2014/5/21
2014年バイオスーパーコンピューティング・ソフト講習会シリーズ

「CafeMol」粗視化分子モデル計算ソフト講習会

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CafeMol (www.cafemol.org)

- Features are;
  - Various CG models
    - protein/DNA/RNA
    - multiple basin model
    - accurate CG model
  - Simulating protein-at-work
    - “switching”
- Under development
  lipid

- Developer

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CafeMol 2.1 (2013/7)
source & manual released

Overview of CafeMol

- General-purpose coarse-grained (CG) biomolecular modeling and simulation software
  - Protein: 1 bead / 1 amino acid
  - Nucleic acid:
    3 beads (sugar, base, phosphate) / nucleotide
  - Lipid: ~3 beads / lipid
- Written by FORTRAN90 with MPI and Open MP
- Large-scale simulation
  - ～”millisecond” event by K-computer
- Version 1.0 is released (only protein) (2010/12/27)
  - Version 2.0 (protein, DNA, RNA) (2012/5/31)
  - Version 2.1 (protein, DNA, RNA) (2013/7/1)

Menu

1. Molecular dynamics simulation
2. Coarse-grained models
3. Simulation methods & Implementation
4. Selected applications

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1. Molecular dynamics simulation
2. Coarse-grained models
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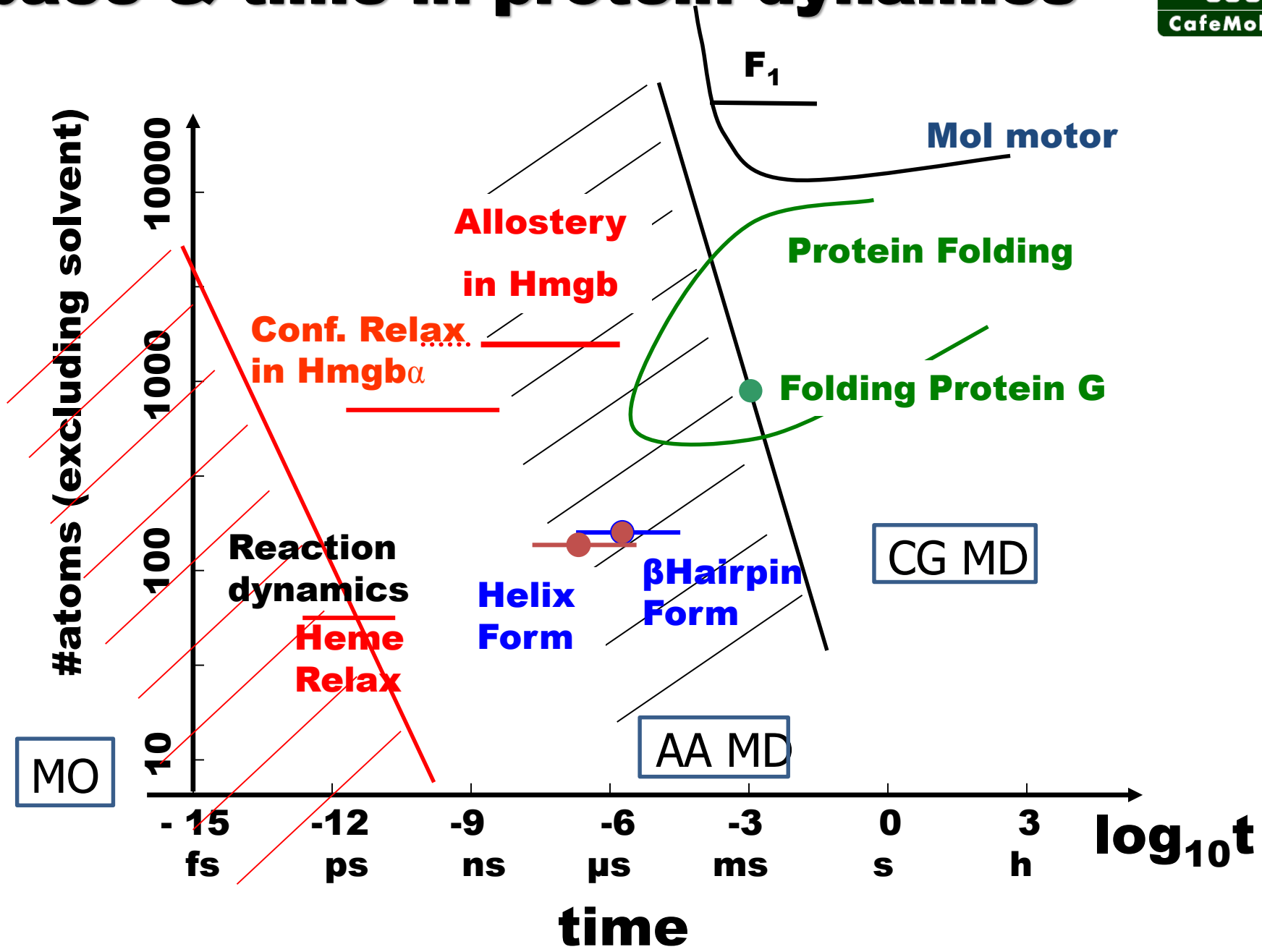
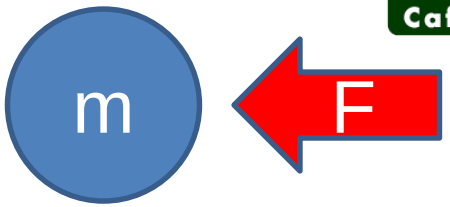
Biomolecular simulations

- Molecular orbital(MO) method
  - quantum mechanics
    - chemical reaction
- Molecular dynamics(MD) method
  - classical mechanics
    - conformational change of biomolecules
- Continuum method
  - elastic model
    - muscle contraction
  - fluid dynamics
    - blood flow

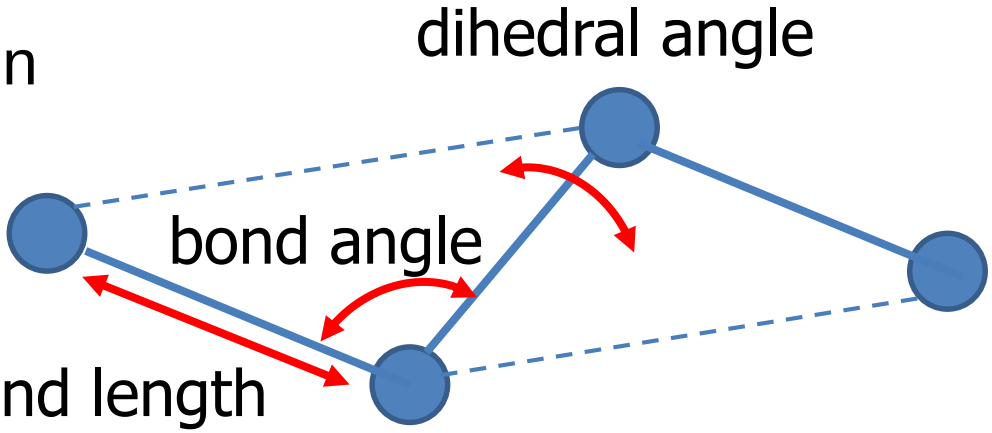
Space & time in protein dynamics



Molecular dynamics



- Calculate molecular movement
  - Classical mechanics
  - Numerically integrate Newton's equation of motion
  - m(mass) x a(acceleration) = F(force)
  - interaction parameters are derived from MO
- Interaction
  - bond length, bond angle, dihedral angle
  - van der Waals interaction
  - electrostatic interaction

