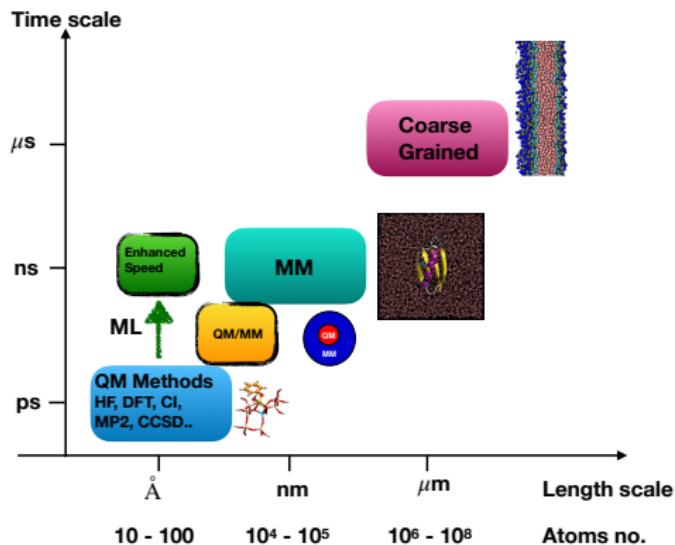


Molecular Modelling and Simulations



Shampa Raghunathan

Outline

1 Introduction

2 Bonded Interactions

- bonds
- angles
- torsions

3 Nonbonded Interactions

4 Derivatives of molecular mechanics energy functions

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Why do we need to do simulations?

Simulation is a useful complement, because it can :

- ▶ Explain experiment
- ▶ Aid experiment; in-silico drug discovery, protein engineering
- ▶ Find structure and function relationship at molecular level

Definitions: modeling and simulation

A **model** is an idealization of real behavior, i.e., an approximate description based on empirical and/or physical reasoning.

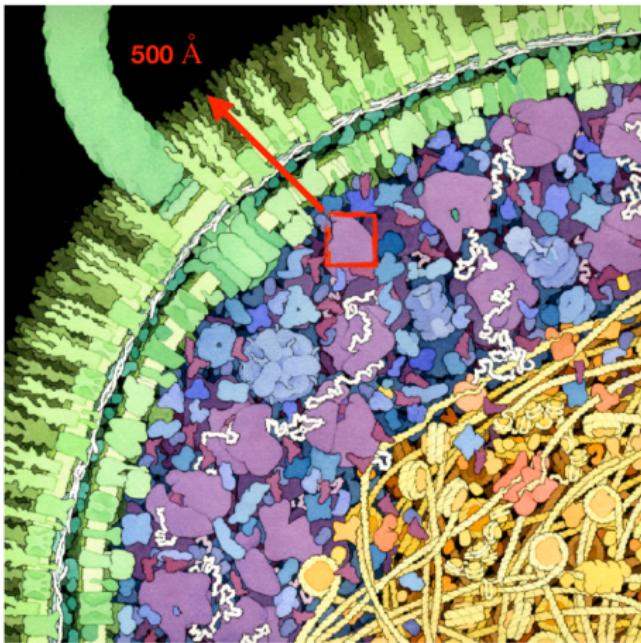
A **simulation** is a study of the dynamical response of a modeled system found by subjecting **models** to inputs and constraints that simulate real events.

A **simulation** does not mimic reality, rather it mimics a **model** of reality.

Can one separate **simulations** from the underlying **model**?
Accuracy & validity?

Richard LeSar, Iowa State University

Inconclusive experiments



Extreme simplification

Limited force field accuracy

Large gaps in timescales

Illustration: Nilsson, L., Karolinska Institute, Stockholm.

