAL POTENTIAL ENERGY



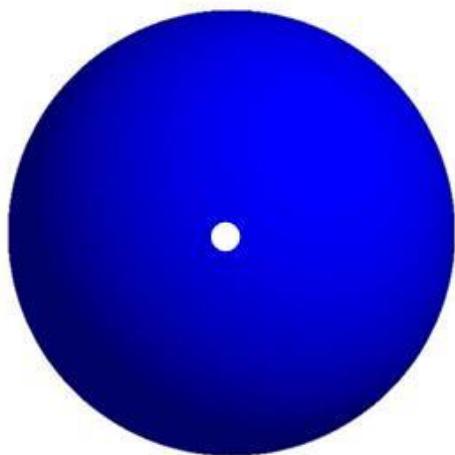
- The total potential energy or enthalpy fully defines the system,  $U$ .

- The forces are the gradients of the energy.

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

- Energy minima are stable as the net forces are zero.

# WHAT IS AN ATOM?



- A solid object.

It occupies space

- A position in space

It has (x,y,z) coordinates.

Remember we are ignoring

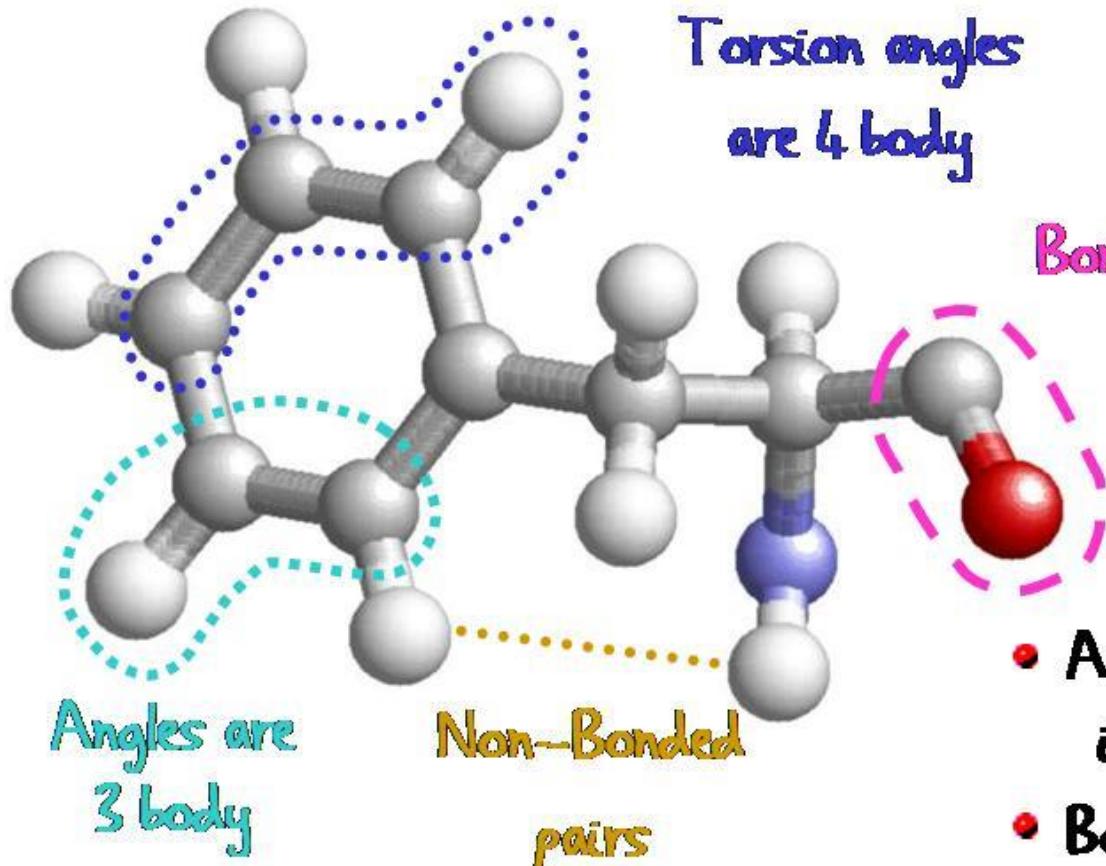
Quantum Mechanics

- It carries electric charge.

Positive or negative.

Partial (less than 1 electron).

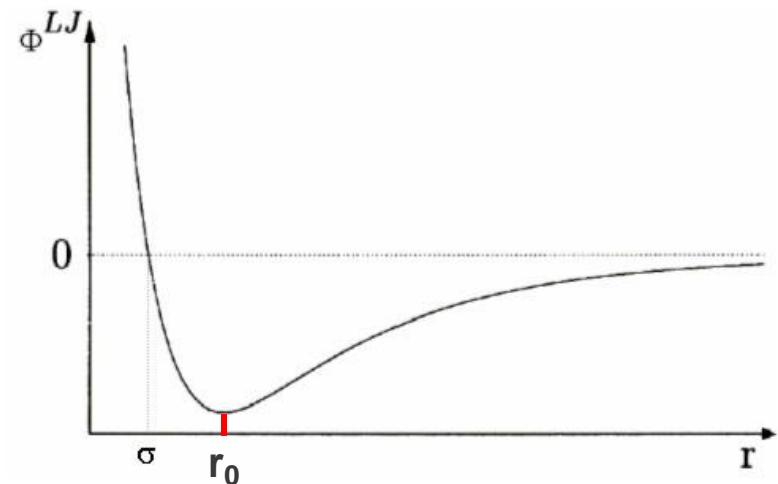
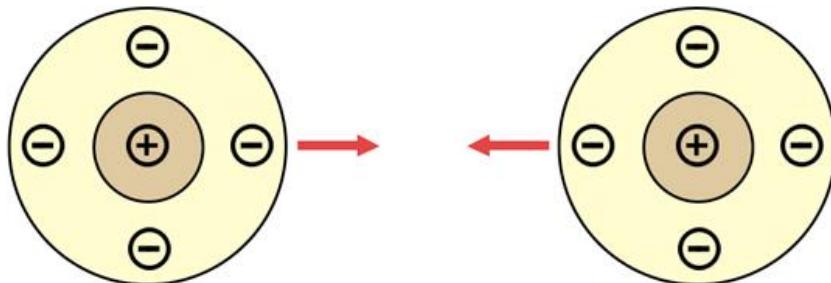
# WHAT IS A MOLECULE?



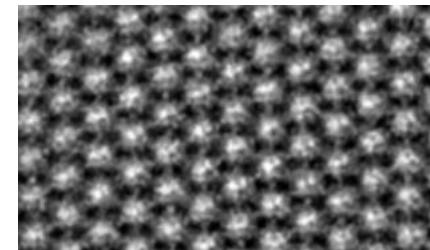
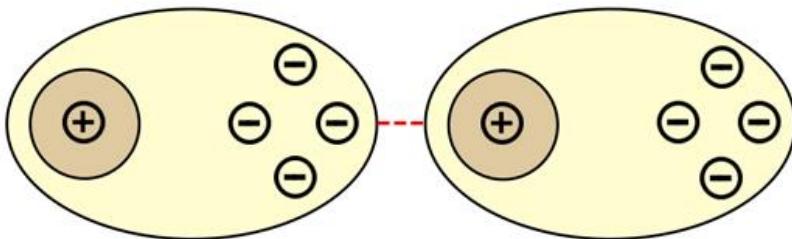
- Atoms are connected in a simple graph.
- Bonded Interactions:  
2, 3, 4 body.
- Non-Bonded Interactions.

# Atomic properties

atomic radius



transient polarisation and attraction

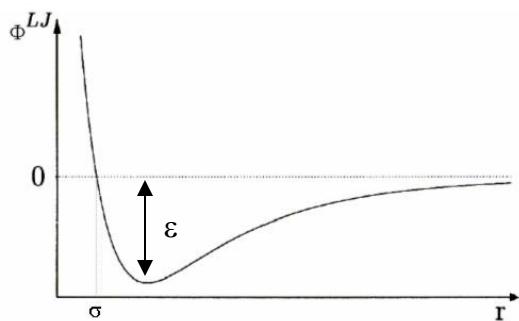


metal crystals, Pauling

# Atomic properties

## atomic radius

### Lennard-Jones potential



### 12-6 potential

$$E(r) = 4\varepsilon \left[ \left( \frac{\sigma}{r} \right)^{12} - \left( \frac{\sigma}{r} \right)^6 \right]$$

Cross diameter:  $\sigma$ , depth of potential valley:  $\varepsilon$

Different atoms:

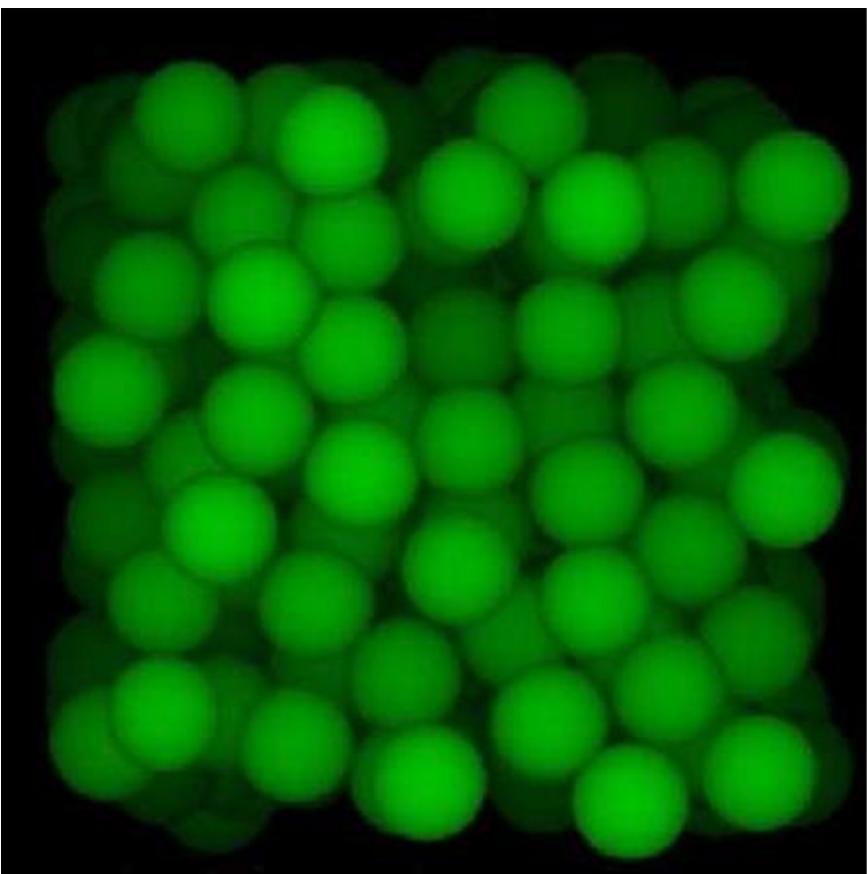
$$\sigma_{AB} = \frac{1}{2}(\sigma_{AA} + \sigma_{BB})$$

$$\varepsilon_{AB} = \sqrt{\varepsilon_{AA} \varepsilon_{BB}}$$

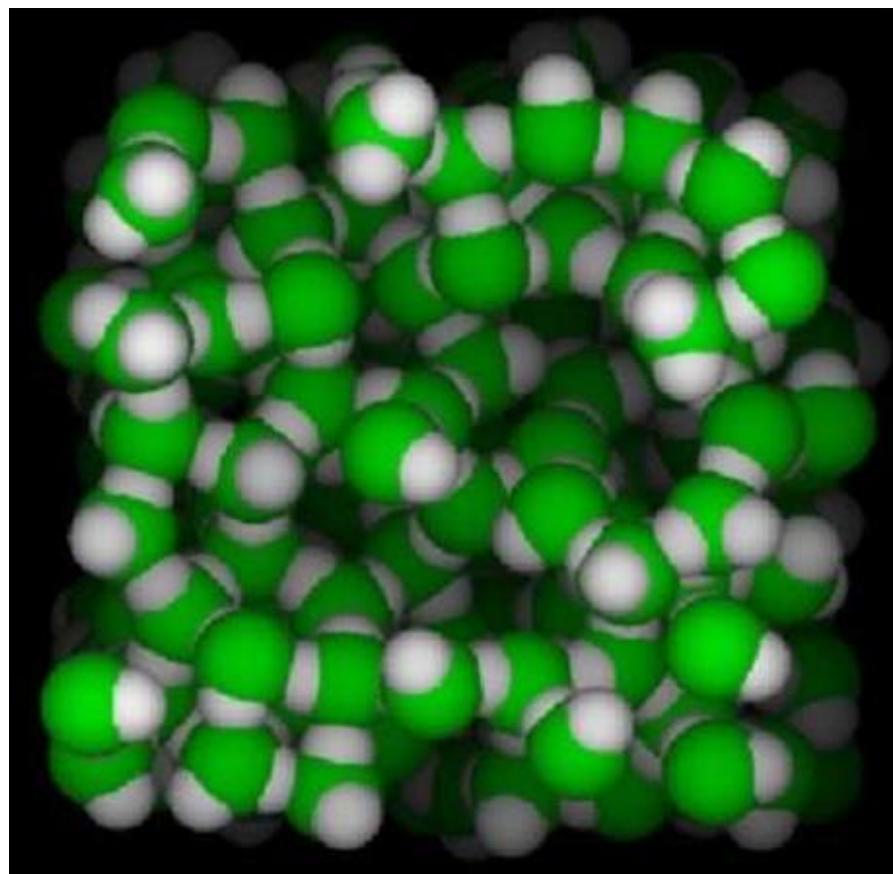
1,4 interaction represent a special case (scaling 1/1.2)

## semi-empirical (simulation of liquids)

# Atomic properties



argon



water

# Atomic properties

## atomic charge

### electrostatic interactions

$$\varphi(\vec{r}) = \frac{1}{4\pi\epsilon_0} \left[ \frac{\textcolor{blue}{q}}{r} + \frac{\vec{\mu} \cdot \vec{r}}{r^3} + \frac{1}{2} \frac{\vec{r} \cdot \textcolor{magenta}{Q} \cdot \vec{r}}{r^5} + \dots \right]$$

### Coulomb law

$$E(el) = \sum_{i=1}^N \sum_{j=i+1}^N \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

## Problems:

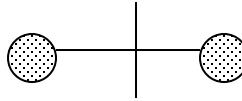
- atomic charges (*non-physical parameter, conformation dependent*)
- $\epsilon_0$  (*dielectric inhomogeneity of proteins*)
- higher order interactions are ignored  
(*dipole-dipole, dipole-quadrupole, etc.*)