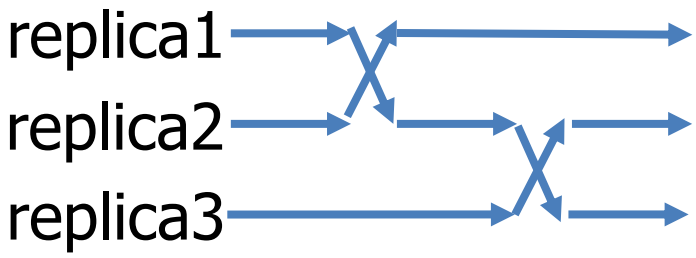


Constant temperature dynamics

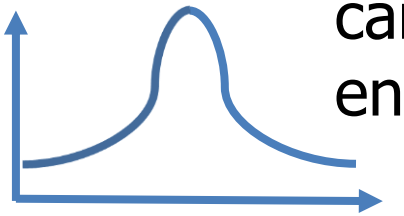
- Berendsen thermostat
  - rescale velocity to control temperature
  - not canonical distribution
- Nose-Hoover thermostat
  - rescale velocity using artificial particles
  - canonical distribution
- Langevin dynamics
  - random force and viscosity
  - fluctuation-dissipation theorem
  - canonical distribution

Generalized ensemble methods

- Generalized ensemble methods
  - accelerate conformational sampling
  - only obtain equilibrium variables

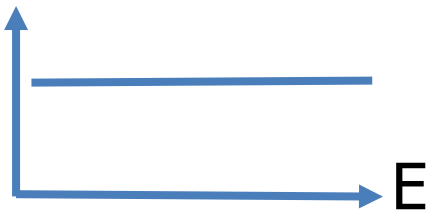


- Replica exchange molecular dynamics(REMD)
  - simulate many copies at different temperatures
  - exchange configuration at proper probability
  - extension to interaction parameters
- Multicanonical method
  - sample “flat histogram” on energy
  - iterative learning of “the density of states”



canonical ensemble

multicanonical ensemble



Menu

1. Molecular dynamics simulation
2. Coarse-grained models
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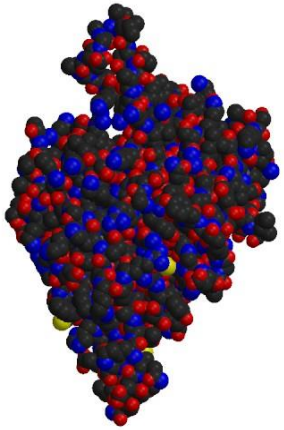
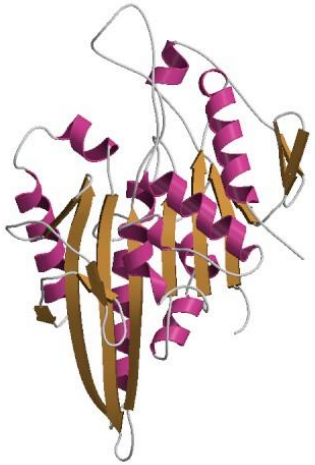
Why coarse-grained model ?



coarse-grained



Reducing the number of particles to 1/100

- 1 amino acid residue →1 particle ($C_\alpha$atom)
- No water molecule
  (included in potential energy)

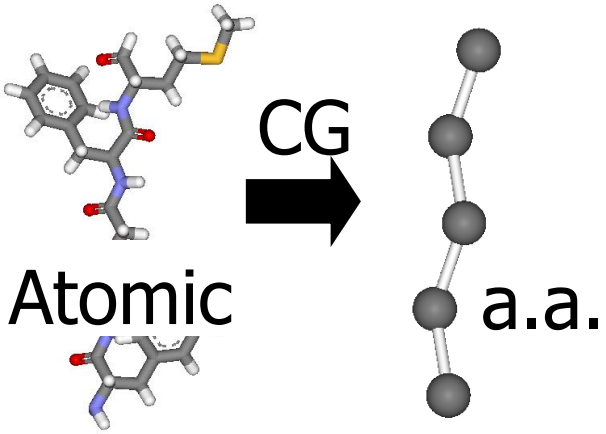
Protein folding and
functional conformational change

10^6 times speed up

- Reducing the number of particles
- Enlarge time step
- Low friction

AA: 100PC 1week → CG: 1PC 1minute!!

Models and energy functions



1 beads / 1 amino acid

A. Go-like model
B. Atomic interaction based CG(AICG) model
C. Flexible local potential(FLP) model
D. AICG2+ model
E. Multiple basin model
F. DNA/RNA model
G. Elastic network model
H. Electrostatic and hydrophobic interactions
I. Explicit and implicit ligands

Go-like model

C. Clementi, H. Nymeyer, and J.N. Onuchic, J. Mol. Biol. (2000)

Based on the energy landscape theory

Structure based

$$V_{protein} = V_{local} + V_{go} + V_{ex}$$

$$V_{local} = K_b \sum_i \left(r_{i,i+1} - r_{0i,i+1} \right)^2 + K_\theta \sum_i \left(\theta_i - \theta_{0i} \right)^2$$

$$+ K_\phi^1 \sum_i \left(1 - \cos\left(\phi_i - \phi_{0i} \right) \right) + K_\phi^3 \sum_i \left(1 - \cos 3\left(\phi_i - \phi_{0i} \right) \right)$$

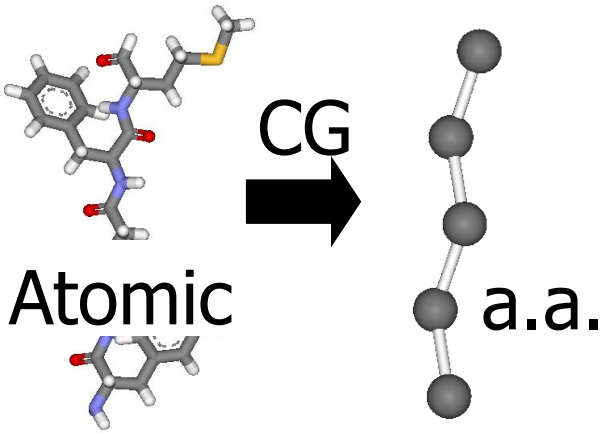
$$V_{go} = \varepsilon_{go} \sum_{i,j}^{native} \left[5 \left(\frac{r_{0ij}}{r_{ij}} \right)^{12} - 6 \left(\frac{r_{0ij}}{r_{ij}} \right)^{10} \right]$$

$$V_{ex} = \varepsilon_{ex} \sum_{i,j}^{nonnative} \left(\frac{\sigma}{r_{ij}} \right)^{12}$$

