

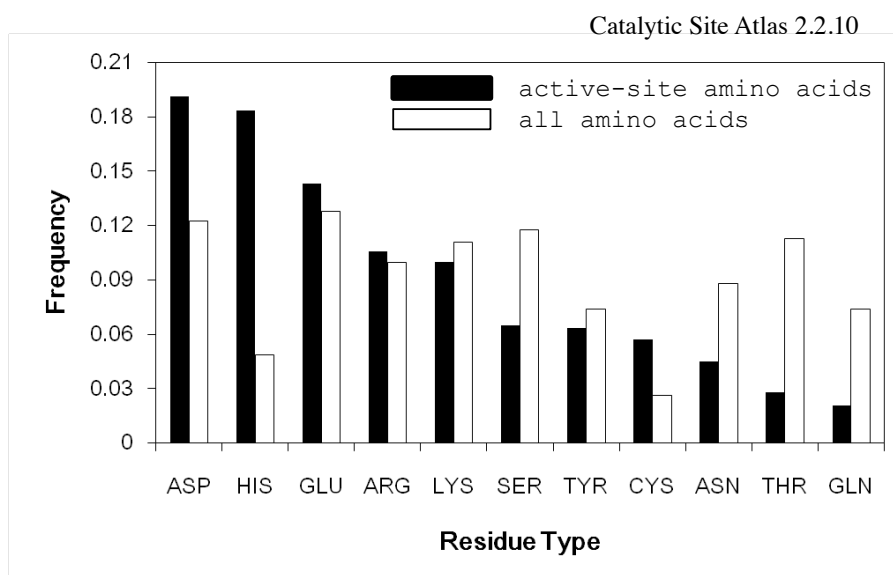
Structural Bioinformatics
or
Computational Structural Biology

黃鎮剛
交通大學
生物資訊所

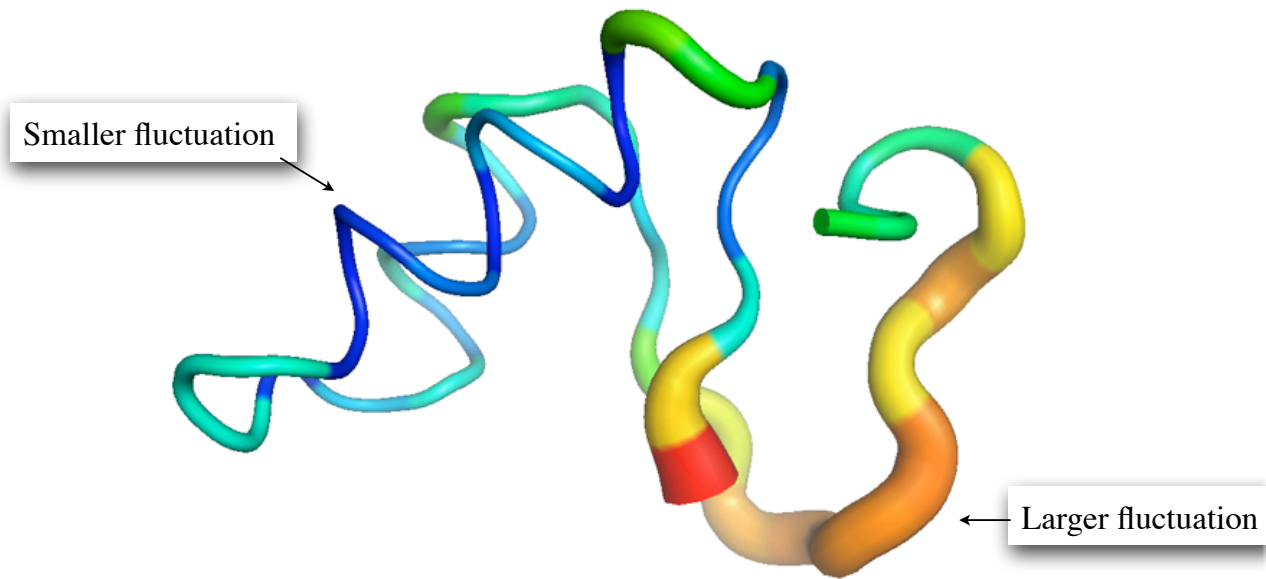
- Molecular Simulation
- Structure prediction
 - 2nd structure prediction; 3D structure prediction; Protein complex prediction
- Protein binding sites prediction
 - Protein - ligand prediction; protein-protein
- Novel protein structure

