

# Classical Force Fields for Simulations

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## Outline

- Potential Energy Function
- All-atom Vs. United Atom force fields
- Protein force fields
- Nucleic acid force fields
- Lipid force fields
- Carbohydrate force fields
- Heterogeneous Biomolecular systems
- Force field transferability

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## Intra- and Inter-molecular Forces

- Molecular Forces tell us how atoms move
- The forces due to intra- and inter-molecular interactions comes from the potential energy of each atom,  $U(R)$
- Intra-molecular Potentials
  - Bond stretching
  - Bond Angles
  - Torsional terms
- Inter-molecular Potentials
  - Van Der Waals interactions
  - Electrostatic Interactions
  - Hydrogen Bonding

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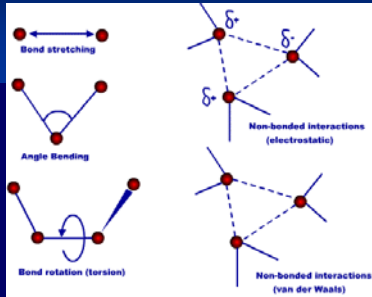
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## Contributions to a Molecular Mechanics Force Field



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## Potential Energy Function

$$U(\vec{R}) = \sum_{\text{bonds}} K_b (b - b_0)^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_0)^2 + \sum_{\text{dihedral}} K_\chi \left( 1 + \cos(n\chi - \delta) \right) + \sum_{\text{impropers}} K_{\text{imp}} (\varphi - \varphi_0)^2 + \sum_{\text{nonbond}} \left( \epsilon_{ij} \left[ \left( \frac{R}{r_{ij}} \right)^{12} - \left( \frac{R}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{\epsilon r_{ij}} \right)$$

- A force field is an equation which expresses the potential energy as a function of the positions of the atoms.

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## Bonds and Angles

$$E_{\text{bond-stretch}} = \sum_{1,2 \text{ pairs}} K_b (b - b_0)^2$$

$$E_{\text{bond-bend}} = \sum_{\text{angles}} K_\theta (\theta - \theta_0)^2$$

- a harmonic potential
- atoms are separated by one covalent bond, i.e., 1,2-pairs.
- also represented by a harmonic potential.
- Values of  $\theta_0$  and  $K_\theta$  depend on chemical type of atoms constituting the angle.

These two terms describe the deviation from an ideal geometry; effectively, they are penalty functions and that in a perfectly optimized structure, the sum of them should be close to zero.

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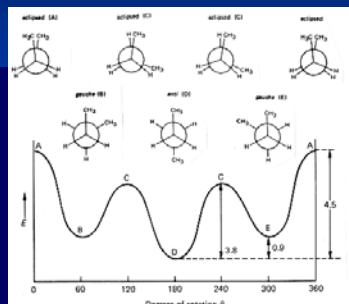
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## Torsion angle potential function

$$\sum_{\text{dihedral}} \times K_n \left( 1 + \cos(n\chi - \delta) \right)$$



- This models steric barriers between atoms separated by 3 covalent bonds (1,4 pairs)

- This potential is assumed to be periodic and is often expressed as a cosine function.

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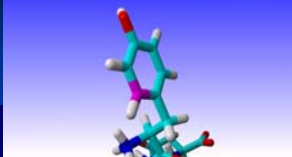
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## Improper Dihedral Forces



$$\sum_{\text{improper}} K_{\text{imp}} (\varphi - \varphi_0)^2$$

The improper dihedral term is used to maintain chirality and planarity

## Improper Dihedral Angles

- This Tyr has a planar ring. The forces which keep this ring planar are called "improper dihedrals"

- 'Improper dihedrals' are a special form of dihedral angles. The associated forces involve a central and three bound atoms.

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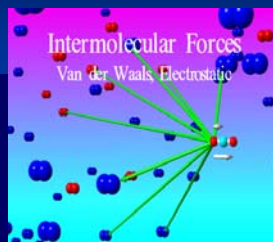
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## Inter-Molecular Forces



- There are intermolecular forces on all atoms that belong to different molecules or are separated by more than three bonds.

- To save processor time, intermolecular forces are usually only calculated for atoms close by, not all atoms in the system.

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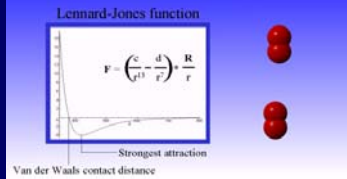
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## Van Der Waals Interactions

### Van der Waals Forces



- Correlated motions of electrons in neighboring atoms create temporary dipoles of the same orientation - the atoms attract.
- This attraction is called a 'Van der Waals' force. In the force field, it is approximated with a 'Lennard-Jones' function.