# Atomic properties

atomic charge – arbitrary, atoms have no clear boundaries

## Mulliken analysis

*basis set dependent!*



$$\mathbf{D}_{\mu\nu} = 2 \sum_i \mathbf{C}_{\mu i} \mathbf{C}_{\nu i}^*$$

$$\mathbf{P}_{\mu\nu} = \mathbf{D}_{\mu\nu} \mathbf{S}_{\mu\nu}$$

electron density  $\sum_{\mu} P_{\nu\mu}$

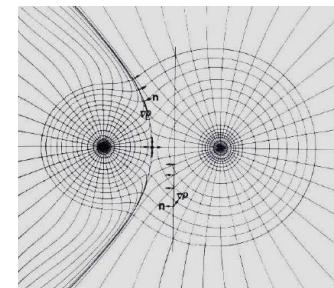
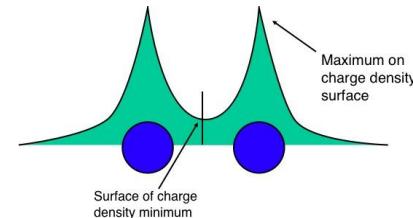
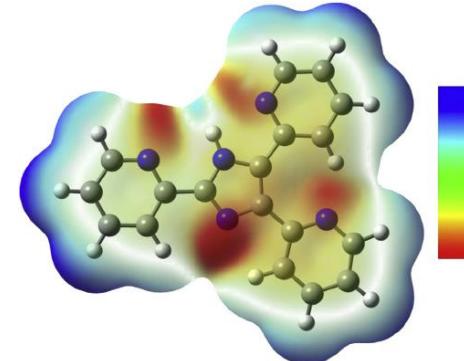
## Bader analysis

*based on electron density*

gradient field vector of  $\rho$ , zero-flux surfaces

Laplacian of  $\rho$

$$\nabla \rho(r_s) \bullet n(r_s) = 0$$

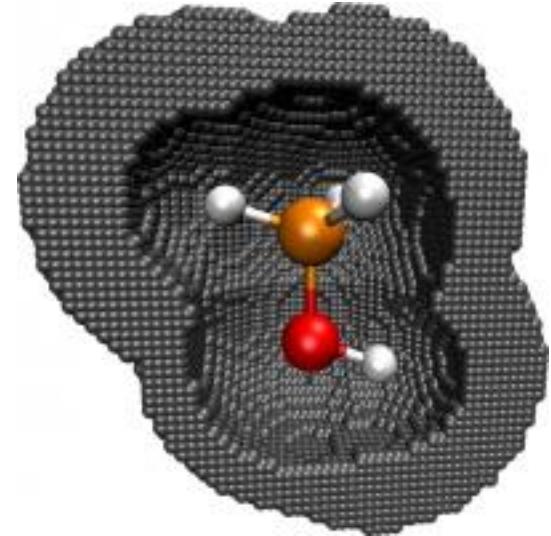


# Atomic properties

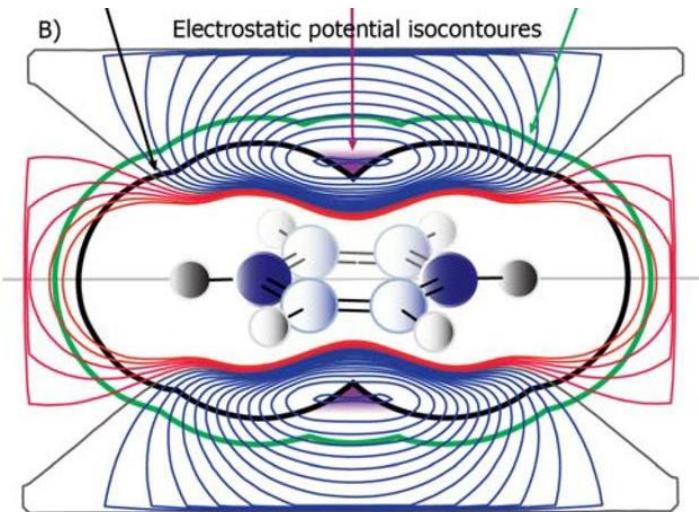
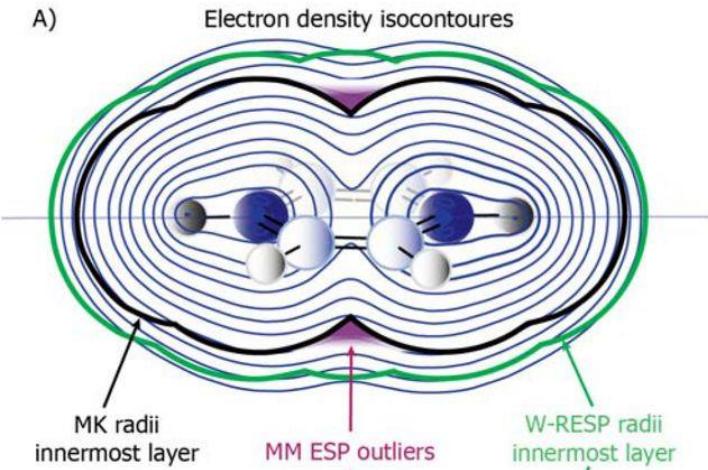
## atomic charge

### Fitting to electrostatic potential (RESP)

$$\phi(r) = \phi_{mag}(r) + \phi_{el}(r) = \sum_{N=1}^M \frac{Z_A}{|r - R_N|} - \int \frac{dr' \rho(r)}{|r' - r|}$$



$$R = \sum_{i=1}^N w_i (\phi_i^0 - \phi_i^{calc})^2$$

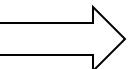


# Atomic properties

## atomic charge

Parametrisation of charges

Environmental effects:

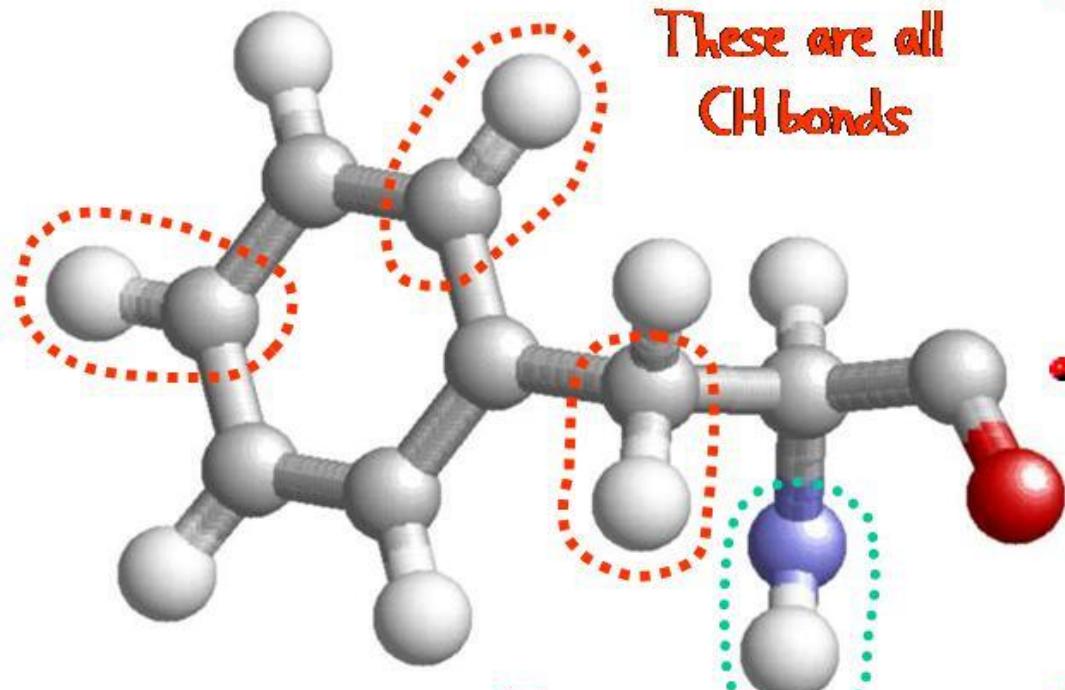
Smaller charge separation in gas phase  polarisation

- higher basis set
- larger fragments
- longer simulations

Effect of geometry: averaging conformers

Polarizable force fields ---- TEST!

# FORCES BETWEEN ATOMS



- Total energy is sum of individual contributions:  
Terms are additive.
- Energy terms transferable:  
A bond is a bond in any environment.
- Ignore quantum effects:  
Atoms are like balls,  
forces like springs.

# Force fields

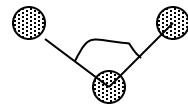
$$E(r^N) = \sum_{bonds} \frac{k_i}{2} (l_i - l_{i,0})^2 + \sum_{angles} \frac{k_i}{2} (\theta_i - \theta_{i,0})^2 + \\ + \sum_{torsions} \frac{V_n}{2} (1 + \cos(n\omega - \gamma)) + \\ + \sum_{i=1}^N \sum_{j=i+1}^N \left( 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \right)$$

## Parameters:

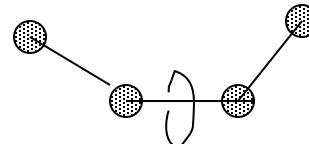
- force constants ( $k, V$ )
- equilibrium values ( $l_{i,0}, \theta_{i,0}$ )
- atomic data ( $q_i, \epsilon_i, \sigma_i$ )



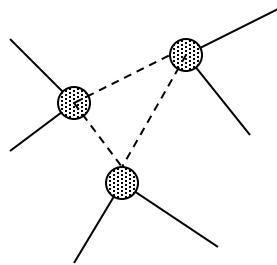
Bond stretch



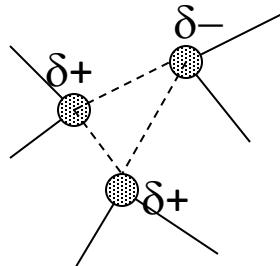
Angle bend



Torsion



van der Waals



electrostatics

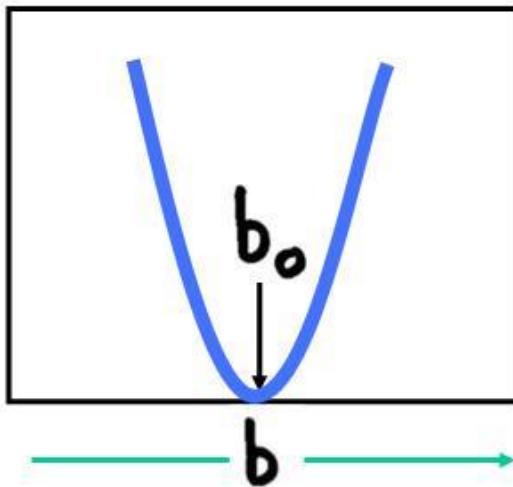
# Force field terms

## BOND STRETCHING

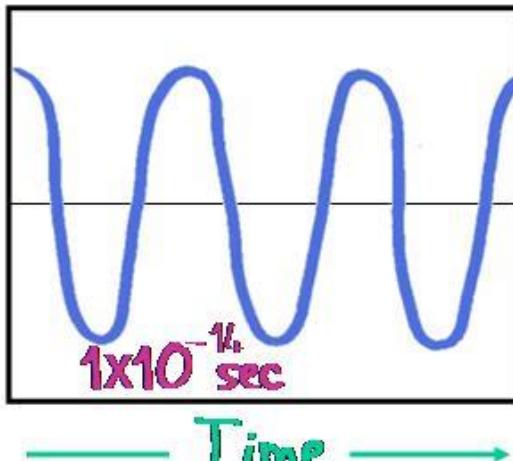


b

- Energy,  $U$

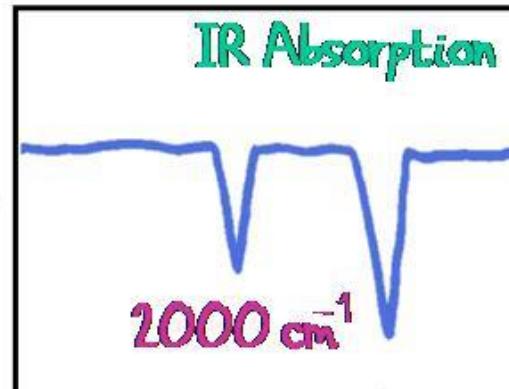


- Amplitude



- Just a spring.
- Simple quadratic form.
- $U(b) = \frac{1}{2} K_b (b - b_0)^2$
- Get  $b_0$  from x-ray.
- Get  $K_b$  from spectroscopy.

- Absorption



# Force fields

## Bond stretch



Harmonic approximation:

$$E(l) = \frac{k}{2}(l - l_0)^2 \quad \text{Hook law}$$

Anharmonic approximation

$$E(l) = D_e \{1 - \exp[-a(l - l_0)]\}^2$$

Morse potential

Extension:

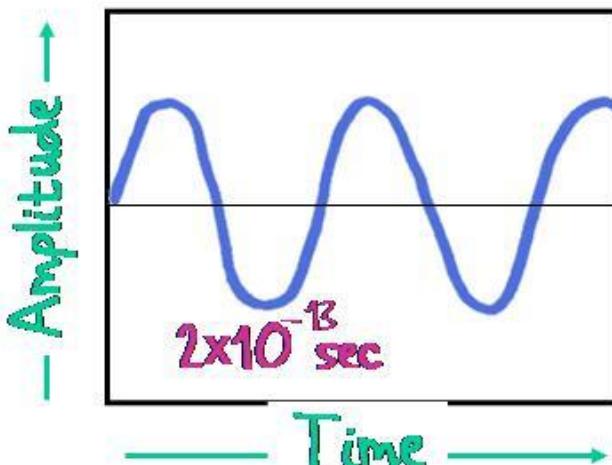
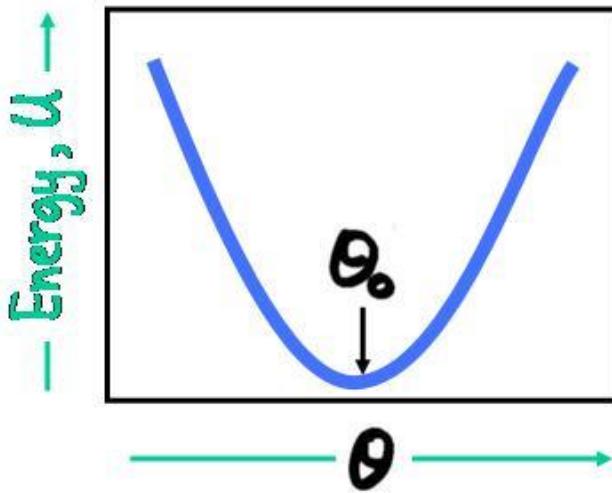
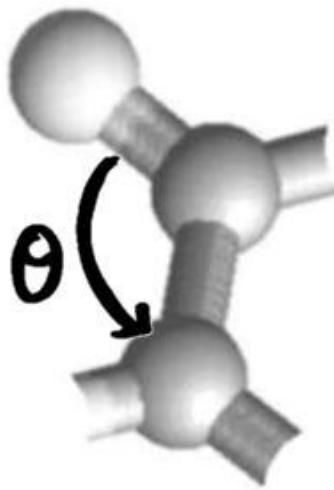
$$E(l) = \frac{k}{2}(l - l_0)^2 [1 - k'(l - l_0) - k''(l - l_0)^2 - k'''(l - l_0)^3 \dots]$$

Parameter determination :

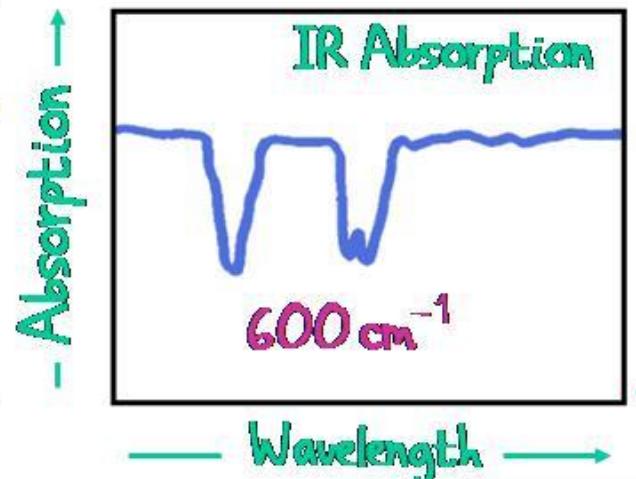
*ab initio* calculation, geometria optimisation, vibrational analysis

# Force field terms

## BOND ANGLE BENDING



- Simple quadratic form.  
$$U(\theta) = \frac{1}{2} K_\theta (\theta - \theta_0)^2$$
- Get  $\theta_0$  from x-ray
- Get  $K_\theta$  from spectroscopy.

