MD Simulation
Part III

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MD Simulation Summary

- Molecular Mechanics (MM) consists of identifying the optimal structural conformer by utilizing various optimization techniques
- Molecular Dynamics Simulation (MD) consists of observing the trajectory of molecular segments energized by internal or external forces
  - Utilizes Newtonian laws of physics (classical physics)
  - Focused on solving Newton's equation of motion:

$$m_i \frac{d^2 x_i}{dt^2} = -\nabla_{x_i} E_{Total}$$

Solution to the Newtonian Equation of Motion

- Two possible approaches can be envisioned:
- Pseudo analytical solution:

$$E_{Total} = \omega_{Bond} E_{Bond} + \omega_{Angle} E_{Angle} + \omega_{dih} E_{Dih} + \cdots$$

$$E_{Bond} = \sum_{bonds} k_b \left(r - r_0\right)^2 = \sum_{bonds} k_b \left(\delta x_i^2 + \delta y_i^2 + \delta z_i^2 - r_0\right)^2$$

- Pure numerical solution:

$$\begin{cases} m_i \dfrac{d^2 x_i}{dt^2} = -\nabla_{x_i} E_{Total} \\ x_i^1 = x_i^0 + \underbrace{\boxed{v_i^0 \Delta t}}_{\text{External forces}} - \overbrace{\boxed{\nabla_{x_i^0} \left(E_{Total}\right) \dfrac{\Delta t^2}{2 m_i}}}^{\text{Internal forces}} \end{cases}$$

Pros and Cons of the Two Approaches

- Analytical solution:
  - Complete
  - Extensive and unmanageable
    - A system of differential equations consisting of tens of thousands of equations and unknowns
- Numerical solution:
  - Only an approximation
  - Easy to compute and manage
  - Choice of Δt is critical
    - Δt too large will lead to gross approximation
    - Δt too small will lead to long computation time

Protein Structure Homology

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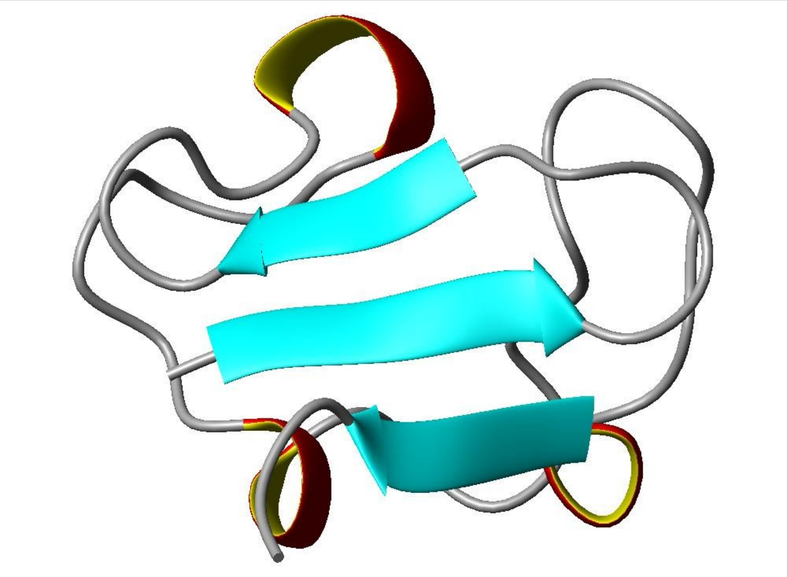
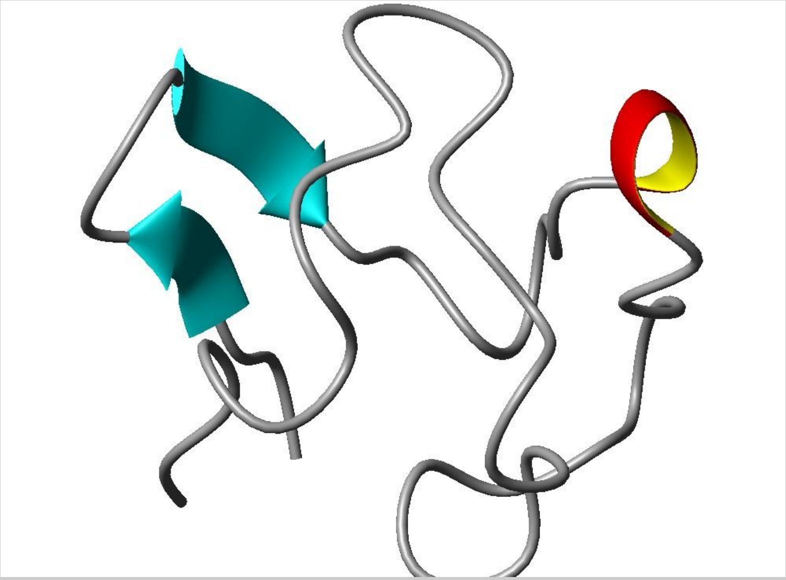
Protein Structure Homology

- Are the following two structures the same?
- Are they similar?