θ: bond angle
ϕ: dihedral angle
(0 means native state)

$K_b = 100\varepsilon$
$K_\theta = 20\varepsilon$
$K_\phi^1 = \varepsilon$
$K_\phi^3 = 0.5\varepsilon$
$\varepsilon_{go} = 0.18\varepsilon$
$\varepsilon_{ex} = \varepsilon$
σ= 4A
ε=1.0kcal/mol

Atomic interaction based CG (AICG) model



W. Li, P. Wolynes, S. Takada, PNAS (2011)

$$V = \sum_i k_b^i (r^i - r_0^i)^2 + \sum_i k_a^i (\theta^i - \theta_0^i)^2 + \sum_i \{\varepsilon_{\phi,1}^i [1 - \cos(\phi^i - \phi_0^i)] + \varepsilon_{\phi,3}^i [1 - \cos 3(\phi^i - \phi_0^i)]\} + \sum_{i>j-3}^{native} \varepsilon^{ij} [5(r_0^{ij}/r^{ij})^{12} - 6(r_0^{ij}/r^{ij})^{10}] + \sum_{i>j-3}^{non-native} \varepsilon (C/r^{ij})^{12}$$

Wenfei Li

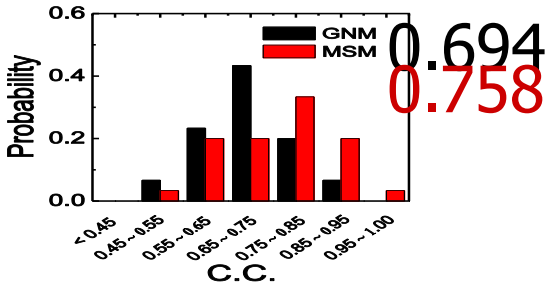
1) Contact energy ε_{ij} from pairwise all-atom (AA) energy

$$E^{IJ}(R_{IJ}) = \sum_{i \in I} \sum_{j \in J} u_{AA}(r_{ij}) \qquad u_{AA}(r) = V(r) + \Delta G_{pol}^{GB}(r) + \Delta G^{SA}(r)$$

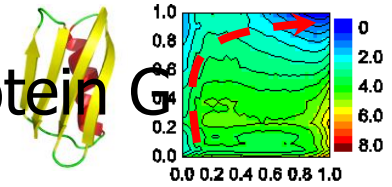
2) Coefficients fitted by AA-derived fluctuation (23 proteins)

param	K_b	K_a^G	k_a^H	k_a^E	k_a^T	k_a^C	ε_ϕ^G	ε_ϕ^H	ε_ϕ^E	ε_ϕ^T	ε_ϕ^C	ε_{nloc}
Av.	109.94	13.40	40.03	17.32	19.35	11.70	0.29	1.76	1.32	0.82	0.81	0.37

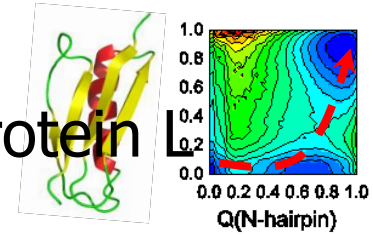
Test for fluctuation, structural change, & folding



Protein G



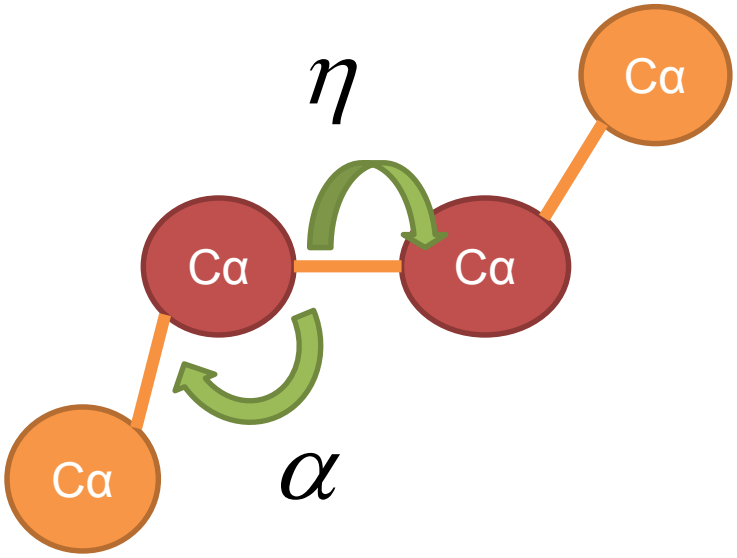
Protein L



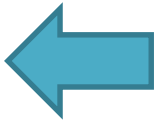
Flexible local potential(FLP) model

T. Terakawa, and S. Takada, Biophys. J. (2011)

Probability distributions to CG potential
for flexible local potentials



$P_a(\alpha)$
$P_d(\eta)$



RCSB PDB PROTEIN DATA BANK
Loop segment library

Boltzmann inversion; prob. to pot.

$$V_a = -k_B T \frac{\ln P_a(\alpha)}{\sin \alpha} \qquad V_d = -k_B T \ln P_d(\eta)$$

AICG2+ model

W. Li, T. Terakawa, W. Wang, S. Takada, PNAS (2012)

improved AICG model + FLP model

$$V = \sum_I k_b (r^I - r_0^I)^2$$

$$+ \sum_I V_a^I(\theta^I) + \sum_I V_{dih}^I(\phi^I)$$

$$+ \sum_{J=I+2} \varepsilon_{1,3}^{IJ} \exp\left(-\frac{(r^{IJ} - r_0^{IJ})^2}{2w^2}\right) + \sum_{J=I+3} \varepsilon_{1,4}^{IJ} \exp\left(-\frac{(\phi^I - \phi_0^I)^2}{2w_\phi^2}\right) +$$

$$+ \sum_{I>J+3}^{native} \varepsilon_{nloc}^{IJ} [5(r_0^{IJ} / r^{IJ})^{12} - 6(r_0^{IJ} / r^{IJ})^{10}] + \sum_{I>J+3}^{non-native} \varepsilon (C / r^{IJ})^{12}$$