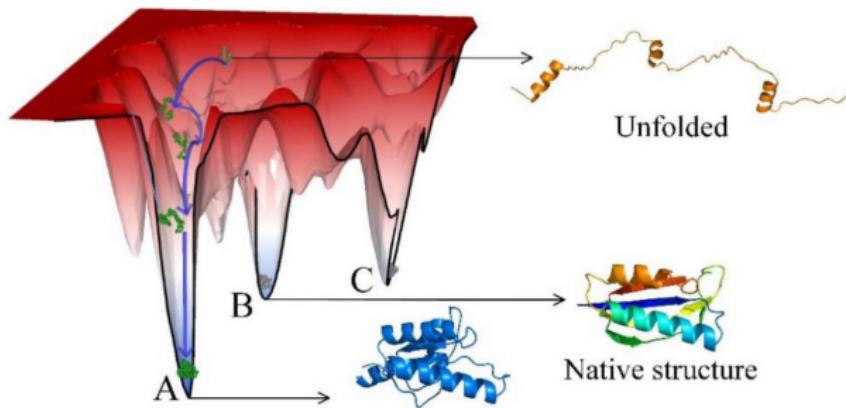
The Ergodic hypothesis states

$$\langle A \rangle_{ensemble} = \langle A \rangle_{time}$$

Ensemble average = Time average

Experiment \equiv Simulations

(macroscopic) (microscopic)



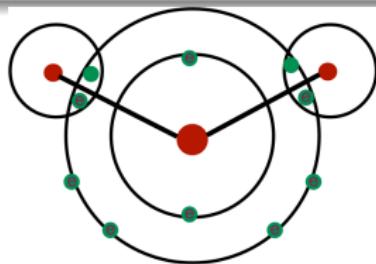
- ▶ Large systems
- ▶ Chemical processes

Illustration: Zhao, K.-L. et al., bioRxiv.

Recap... and next...

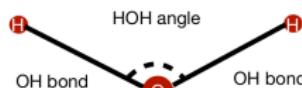
Quantum mechanics

- ▶ Fundamental entity: electrons
- ▶ Building blocks: atomic orbital basis
- ▶ Approx.: N-electron problem converted to N no. of 1-electron problems



Molecular mechanics

- ▶ Fundamental entity: atoms
- ▶ Analytic potentials
- ▶ Approx.: Potentials are fitted to exp. and/or QM data

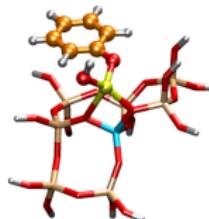


Computational Tools

Quantum Mechanics (QM)

Electronic structure, (Schrödinger)

- More accurate
- More expensive, small systems

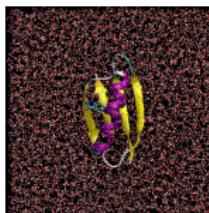


10–100 atoms
10–100 ps

Classical Molecular Mechanics

Empirical forces, (Newton)

- Less accurate
- Less expensive, large systems



10^4 – 10^5 atoms
10–100 ns

Combined QM/MM



10^4 – 10^5 atoms
10–100 ps

Books

Jensen, F. (2017). Introduction to Computational Chemistry. John Wiley & Sons.

Cramer, C. J. (2013). Essentials of Computational Chemistry: Theories and Models. John Wiley & Sons.

Leach, A. R. (2001). Molecular Modelling: Principles and Applications. Pearson Education.

LeSar, R. (2013). Introduction to Computational Materials Science: Fundamentals to Applications. Cambridge University Press.

Allen, M. P., & Tildesley, D. J. (2017). *Computer simulation of liquids*. Oxford university press.

Aim to simulate processes

Polypeptide folding
Biomolecular associations
Membrane transportsations
Solvent partitioning