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## Electrostatic Interactions

$$E_{\text{electrostatic}} = \sum_{\text{nonbonded pairs}} \frac{q_i q_j}{\epsilon r_{ij}}$$

- Coulombic potential
- $\epsilon$  is the effective dielectric function and  $r_{ij}$  is the distance between two atoms having charges  $q_i$  and  $q_j$

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## Limitations of Potential Energy Function

- there is a certain amount of grouping in order to minimize the number of atom types, this can lead to **type-specific errors**
- The simultaneous interaction between three or more atoms is not calculated. **polarization effects are not explicitly included** in the force field
- potential energy function **does not include entropic effects**

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## All-Atom Vs. United Atom Force Fields

- Treat all atoms in the molecule: all-atom ff
- Neglect H atoms and make adjustments in the non-bond parameters of the atom to which the H is attached: Extended or United atom ff
- Explicitly include polar hydrogens
- Certain interactions are poorly treated

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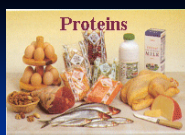
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## Protein Force Fields

- Majority of protein MD (excl. protein folding) is done using all-atom force fields
  - OPLS/AA
  - CHARMM22
  - AMBER

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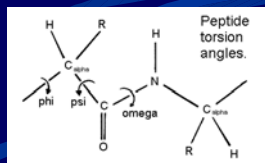
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## CHARM22 and AMBER

- Optimized based on TIP3P water model
- Intra-molecular parameters from experimental and QM data
  - Reproduction of vibrational spectra for optimization of force constants
- The inclusion of 2D dihedral energy grid correction improves  $\phi$ ,  $\psi$  sampling (work on progress)



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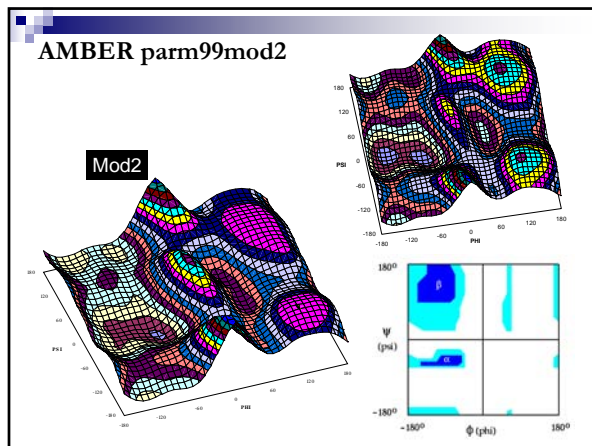
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## Knowledge based force fields

- Also called Free Energy force fields
- Used in Protein folding studies
- Are parameterized to directly yield free energies
  - ECEPP : one of the earliest ff
  - UNRES

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## Nucleic Acid Force Fields

- Oligo-nucleotides are POLY-ANIONIC
- Challenges:
  - treatment of their conformational energies
  - their interaction with aq. solvent environment
- Nucleic acid ff:
  - Cornell et al AMBER (parm94) and CHARMM all atom
  - Both produced stable simulations

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## Nucleic Acid ff and their problems



### ■ CHARMM:

- strong tendency towards A form DNA -> lead to re-optimization of CHARMM all atom nucleic acid ff -> CHARMM27

### ■ AMBER:

- Problems with sugar pucker and helical repeat -> modification of selected torsion parameters -> parm98/99

### ■ New: BMS (Bristol-Myers-Squibb)

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## Optimization involved differences

### ■ AMBER

- Internal parameters from small molecules via reproduction of geometries, vibrational spectra and conformational energies
- These parameters applied to larger model compds. With adjustments with dihedral parameters
- Partial charges from RESP
- Optimization of torsional parameters-> applied to nucleotides

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## Optimization involved differences

### ■ CHARMM27

- Internal parameters from small molecules via reproduction of geometries, vibrational spectra and conformational energies (same as AMBER)
- Partial charges from supramolecular approach
- Optimization in part by reproduction of conformational energies of larger model compounds

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## Optimization involved differences

- BMS based on
  - AMBER RESP charges
  - CHARMM based internal parameters
  - CHARMM/Quanta internal parameters for sugars and phosphodiester backbone
  - Final optimization was based on surveys of the NDB with proper treatment of equilibrium between A and B form of DNA as a function of water activity

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## Other force fields

- GROMOS, MOS, MMFF, CVFF, OPLS
- FLEX (from JUMNA): knowledge based ff for nucleic acids

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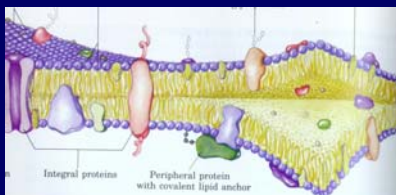
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## Lipid Force Fields

- Liquid crystalline nature of lipid bilayers
  - ⇒ absence of high resolution experimental structures
  - ⇒ Absence of structural target data needed for optimization