Multiple-basin model for proteins

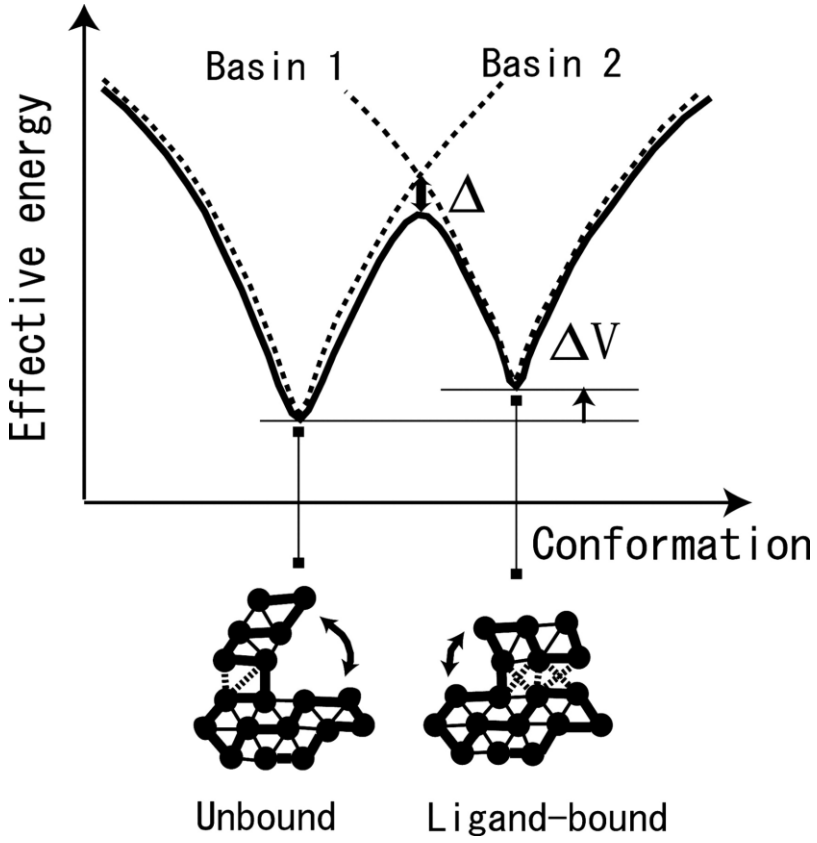
K. Okazaki, N. Koga, S. Takada, J.N. Onuchic, and P.G. Wolynes, PNAS (2006)

Use of 2 references

$$\begin{pmatrix} V(R|R_1) & \Delta \\ \Delta & V(R|R_2)+\Delta V \end{pmatrix}\begin{pmatrix} c_1 \\ c_2 \end{pmatrix} = V_{MB}\begin{pmatrix} c_1 \\ c_2 \end{pmatrix}$$

$$V_{MB} = \frac{V(R|R_1)+V(R|R_2)+\Delta V}{2} - \sqrt{\left(\frac{V(R|R_1)-V(R|R_2)-\Delta V}{2}+\Delta\right)}$$

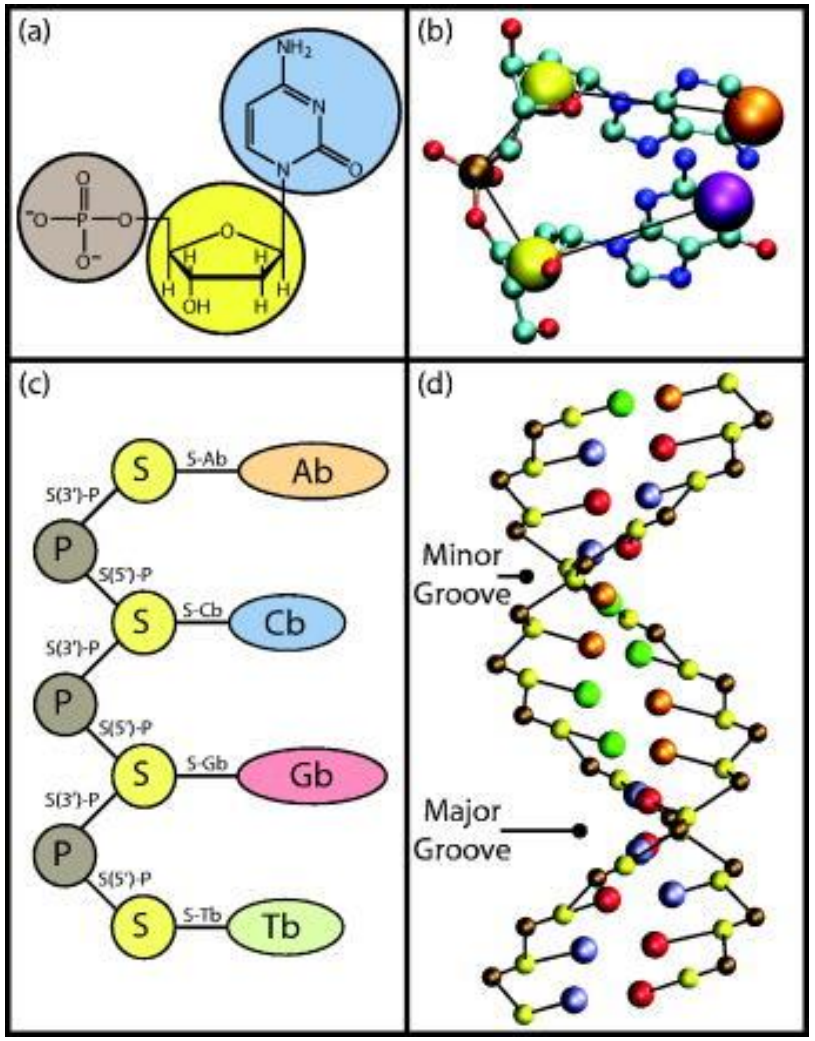
$$\chi = \log\left(\frac{c_2}{c_1}\right)$$



CG DNA model

T.A. Knotts IV, N.Rathore, D.C. Shwartz, and J.J. Pablo, J. Chem. Phys. (2007)

- Three interactions sites
  - Phosphate
  - Sugar
  - Base
- Reproduce various DNA behavior
  - Salt-dependent melting
  - Bubble formation
  - Mechanical properties