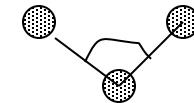


# Force fields

## Angle bending

Harmonic approximation:

$$E(\theta) = \frac{k}{2} (\theta - \theta_0)^2$$



Angle bend

Anharmonic approximation

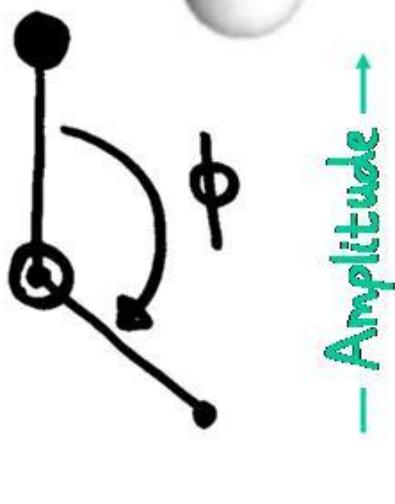
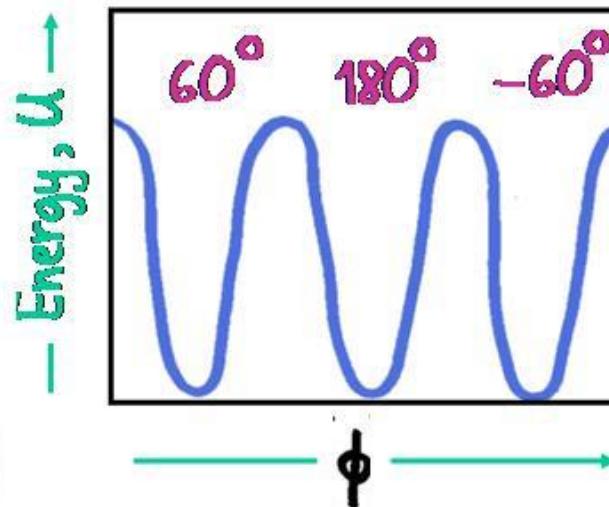
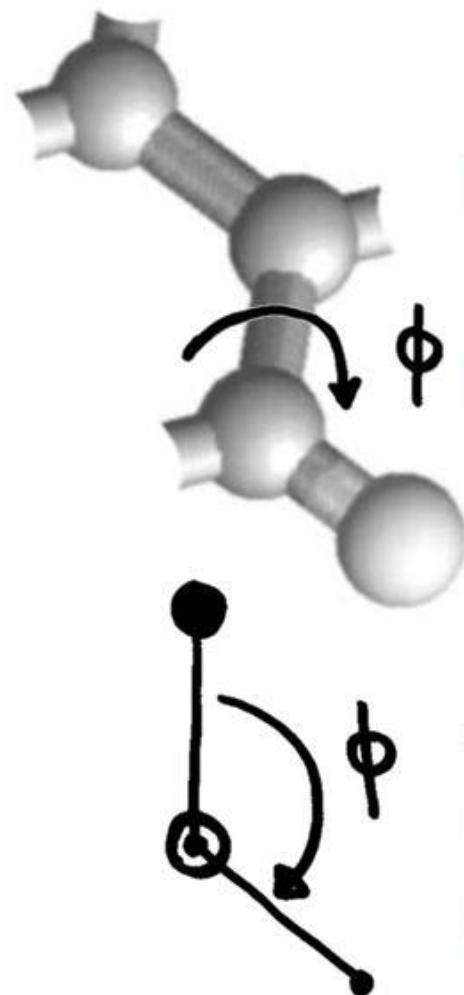
$$E(\theta) = \frac{k}{2} (\theta - \theta_0)^2 [1 - k'(\theta - \theta_0) - k''(\theta - \theta_0)^2 - k'''(\theta - \theta_0)^3 \dots]$$

Parameter determination :

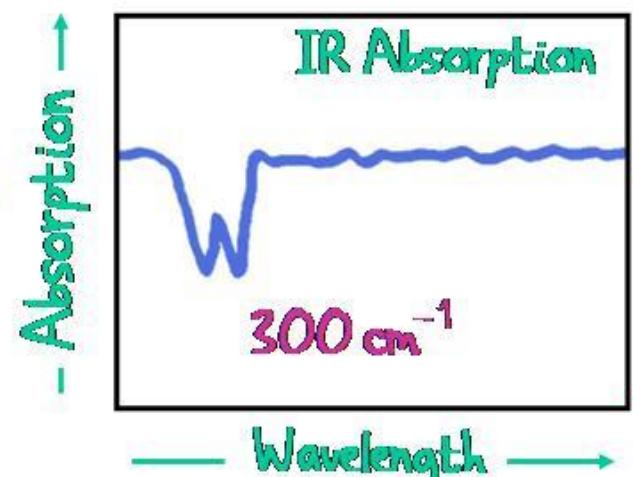
*ab initio* calculation, IR spectroscopy, vibrational analysis

# Force field terms

## BOND TWISTING



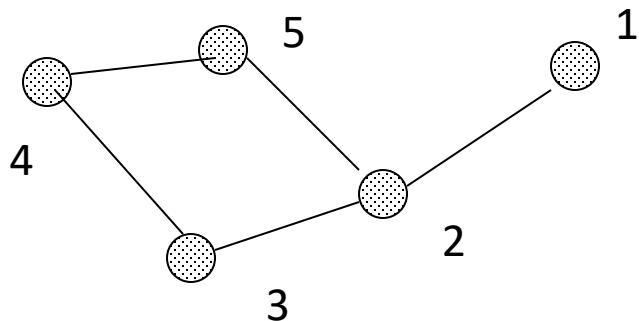
- Simple periodic form.
- $$U(\phi) = K_\phi [1 - \cos(n\phi + \delta)]$$
- $K_\phi \sim 2 \text{ kcal/mol}$
  - $n = 2, 3, 6$  by symmetry.



# Force fields

## Torsion

Planar systems:  
“improper torsion”

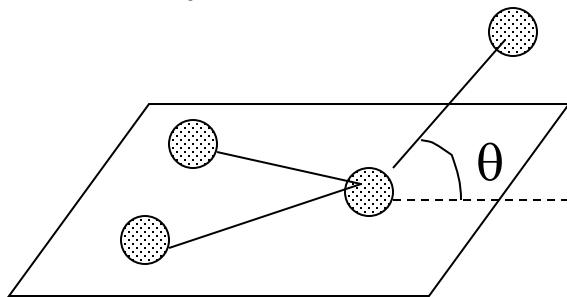


$$E(\omega) = \sum_{n=0}^N \frac{V_n}{2} [1 + \cos(n\omega - \gamma)]$$

1-5-3-2      (not 1-2-3-4)

$$E(\omega) = k(1 - \cos 2\omega)$$

“out-of-plane torsion”



Planar systems: out of plane angles

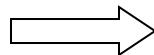
$$E(\theta) = \frac{k}{2} \theta^2$$

# Force fields

## Parametrisation

*ab initio* potential map :

MP2/TZP, DFT method  
Gas phase



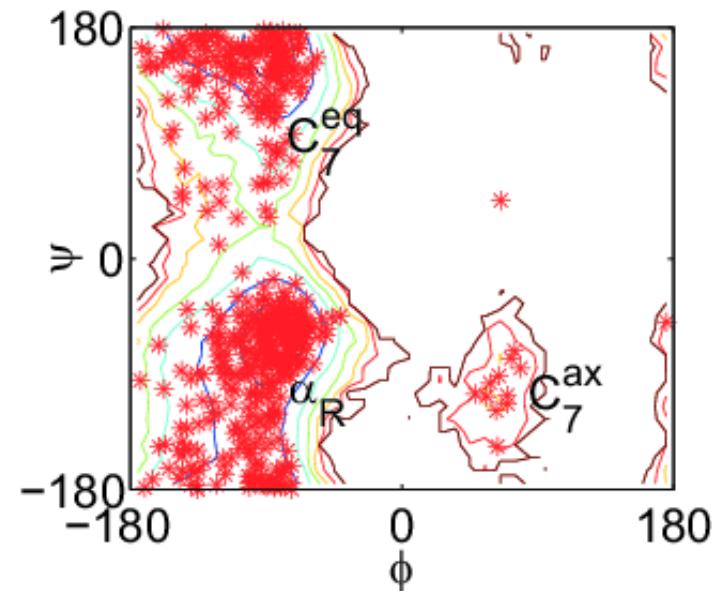
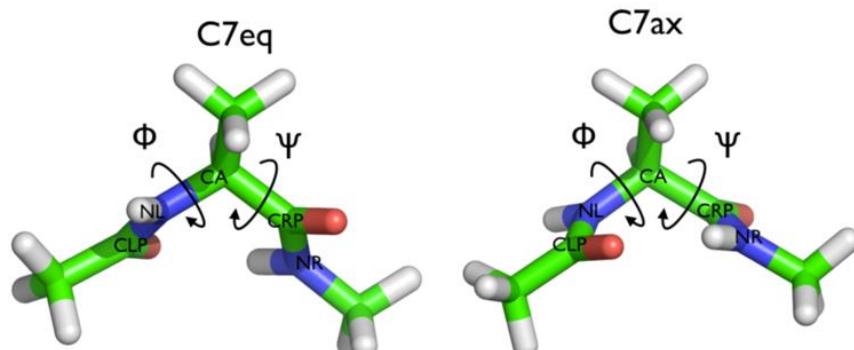
geometric parameters  
force constants

problem:

energy minimum of dipeptides are different than  
that of oligopeptides

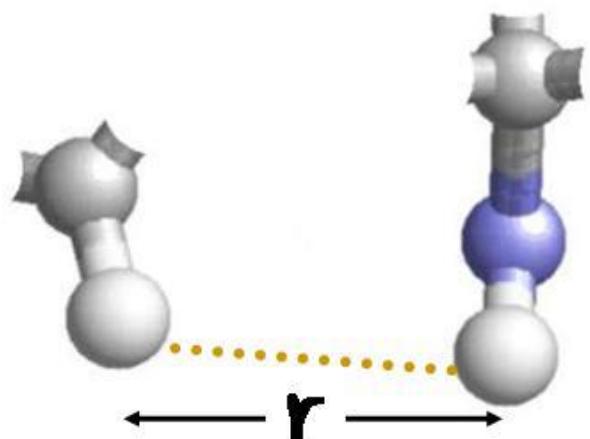
solution:

- fit to high resolution structures
- solution structures (NMR)



# Force field nonbonded terms

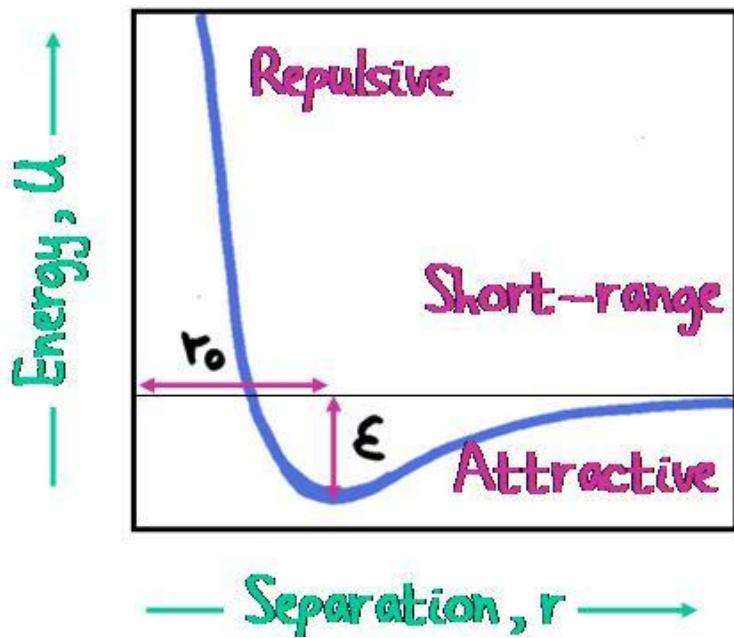
## VAN DER WAALS INTERACTION



- Weak interaction

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

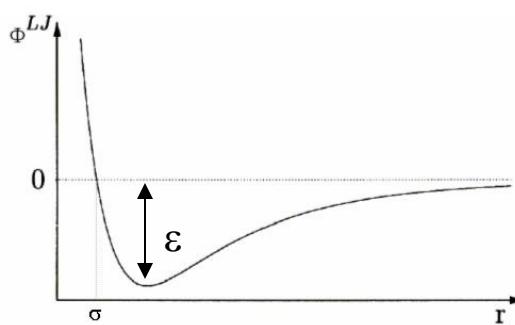
$$\epsilon \sim 0.2 \text{ kcal/mol}, r_0 = 3.5 \text{ \AA}$$



- Same form for all atoms.
- Can be large for a large molecule.