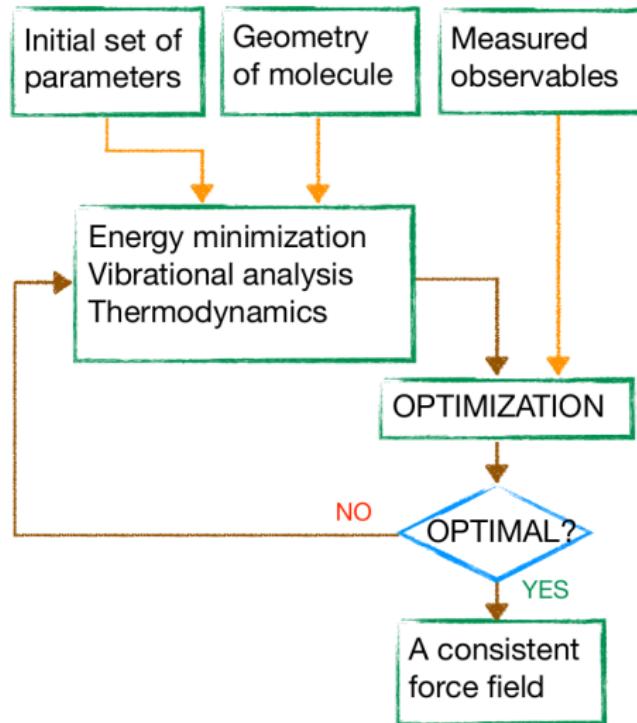
thermodynamics, weak
nonbonded interactions
Classical MD
atomic degrees of free-
dom (system+solute)

Chemical reactions
Catalytic processes
Photochemical reactions



Strong bonded forces
Quantum MD
electronic, nuclear de-
grees of freedom

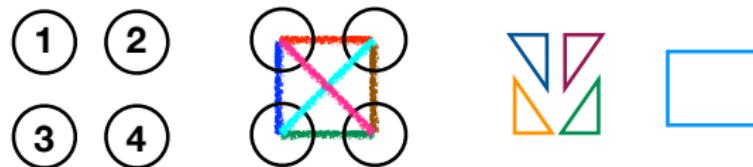
How do we create models?



Building an MD model

- ▶ Define potential energy functions, $\mathbf{V}(\mathbf{r})$ to model molecular interactions
- ▶ Compute forces on each atom $\mathbf{F} = \nabla \mathbf{V}(\mathbf{r})$

Models in MD simulations



$$V(\mathbf{r}) = \sum_i v_1(\mathbf{r}_i) + \sum_i \sum_{j>i} v_2(\mathbf{r}_i, \mathbf{r}_j) + \sum_i \sum_{j>i} \sum_{k>j>i} v_3(\mathbf{r}_i, \mathbf{r}_j, \mathbf{r}_k) + \dots$$

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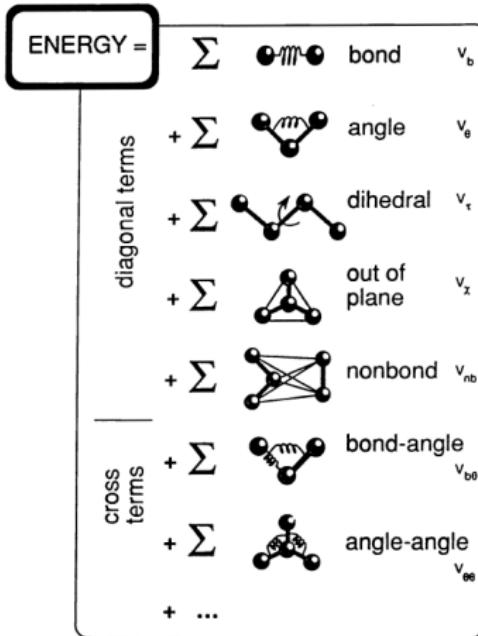
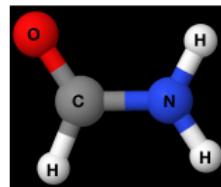
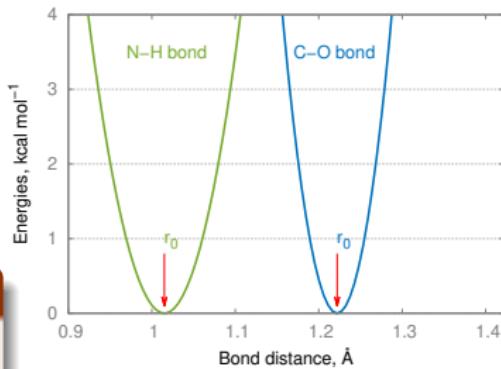


Figure 1 Schematic of molecular force field expression. Diagonal terms refer to interactions that can be expressed as a function of a single internal coordinate, whereas cross terms introduce coupled interactions involving two or more coordinates.