3SPN.1 force field

E.J. Sambrisiki, D.C. Schwartz, and J.J. de Pablo,Knotts, Biophys. J. (2009)

$$V_{dna} = V_{local} + V_{stack} + V_{bp} + V_{ex} + V_{qq} + V_{solv}$$

$$V_{local} = K_{b1}\sum_i \left(r_{i,i+1} - r_{0i,i+1}\right)^2 + K_{b2}\sum_i \left(r_{i,i+1} - r_{0i,i+1}\right)^4$$

$$+ K_\theta \sum_i \left(\theta_i - \theta_{0i}\right)^2 + K_\phi \sum_i \left(1 - \cos\left(\phi_i - \phi_{0i}\right)\right)$$

$$V_{stack} = 4\varepsilon_1 \sum_{i,j}^{Nst} \left[\left(\frac{\sigma_{0ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{0ij}}{r_{ij}}\right)^{6} \right]$$

$$V_{bp} = \sum_{i,j}^{Nbp} 4\varepsilon_{bpi} \left[5\left(\frac{r_{0ij}}{r_{ij}}\right)^{12} - 6\left(\frac{r_{0ij}}{r_{ij}}\right)^{10} \right]$$

$$V_{ex} = 4\varepsilon_1 \sum_{i,j}^{Nex} \left[\left(\frac{\sigma_0}{r_{ij}}\right)^{12} - \left(\frac{\sigma_0}{r_{ij}}\right)^{6} \right] + \varepsilon_1 \,(if\ r_{ij} < d_{cut}),$$

$$= 0\ (if\ r_{ij} > d_{cut})$$

θ: bond angle
ϕ: dihedral angle
(0 means B-type DNA)

Structre-based interaction

$K_{b1} = 1\varepsilon$
$K_{b2} = 100\varepsilon$
$K_\theta = 1400\varepsilon$
$K_\phi = 28\varepsilon$
$\varepsilon_{bpGC} = 2.532\varepsilon$
$\varepsilon_{bpAT} = 2.0\varepsilon$
ε =0.1839kcal/mol

3SPN.1 force field (electrostatic and solvation interaction)

$$V_{qq} = \sum_{i,j}^{N} \left(\frac{q_i q_j}{4\pi\varepsilon_0 \varepsilon(T,C) r_{ij}} \right) e^{-r_{ij}/\kappa_D}$$

Debye-Huckel theory

$$\varepsilon(T,C) = \varepsilon(T) a(C)$$

ε=78

$$\varepsilon(T) = 249.4 - 0.788T/K + 7.20\times10^{-4}(T/k)^2$$

$$a(C) = 1.000 - 0.2551C/M + 5.151\times10^{-2}(C/M)^2 - 6.889\times10^{-3}(C/M)^3$$

Debye length

$$\kappa_D = \left(\frac{\varepsilon_0 \varepsilon RT}{2N_A^2 e_q^2 I} \right)$$

$$V_{solv} = \sum_{i<j}^{N_{solv}} \varepsilon_s \left[1 - e^{-a(r_{ij}-r_s)} \right]^2 - \varepsilon_s$$

$$\varepsilon_s = \varepsilon_N A_I$$

$$e_N = e_0 (1 - [1.40418 - 0.268231 N_{nt}]^{-1})$$

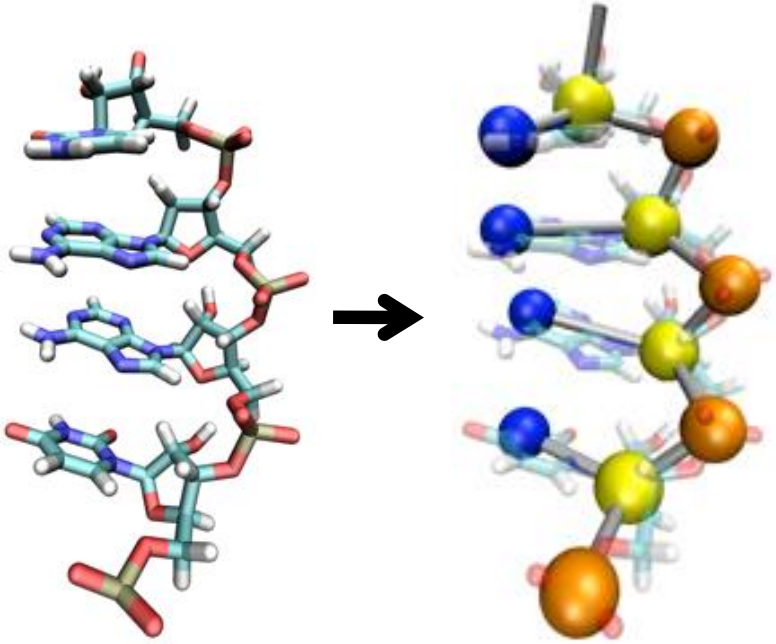
$$A_I = 0.474876 (1 + \{0.148378 + 10.9553[Na^+]\}^{-1})$$

α^{-1} = 5.333A
r_s = 13.38A
$\varepsilon_0 = 0.504982\varepsilon$

CG RNA model

N. Hori, and S. Takada, JCTC (2012)

1 nucleotide = 3 beads



- Phosphate (phosphorus atom)
- Sugar (center of ribose ring)
- Base (pyrimidine: N1 atom)
  (purine: N3 atom)

CG RNA model (local)

$$V_{\text{total}} = V_{\text{local}} + V_{\text{stack}} + V_{\text{basepair}} + V_{\text{nonlocal}} + V_{\text{exclude}}$$