From protein structure to active protein

The distribution of amino acid types



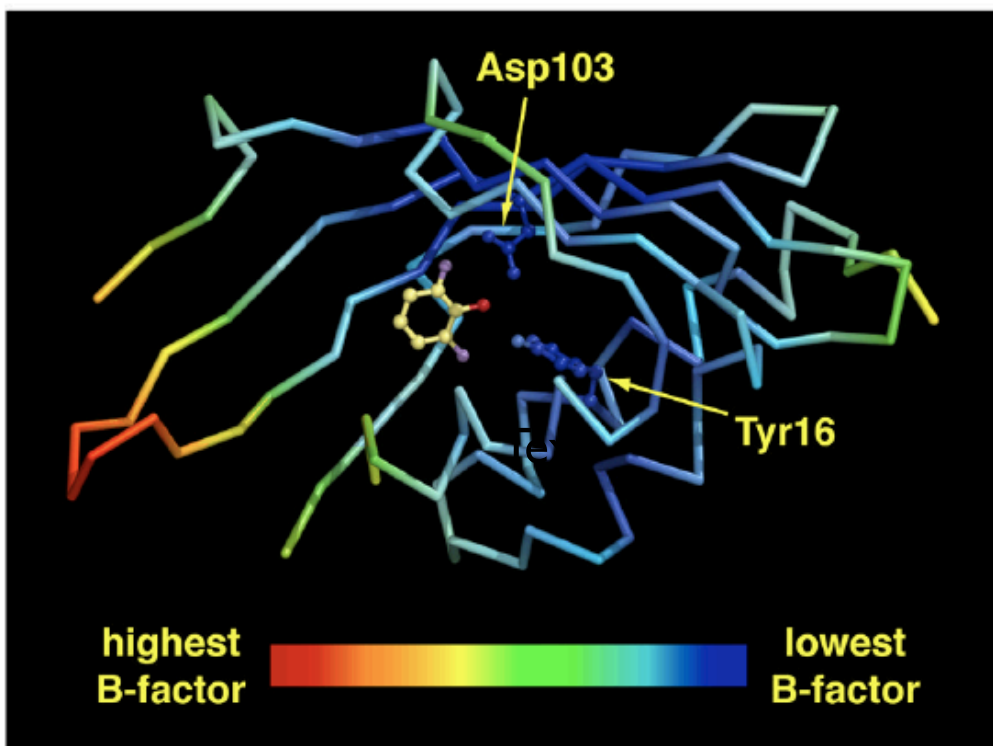
B-factors



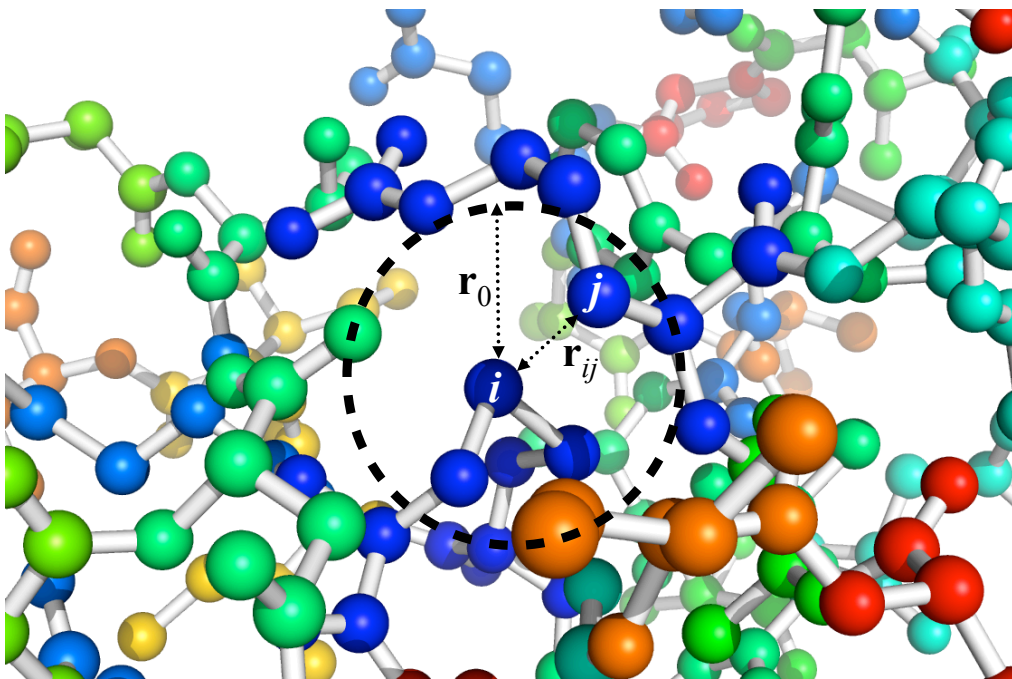
$$B_i = (8\pi^2 / 3) \langle \delta \mathbf{x}_i \cdot \delta \mathbf{x}_i \rangle$$

5

c)



JACS (2009) 140: 13696, Testing Geometrical Discrimination within an Enzyme Active Site:



$$v_i = \sum_j h(r_0 - r_{ij})$$

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Figure 2

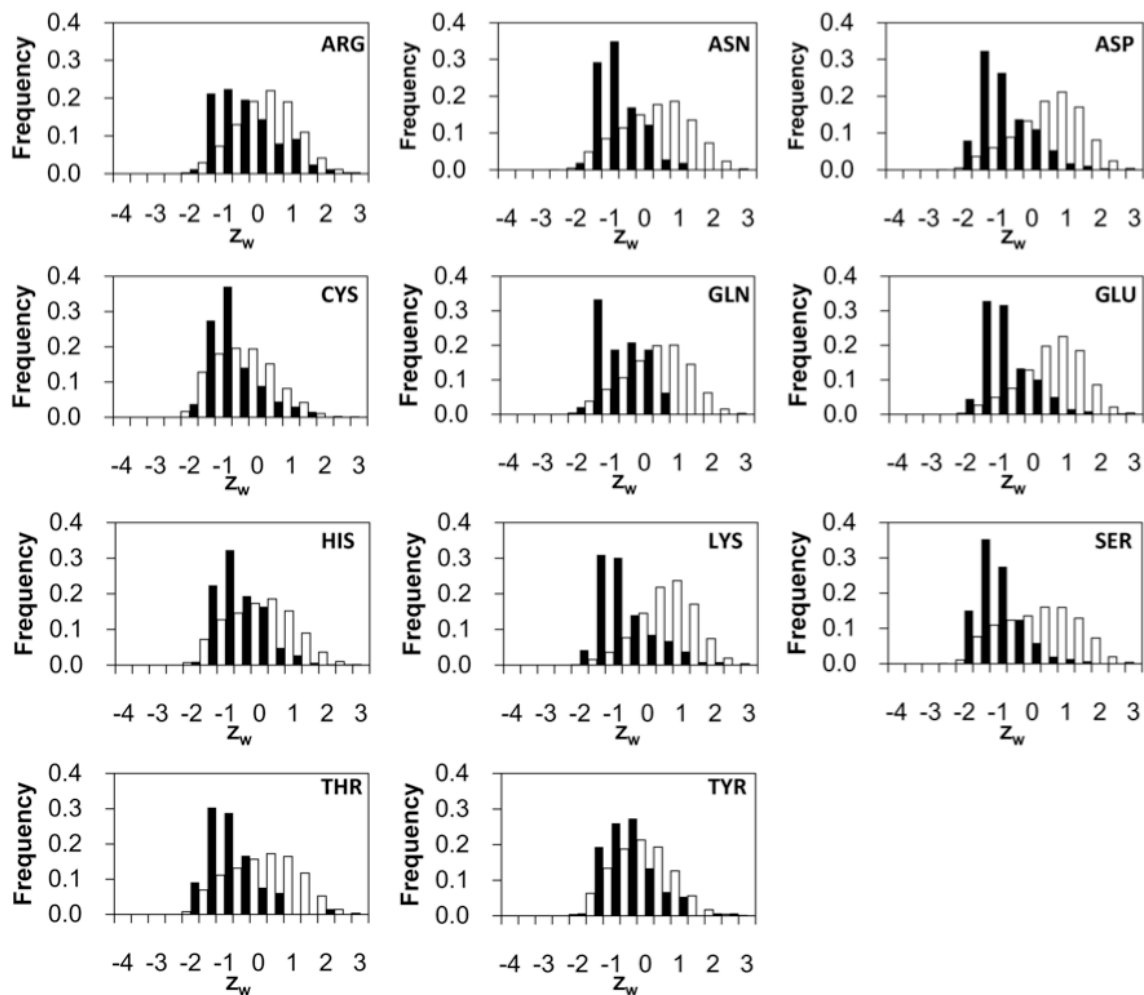


Figure 1

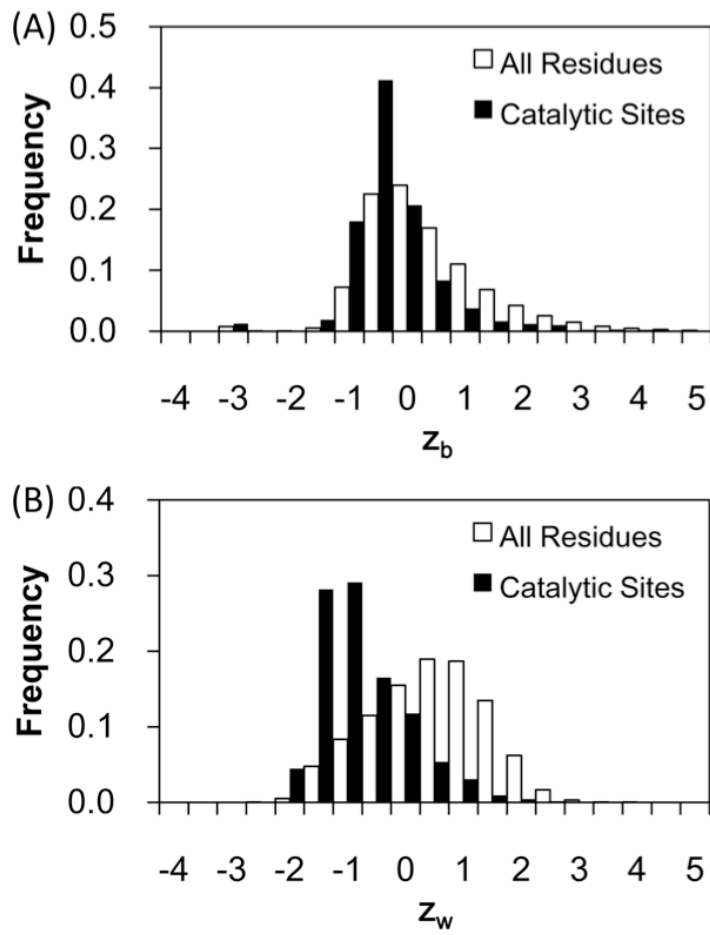


Figure 3

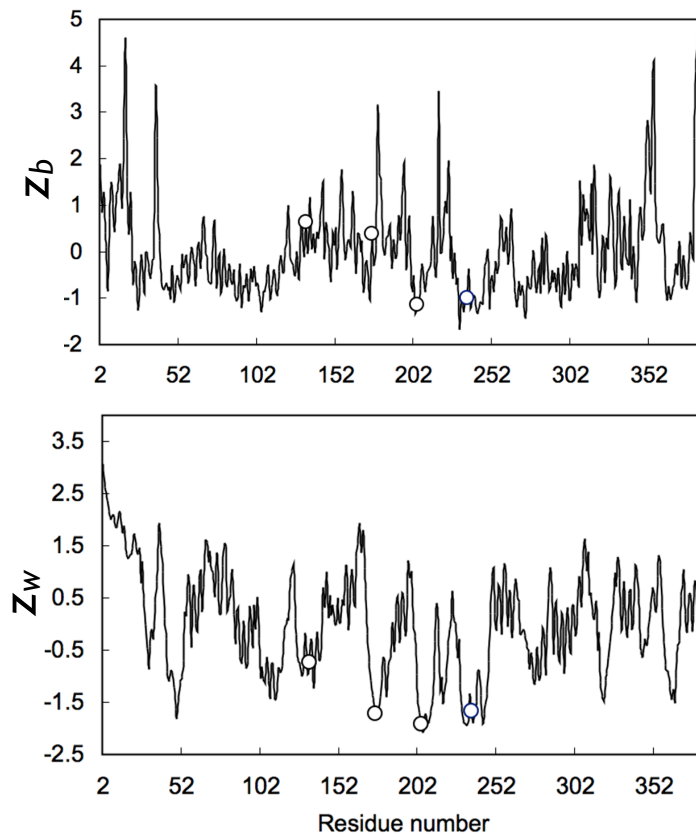
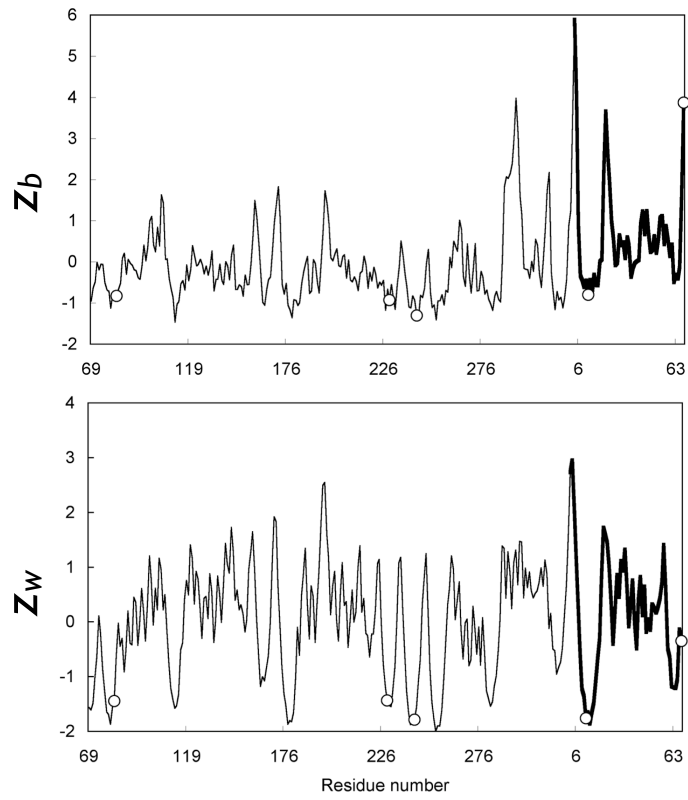
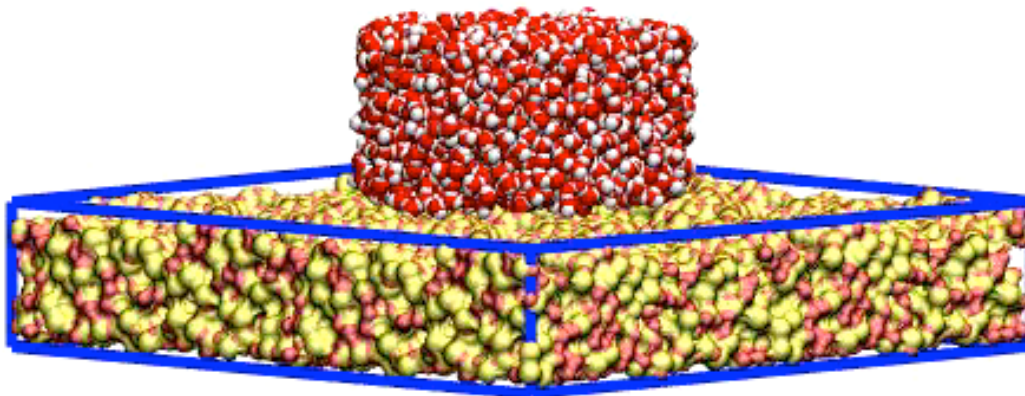