Illustration: Ponder, J., Washington University.

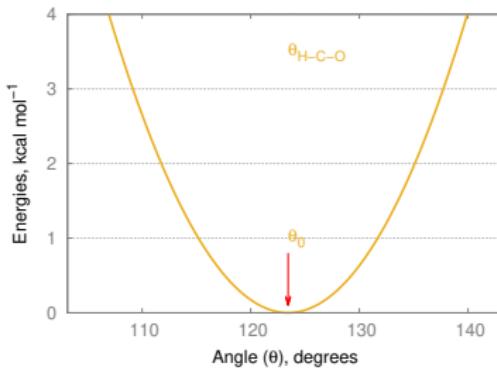
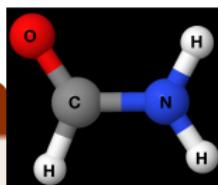
Bond

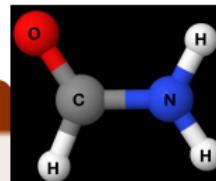
$$v_b = \frac{k_b}{2} (r - r_0)^2$$



Angles

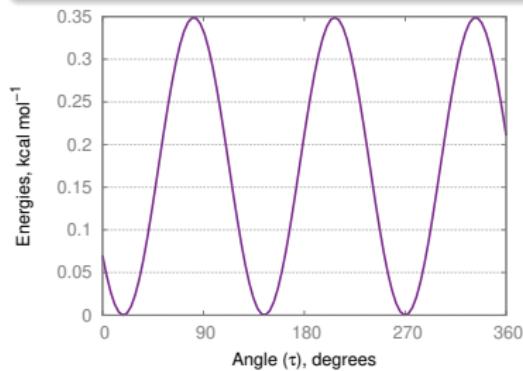
$$v_\theta = \frac{k_\theta}{2}(\theta - \theta_0)^2$$

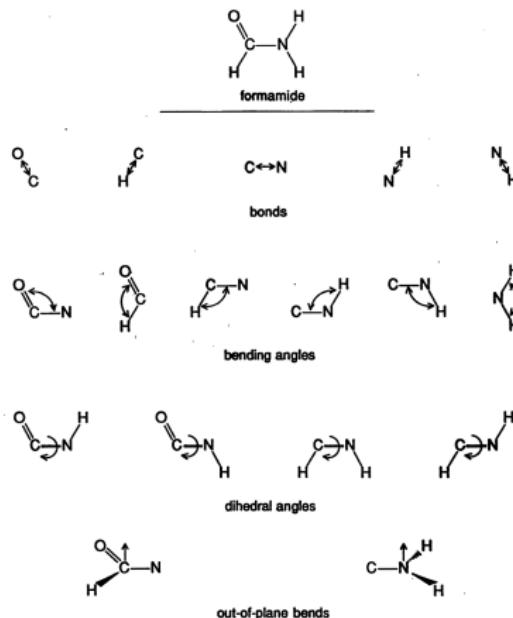




Torsions

$$v_\tau = \frac{k_\tau}{2}(1 + \cos(n\tau - \gamma))$$





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Lecture 2

Nonbonded Interactions

$$V_{ij} = \underbrace{\frac{q_i q_j}{r_{ij}}}_{\text{Coulomb}} + 4\epsilon \underbrace{\left[\left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^6 \right]}_{\text{Lennard-Jones potential}}$$

$$V_{ij} = \underbrace{\frac{q_i q_j}{r_{ij}}}_{\text{Coulomb}} + \underbrace{A_{ij} \exp\left(-\frac{r_{ij}}{\rho_{ij}}\right) - \frac{C_{ij}}{r_{ij}^6}}_{\text{Buckingham potential}}$$

vdW interactions, short-range

ϵ : well-depth, σ : collision diameter, r_{\min} : distance at minimum

$$r_{\min} = 2^{1/6} \sigma$$

$$r_{\min,ij} = r_{\min,i} + r_{\min,j}, \quad \epsilon = \sqrt{\epsilon_i \epsilon_j}$$