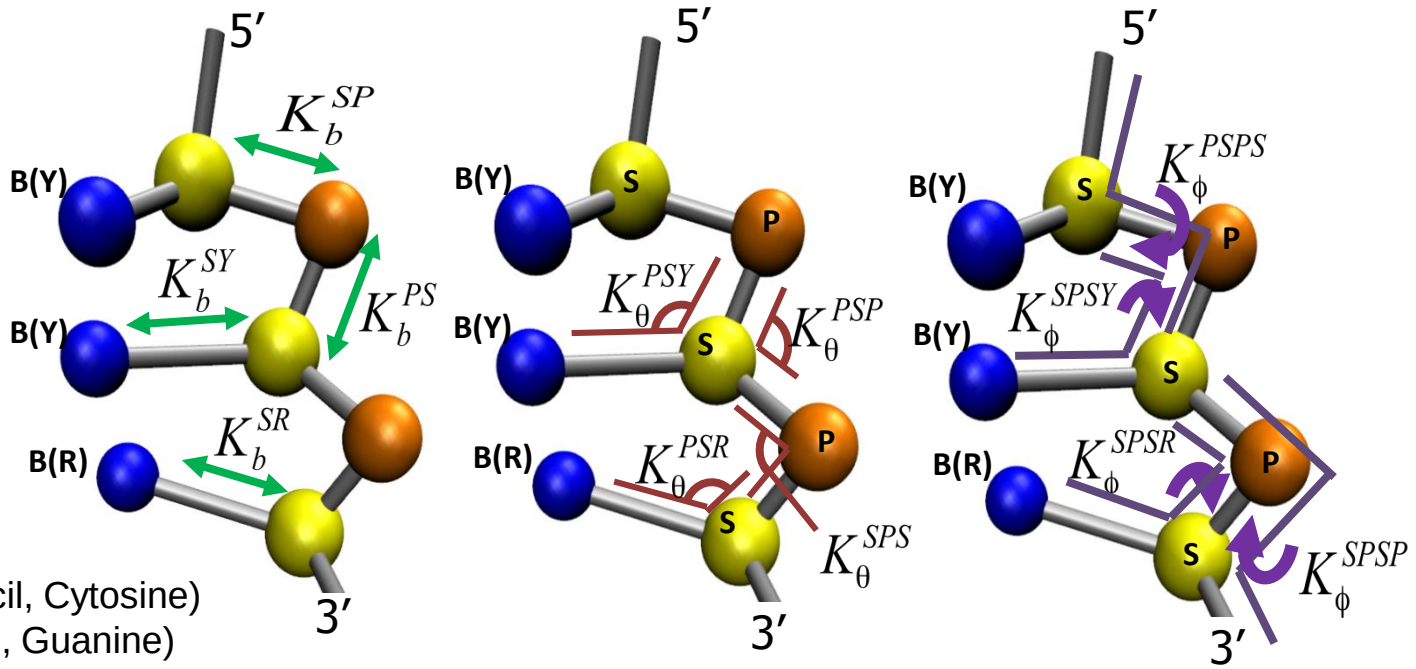
Bond length **Bond angle**

Local

$$V_{local} = \sum_{ibd\in \substack{PS,\\ SP,\\ SB}} K_b^{\eta}(r_{ibd} - r_{ibd}^{(0)})^2 + \sum_{iba\in \substack{PSP,\\ SPS,\\ SPB}} K_{\theta}^{\eta}(\theta_{iba} - \theta_{iba}^{(0)})^2$$

$$+ \sum_{idih\in \substack{PSPS,\\ SPSP,\\ SPSB}} \{K_{\phi}^{\eta}(1 - cos(\phi_{idih} - \phi_{idih}^{(0)})) + 0.5K_{\phi}^{\eta}(1 - cos3(\phi_{idih} - \phi_{idih}^{(0)}))\}$$

Dihedral angle



Base type
Y : Pyrimidine (Uracil, Cytosine)
R : Purine (Adenine, Guanine)

CG RNA model (nonlocal)

CafeMol

Nonlocal

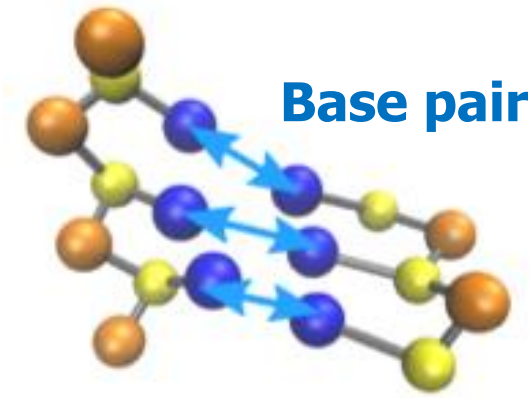
Reference (X-ray structure's) value

$$V_{\mathrm{contact}} = \sum_{i,j \in S,B}^{\text{native contact}} \varepsilon_\xi \left[5 \left(\frac{r_{ij}^0}{r_{ij}} \right)^{12} - 6 \left(\frac{r_{ij}^0}{r_{ij}} \right)^{10} \right]$$

$\varepsilon_\xi = \varepsilon_{BP3}$

$\varepsilon_\xi = \varepsilon_{BP2}$

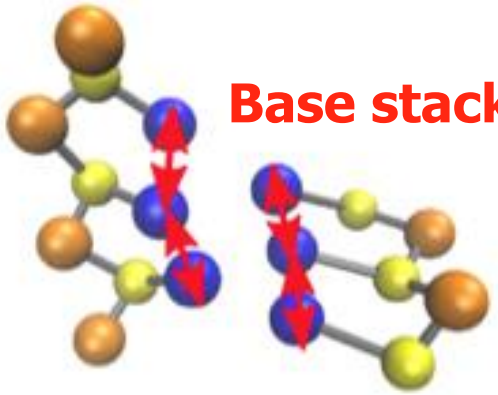
Base pair



Base pair

$\varepsilon_\xi = \varepsilon_{\mathrm{ST}}$ Base stack

$\varepsilon_\xi = \varepsilon_{con}^{\eta}$ Contact (Other)



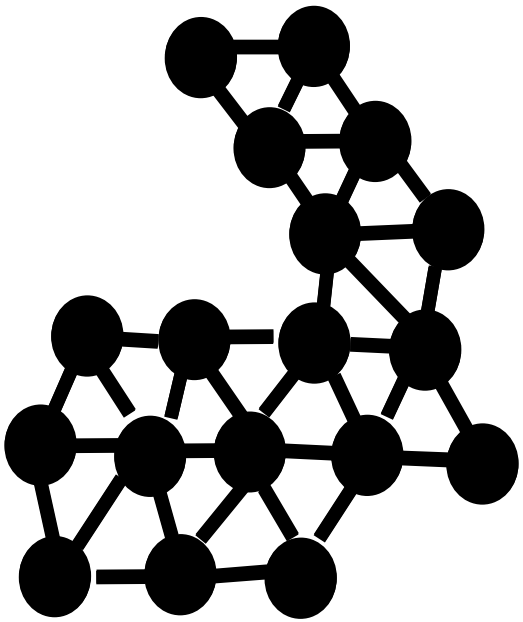
Base stack

$$V_{exclude} = \sum_{i,j}^{\text{non-native}} \varepsilon_{ex} \left(\frac{\sigma}{r_{i,j}} \right)^{12}$$