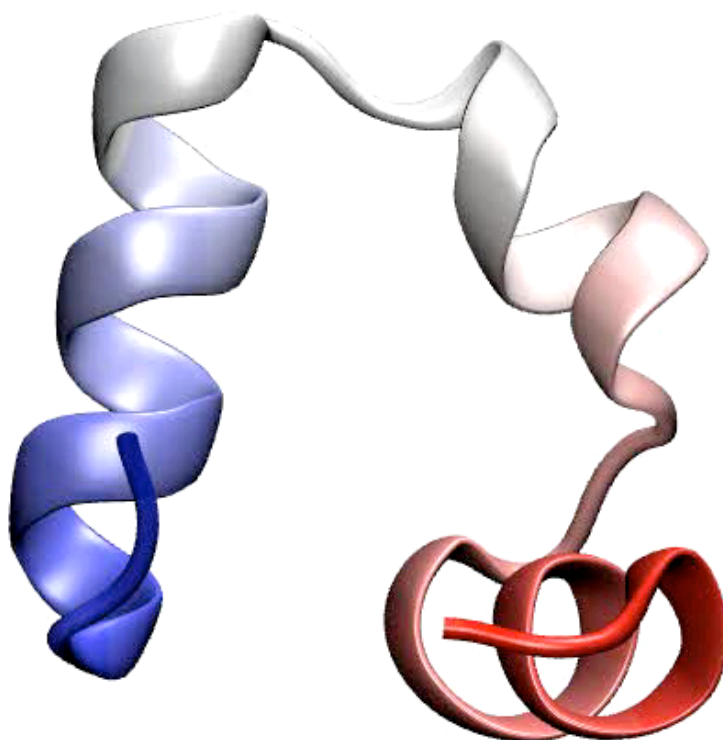
Figure 4



Molecular Simulation



Simulation of water drop in a hydrophobic surface

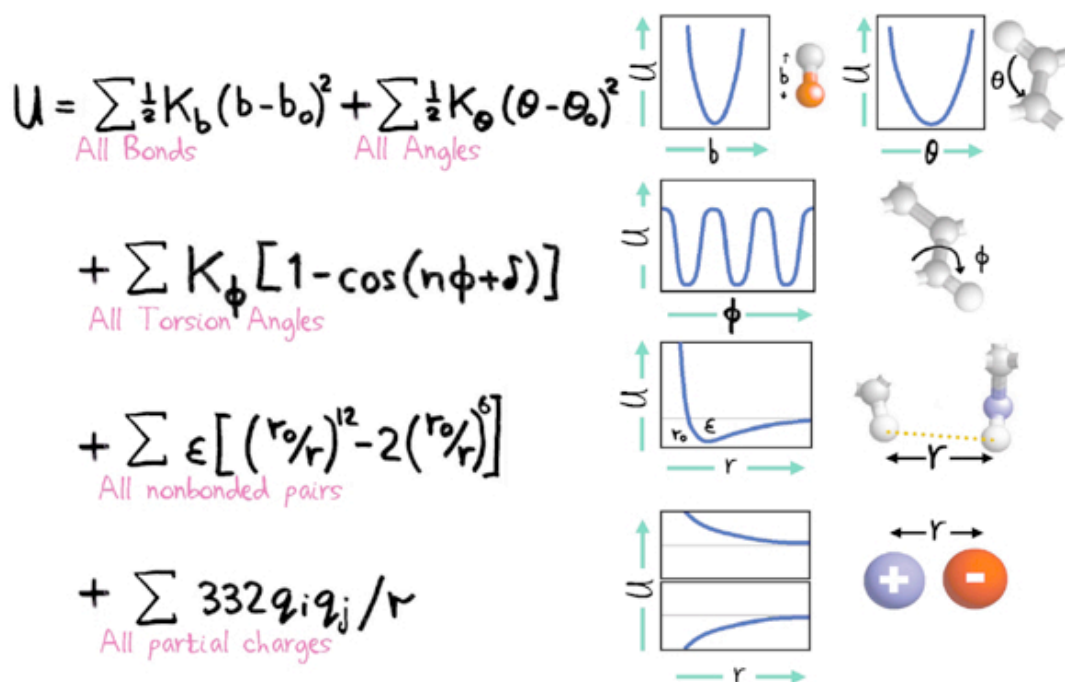


Villin Folding

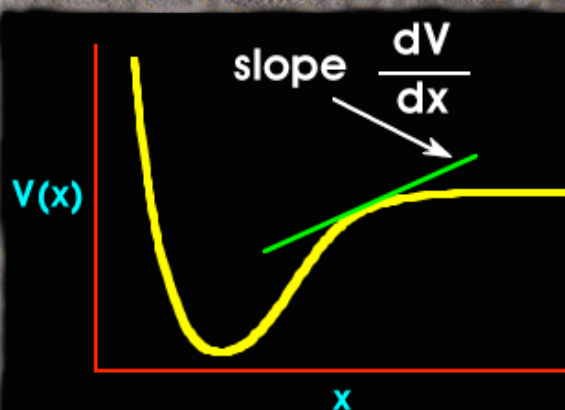
Molecular simulation of biological systems

- BIOLOGY
- Computer science
- Physics
- Chemistry
- Statistics
- ...

Empirical force field



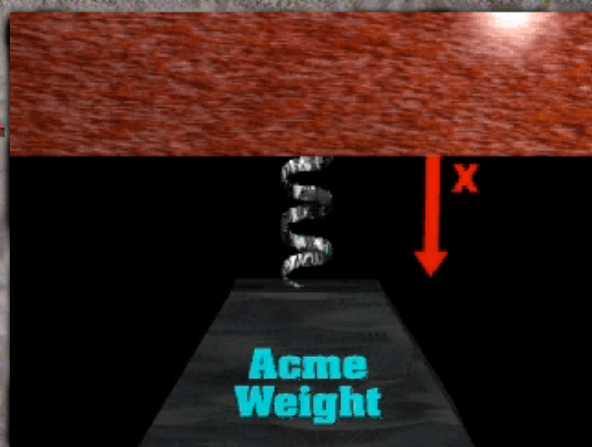
Molecular Dynamics



We need to know the potential energy $V(x)$ to compute the dynamics $x(t)$. How can we describe $V(x)$ for a molecule?

Molecular Dynamics

Newton's 2nd Law

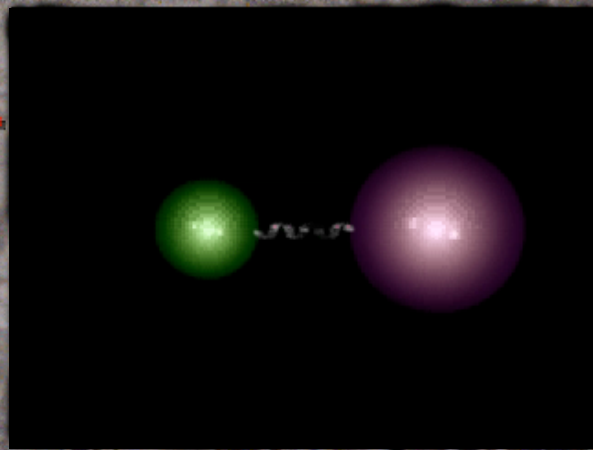
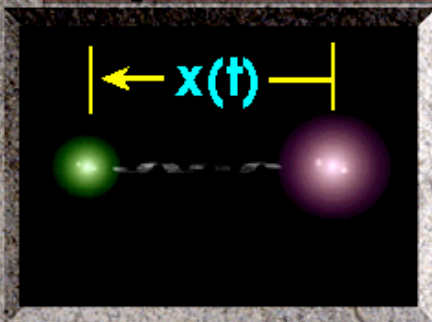


$$-\frac{dV}{dx} = F = ma = m \frac{d^2 x}{dt^2}$$

Potential Energy

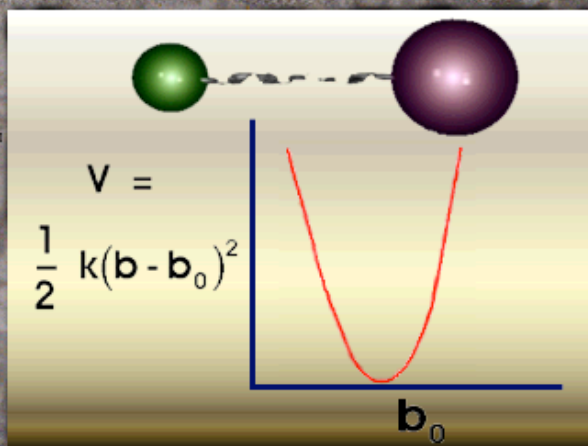
Position

Biomolecular Dynamics



How do we find out the motion of the atoms in a molecule, the $x(t)$?

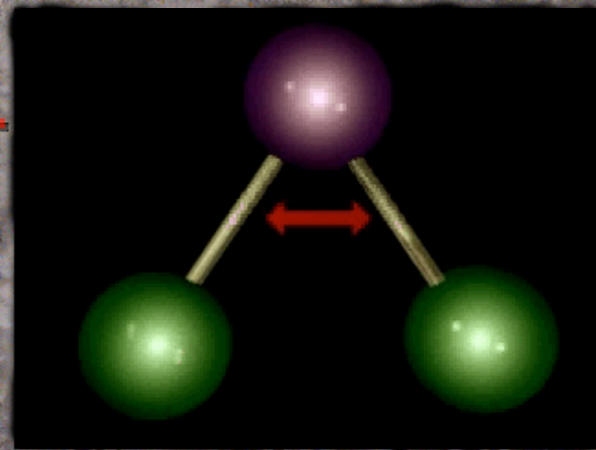
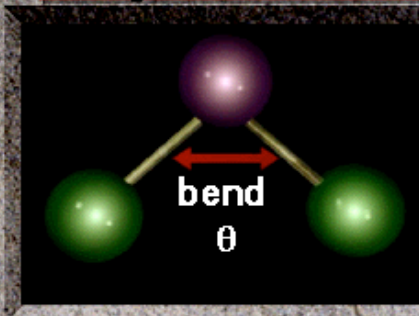
Molecular Dynamics



$$V_{\text{bonded}} = \sum_{\text{bonded pair of atoms}} \frac{1}{2} k(b - b_0)^2$$