# Force fields nonbonded terms

## van der Waals



12-6 potential

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

Cross diameter:  $\sigma$ , depth of potential valley:  $\epsilon$

Different atoms:

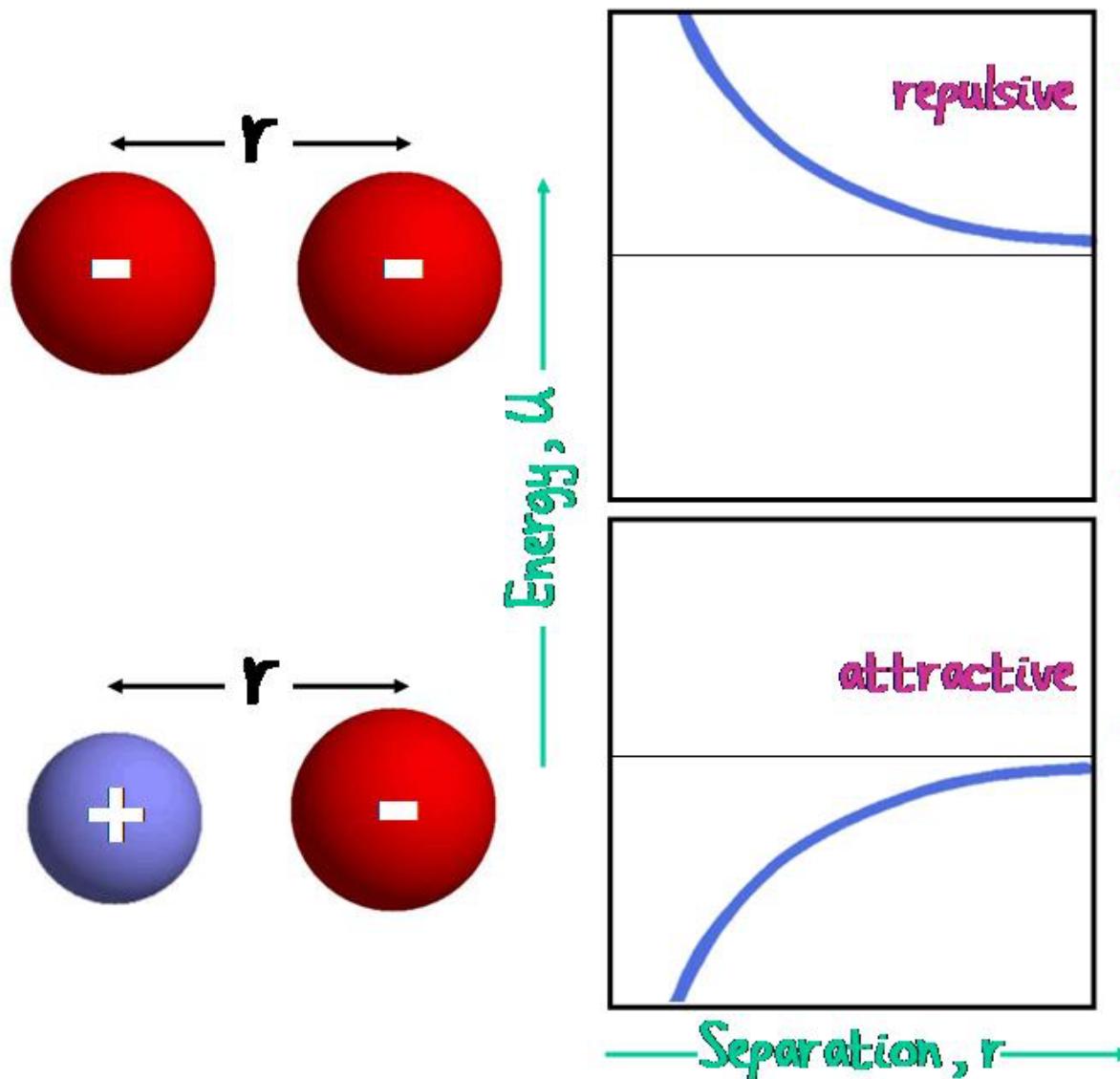
$$\sigma_{AB} = \frac{1}{2}(\sigma_{AA} + \sigma_{BB})$$

$$\epsilon_{AB} = \sqrt{\epsilon_{AA} \epsilon_{BB}}$$

1,4 interaction represent a special case (scaling 1/1.2)

# Force field nonbonded terms

## ELECTROSTATICS INTERACTION



- Long-range.  
Repulsive & attractive.

$$U(r) = 332 q_i q_j / r$$

- All atoms carry partial charges.
- Charge depends on:  
nature of atom,  
state of ionization,  
environment.

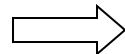
# Force fields nonbonded terms

## van der Waals parameters

Old days: *ab initio* calculations in gas-phase

Problem:

many-body interactions



effective pair-potentials

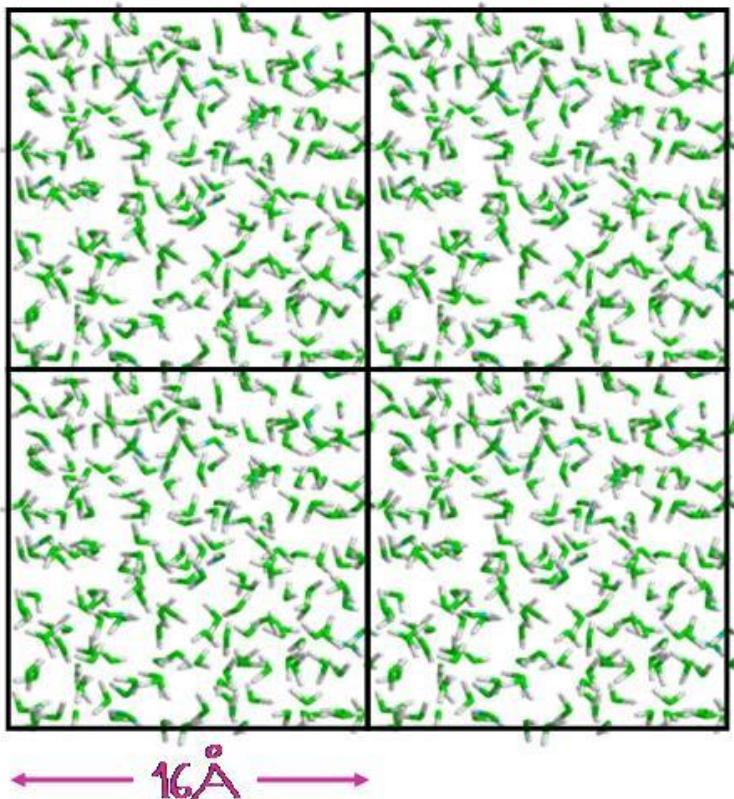
Solution:

Parameter testing simulations in solution

Comparison of experimental and computed properties

- geometry, pair correlation functions
- heat capacity, internal energy
- dipole moment, dielectric constant
- density

# SIMULATING LIQUIDS



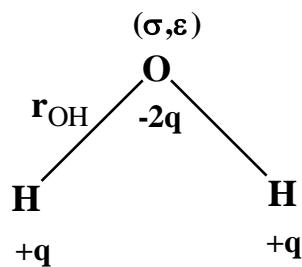
- Periodic box with 216 water molecules. Simulate motion for 100 ps.
- Calculate key experimental properties:
  - Heat of vaporization
  - Structure.
  - Internal pressure
  - Diffusion constant
- Compare with experiment and calibrate.

Rahman & Stillinger 1970

# Parametrisation issue

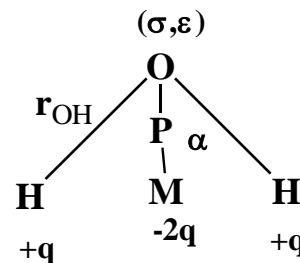
## Water

3 point model



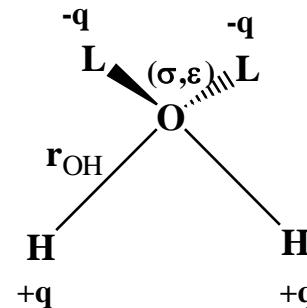
SPC, SPC/E, TIP3P

4 point model



TIP4P  
polarizable:  
BSV, Chialvo-Cummings,  
Dang-Chang, PPC

5 point model



ST2, TIP5P

Reproduced properties:

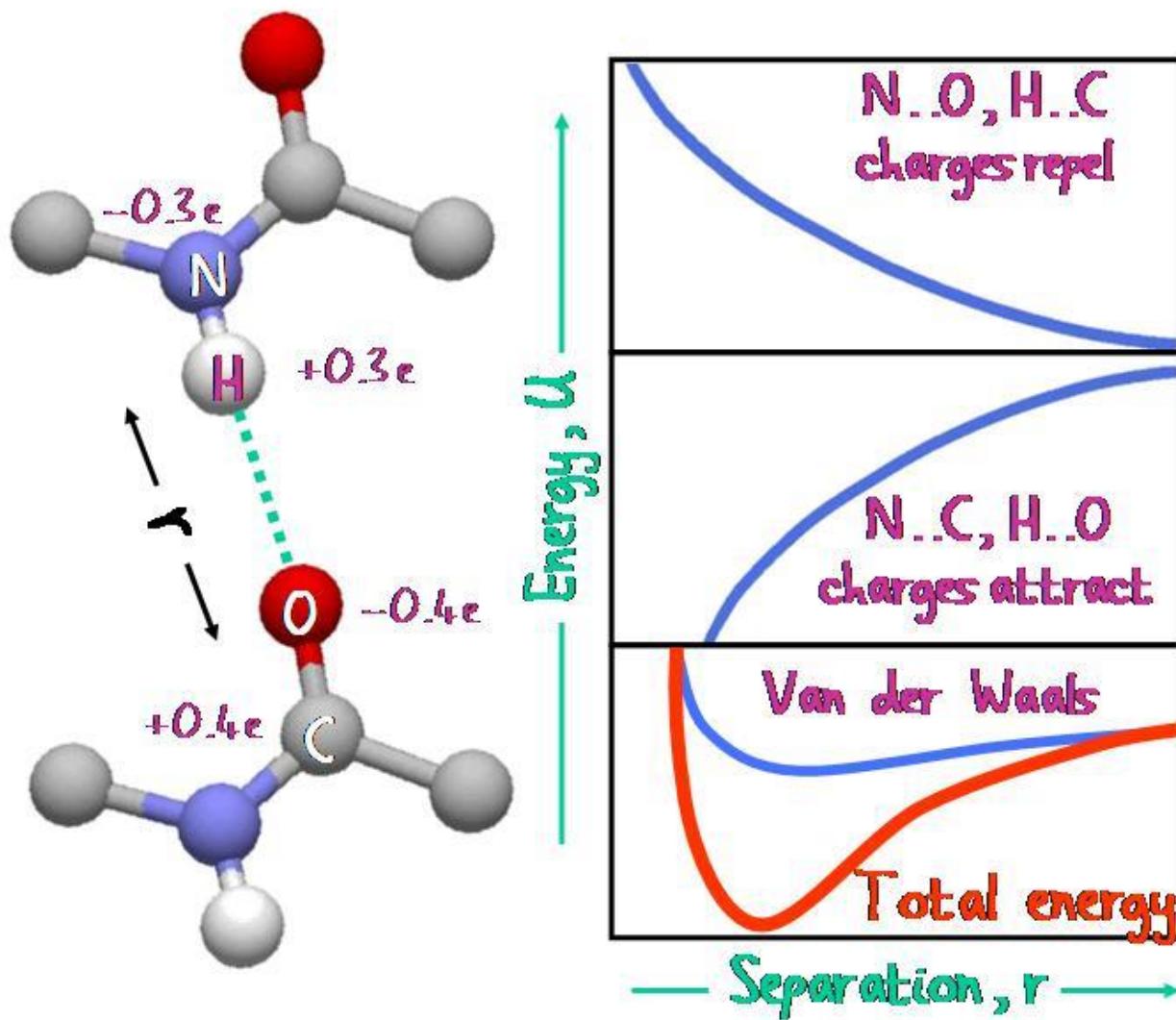
SPC, TIP4P: structure, thermodynamics, dynamics

SPC/E: average polarizability of molecules

BSV: dielectric constant, structure

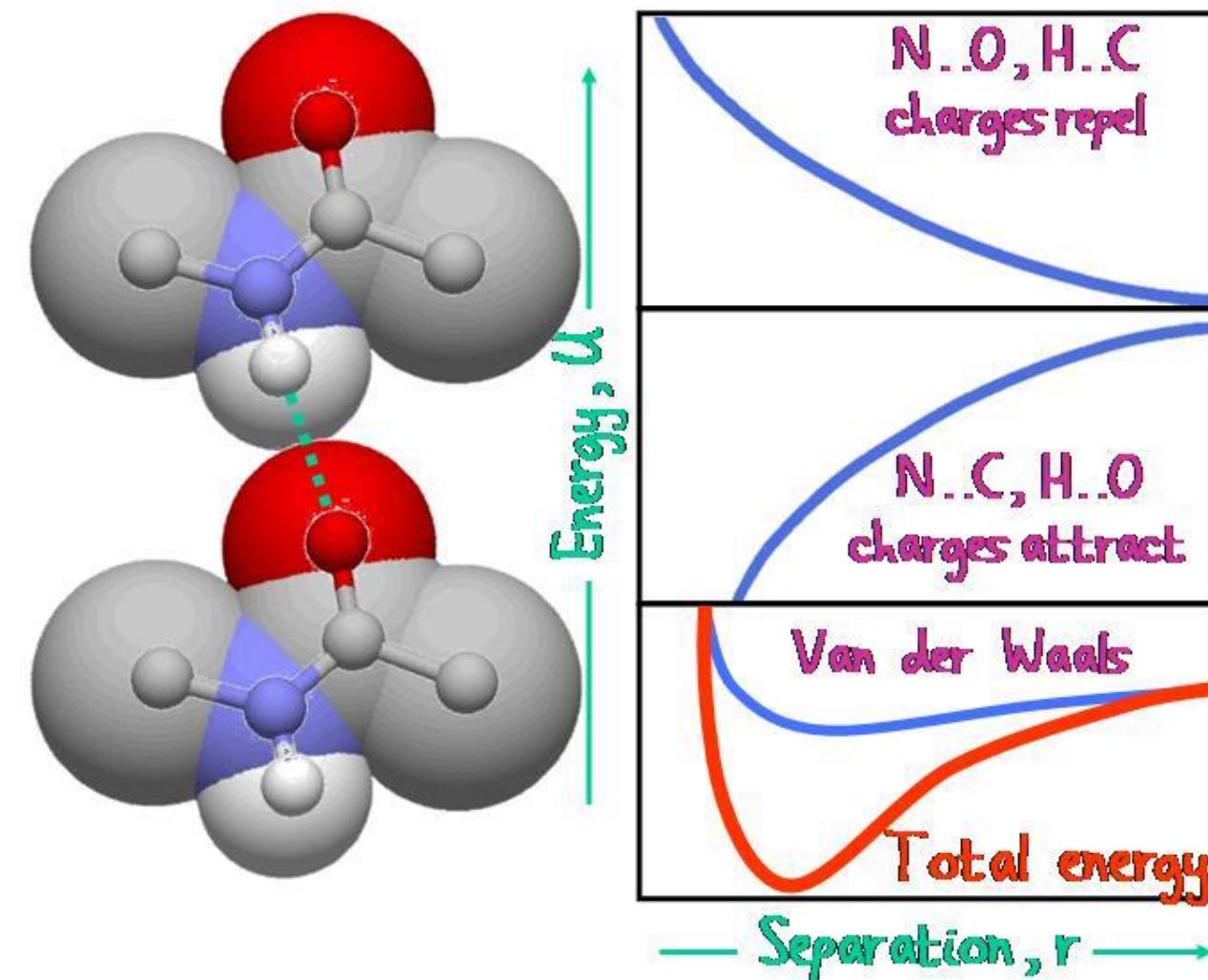
Density maximum: BSV, PPC (SPC, SPC/E no max., TIP4P –30 °C max.)

