Molecular Dynamics Simulations

SS 2007

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Literature:

Karplus, M., Petsko, G. A. (1990) Nature, 347, 631.
Molecular dynamics simulations in biology,

van Gunsteren et al. (2006) Angewandte Chemie 45, 4064
Biomolecular modeling: Goals, Problems, Perspective.

van der Spoel et al. (2005) Journal Computational Chemistry 26, 1701
GROMACS: Fast, Flexible, and Free

Additional Reading:
Leach A. R. 2nd edition (2001)
Molecular modelling: Principles and applications

How to find me:

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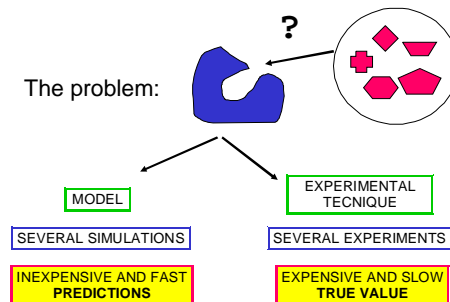villa@theochem.uni-frankfurt.de

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Outline meetings

- Introduction
- Models
- Empirical force fields

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The problem:

MODEL		EXPERIMENTAL TECNIQUE
SEVERAL SIMULATIONS		SEVERAL EXPERIMENTS
INEXPENSIVE AND FAST PREDICTIONS		EXPENSIVE AND SLOW TRUE VALUE

Simulation route vs experimental route

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EXPERIMENT	RESOLUTION	SIMULATION
10^{23} MOLECULES		1 MOLECULE
1 (milli)second		10^{-15} second
	SYSTEM SIZE	
10^{-3} meter		10^{-9} meter
10^{3-5} second		10^{-6} second

| Low resolution, large scale complex physical interaction | High resolution, small scale simple physical interaction |

Simulation and experiment are complementary

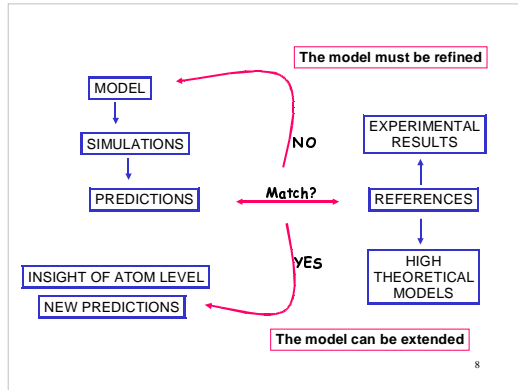5

What is molecular modelling?

- *Molecular*: refers to molecules
- *Model*: simplified or idealized description of a system or process devised to facilitate calculations and predictions
- *Molecular modelling* is thus concerned with ways to mimic and predict (simulate) the behavior of molecules and molecular systems

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The model must be refined

MODEL → SIMULATIONS → PREDICTIONS ← Match? → REFERENCES ← EXPERIMENTAL RESULTS

NO

YES

INSIGHT OF ATOM LEVEL

NEW PREDICTIONS

HIGH THEORETICAL MODELS

The model can be extended

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Choices in the modeling

Degrees of freedom → Which particles are defined

Interactions — How the particles interact

Boundary Conditions — Under which conditions (shape, temperature, pressure, etc.)

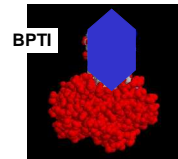Methods — How is the conformational space sampled

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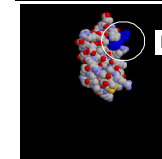**Trypsion and Basic PanceaticTrypsin Inhibitor (BPTI)**

Complexes
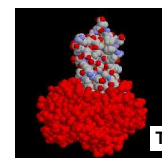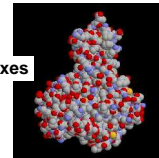
Trypsin

BPTI

BPTI

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Choice of Degrees of Freedom: Level of Modelling

Asp
Phe
Cys
Leu

What to include?
All atoms

Example: Sites in BPTI (Basic Panceatic Trypsin Inhibitor)
All atoms   ~ 1000

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Choice of Degrees of Freedom: Level of Modelling

Asp
Phe
Cys
Leu

What to include?
residues

Example: Sites in BPTI (Basic Panceatic Trypsin Inhibitor)
All atoms   ~ 1000
Residues   ~ 58