Superimposing Structures

- Options-Dialogs-RMSD
- Fit structures using Root-Mean-Square-Deviation (RMSD) of backbone atomic positions

1. Superpose the centers of masses between the two sets of atoms
2. Optimally rotate the two proteins such that:

$$R^*_{3\times 3} X_{3\times n} = Y_{3\times n}$$

$$D^*(X, Y) = \sqrt{\frac{1}{N} \sum_{i=1..n} \left(x_i - y_i\right)^2}$$

3. Can use Singular Value Decomposition to obtain R*

Superimposing Structures

- Options-Dialogs-RMSD
- Fit structures using Root-Mean-Square-Deviation (RMSD) of backbone atomic positions
    1. Superpose the centers of masses between two proteins

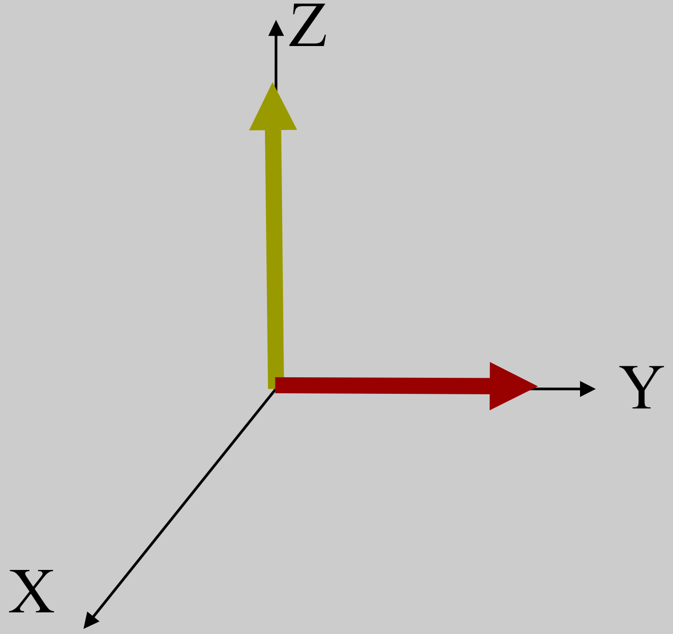
$$RMSD = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(A_1^i - A_2^i\right)^2}$$

    1. Optimally rotate the two proteins such that:

- Difference is measured in units of angstrom (Å).
- Backbone RMSD of 3.5 or less is significant.
- Backbone RMSD of 2.0 or less is good.
- Backbone RMSD of less than 1.0 means identical structures.

Rotation of Molecules in Space

- Fundamentally, rotation of objects in space
- A limited version of technology from gaming industry
- The coordinates of objects in space can be computed by rotation matrices
- Rotations can be about the X, Y, Z or any arbitrary axis.
  - Where would the point (0,1,0) be after a rotation of 90° about the X axis. Counter clockwise is positive rotation.
  - Rotate (0,0,1) by 180° about Z.
  - Rotate (1,2,3) 23.5° about the vector (1,3,2).



Rotation Operators (Matrices)

- Rx, Ry and Rz denote rotations about X, Y and Z respectively
- Example:
  - Rotate (1,2,5) by 45° about y

$$R_x(\alpha)=\begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos(\alpha) & -\sin(\alpha) \\ 0 & \sin(\alpha) & \cos(\alpha) \end{bmatrix}$$

$$R_y(\alpha)=\begin{bmatrix} \cos(\alpha) & 0 & \sin(\alpha) \\ 0 & 1 & 0 \\ -\sin(\alpha) & 0 & \cos(\alpha) \end{bmatrix}$$

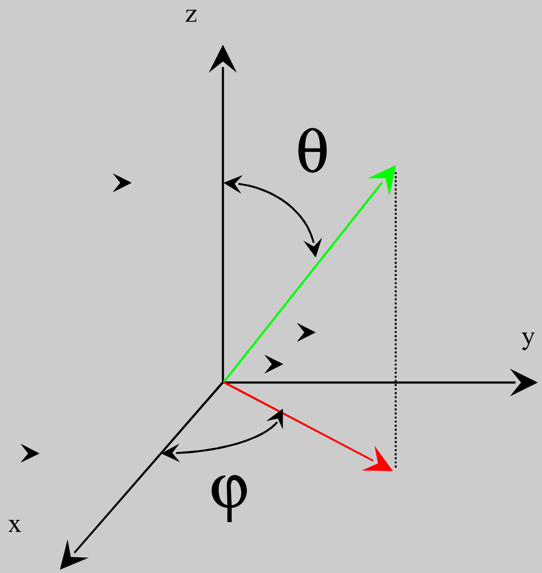
$$R_z(\alpha)=\begin{bmatrix} \cos(\alpha) & -\sin(\alpha) & 0 \\ \sin(\alpha) & \cos(\alpha) & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

Euler Rotation

- Any set of vectors can be rotated to any other orientation (as long as the internal relationship is maintained) by three rotations.
- Any two consecutive rotations can not be about the same axis.
  - Valid: XYX, ZYZ, ZYX, …
  - Invalid: XXY, ZYY, …
- Normally use ZYZ
- How would you derive the final ZYZ rotation?

Rotation About any Arbitrary Axis

- Two types of rotation:
  - Active rotation: rotation of the space.
  - Passive rotation: rotation of the axes.
- Can represent the arbitrary axis of rotation in its spherical coordinates (θ,ϕ)
- Then:



$$R_V^A(\alpha)=R_Y^P(-\theta)\,R_{Z'}^P(-\varphi)\,R_{Z'}^A(A)\,R_{Z'}^P(\varphi)\,R_Y^P(\theta)$$