BINF 731

Protein Structure Analysis

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Protein Modeling Methods



 Knowledge-based methods: homology modeling fold recogniion

HP Lattice Models



Free energy surface in protein simulation



M.Karplus and J. A. McCammon, 2002



Energy Minimazation



Molecular dynamics



YSNSG cyclopeptide as observed along the 20 ns molecular dynamics trajectory (Thevenard et al., 2006)

Molecular dynamics

taken at 5-ps intervals along a 100-ps molecular dynamics trajectory. Bubb et al., 1999

Twenty energy minimized structures

Molecular Dynamics

- Model system
- Initial conditions
- Boundary conditions
- Integration algorithm
- Constraints
- Ensemble
- Results

Potential Energy Function and Force Field

$$\begin{split} V(\vec{R}) &= \sum_{\text{bonds}} K_{\text{d}} (d - d_0)^2 + \sum_{\text{Urey-Bradley}} K_{\text{UB}} (S - S_0)^2 + \\ &\sum_{\text{angle}} K_{\theta} (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} K_{\chi} (1 + \cos(n\chi - \delta)) + \\ &\sum_{\text{impropers}} K_{\phi} (\phi - \phi_0)^2 + \\ &\sum_{\text{nonbond}} \left\{ \in_{ij} \left[\left(\frac{R_{ij}}{r_{ij}} \right)^{12} - \left(\frac{R_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{\in_{i} r_{ij}} \right\} \end{split}$$

Force Field Development and Parametrization



Molecular Dynamics

$$F_{i}=m_{i} a_{i}$$

$$a_{i} = dv_{i} / dt$$

$$v_{i} = dr_{i} / dt$$

$$- dE / dr_{i} = F_{i}$$

$$- dE / dr_{i} = m_{i} d^{2}r_{i} / dt^{2}$$

L.-P. Wang et al., 2014

Periodic Boundary Conditions





Periodic Boundary Conditions



MD cycle and integration algorithm



Characteristic Time Scales for Protein Motions

event	spatial extent (nm)	amplitude (nm)	time (s)	appropriate simulations			
bond-length vibration	0.2-0.5	0.001-0.01	10 ⁻¹⁴ -10 ⁻¹³	QM methods			
elastic vibration of globular domain	1.0-2.0	0.005-0.05	10.15-10.11	conventional MD			
rotation of solvent-exposed side chains	0.5-1.0	0.5-1.0	10 ⁻¹¹ -10 ⁻¹⁰	conventional MD			
torsional libration of buried groups	0.5-1.0	0.05	10 ⁻¹¹ -10 ⁻⁹	conventional MD			
hinge bending (relative motion of globular domains)	1.0-2.0	0.1-0.5	10.11-10.2	Langevin dynamics, enhanced sampling MD methods?			
rotation of buried side chains	0.5	0.5	10-4-1	enhanced sampling MD methods?			
allosteric transitions	0.5-4.0	0.1-0.5	10'5-1	enhanced sampling MD methods?			
local denaturation	0.5-1.0	0.5-1.0	10 ⁻⁵ -10 ¹	enhanced sampling MD methods?			
loop motions	1.0-5.0	1.0-5.0	10 ⁻⁹ -10 ⁻⁵	Brownian dynamics?			
rigid-body (helix) motions		1.0-5.0	10 ^{.9} -10 ^{.6}	enhanced sampling MD methods?			
helix-coil transitions		>5.0	10 ⁻⁷ -10 ⁴	enhanced sampling MD methods?			
protein association	≫1.0			Brownian dynamics			

S. A. Adcock and J. A. McCammon, 2006

MD Ensemble

Microcanonical ensemble (NVE) :

The thermodynamic state characterized by a fixed number of atoms, N, a fixed volume, V, and a fixed energy, E. This corresponds to an isolated system.

Canonical Ensemble (NVT):

This is a collection of all systems whose thermodynamic state is characterized by a fixed number of atoms, N, a fixed volume, V, and a fixed temperature, T.

Isobaric-Isothermal Ensemble (NPT):

This ensemble is characterized by a fixed number of atoms, N, a fixed pressure, P, and a fixed temperature, T.

Grand canonical Ensemble (μVT):

The thermodynamic state for this ensemble is characterized by a fixed chemical potential, m, a fixed volume, V, and a fixed temperature, T.

Temperature in molecular dynamics

$$U_{kin} = \sum \frac{1}{2}m_i v_i^2 = \frac{3}{2}NkT$$

N – number of atoms k – Boltzmann constant T – absolute temperature

MD of proteins: Solvent model





MD simulation of ubiquitin (400 ps)

MD of proteins: radial distribution functions



MD of proteins: radial distribution functions



MD of proteins: mobile regions



Adopted from W.F.VanGunsteren (2001)

MD of proteins: Conformational change



A set of structures on the reaction path showing the behavior of a single subunit (apical domain, green; intermediate domain, yellow; intermediate domain, yellow; equatorial domain, red; and ATP, blue). Structures 1–3 correspond to the first stages associated with ATP binding; 4–6 correspond to the second stage involving GroES binding. The early downward motion of the intermediate domain (commare 114) with 12 domain (compare [1,t] with [2]and [6,r"]) is the trigger for the overall transition.

M.Karplus and J. A. McCammon, 2002

MD of proteins: scale of simulation



Adopted from J.C.Phillips et al. (2005)

314,000 atoms 10 ns

MD of proteins: long runs



Adopted from I.D.Kuntz and P.Kollman (2001)

MD of proteins: long runs



MD of proteins: performance

	Simulation setup							Performance, ps/day			
6	System	FF	virtH	Water	Coulomb	IJ	ia32	x86-64	ррс		
19	Vil	G	no	TIP3P	cutoff 0.8	cutoff 0.8	9744	9574	14,385		
	Vil	G	yes	TIP3P	cutoff 0.8	cutoff 0.8	16,900	16,895	23,681		
	Vil	G	yes	TIP3P	RF 1.0	cutoff 1.0	10,308	9719	12,934		
	System (PDB ID	1 Num ID) of at		nber toms	Approperfo (μs/m	Approximate performance (µs/machine-day					
14	*DHFR ((5DFR)	23,5	58	17.4						
2(aSFP (1SFP)		48,423		11.7	11.7					
	FtsZ (1FSZ)		98,236		5.7	5.7					
	T7Lig (1A01)		116,650		5.5						
	bILAP (1BPM)		132,	132,362		4.8					

MD: Reversible folding of peptides



MD: Reversible folding of small proteins



K. Lindorff-Larsen et al., 2011

MD: Reversible folding of small proteins



Formation of topology, native contacts, and secondary structure during protein folding.

- (A) The three panels show the accumulation of native secondary structure, nonlocal native contacts, and native topology during a single folding event for α3D
 (B) The 24 transitions of α3D in a scatter plot are represented, with each of the black points corresponding to the time series integral for a single folding event
- event (C) Each point shows the average value
- over all folding and unfolding events observed for one protein. Each point is labeled with the PDB code of the anoted with the PDB code of the relevant protein. Most proteins fall below the diagonal in these plots, showing that topology and secondary structure develop earlier than the full set of native contacts.

K. Lindorff-Larsen et al., 2011