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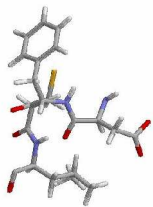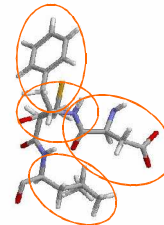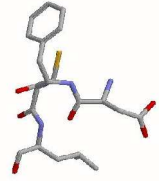
Choice of Degrees of Freedom: Level of Modelling

Asp
Phe
Cys
Leu

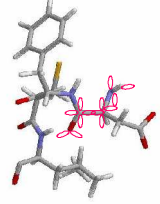What to include?
Heavy atoms

Example: Sites in BPTI (Basic Panceatic Trypsin Inhibitor)
All atoms ~ 1000
Heavy atoms (no hydrogens) ~ 450

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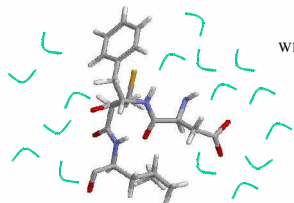Choice of Degrees of Freedom: Level of Modelling

Asp
Phe
Cys
Leu

What to include?
All atoms
electrons

Example: Sites in BPTI (Basic Panceatic Trypsin Inhibitor)
All atoms ~ 1000
All electrons ~ 3500
(external shell)

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Choice of Degrees of Freedom: Level of Modelling
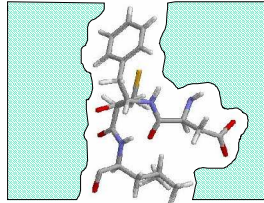
Asp
Phe
Cys
Leu

What to include?
Explicit Solvent

Example: Sites in BPTI (Basic Panceatic Trypsin Inhibitor)
All atoms ~ 1000
waters ~ 7500

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Choice of Degrees of Freedom: Level of Modelling

Asp
Phe
Cys
Leu

What to include?
Solvent effects?
• reaction field
• mean force
(+fluctuations)
(+delay)

Example: Sites in BPTI (Basic Panceatic Trypsin Inhibitor)
All atoms ~ 1000

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How do we represent our protein?
Which degrees of freedom to include?

more costly (less can calculate)

less physically relevant

Include

- electrons and nuclei
- all atoms
- united non-polar (CH₁, CH₂, CH₃) atoms
- united polar groups
- united amino-acid residues
  represent by: 1 particle
               2 particles
               ...
- whole molecule as
  sphere
  rod
  disk

Consideration

→ Quantum Mechanics
→ hydrogen atoms
→ polar hydrogens
→ no hydrogens

→ no atoms

→ no internal degrees of freedom

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How do we represent the solvent?
Which degrees of freedom to include?

more costly (less can calculate)

less physically relevant

Include

•Explicit
• electrons and nuclei
• all atoms
• whole molecule as sphere

•Implicit
•solvent effect is included using
analytic form

•No solvent

Consideration

→ Quantum Mechanics
→ hydrogen atoms
→ no internal degrees of freedom

→ Reactions fields
   Mean force

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Factors that Determine Reliability

• *the model must encompass* *the property of interest*

•*the simulation time >> time scale of the process to be investigated*

To Match Reality

• The Model (force field)
Is the model fitted to the property of interest?

•Time Scale.
Is the process spontaneous or enforced?

•Know what is reality.
Are we fitting to just another model?

Interactions

Molecular Mechanics

The term molecular mechanics refers to the use of classical (Newtonian) mechanics to model atomistic or molecular systems. The potential energy of a system is calculated using force fields.

Force field

Force field refers to the analytical functions and the parameter sets used to describe the potential energy of a system of particles (typically but not necessarily atoms). Force field functions and parameter sets are derived from both experimental work and high-level quantum mechanical calculations.