Harmonic Oscillator

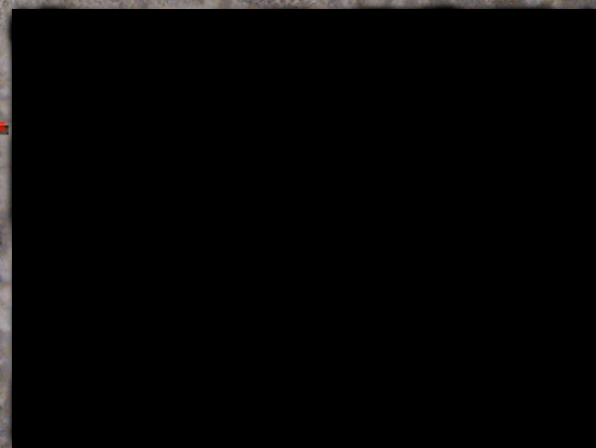
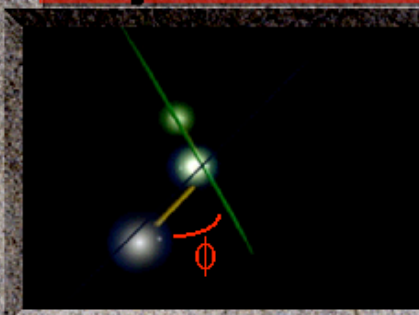
Molecular Dynamics



$$V_{\text{bend}} = \sum_{\text{bond angles}} \frac{1}{2} k_{\theta} (\theta - \theta_0)^2$$

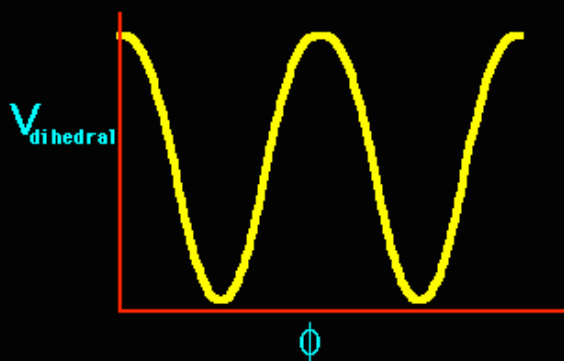
Harmonic Oscillator

Molecular Dynamics



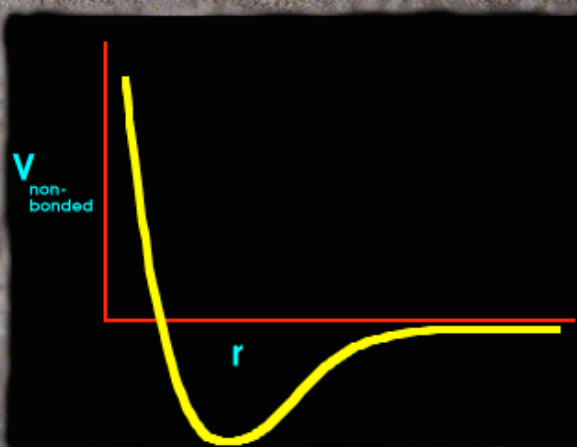
$$V_{\text{dihedral}} = \sum_{\text{dihedral angles}} k_{\phi} [1 + \cos(n\phi - \delta)]$$

Molecular Dynamics



$$V_{\text{dihedral}} = \sum_{\text{dihedral angles}} k_{\phi} [1 + \cos(n\phi - \delta)]$$

Molecular Dynamics



$$V_{\text{nonbonded}} = \sum_{\text{nonbonded pairs of } i, j \text{ atoms}} V_{\text{nb}}(r) + \frac{q_i q_j}{\epsilon r}$$

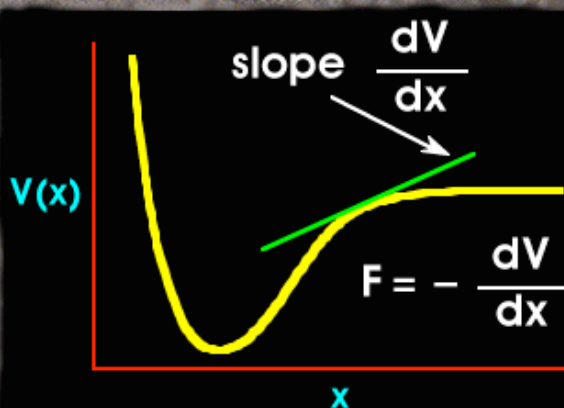
charges on atoms \rightarrow $q_i q_j$
 \uparrow
dielectric constant ϵ

Molecular Dynamics

Force (x) →



$$F(x) = m \frac{d^2 x}{dt^2}$$



How can we find out how the atoms in a molecule move? Let's look at a simple example, in which a single atom feels a force $F(x)$ only in the x direction.

Molecular Dynamics

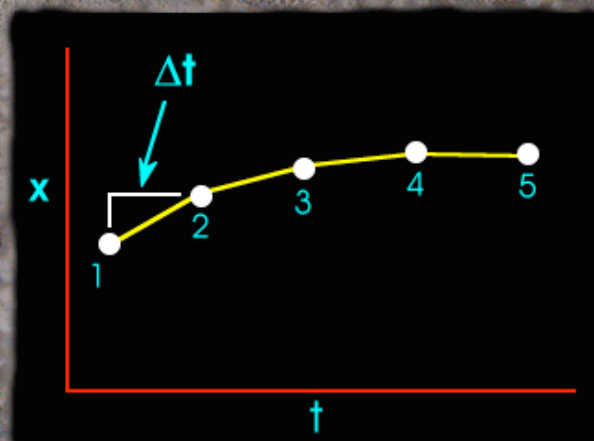
Force (x) →



$$F(x) = m \frac{d^2 x}{dt^2}$$

Now we want to find the trajectory, $x(t)$, of that atom. Assume that at time t , the atom is at position x_1 , with velocity $v_1 = \frac{dx_1}{dt}$, and acceleration $a_1 = \frac{d^2 x_1}{dt^2} = m^{-1} F(x_1)$.

Molecular Dynamics

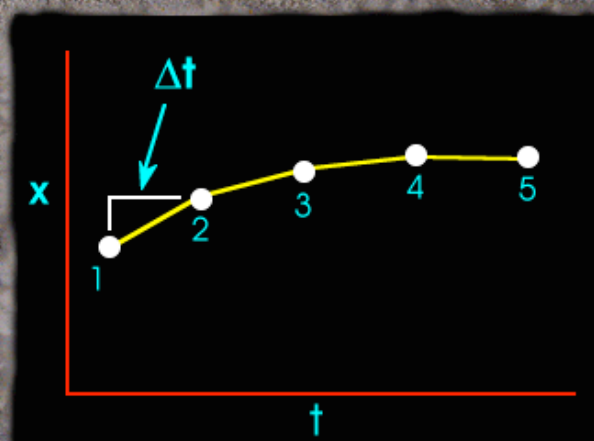


Approximately,

$$x_2 = x_1 + v_1 \Delta t$$

$$v_2 = v_1 + a_1 \Delta t = v_1 + m^{-1} F(x_1) = v_1 - m^{-1} \left. \frac{dV}{dx} \right|_{x_1}$$

Molecular Dynamics



Approximately,

$$x_3 = x_2 + v_2 \Delta t$$

$$v_3 = v_2 + a_2 \Delta t = v_2 + m^{-1} F(x_2) = v_2 - m^{-1} \left. \frac{dV}{dx} \right|_{x_2}$$

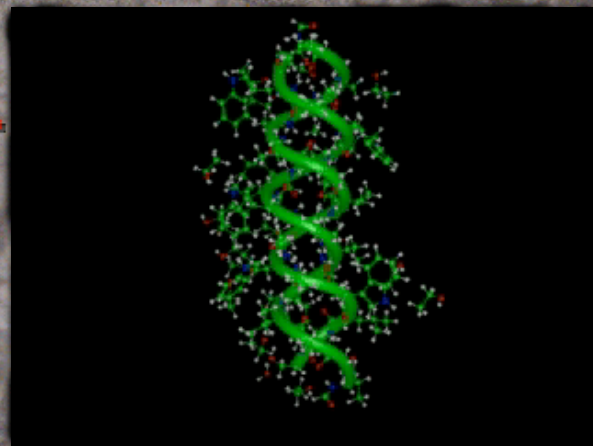
Molecular Dynamics

In general, if we are given the initial position x_1 , and velocity v_1 , of the atom, and the potential energy $V(x)$ which it feels, we can thus, step by step, compute its positions $x_1(t_1), x_2(t_2), x_3(t_3), \dots$ by

$$x_i = x_{i-1} + v_{i-1} \Delta t \quad v_i = v_{i-1} - m^{-1} \left. \frac{dV(x)}{dx} \right|_{x_{i-1}}$$