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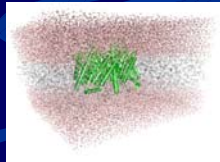
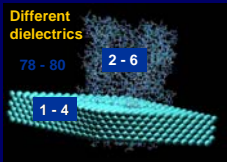
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## Lipid Force Fields

- Both all atom and extended atom ff available
- United atom ff is advantageous for lipids
  - GROMOS96 (most commonly used)
  - Force field by Berger et al



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## Parameter development in CHARMM for use as lipid ff

- Optimization of ff targeting small molecules
- High densities for glycerolphosphorylcholine and cyclopentylphosphorylcholine + limitations with nucleic acid ff => re-optimization in the phosphate parameters
- Application of new LJ parameters → CHARMM27

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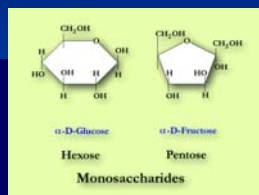
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## Carbohydrate force fields

- Challenges:
  - With mono-saccharides, the conformational properties are dominated by a subtle balance of inter- and intra-molecular **H-bonding**
  - Significant number of **different types** of mono-saccharides of biological interest



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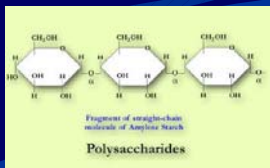
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## Challenges (...contd.)

- Different **functional groups** involved like acetamido, amino, sulfate, uronic acid etc
- In polysaccharides, chemical connectivities like **glycosidic bonds** are present
- Presence of multiple O (or N) → **delocalization** of O lone pairs



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## Carbohydrate Force Fields

- Recently MM4 ff reported
  - Developed for gas phase (applicability for condensed phase simulations are unclear)
  - Treats alcohols, ethers and hexoses
- Commercial CHARMM package (for gas phase)
- CHEAT (variant of commercial CHARMM ff)
  - Knowledge based approach
  - Hydroxyl groups are treated as extended atoms

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## Carbohydrate force fields

- Gas phase-based ff useful for understanding general conformational properties
- CHARMM based ff (designed to be used with explicit solvent)
  - Brady and coworkers: ff limited to hydroxyl substituents
  - Reiling et al
- GROMOS based
  - United atom model
  - Variations by Ott and Meyer

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## AMBER based Carbohydrate force fields

- Glennon and Merz: hexapyranose ff (semi-empirical calculations to assign partial atomic charges)
- GLYCAM by Wood and coworkers
  - Unique partial atomic charges for atoms
  - Ensemble averaging in charge determination
  - Additional optimization of internal parameters
  - 1, 4 scale factor of 1.0
- AMB99C
- Kollman and co-workers: adjustment of torsional parameters (accurate but for monomers only)
- SPACIBA (specialized...gen. applicability is questionable)
- OPLS

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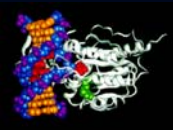
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## Heterogeneous Bio-molecular Systems

- Non-bonded interactions between different aspects of the ff should be properly balanced when employing empirical ff for heterogeneous systems
- Use parameters which are part of the same force field
- Range of molecules that a ff covers should be taken into account

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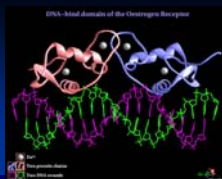
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## Heterogeneous Biomolecular Systems

- CHARMM22 and CHARMM27
  - Most extensively used
  - Include proteins, NA, lipids and carbohydrates
  - Performed on DNA-protein, DNA-lipid and protein-lipid complexes
- OPLS

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## Force Field Transferability

- There is application of empirical force field parameters to molecules not explicitly included during the parameter optimization.
  - Simplicity of form of the potential energy function limits transferability.
  - Extended potential energy function, including cross terms, increases transferability.
- Transferability is relative; the more you extrapolate the less the accuracy of the force field. Even in cases when the extrapolation is small, the force field can fail.

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## Force Field Transferability

- Empirical ff used in drug design and development
- Need parameters for drug like molecules
- Examples of ff: MMFF, CVFF, CHARMM, COMPASS, CFF, MM2/MM3/MM4, Dreiding and Tripos (sacrifice quality of nonbond interactions)
- MMFF and COMPASS include nonbond interactions
- AMBER has been designed to help transferability (automated methods for parameter assignment)
- CHARMM is limited in transferability

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## Summary

- Force field “quality” is defined by the parameters used in its creation. Two force fields with exactly the same “form” (i.e., a four term force field) can yield remarkably different results, depending on the parameterization.
- **Transferability** of the functional form and parameters is an important feature of a force field.
- force fields are **empirical**. There is no “correct” form of a force field

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# Thank You

## Acknowledgement

- Prof. Robert Rizzo
- Simmerling Lab members

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