# HYDROGEN BONDS 1



- No special forces.
- Geometry allows good interaction combining van der Waals and electrostatic terms.
- Strong attraction with a minimum 5 kcal/mol deep at  $r=2.8 \text{ \AA}$ .

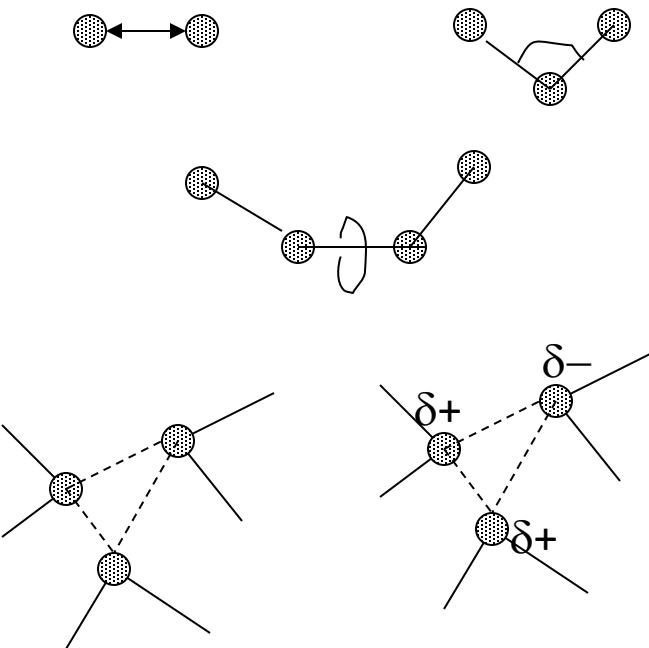
# HYDROGEN BONDS 2



- Very directional.
- Directionality due to repulsion between the other atoms in the system.
- Do not need a special directional term even for water molecules.

# Parametrisation issue

$$E(r^N) = \sum_{bonds} \frac{k_i}{2} (l_i - l_{i,0})^2 + \sum_{angles} \frac{k_i}{2} (\theta_i - \theta_{i,0})^2 + \\ + \sum_{torsions} \frac{V_n}{2} (1 + \cos(n\omega - \gamma)) + \\ + \sum_{i=1}^N \sum_{j=i+1}^N \left( 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \right)$$



Parameters:

- force constants ( $k, V$ )
- equilibrium values ( $l_{i,0}, \theta_{i,0}$ )
- atomic data ( $q_i, \epsilon_i, \sigma_i$ )



Magicians

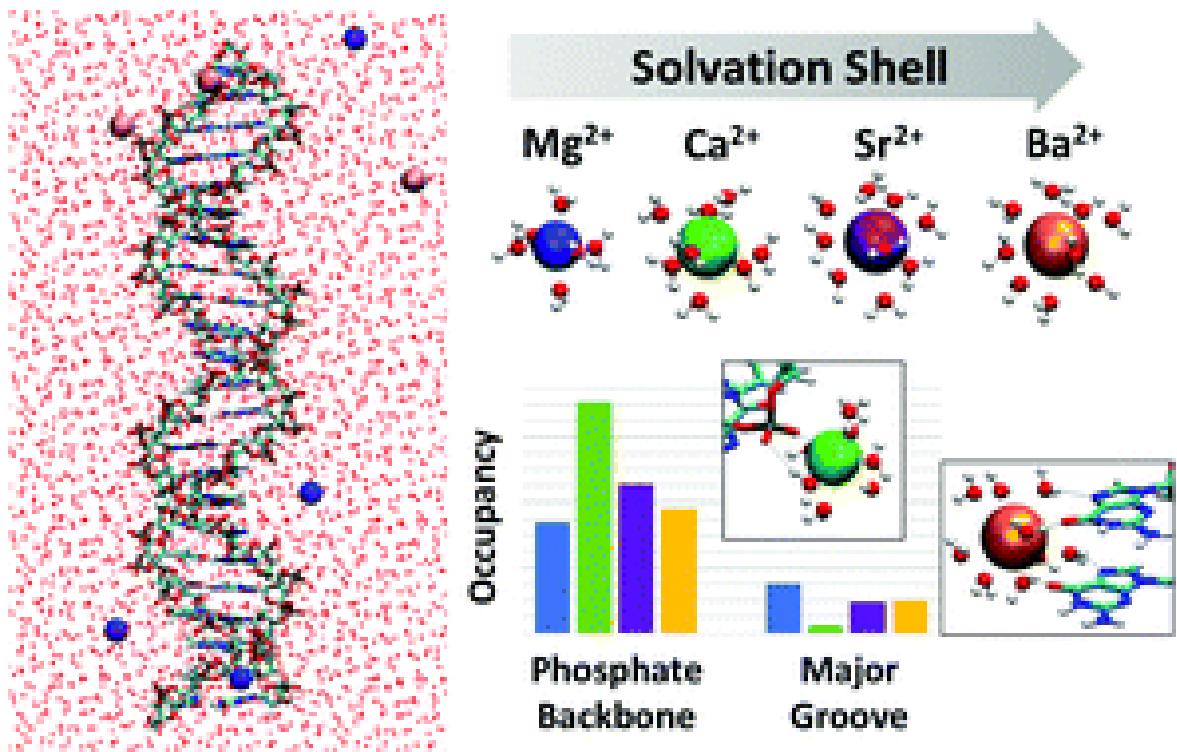
# Parametrisation issue



Making a soup

*“computational recipes”*

# Unphysical results



DNA may fall apart with some force fields

*electrostatics is not handled properly  
ions missing  
simulation is ‘too’ long  
different water model*

# Force field classics

## Biomolecules:

AMBER            Kollman group (USF, Scripps)  
CHARMM          Karplus group (Harvard)

## Solution phase:

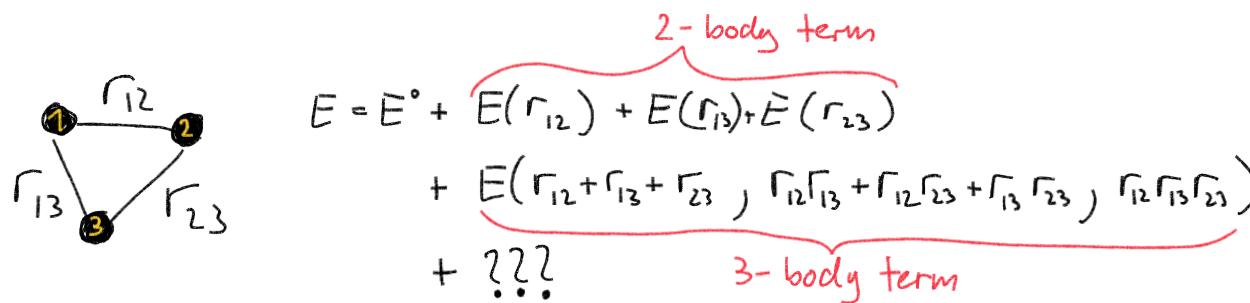
OPLS            Jorgensen group

## Organic compounds

GROMOS        Berendsen, van Gunteren (united atom)  
MM              Allinger group  
CVFF            Lifson, Hagler (Discover)  
TRIPOS          SYBYL  
ECEPP           Scheraga, Némethy

# Force fields today

- Thousands of different empirical force fields, each specific to a system and application
- Since the early 2000s, two things have changed:
  - More and faster computers enabled large scale data collection
  - Explicit inclusion of symmetry enables non-empirical functional forms that can converge to the true potential energy function
  - Machine learning methods taught us how to control fits with a large number of parameters



Invariance wrt  
- rotations  
- permutations

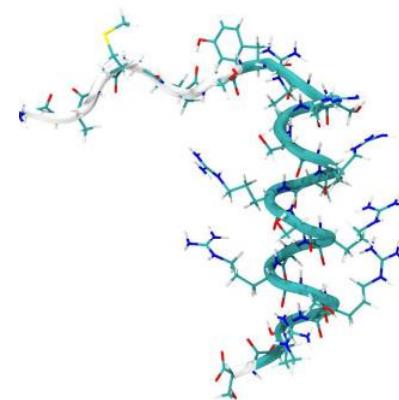
Each body order fit with a large number of polynomials

⇒ very accurate

scales exponentially with number of atoms !

# Parametrisation issue

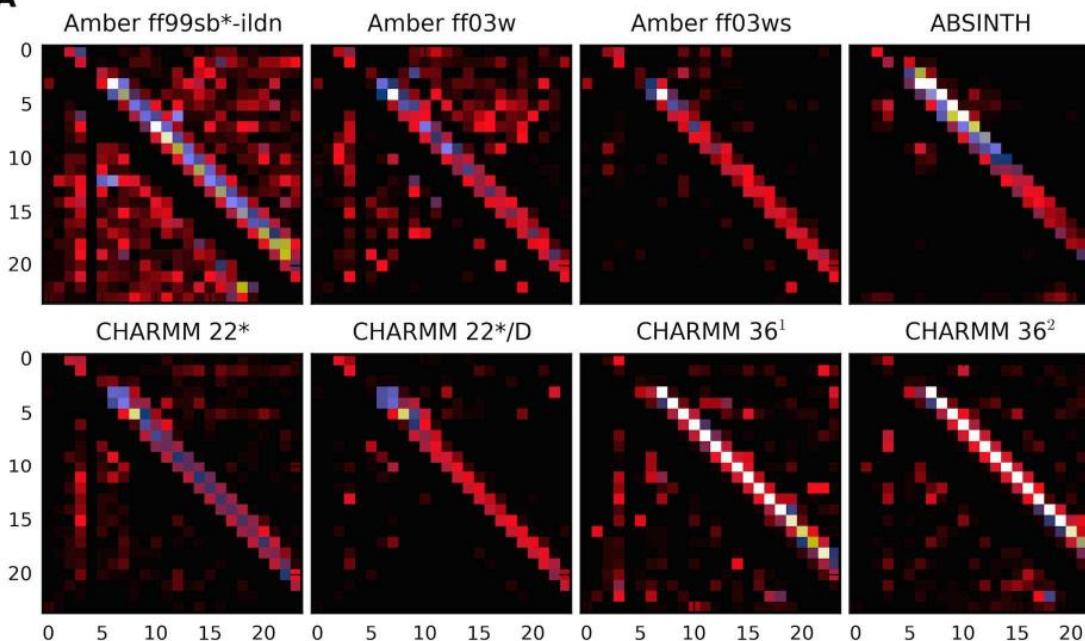
Force Field (Abbreviation)	Peptide Force Field	Water Model
Amber ff99sb*-ildn (a99sb)	Amber ff99sb*-ildn <sup>33</sup>	TIP3P <sup>55</sup>
Amber ff03w (a03w)	Amber ff03w <sup>34</sup>	TIP4P-2005 <sup>56</sup>
Amber ff03ws (a03ws)	Amber ff03ws <sup>51</sup>	TIP4P-2005 <sup>56</sup>
ABSINTH (ABS)	OPLS-AA/L <sup>57</sup>	ABSINTH implicit solvent <sup>21</sup>
CHARMM 22* (c22*)	CHARMM 22* <sup>33</sup>	charmm-modified TIP3P <sup>31</sup>
CHARMM 22* (c22*/D)	CHARMM 22* <sup>33</sup>	TIP4P-D <sup>26</sup>
CHARMM 36 <sup>1</sup> (c36 <sup>1</sup> )	CHARMM 36 <sup>58</sup>	TIP3P <sup>55</sup>
CHARMM 36 <sup>2</sup> (c36 <sup>2</sup> )	CHARMM 36 <sup>58</sup>	charmm-modified TIP3P <sup>31</sup>



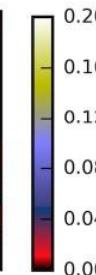
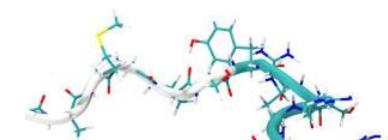
nucleoporin peptide

# Parametrisation issue

A

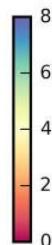
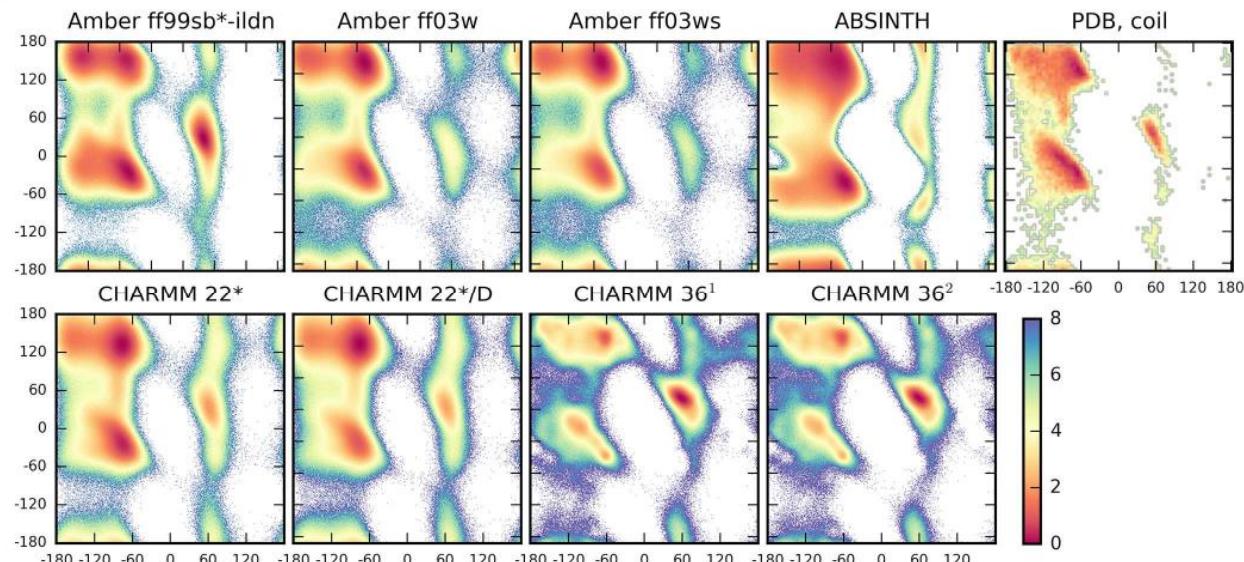