Force Fields

Gas Phase

•CFF/CVFF
•EFF93
•MM2/MM3
•QMFF/CFF93

Condensed Phase

•AMBER
•CHARMM
•CHARMm/QUANTA
•ECEPP/3
•ENCAD
•GROMOS
•OPLS
•Tripos

Classical potential energy

Total energy of a system of N particles

$$H(\mathbf{p},r,m) = K(\mathbf{p},m) + V(\mathbf{r})$$

kinetic energy

$$K(\mathbf{p},m) = \Sigma i\ \mathbf{p}_i\ m_i$$

potential energy

$$V(\mathbf{r}) = V(\{\mathbf{r}_i\})$$

$\mathbf{p}_i$ is momenta, m_i is the mass, $\mathbf{r}_i$ is the position of each particle

Classical approximation
Particles ≡ Atoms (no electrons are included)

Why is it still a reasonable approximation?

Electrons are > 1000 times lighter than nuclei
      move > 1000 times faster
      "see" motionless nuclei

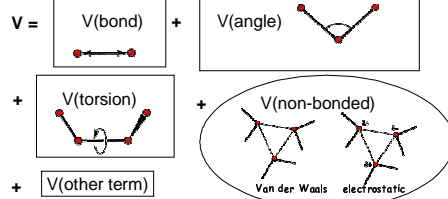Nuclei "see" an instantaneously adjusting bath of electrons

see Born-Oppenheimer approximation

Classical nuclei approximation valid for:
  Heavy nuclei **(protons ?)**
  Low frequency motions **(bond-stretching vibrations?)**
  High-enough temperatures

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Empirical force fields

Given a set of particles the force field is the potential function
describing the inter-atomic interactions

V =   V(bond) **+**   V(angle)

+   V(torsion) **+**   V(non-bonded)

                              Van der Waals electrostatic

+   V(other term)

Classical force field does not account
for the quantum mechanical nature of the microscopic world! 26

Empirical force fields

Empirical force fields

Set of potential functions   Set of parameters

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Empirical force field: a example of analytical form

$$V(r_1, r_2, ..., r_N) = \sum_{bonds} \frac{1}{2} K_b (b - b_0)^2 + \sum_{angles} \frac{1}{2} K_\theta (\theta - \theta_0)^2$$

$$+ \sum_{torsions} \frac{1}{2} K_\xi (\xi - \xi_0)^2$$

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

bonded-interactions

$$+ \sum_{pairs} [C_{12}(i,j)/r_{i,j}^{12} - C_6(i,j)/r_{i,j}^{6}] + q_i q_j / 4\pi\varepsilon_0 \varepsilon r_{i,j}$$

non-bonded interactions

Every force field has his own analytical functions and set of parameters

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Bond stretching

V(bond)

−Harmonic potential:
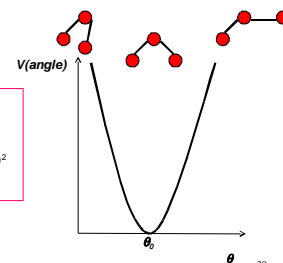
$V(bond) = 1/2\ K_b\ (b - b_0)^2$

•Most commonly used

V(bond)

          b_0 *b*

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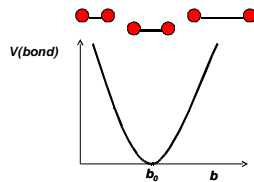
Angle bending

V(angle)

V(angle)

−Harmonic potential:

$V(angle) = 1/2\ K_\theta\ (\theta - \theta_0)^2$

        θ_0 *θ*

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Torsion terms

V(torsion)

Cosine expansion:

$V(torsion) = K_\phi [1 + \cos(n\phi + \delta)]$

$V(torsion)$

ϕ

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van der Waals interactions (interactions between atoms independent of net charge).

A. short range repulsion due to electron overlap — exponential

B. medium range attraction due to dispersion (induced dipoles)

$V_R = \dfrac{3 I \alpha_i \alpha_j}{4 r_{ij}}$

To avoid treating all electrons explicitly use effective potentials

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Non-Bonded Interactions

V

Lennard-Jones (6-12) potential

$V_{vdw} = \dfrac{A}{r^{12}} - \dfrac{B}{r^6}$

or

$V_{vdw} = 4\varepsilon\left[\dfrac{\sigma^{12}}{r^{12}} - \dfrac{\sigma^6}{r^6}\right]$