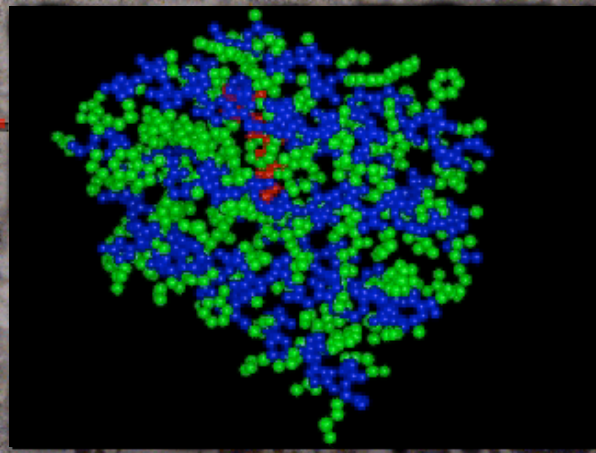
and thus approximately compute its trajectory $x(t)$. We call this process **integrating the equations of motion to find the trajectory**.

Molecular Dynamics



These same ideas may be generalized to compute the trajectories of all the atoms in a biomolecule, if we are given the initial positions and velocities of all the atoms, and the potential energy V of the molecule, such as we just defined, $V = V_{\text{bonded}} + V_{\text{bend}} + V_{\text{dihedral}} + V_{\text{nonbonded}}$

Biomolecular Dynamics



In this way, we can at least learn about the short time and distance scale motions involved in chemical reactions, enzyme-substrate interactions, and local interactions of biomolecules with their environment. As computers get faster, and scientists get more clever in using them, the accessible time and distance scales will keep increasing.

Molecular Dynamics

$$U = \sum_{\text{All Bonds}} \frac{1}{2} K_b (b - b_0)^2 + \sum_{\text{All Angles}} \frac{1}{2} K_\theta (\theta - \theta_0)^2$$

$$+ \sum_{\text{All Torsion Angles}} K_\phi [1 - \cos(n\phi + \delta)]$$

$$+ \sum_{\text{All nonbonded pairs}} \epsilon \left[\left(\frac{r_0}{r} \right)^{12} - 2 \left(\frac{r_0}{r} \right)^6 \right]$$

$$+ \sum_{\text{All partial charges}} 332 q_i q_j / r$$

Empirical Force Field

Classical equations of motion

$$H = T + U$$

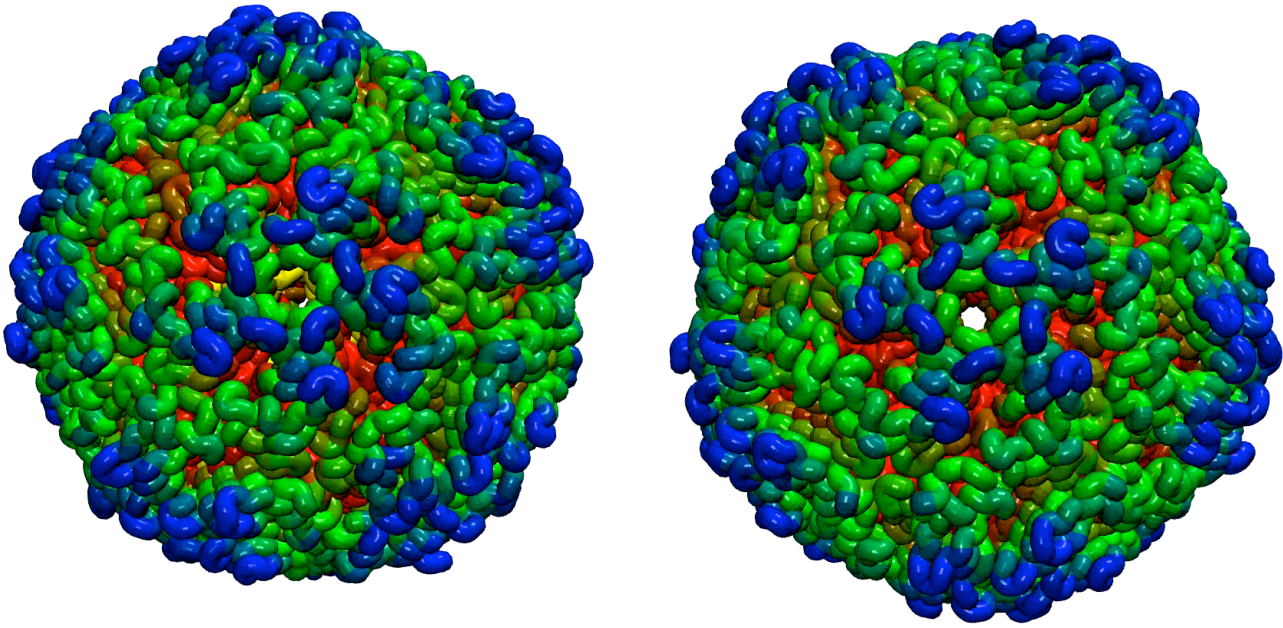
$$\dot{\mathbf{p}} = - \frac{\partial H}{\partial \mathbf{q}}$$