H-bond contact maps



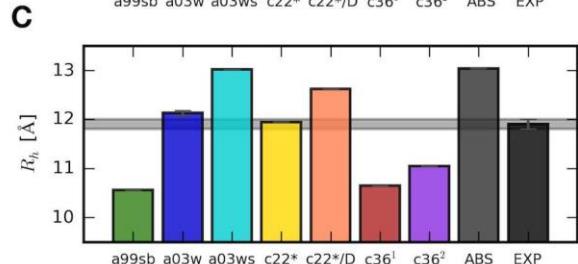
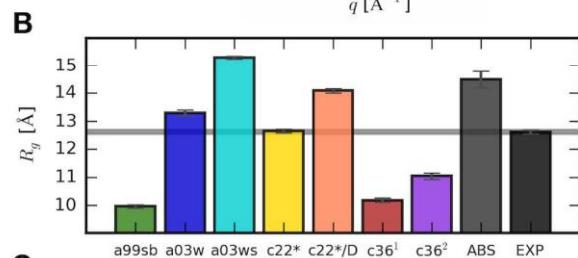
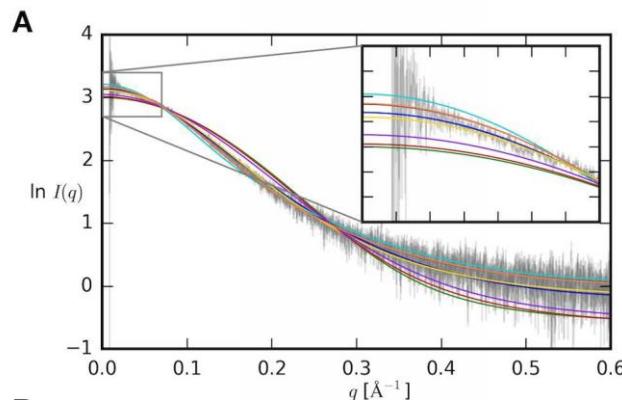
nucleoporin peptide

backbone dihedrals

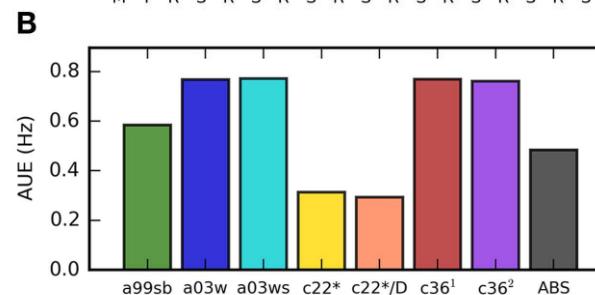
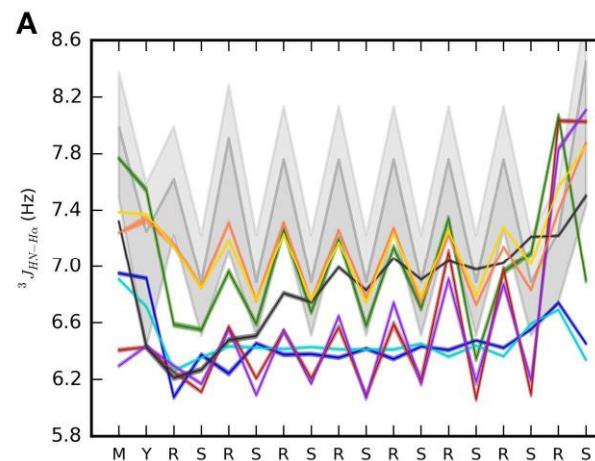


