

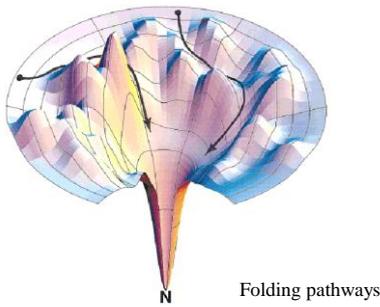
# Protein Structure Analysis

Iosif Vaisman

2023

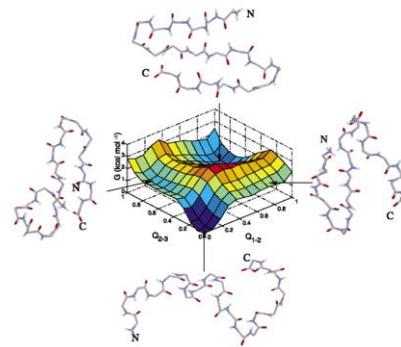
- **Ab initio methods:**  
solution of a protein folding problem  
search in conformational space
- **Energy-based methods:**  
energy minimization  
molecular simulation
- **Knowledge-based methods:**  
homology modeling  
fold recognition

## HP Lattice Models



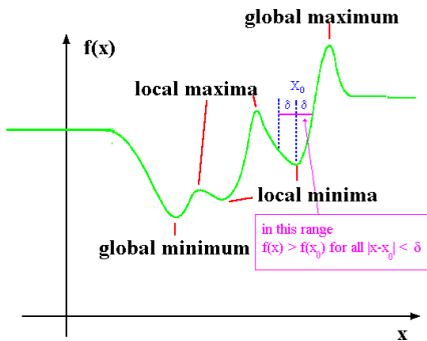
Chan & Dill, 1998

## Free energy surface in protein simulation

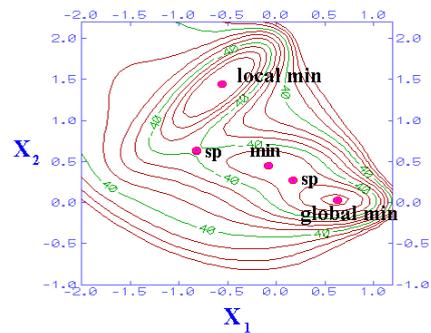


M.Karplus and J. A. McCammon, 2002

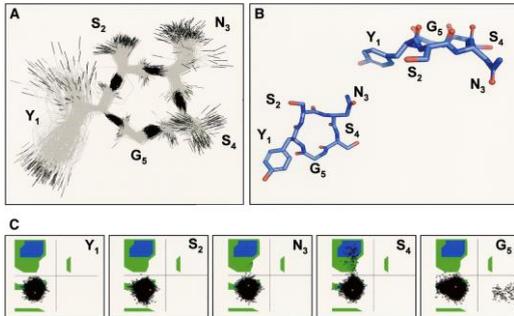
## Energy Minimization



## Energy Minimization

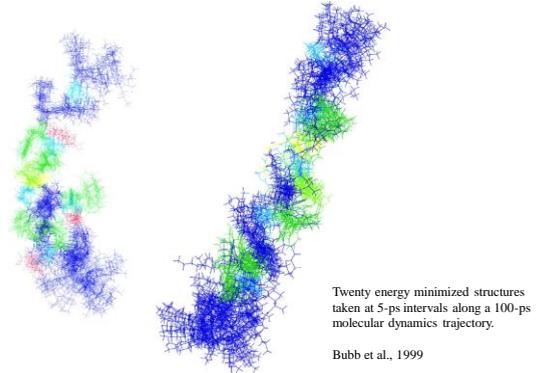


## Molecular dynamics



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

## Molecular dynamics



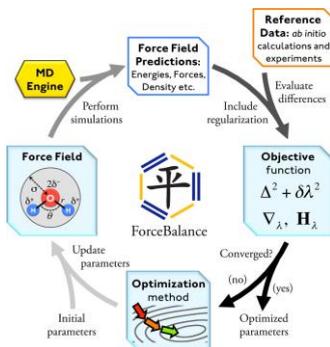
## Molecular Dynamics

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

## Potential Energy Function and Force Field

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

## Force Field Development and Parametrization



L.-P. Wang et al., 2014

## Molecular Dynamics

$$\mathbf{F}_i = m_i \mathbf{a}_i$$

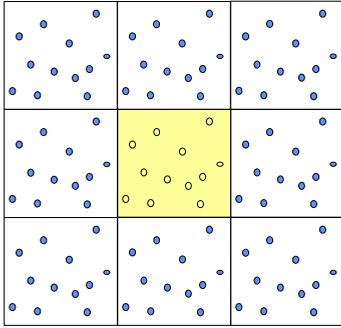
$$\mathbf{a}_i = d\mathbf{v}_i / dt$$

$$\mathbf{v}_i = d\mathbf{r}_i / dt$$

$$-dE / d\mathbf{r}_i = \mathbf{F}_i$$

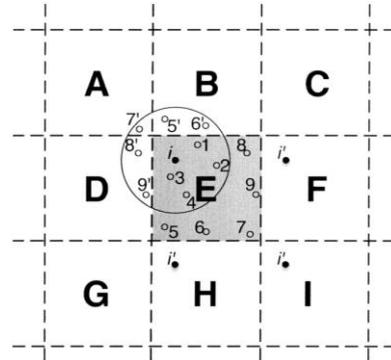
$$-dE / d\mathbf{r}_i = m_i d^2\mathbf{r}_i / dt^2$$

