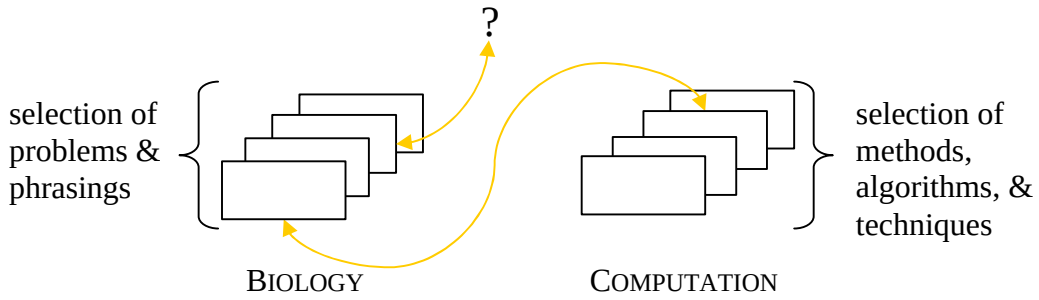
MIT 6.581/20.482J

FOUNDATIONS OF ALGORITHMS AND COMPUTATIONAL TECHNIQUES IN SYSTEMS BIOLOGY
Spring 2006

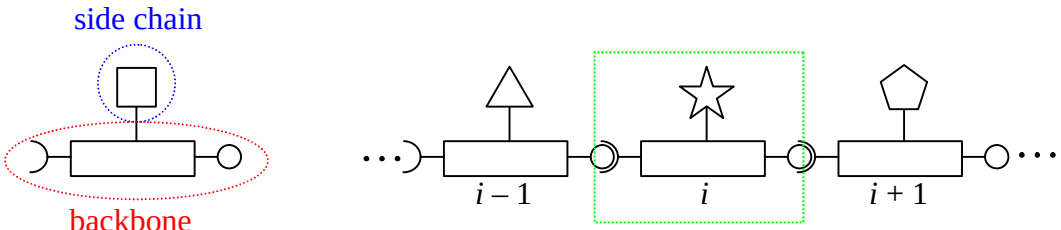
9 February 2006
Thursday

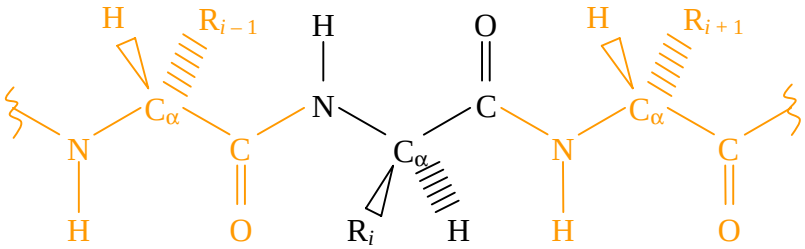
LECTURE 2 : MODELS OF PROTEINS



Fundamental role of models:
- Understanding
- Prediction
- Design

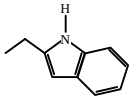
DNA – mRNA – Protein
(genome)



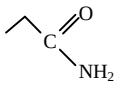
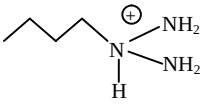


The "R_i" groups are chosen from the common 20 amino acid side chains – chemical diversity

(1) size: small – large
R_{Gly} : –H ⟶ R_{Trp}



(2) polarity: hydrophobic – polar – charged

R_{Leu} :  – R_{Asn} :  – R_{Arg} : 

(3) uniformity of character

(4) local backbone flexibility

Gly – Pro
(flexible) (rigidity)

Coordinate systems:

1) Absolute Cartesian Coordinates

$$\vec{\mathbf{X}} = \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \\ \vdots \\ x_{3N-1} \\ x_{3N} \end{bmatrix}$$

x_1, x_2, x_3: cartesian coordinates of 1st atom

x_{3N-1}, x_{3N}: N^{th} atom

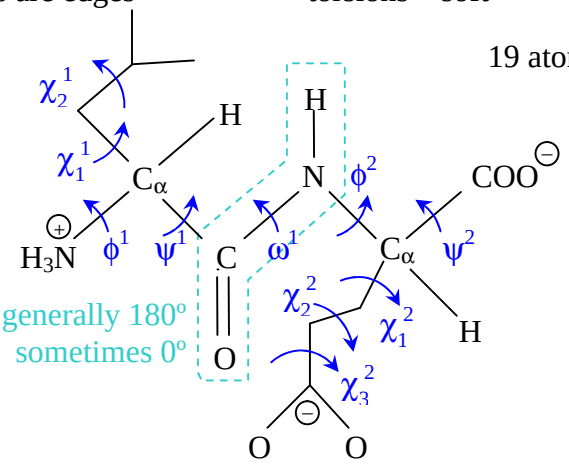
2) Relative Coordinates – Internal

Think of the molecules as graphs where

- atoms are vertices
- bonds are edges

bond lengths & bond angles – rigid

torsions – soft



Desire : Mapping $\vec{\mathbf{X}}^{3N} \rightarrow E\left(\vec{\mathbf{X}}^{3N}\right)$

"energy" scalar value

$\Rightarrow$ Bias toward <u>mechanistic</u> basis for model

Chemistry – Physics (Quantum Mechanics)

Schrödinger Equation: $i\hbar\frac{\partial\Psi}{\partial t} = -\frac{\hbar^2}{2m}\nabla^2\Psi + V(x)\Psi(x,t) \equiv \hat{H}\Psi(x,t)$ (nuclear & electrons)

<u>Linus Pauling</u>

Observations:

- bond lengths, angles – fixed
- torsions – "soft" & sinusoidal
- atoms appear to have a fixed spherical size & approach to contact neighbors
- complementary electrostatics

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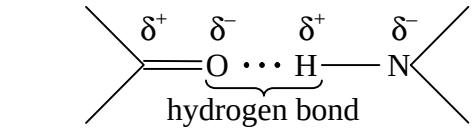

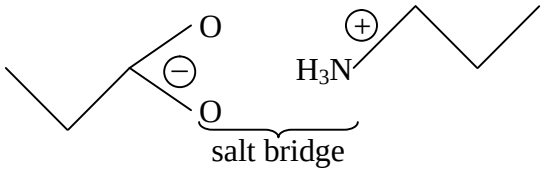

Molecular Mechanics Potential:

$$E\left(\vec{\mathbf{X}}^{3N}\right) = U_{\text{COVALENT}} + U_{\text{NON-COVALENT}}$$

bonded; through space

$$U_{\text{COVALENT}} = \sum_{i:\text{bonds}} \tfrac{1}{2} k_{b,i}\left(b_i - b_{o,i}\right)^2 + \sum_{i:\text{angles}} \tfrac{1}{2} k_{q,i}\left(q_i - q_{o,i}\right)^2 + \sum_{i:\text{impropers}} \tfrac{1}{2} k_{\Phi,i}\left(\Phi_i - \Phi_{o,i}\right)^2 + \sum_{i:\text{torsions}} \tfrac{1}{2} k_{f,i}\left[1 + \cos\left(n_i f_i - d_i\right)\right]$$

$$U_{\text{NON-COVALENT}} = \underbrace{\sum_{i>j}\left(\frac{B_{ij}}{r_{ij}^{12}} - \frac{C_{ij}}{r_{ij}^{6}}\right)}_{\text{van der Waals}\ \rightarrow\text{Lennard-Jones}} + \underbrace{\sum_{i>j}\frac{q_i q_j}{e\, r_{ij}}}_{\text{Electrostatics}\ \rightarrow\text{Coulombic}}$$