# Parametrisation issue

dimensions

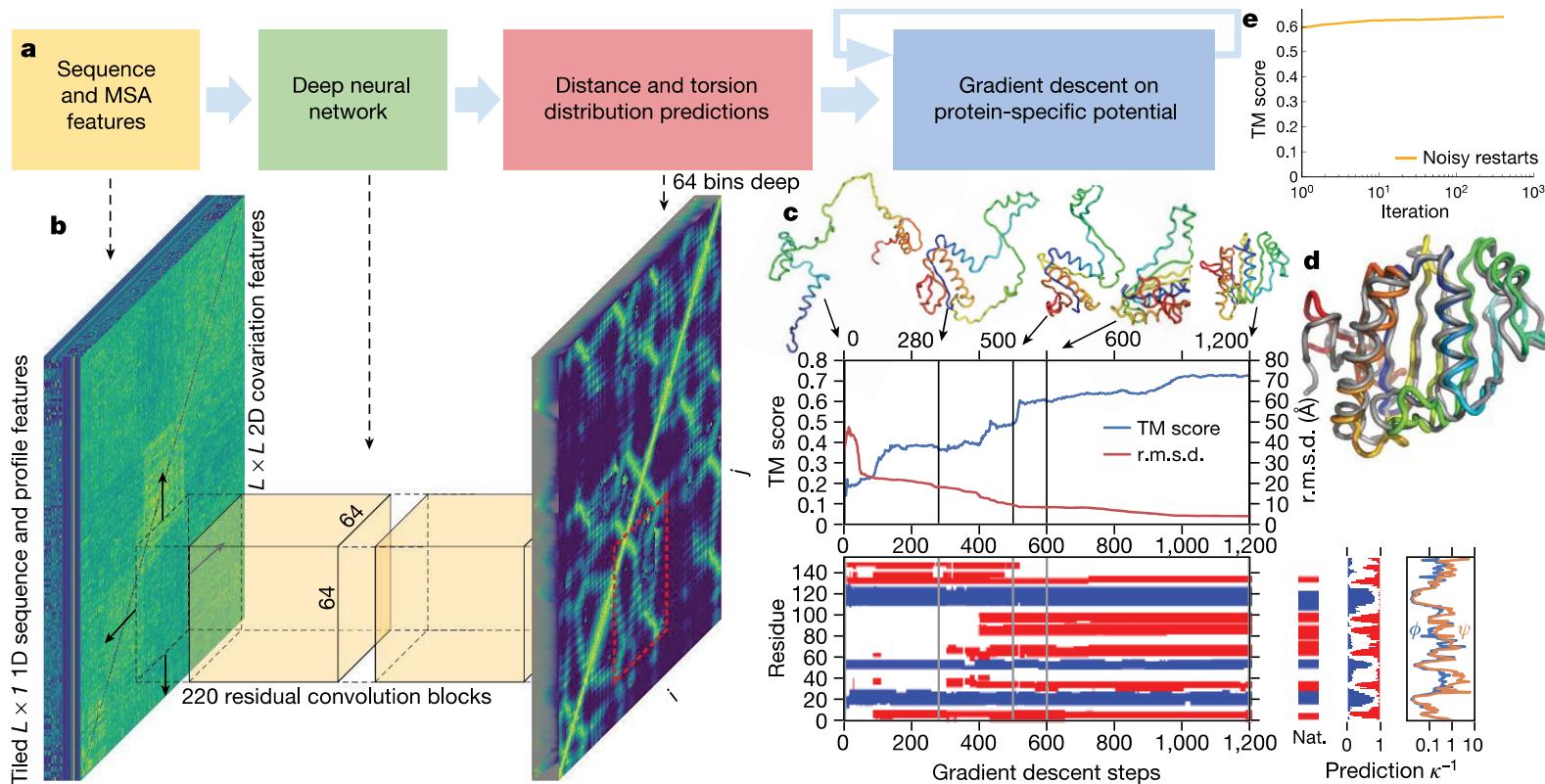


NMR couplings



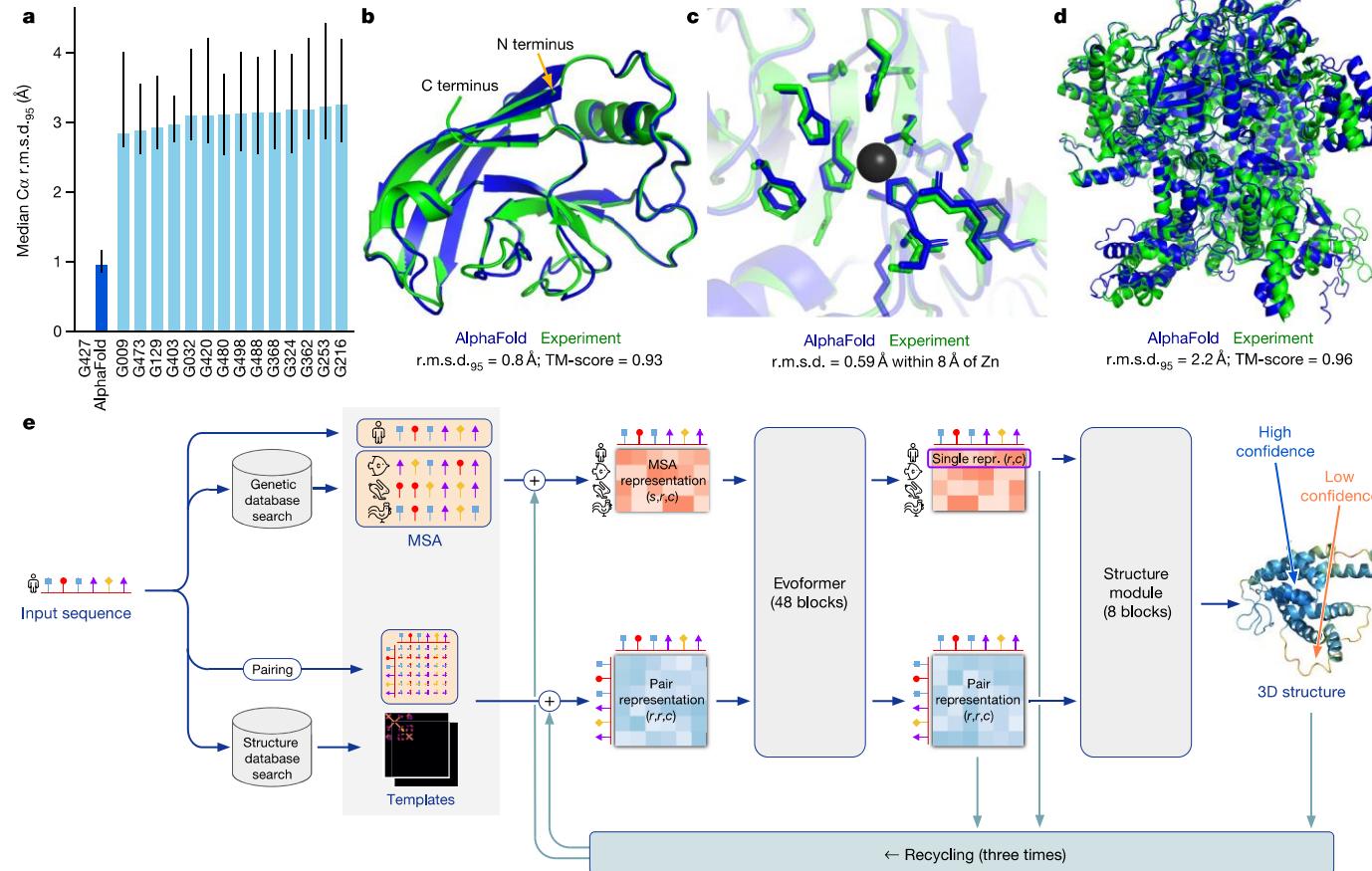
# Machine learning

## AlphaFold – Protein structure predictions

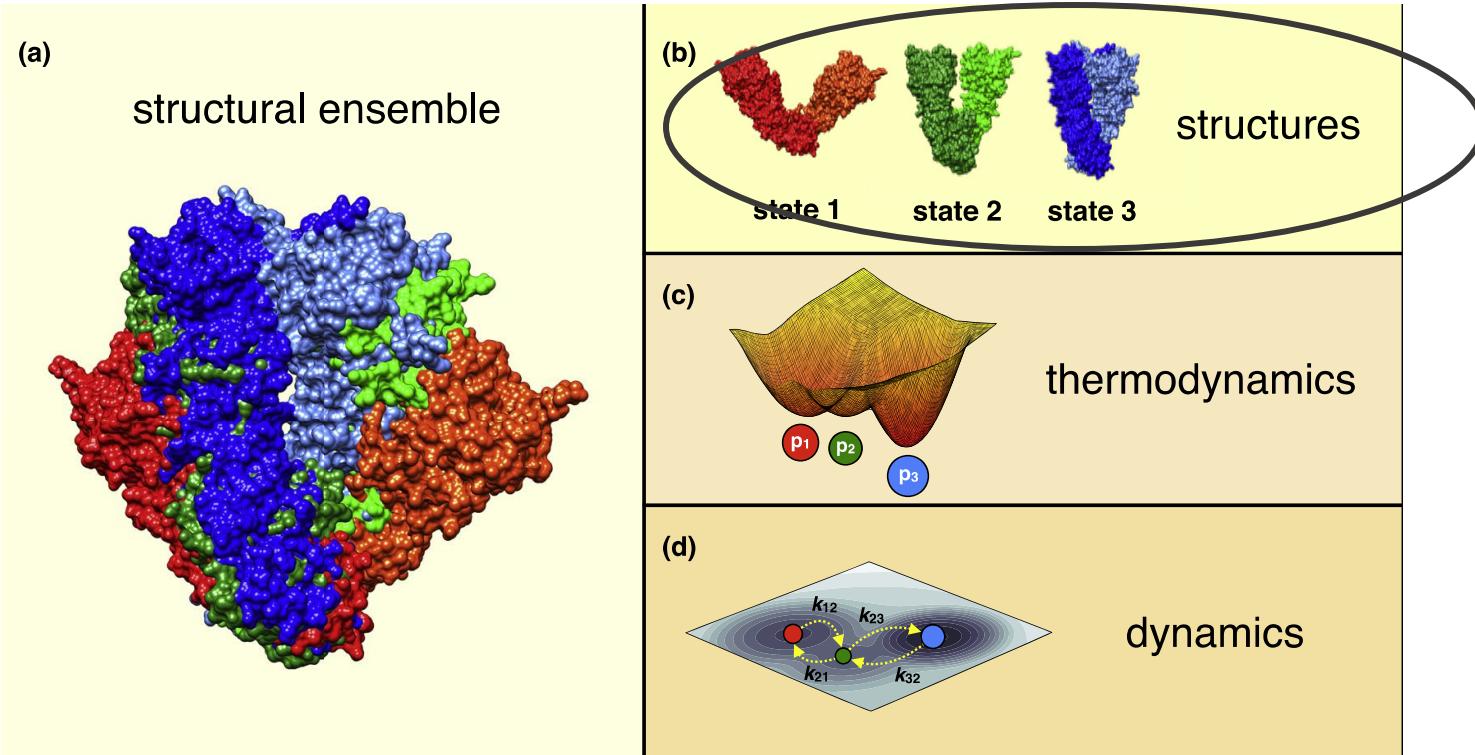


# Machine learning

## AlphaFold – Protein structure predictions



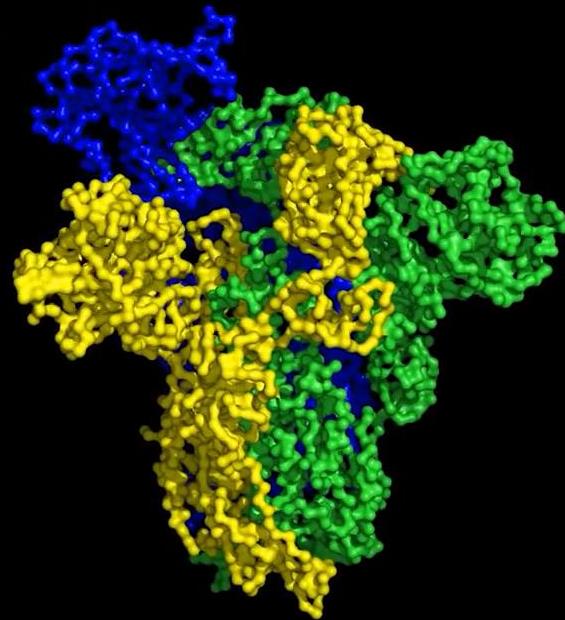
# Questions



**proteins are complicated, many things matter**

*(solvent, ions, concentration, partners, modifications, localisation)*

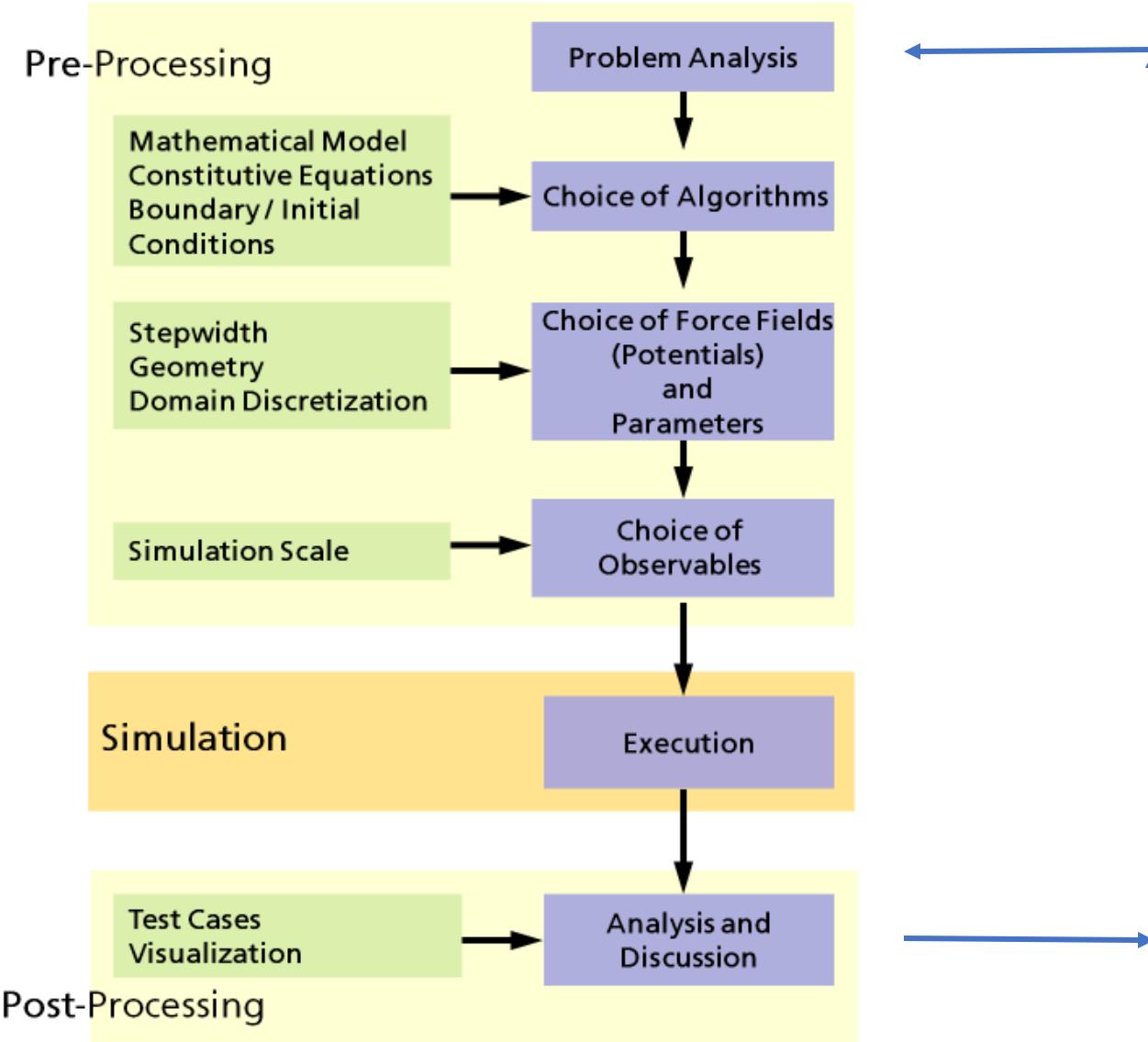
# Conformations and motions



(SARS-CoV2)

vibrations help virus penetration into the cell

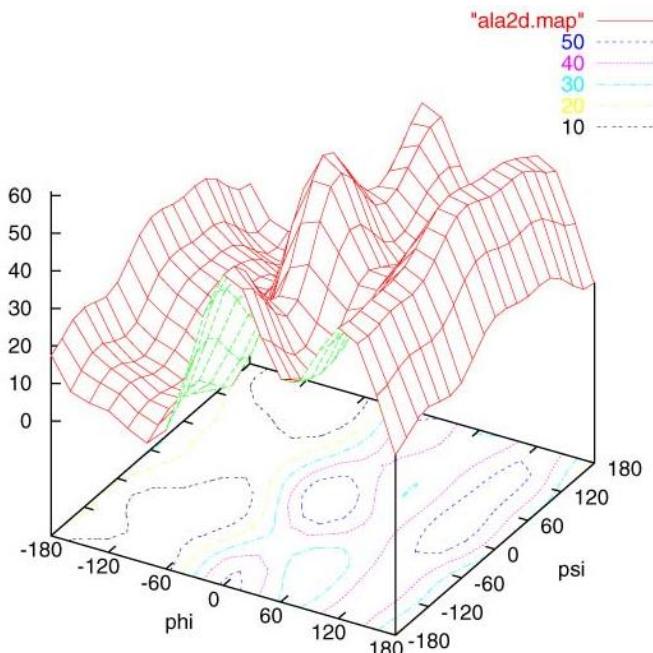
# Computer simulations



# Simulation techniques

## Molecular Mechanics (MM)

Potential energy surface (multi-variable function)



Shape

- minima
- maxima
- saddle points



stable conformations  
conformational transitions

# Molecular mechanics

## Goals:

- determine optimal geometry (global energy minima)
- identify stable conformers
- determine conformer ratios
- characterise pathway of conformational transition
- remove steric clash
- determine main movement directions

# Molecular mechanics

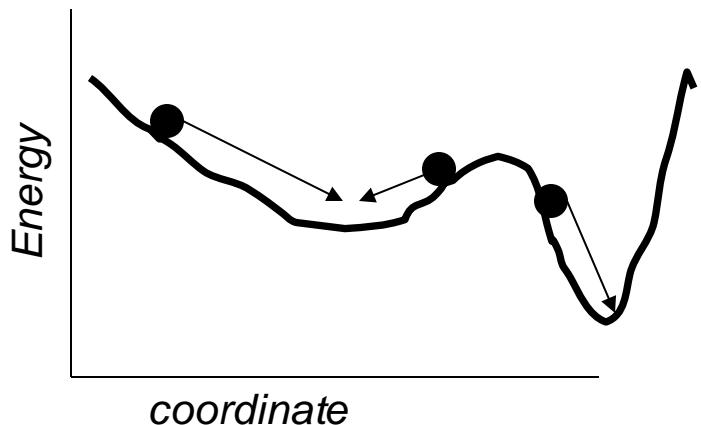
**Optimisation problem:**

$$\frac{\partial f}{\partial x_i} = 0$$

$$\frac{\partial^2 f}{\partial x_i^2} > 0$$

MM: optimisation in *Descartes coordinates*

QM: optimisation in *intrinsic coordinates*



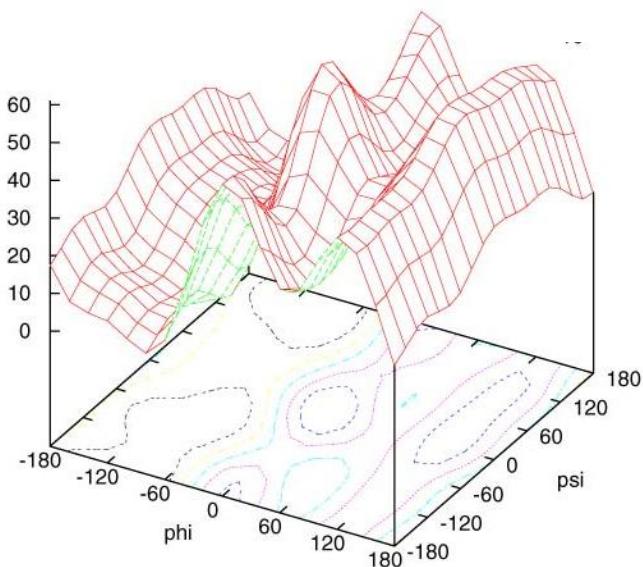
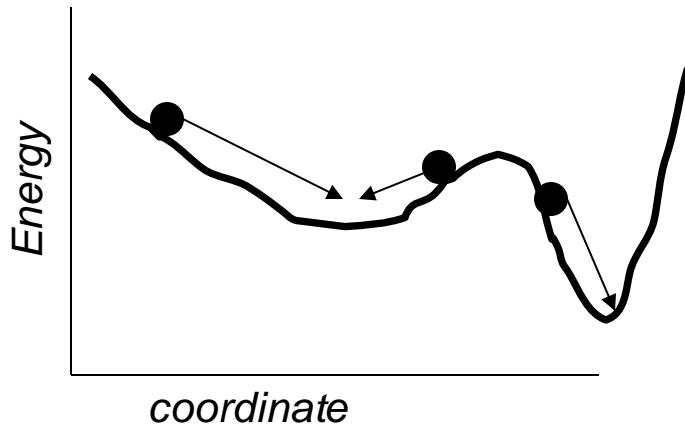
determine the position of the closest local minimum

# Molecular mechanics

Optimisation techniques:

steepest descent  
conjugate gradient  
Newton-Raphson

determine the position of the closest  
local minimum



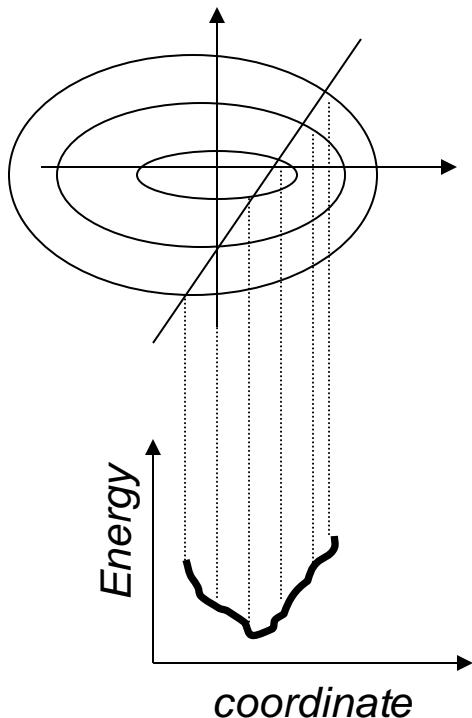
# Molecular mechanics

## Optimisation techniques

### *Steepest descent*

direction is parallel with force

$$s_k = -g_k / \|g_k\|$$



line search



fitting (quadratic)



step; new direction:

$$g_k g_{k-1} = 0$$

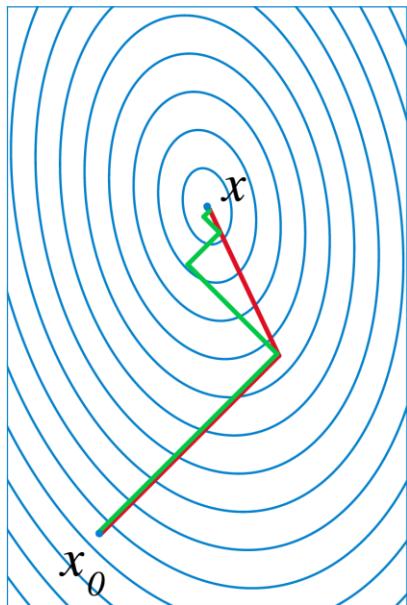
$$x_{k+1} = x_k + \lambda_k s_k$$

# Molecular mechanics

## Optimisation techniques

### *Conjugate gradient*

direction depends on previous steps



$$v_k = -g_k + \gamma_k v_{k-1}$$

$$\gamma_k = \frac{g_k g_k}{g_{k-1} g_{k-1}}$$

$$g_i g_j = 0$$

$$g_i v_j = 0$$

fewer steps are enough

# Molecular mechanics

## Optimisation techniques

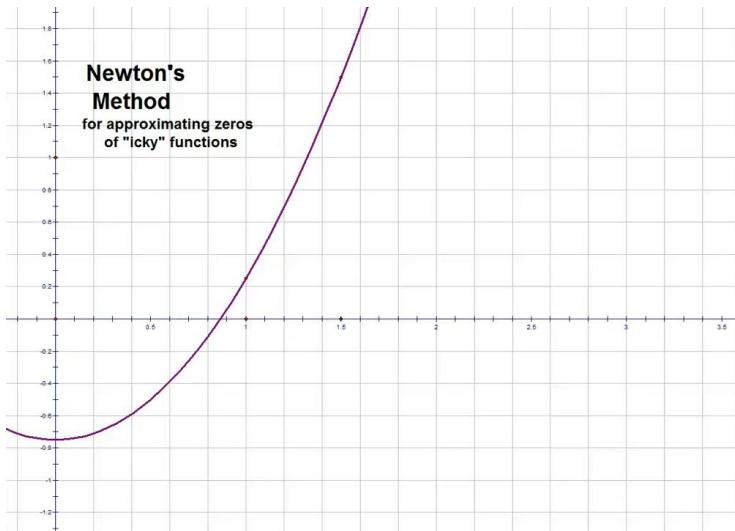
### **Newton-Raphson**

in case close to minimum

$$x_1 = x_0 - \frac{f(x_0)}{f'(x_0)}$$

$$x_{n+1} = x_n - \frac{f(x_n)}{f'(x_n)}$$

$x_0$  is a guess



# Molecular mechanics

## Method of choice

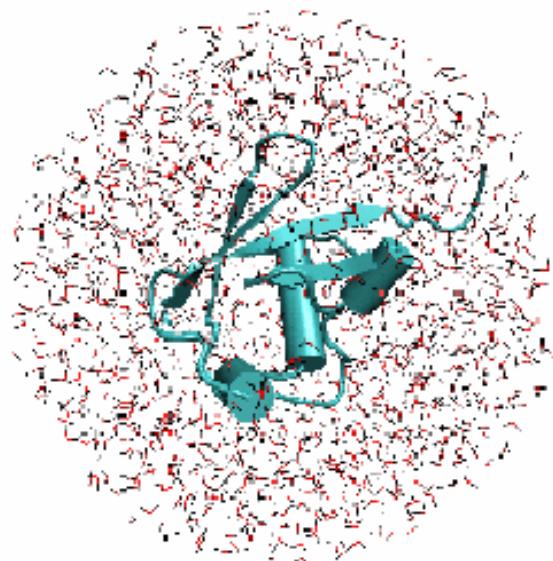
1. far from minimum: slower, precise method
2. close to minimum: fast, less precise method