## Periodic Boundary Conditions



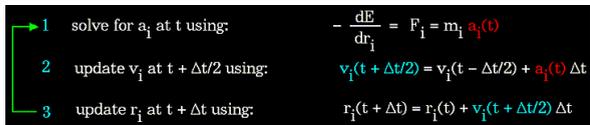
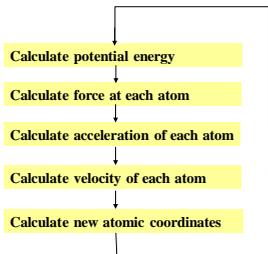
J. Jensen, [animation](#)

## Periodic Boundary Conditions



Adopted from D.van der Spoel et al. (2005)

## 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	$10^{-12}$ - $10^{-11}$	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	$10^{-11}$ - $10^{-7}$	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	$10^{-8}$ - $10^{-5}$	Brownian dynamics?
rigid-body (helix) motions	1.0-5.0	1.0-5.0	$10^{-8}$ - $10^{-6}$	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 ( $\mu$ V $T$ ):

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

## Temperature in molecular dynamics

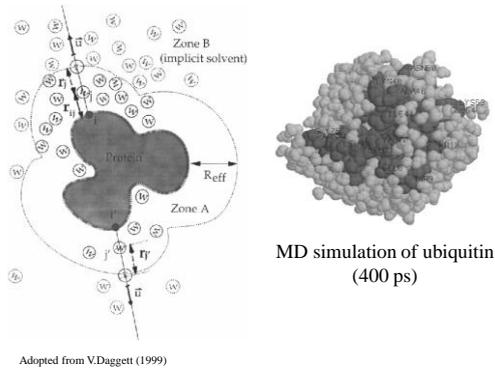
$$U_{kin} = \sum \frac{1}{2} m_i v_i^2 = \frac{3}{2} NkT$$

$N$  – number of atoms

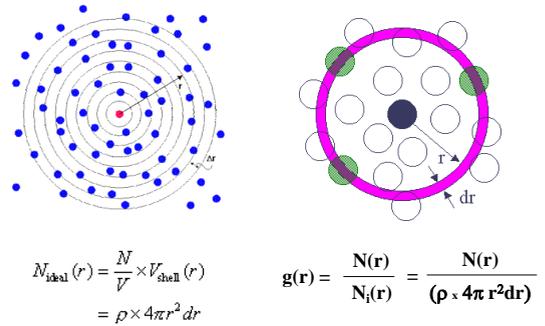
$k$  – Boltzmann constant

$T$  – absolute temperature

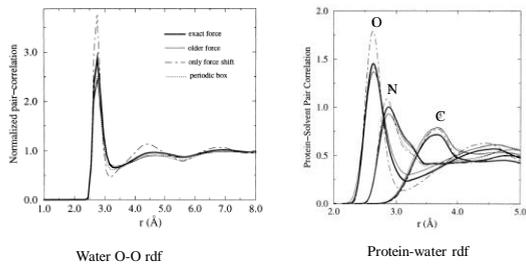
## MD of proteins: Solvent model



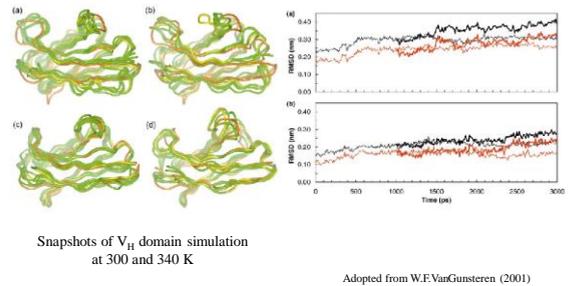
## MD of proteins: radial distribution functions



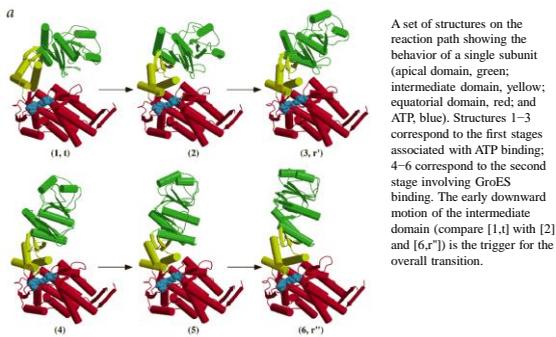
## MD of proteins: radial distribution functions