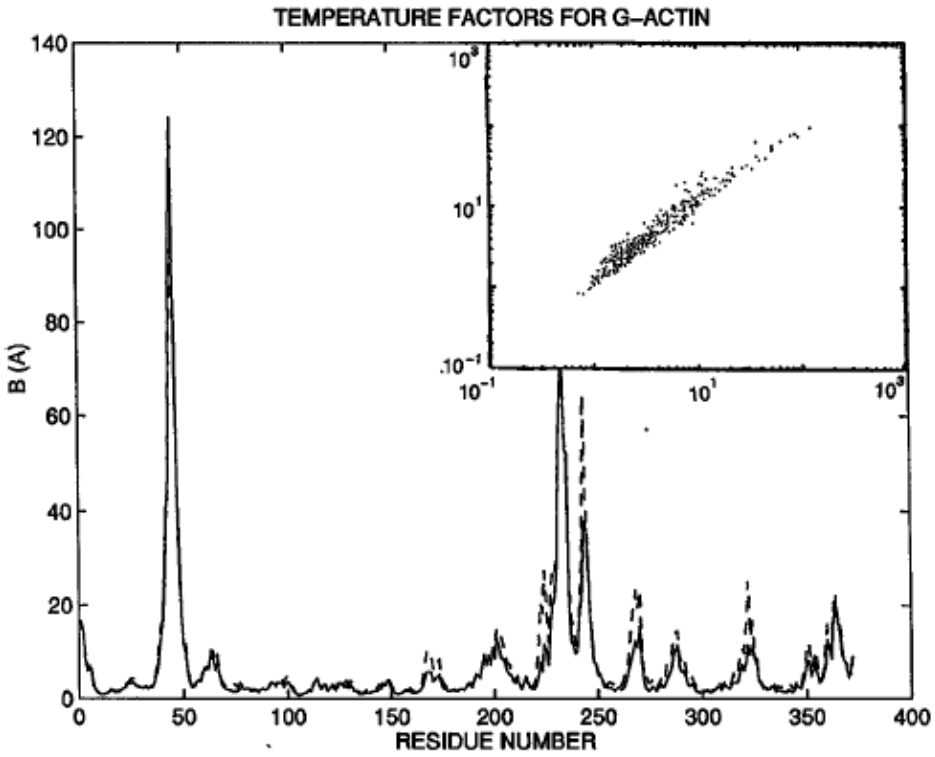
Excluded volume

Elastic network model

$$E = \sum_{ij,s.t.r_{ij}^0 < r_c} K(r_{ij} - r_{ij}^0)^2$$



Atomic fluctuation reproduced by ENM (Tirion96)



Electrostatic and hydrophobic interactions

Debye-Huckel form for electrostatics

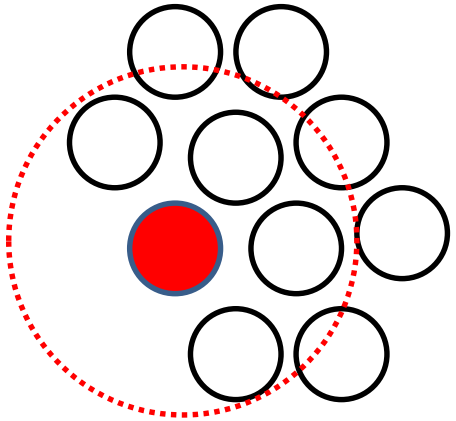
$$V_{\mathrm{ele}} = \sum_{i<j}^{N} \frac{q_i q_j}{4\pi\epsilon_0\epsilon_k r_{ij}} e^{-r_{ij}/\kappa_D}$$

Debye length

$$\kappa_D = \left(\frac{\varepsilon_0 \varepsilon RT}{2N_A^2 e_q^2 I} \right)$$

HP interactions analogous to ASA

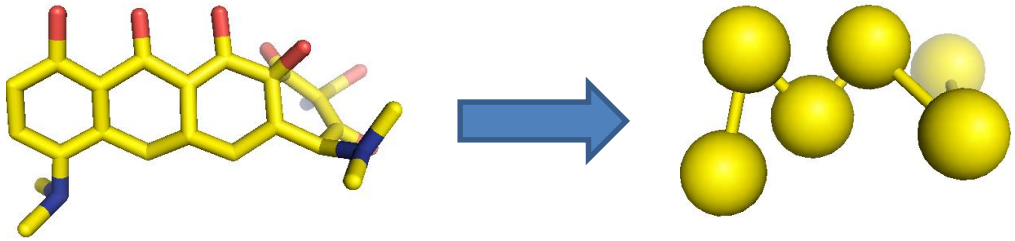
$$V_{\mathrm{HP}} = -c_{\mathrm{HP}} \sum_{i \in \mathrm{HP}} \epsilon_{\mathrm{HP},A(i)} S_{\mathrm{HP}}(\rho_i)$$



Count coordination number
for each hydrophobic particle

Explicit and Implicit ligands

Explicit ligand: as a rigid molecule



Implicit ligand:
MD-MC scheme with ligand-mediated contact

$$V_{protein} \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} V_{protein} + V_{imp-lig}$$

$$V_{imp-lig} = \sum_{\substack{ligand-mediated \\ contact-pairs}} -c_{lig}\varepsilon_{go} \exp\left[-\frac{(r_{ij}/r_{0ij}-1)^2}{2(\sigma/r_{0ij})^2}\right]$$

Menu

1. Molecular dynamics simulation
2. Coarse-grained models
3. Simulation methods & Implementation
4. Selected applications

Simulation method

- Dynamics
  - Newtonian dynamics with Berendsen thermostat
  - Langevin dynamics
  - Multi-Particle Collision dynamics (MPC)
- Time integration
  - velocity Verlet algorithm
- Run mode
  - Constant temperature simulation
  - Simulated annealing
  - Auto-search of Tf
  - Replica exchange method
  - Potential “switching”
- Useful option
  - anchor, bridge, pulling, fix, box

Units in CafeMol

- The length unit is A
  - 1A = 10^{-10}m
- The energy unit is kcal/mol
  - 1kcal/mol = 6.9478pNnm = 0.04337eV
  - $300k_BT$ = 0.6kcal/mol
- The mass unit is cafemol-mass-unit (cafemu)
  - each amino acid has the mass of 10cafemu
  - 1cafemu = 13.7amu = 2.275×10^{-26}kg
- The unit of charge is elementary-electric charge (e)
- The unit time is café time
  - 1cafe time= 1.809×10^{-13}s ~ 200fs
  - intrinsic dynamics is accelerated by coarse-graining the energy landscape

Input and output files

- Input files
  - Input file(.inp)
  - PDB file(.pdb)
  - native-info file(.ninfo)
  - parameter file(.para)
  - AICG files