$$\dot{\mathbf{q}} = \frac{\partial H}{\partial \mathbf{p}}$$

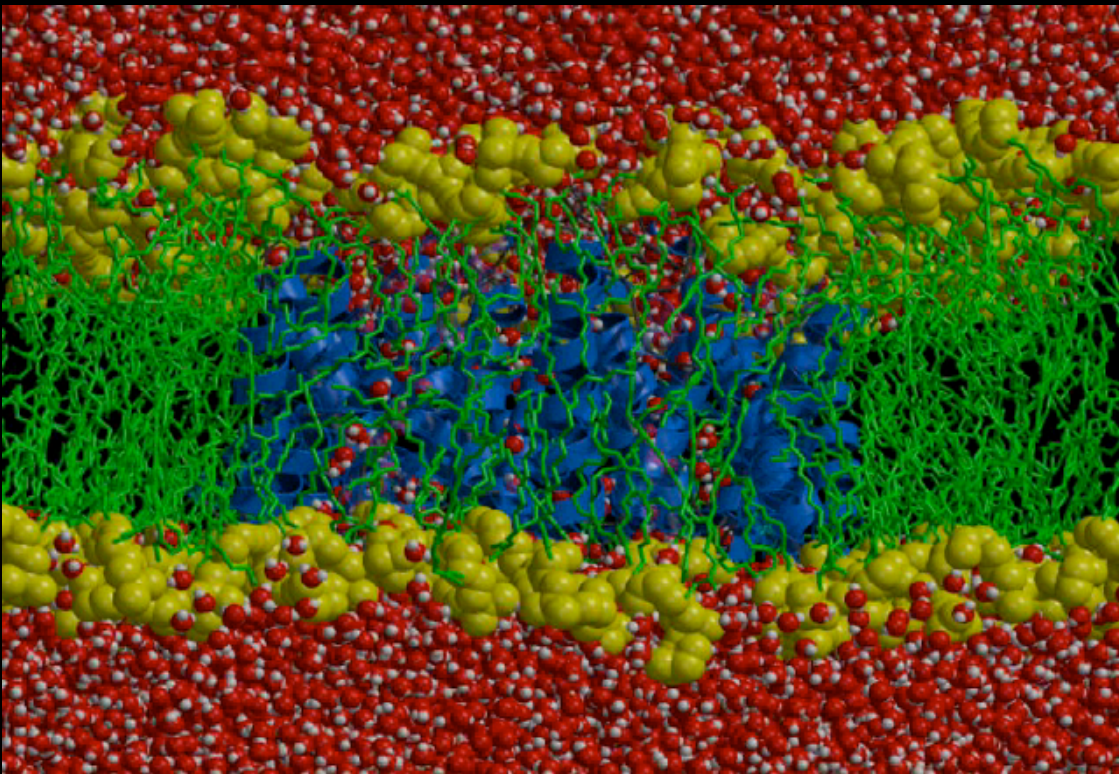
$$\mathbf{q}(t)$$

$$\mathbf{p}(t)$$

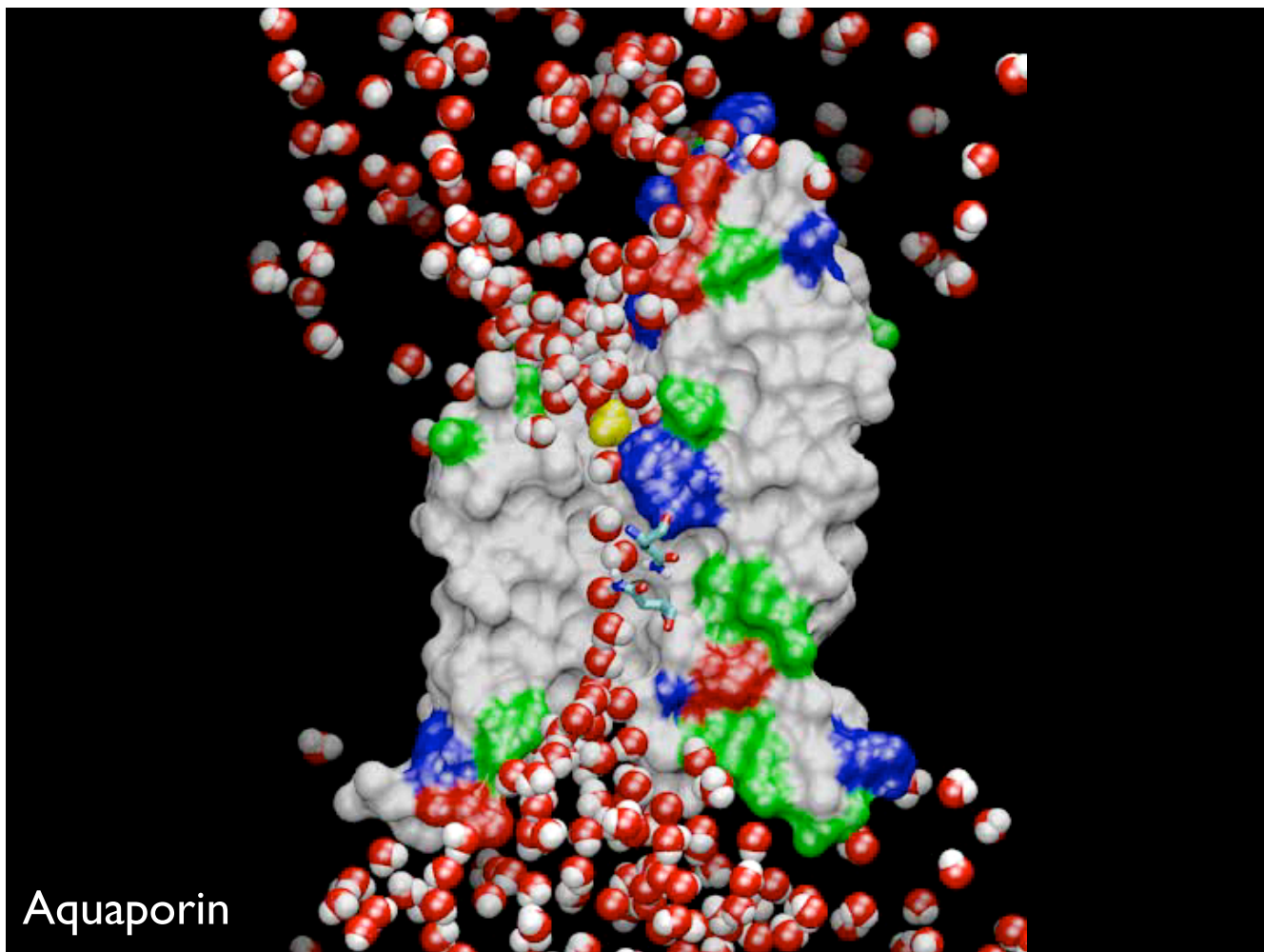
Trajectory integration



Satellite Tobacco Mosaic Virus



Simulation of protein dynamics



Knotted Proteins



Different types of knots

KnotPlot

Vol 438 | 17 November 2005 | 324-324 | doi:10.1038/nature04118

nature

ARTICLES

A light structure domain

Jeremiah R. We

1ztu

A trefoil knot

Phytochromes are found in bacterial, fungal and plant kingdoms. These include photosynthetic potential and pigmentation in bacteria as well as chloroplast development and photomorphogenesis in plants. Phytochromes consist of an amino-terminal domain that binds a single bilin chromophore, followed by a carboxy-terminal dimerization domain that contains a histidine kinase relay. Here we describe the three-dimensional structure of the *Deinococcus radiodurans* phytochrome assembled with its chromophore refined to 2.5 Å resolution, reaffirms Cys 24 as the chromophore attachment site, and reveals an unusually formed solvent-shielded bilin-binding pocket, and reveals an unusually formed structure provides the first three-dimensional glimpse into the photochemical mechanism. The structure helps to explain the evolution of higher plant phytochromes from prokaryotes.

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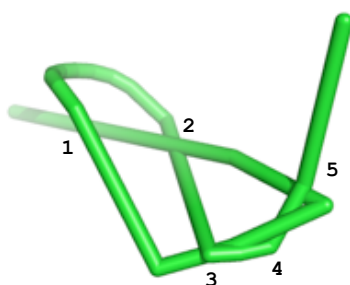
Nature (2005) 438, 324