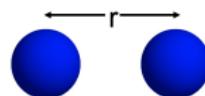
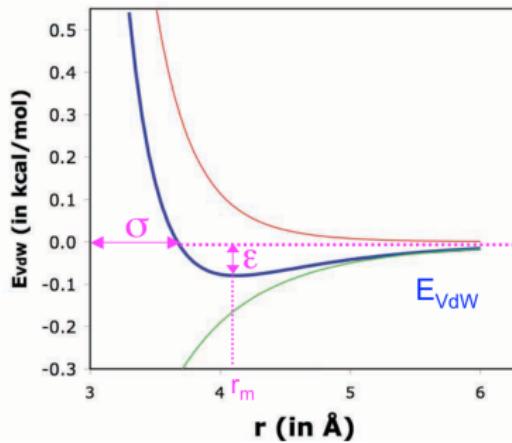
$$\epsilon \left[\left(\frac{r_{\min}}{r_{ij}} \right)^{12} - 2 \left(\frac{r_{\min}}{r_{ij}} \right)^6 \right]$$



Repulsive



Attractive

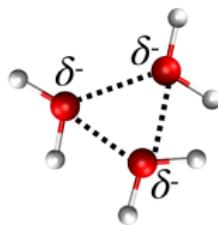


Electrostatic interactions, long-range

ϵ_0 dielectric constant:

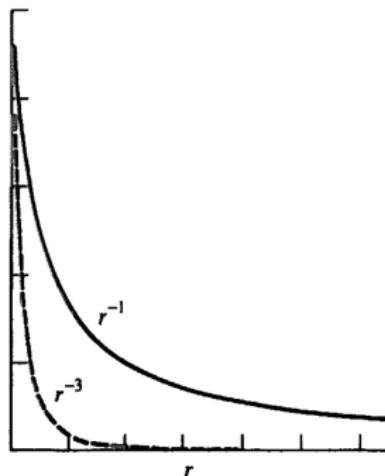
$$V_{\text{elec}} = \frac{q_i q_j}{4\pi \epsilon_0 r_{ij}}$$

1	for vacuum
4–20	for protein core
80	for water



The Coulomb energy decrease as $1/r$; **long-range interactions**

Special techniques are available to deal with the long-range electrostatic interactions as well as vdW interactions.



A typical molecular mechanics force field

“STERIC” Energy

$$\begin{aligned} V(\mathbf{r}^N) = & \sum_{\text{bonds}} \frac{k_{b_i}}{2} (r_i - r_{i,0})^2 + \sum_{\text{angles}} \frac{k_{\theta_i}}{2} (\theta_i - \theta_{i,0})^2 \\ & + \sum_{\text{torsions}} \sum \frac{k_{\tau_i,n}}{2} (1 + \cos(n\tau_i - \gamma)) \\ & + \sum_{i=1}^N \sum_{j=i+1}^N \left(4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{r_{ij}} \right) \end{aligned}$$