*/Step. desc. any; Conj. grad. < 0.1 kcal/mol\* Å<sup>2</sup> ; NR g < 0.01 kcal/mol\* Å<sup>2</sup> /*

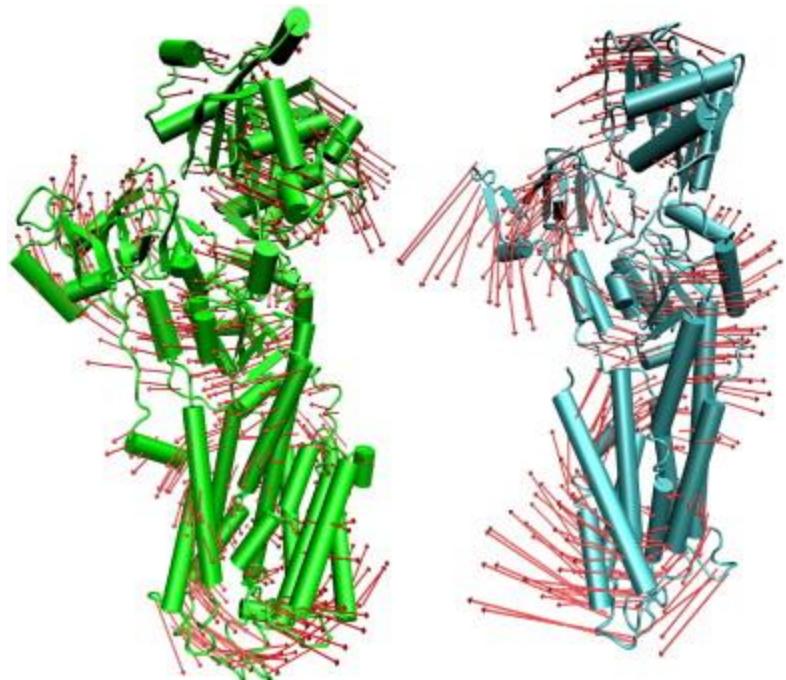
## Strategy (what to optimise):

1. solvent environment
2. ions
3. flexible parts
4. whole protein

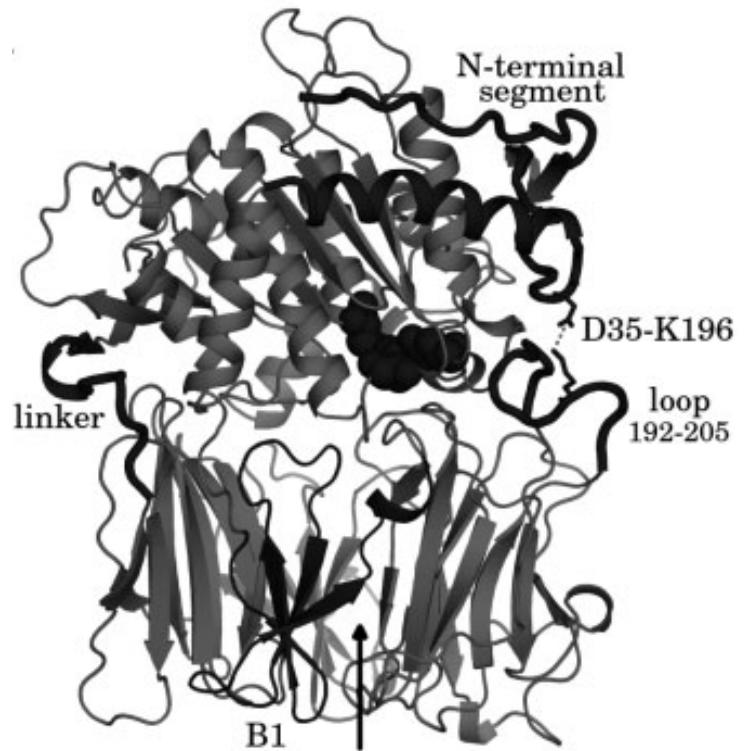
*/constraints are applied/*



# Molecular mechanics – beyond the static picture

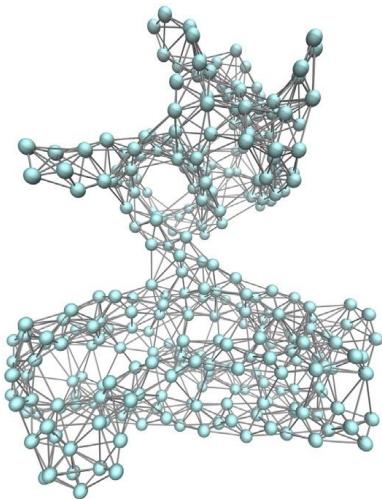


directions of relevant motions



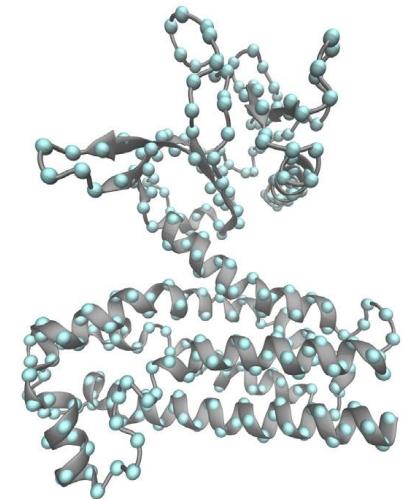
*/beyond available timescales/*

# Elastic network models



set of springs

$$V_{ij}(\mathbf{r}) = \frac{k_{ij}}{2} (\|\mathbf{r}_i - \mathbf{r}_j\| - \|\mathbf{r}_i^0 - \mathbf{r}_j^0\|)^2$$



total energy

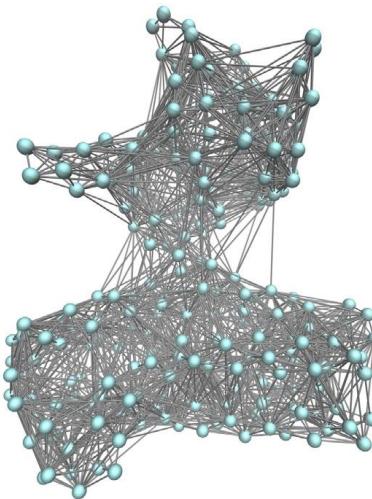
$$V(\mathbf{r}) = \sum_{i=1}^N \sum_{j=i+1}^N V_{ij}(\mathbf{r})$$

$$V(\mathbf{r}) = \frac{1}{2} (\mathbf{r} - \mathbf{r}^0)^T \mathbf{H} (\mathbf{r} - \mathbf{r}^0)$$

*using the Hessian matrix*

determining the eigenvectors and eigenvalues of the Hessian

$$V(\mathbf{r}) = \sum_{m=1}^{3N} \lambda_m ((\mathbf{r} - \mathbf{r}^0)^T \mathbf{v}_m)^2$$



# Molecular mechanics

## *normal mode analysis*

vibrational analysis

$$E(x) = E(x_k) + (x - x_k)E'(x_k) + (x - x_k)^2 E''(x_k)/2 + \dots$$

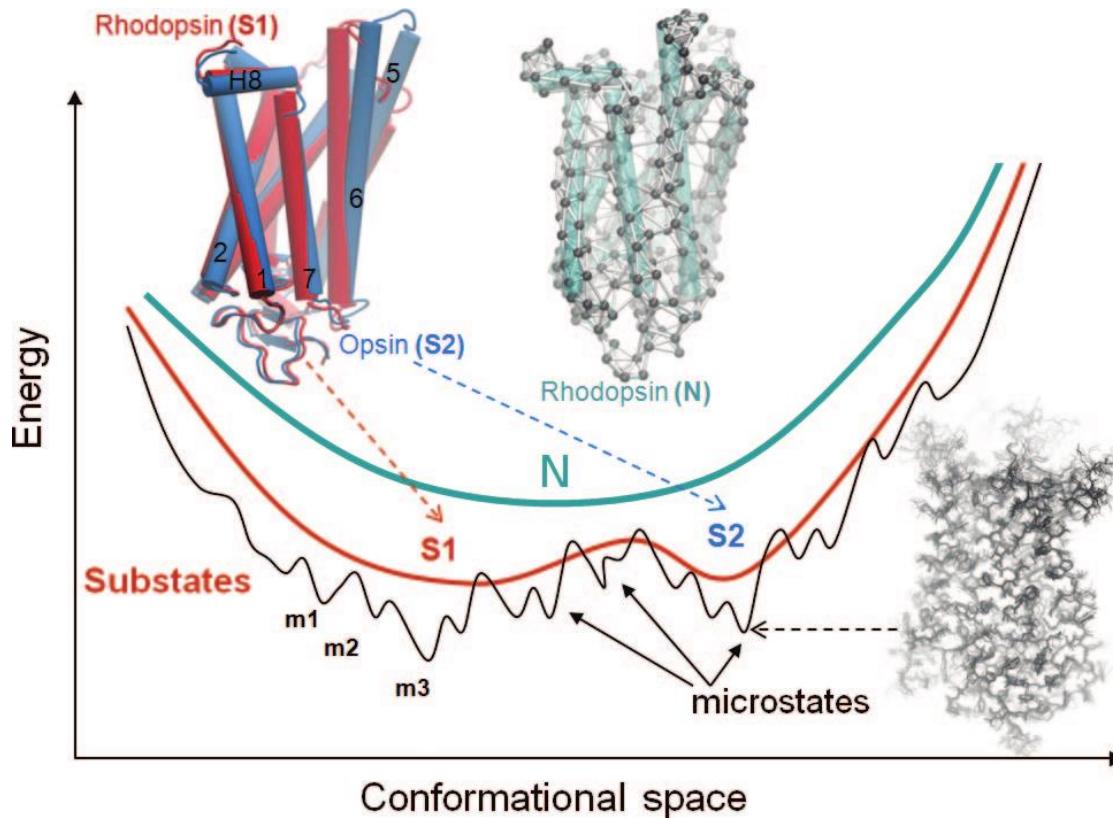
- Hessian matrix  $E''(x_k)$
- Force matrix  $F = M^{-1/2} E'' M^{-1/2}$

decomposition, determination of eigenvectors and eigenvalues

$$\nu_i = \frac{\sqrt{\lambda_i}}{2\pi} \quad |F - \lambda I| = 0$$

# Molecular mechanics

## *normal mode analysis*



*harmonic approximation*

can also be done using quasiharmonic analysis (QHA) [MD trajectories]

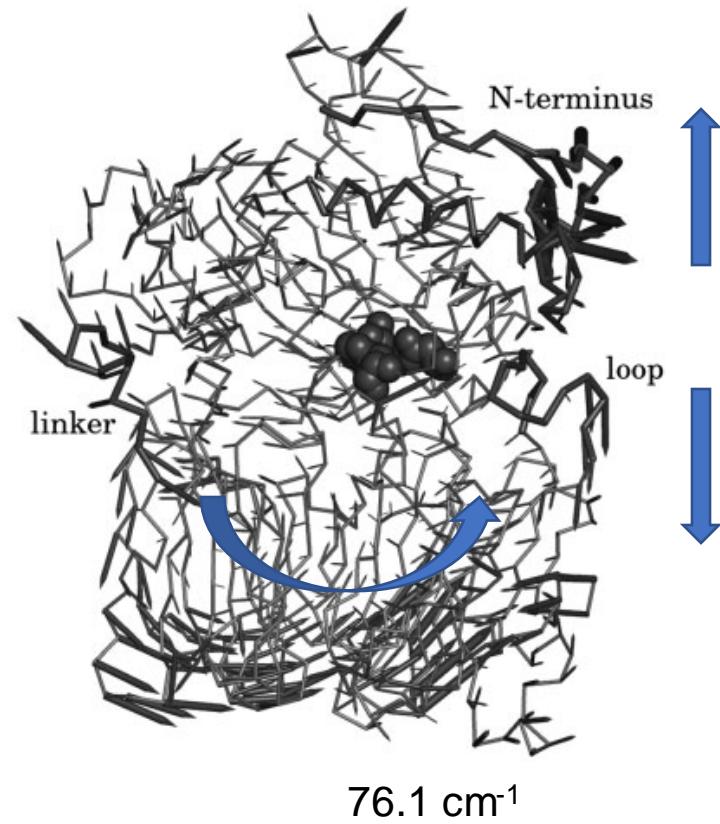
# Molecular mechanics

## *normal mode analysis*

Low frequency motions  $20\text{-}200\text{ cm}^{-1}$

*(domain movement)*

possible to simulate



# Molecular mechanics

## *normal mode analysis*

Calculation of entropy. /harmonic oscillators/

$$TS_{\text{vib}} = \sum_i^{3N-6} \left[ -k_B T \ln(1 - e^{-hv_i/k_B T}) + \frac{hv_i}{e^{hv_i/k_B T} - 1} \right]$$