PyMOL

To find knots by a smoothing algorithm



Ubiquitin Hydrolase
1XD3:A

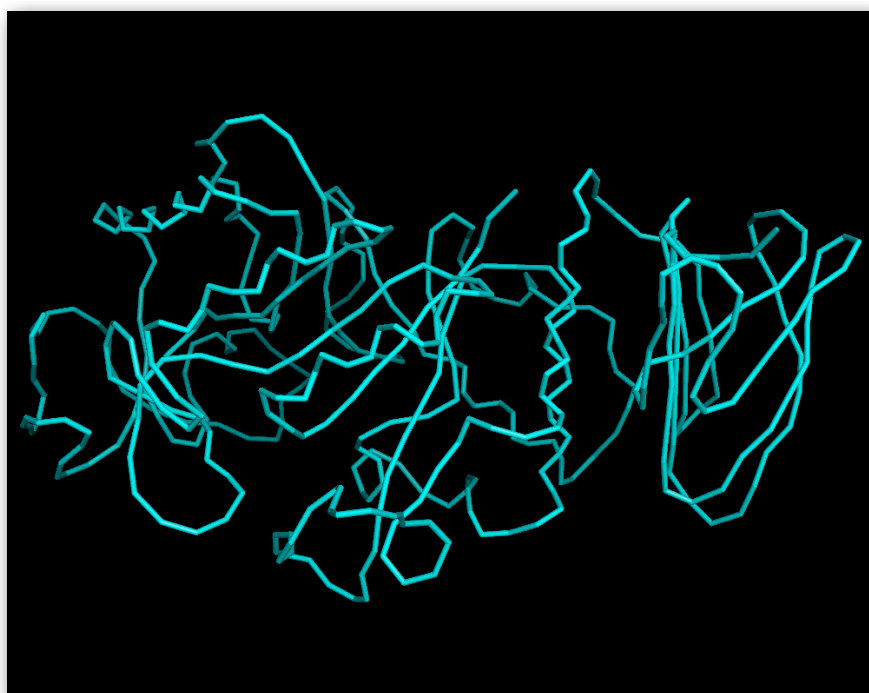


`PyMol: show animation`

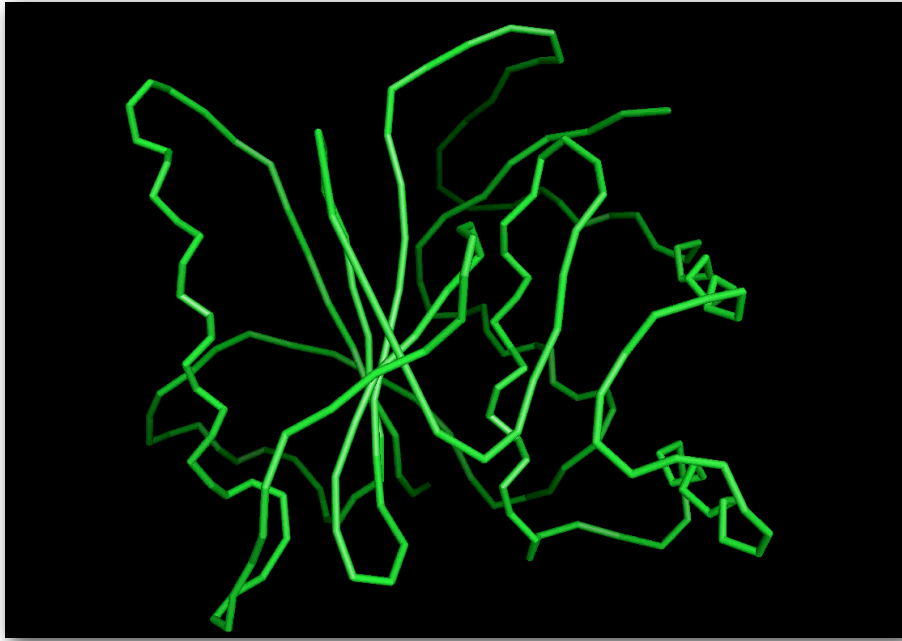
A 5_2 knot

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Smooth the protein backbone

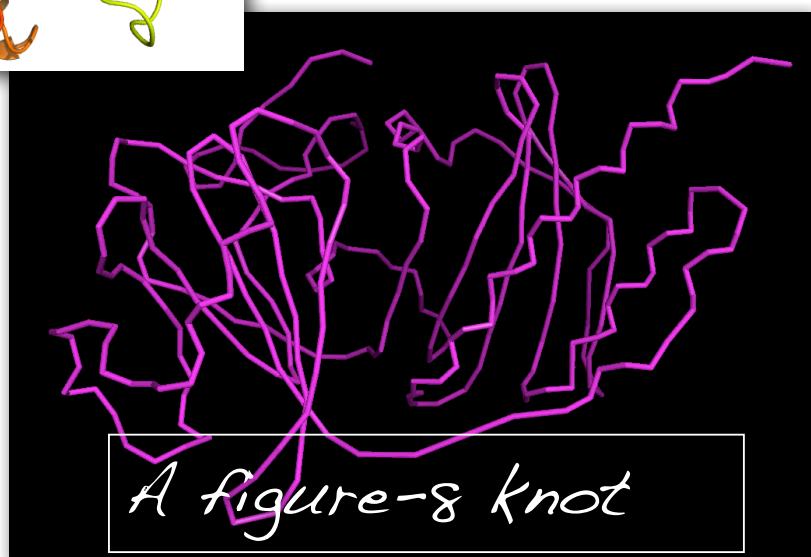
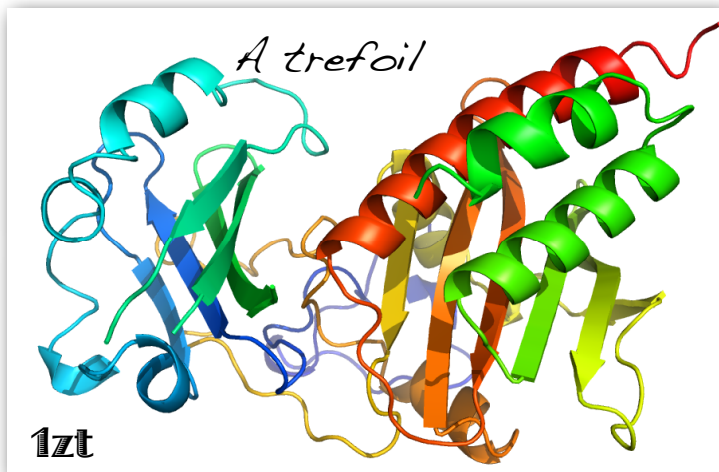


Smooth the protein backbone



Lai et al. NAR, 2007; Taylor Nature (2000)

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pKNOT: The Protein KNOT Server

MBC Molecular Bioinformatics Center
National Chiao Tung University

pKNOT 1.0: the protein KNOT web server

QUERY PROTEINS IN PDB

Enter PDB ID:

QUERY PROTEINS ON THE LOCAL MACHINE

OPTIONS

Ignore breaks in the chain
 Preserve breaks in the chain

OPTIONS

Iteration number:
Collision threshold:

Residue (specify the starting and the ending residues): -

Submit protein structure (in PDB format): no file selected

Lai YL, Yen SC, Yu SH, Hwang JK. pKNOT: the protein KNOT web server. Nucleic Acids Research (2007)

<http://pknot.life.nctu.edu.tw/>

43

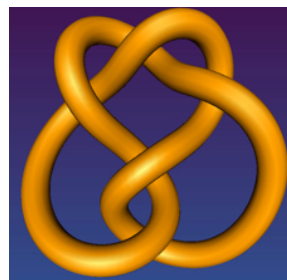
Only 3 types of knot are found in PDB



The trefoil knot



The figure-8 knot



The 5_2 knot

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Families of the Knotted proteins



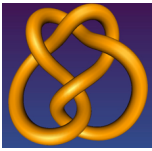
A. The trefoil knot (349)

1. methyltransferase (51)
2. transcarbamylase (20)
3. methionine adenosyltransferase (26)
4. carbonic anhydrase
5. YMPa superantigen (NMR)



B. The figure-8 knot

1. ketol-acid reductoisomerase
2. the chromophore binding domain of bacterial phytochrome
3. the core protein of bluetongue virus
4. a LIM-Idb1-LID chimeric protein (NMR)

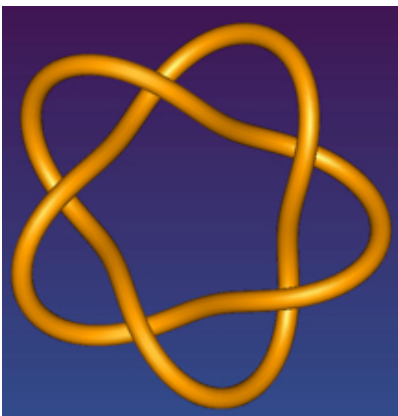


C. The 5_2 knot

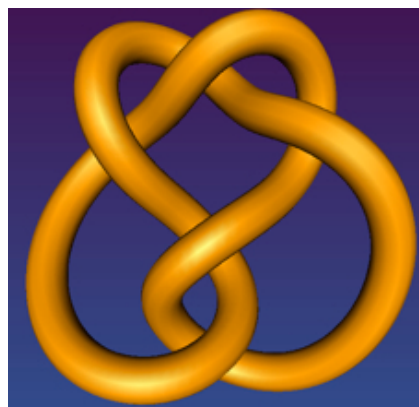
1. ubiquitin c-terminal hydrolase

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Interestingly, there are 2 types of knots with 5 crossings -- 5_1 and 5_2 , but only 5_2 is found in protein



The 5_1 knot



The 5_2 knot