Examples of force fields: CHARMM, AMBER

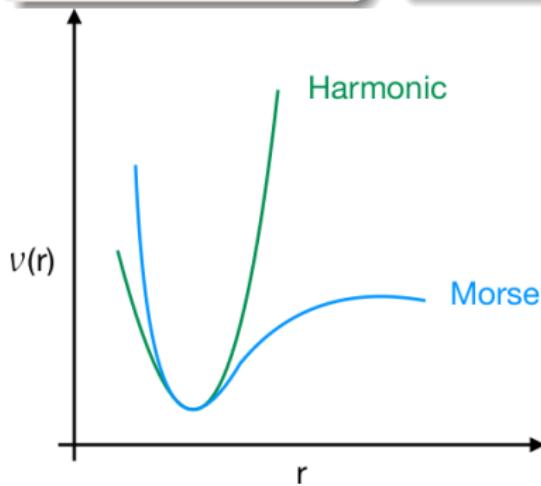
Beyond harmonic approximation

Bond, Harmonic

$$v_b(r) = \frac{k_b}{2}(r - r_0)^2$$

Morse potential

$$v(r) = D_e \{1 - \exp[-a(r - r_0)]\}^2$$

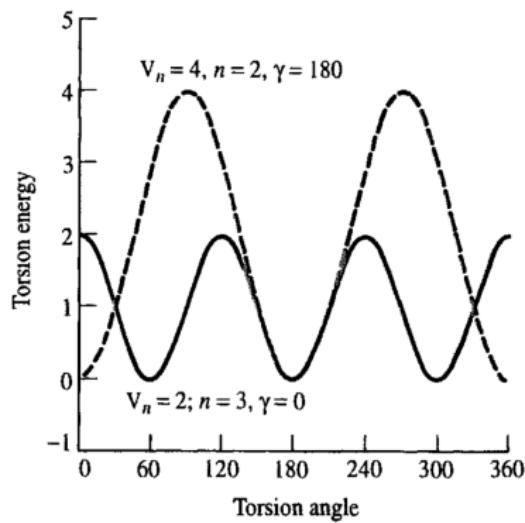


Bond	r_0 (Å)	k kcal mol ⁻¹ Å ⁻²
C _{sp³} –C _{sp³}	1.523	317
C _{sp³} –C _{sp²}	1.497	317
C _{sp²} =C _{sp²}	1.337	690
C _{sp²} =O	1.208	777
C _{sp³} –N _{sp³}	1.438	367
C–N (amide)	1.345	719

Angle	θ_0 (Å)	k kcal mol ⁻¹ deg ⁻¹
C _{sp³} -C _{sp³} -C _{sp³}	109.47	0.0099
C _{sp³} -C _{sp³} -H	109.47	0.0079
H-C _{sp³} -H	109.47	0.0070
C _{sp³} -C _{sp²} -C _{sp³}	117.2	0.0099
C _{sp³} -C _{sp²} =C _{sp²}	121.4	0.0121
C _{sp³} -C _{sp²} =O	122.5	0.0101

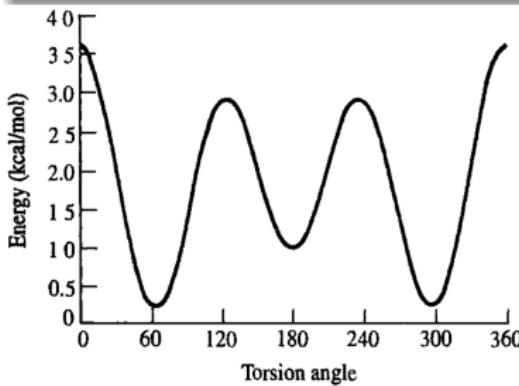
Torsions and beyond

$$v_{\tau} = \frac{k_{\tau,n}}{2}(1 + \cos(n\tau - \gamma))$$



Torsions and beyond

$$v_{\tau_{O-C-C-O}} = 0.25(1 + \cos(2\tau)) + 0.25(1 + \cos(3\tau))$$



In AMBER force field, O–C–C–O torsion angle for $\text{OCH}_2\text{--CH}_2\text{O}$ fragment found in sugars in DNA

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$$r_{ij} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2}$$

$$\frac{\partial v}{\partial x_i} = \frac{\partial v}{\partial r_{ij}} \frac{\partial r_{ij}}{\partial x_i}$$

FFs in internal coordinates; atomic positions in Cartesian coordinates

$$\frac{\partial r_{ij}}{\partial x_i} = \frac{(x_i - x_j)}{r_{ij}}$$

$$\frac{\partial v}{\partial r_{ij}} = \frac{24\epsilon}{r_{ij}} \left[-2 \left(\frac{\sigma}{r_{ij}} \right)^{12} + \left(\frac{\sigma}{r_{ij}} \right)^6 \right]$$

$$f_{x_i} = (x_i - x_j) \frac{24\epsilon}{r_{ij}^2} \left[2 \left(\frac{\sigma}{r_{ij}} \right)^{12} - \left(\frac{\sigma}{r_{ij}} \right)^6 \right]$$