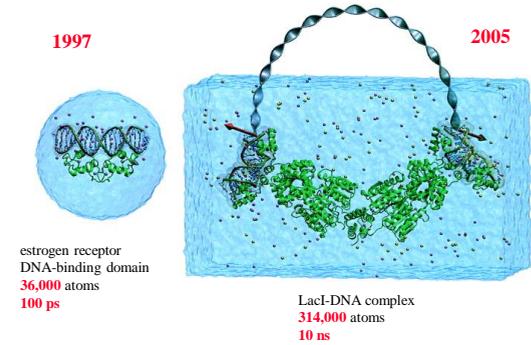
## MD of proteins: mobile regions



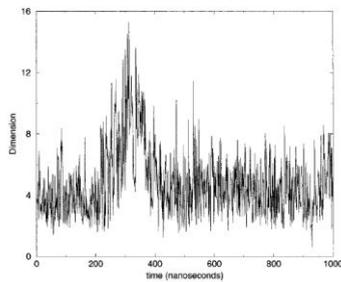
## MD of proteins: Conformational change



## MD of proteins: scale of simulation



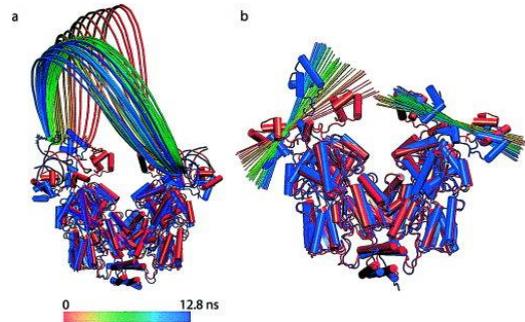
## MD of proteins: long runs



1 microsecond simulation of villin

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

## MD of proteins: long runs



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

## MD of proteins: performance

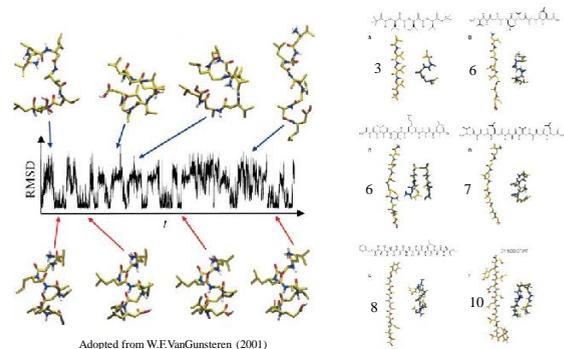
Simulation setup				Performance, ps/day				
System	FF	virtH	Water	Coulomb	LJ	ia32	x86-64	ppc
Vil	G	no	TIP3P	cutoff 0.8	cutoff 0.8	9744	9574	14,385
Vil	G	yes	TIP3P	cutoff 0.8	cutoff 0.8	16,900	16,895	23,681
Vil	G	yes	TIP3P	RF 1.0	cutoff 1.0	10,308	9719	12,934

1999

System (PDB ID)	Number of atoms	Approximate performance (μs/machine-day)
*DHFR (5DFR)	23,558	17.4
aSFP (1SFP)	48,423	11.7
FtsZ (1FSZ)	98,236	5.7
T7Lig (1A01)	116,650	5.5
bILAP (1BPM)	132,362	4.8

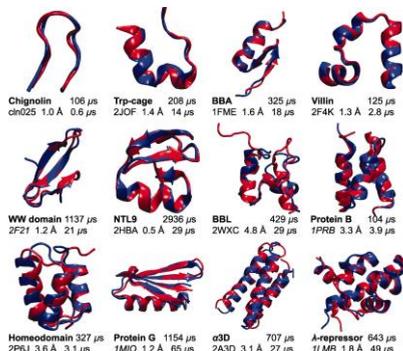
2014

## MD: Reversible folding of peptides



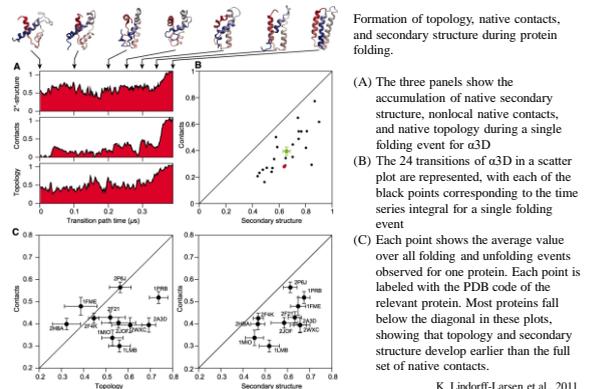
Adopted from W.E.VanGunsteren (2001)

## MD: Reversible folding of small proteins



K. Lindorff-Larsen et al., 2011

## MD: Reversible folding of small proteins



K. Lindorff-Larsen et al., 2011