0

σ

ε

r

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Non-Bonded Interactions

water

$O^{\delta-}$ -0.82e

$H^{\delta+}$ $H^{\delta+}$

0.41e   0.41e

partial charge (**z**) distributions

Coulomb Interactions

$V = \dfrac{z_i z_j}{4\pi\varepsilon_0 r_{ij}}$

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Dipole-Dipole Interactions

N
H

O
C

no-interaction

attractive

repulsive

attractive

$V = \dfrac{\mu_2 \mu_2 \theta}{D r^3}$

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Relative Magnitude of Interactions

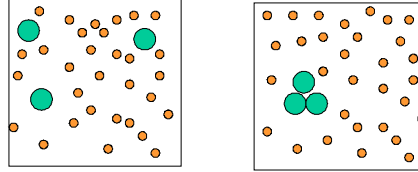| Interaction	Dependence	Approximate magnitude (kJ/mole/nm)
ion-ion	$\propto 1/r$	60
ion-dipole	$\propto 1/r^2$	~8
dipole-dipole	$\propto 1/r^3$	~2
dispersion	$\propto 1/r^6$	~.1

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Other Interactions

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Hydrophobic Effect

What keeps proteins folded?
Why does oil separate from water?
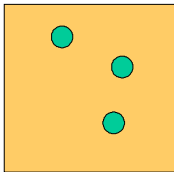Why do people who do not know anyone at parties end up together?

Particles driven together by favorable interaction within environment
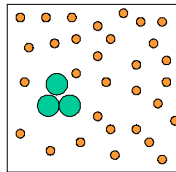*not pairwise additive*

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Hydrophobic Effect

implicit solvent no-aggregation   Explicit solvent aggregation

NOT that particles do not like water. Rather the interaction of water with water stronger.

Entropy of solvent   Sometimes modeled as surface area term

Automatic in explicit solvent simulations

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Empirical force fields

Set of potential functions   Set of parameters

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Parameterization

Bonds	Length	Force Constant
	x-ray (small molecules)	QM
	QM	vibrational spectra
	vibrational spectra	empirically based on bond length
	(standard tables)	weakly dependent geometry

Angles	Equilibrium Angle	Force Constant
	hybridization	QM
	x-ray (small molecules)	vibrational spectra
	QM	weakly dependent on bonds

Dihedral Angles	Multiplicity	Force Constant
	hybridization + substituents	fit to QM profiles (vacuum)
	QM	population distributions
		(experimental)
		strongly dependent on angles, vdw, charges…

Parameterization (cont.)

van der Waals
self-terms
(Lennard-Jones)

Ar, Kr, Xe analytical expressions
(+ LJ phase diagram)

$C_6 \Rightarrow$ Slater-Kirkwood formula
C12 fit to density and pressure
(fixed temperature)

Fit to QM calculations
(not always reliable)

Cross-terms

Combination rules
fit to simple systems

vdw highly correlated with charge distribution

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Parameterization (cont.)

Partial atomic charges non-physical!

Partial Charges

- Fit to QM electron density calculations
- Estimate from electronegativities
- Fit to dipole moments
- Fit to hydrogen bonding energies
- Fit to properties of simple liquids

Dependent on dielectric, vdw's, treatment of long-range, all-atom/united atom, ...

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Parameterization (cont.)

Methanol

Charges(e)	qH	qO	qMe
GR96	0.398	-0.574	0.176
H1	0.431	-0.728	0.297
B3	0.408	-0.674	0.266

Lennard-Jones (10^{-3} kJmole/nm^{12})$^{1/2}$	$(C_{12}^1(O))^{1/2}$	$(C_{12}^2(O))^{1/2}$	$(C_{12}^1(Me))^{1/2}$
GR96	1.1250	1.227	4.5665
H1	1.5839	1.4683	5.7685
B3	1.5250	1.5250	4.4000

density/pressure/heat of vaporization similar (compensation of errors)

Compare to heat of vaporization, mixing enthalpy, diffusion, compressibility, dielectric constant, Debye relaxation times, solvation free energy, ...

all properties cannot be reproduce simultaneously (polarization, Lennard Jones) 44

Force Fields

Gas Phase

- CFF/CVFF
- EFF93
- MM2/MM3
- QMFF/CFF93

Fit to QM + vibrational data
lone pairs/cross terms

Condensed Phase

- AMBER
- CHARMM
- CHARMm/QUANTA
- ECEPP/3
- GROMOS
- ENCAD
- Tripos
- OPLS

Fit to crystal and/or liquid properties

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