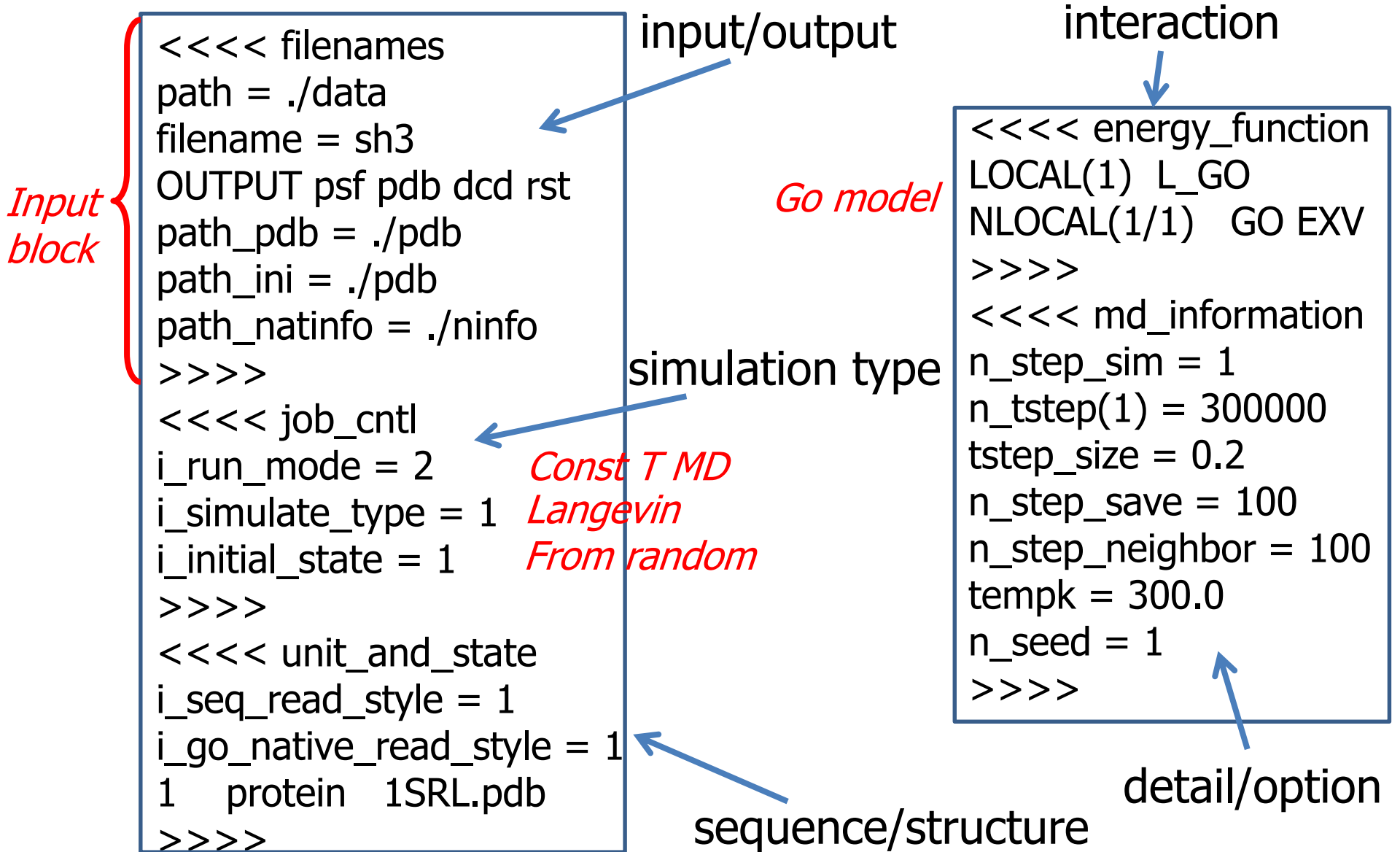
red: essential files

green: frequently used

black: optional files

- Output files
  - data file(.data)
  - time-series file(.ts)
  - native-info file(.ninfo)
  - coordinate and velocity
    - PDB format(.pdb)
    - CARD format(.crd, .vdcd)
  - trajectory
    - PDB format(.movie)
    - DCD coordinate(.dcd, .vdcd)
  - PSF file(.psf)
  - restart file(.rst)
  - replica information file(.rep)

Example of input file (folding simulation of src SH3)



Native-info

all-in-one style

```
<<<< native_info_sim1
NINFO(all/all) f1atp_all.ninfo
>>>>
```

one-by-one style

```
<<<< native_info_sim1
NINFO(1/1) 1      Intra-mol 1
...
NINFO(3/6) 13   Inter-mol 3/6
1= f1atp_alpha_E.ninfo
...
13= f1atp_alphDP_betaDP.ninfo
>>>>
```

native-info file *(alpha_E subunit)*

```
bond  1  1  1  1  2  1  2   3.8132   1.0000   1.0000   100.0000
...
angl  1  1  1  1  2  3  1  2  3  93.2170   1.0000   1.0000   20.0000
...
dihd   1  1  1  1  2  3  4  1  2  3  4  67.0855  1.0000  1.0000  1.0000
...
contact  1  1  1  1  5  1  5  5.9973  1.0000   1  0.3000
...
```

pair ij *nat- distance* *coefficient contact interaction*

Useful option1

■ redefine parameters

dfcontact = 4.5 definition of native contact(default 6.5A)

cdist_rep12 = 6.0 reference distance in excluded interaction(default 4.0A)

rneighbor_dist = 20.0 truncation distance for neighbor list(default 24.0A)

fric_const = 0.02 friction constant(default 0.25)

■ delete interaction

DEL_LGO(mp_{ini}-mp_{las})

DEL_GO($mp_{ini,i}$-$mp_{las,i}$/$mp_{ini,j}$-$mp_{las,j}$)

■ box: fix some particles or units

xbox = boxsize_x

ybox = boxsize_y

zbox = boxsize_z

boxsigma = sigma

$$V_{box} = 0 \qquad (d > 3\sigma),$$

$$= k_{box}\left(\frac{\sigma}{d}\right)^{12} \qquad (0.5\sigma < d < 3\sigma),$$

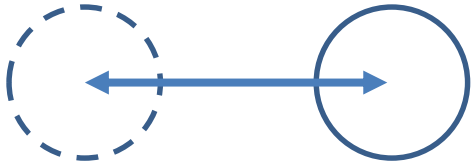
$$= k_{box}\left(\frac{\sigma}{0.5\sigma}\right)^{12}\left(1+12\frac{0.5\sigma - d}{0.5\sigma}\right) \quad (d < 0.5\sigma)$$

Useful option2

- anchor: particle i constrain to some position

ANCH i k_i l_0 x_0 y_0 z_0

$$V_{anchor} = k_i (r_{i0} - l_0)^2 \ (r_{i0} > l_0),$$
$$= 0 \ (r_{i0} < l_0)$$



- bridge: bind I and j particles by a harmonic spring

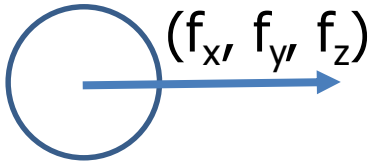
BRIDGE i j k_{ij} l_0

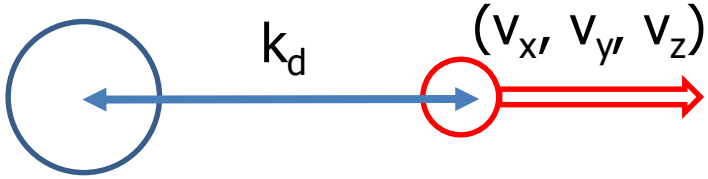
$$V_{bridge} = k_{ij} (r_{ij} - l_0)^2 \ (r_{ij} > l_0),$$
$$= 0 \ (r_{ij} < l_0)$$

- pulling: particle I is pulled by constant force or constant velocity

PULL_CF i f_x f_y f_z

PULL_CV i k_d v_x v_y v_z x_0 y_0 z_0



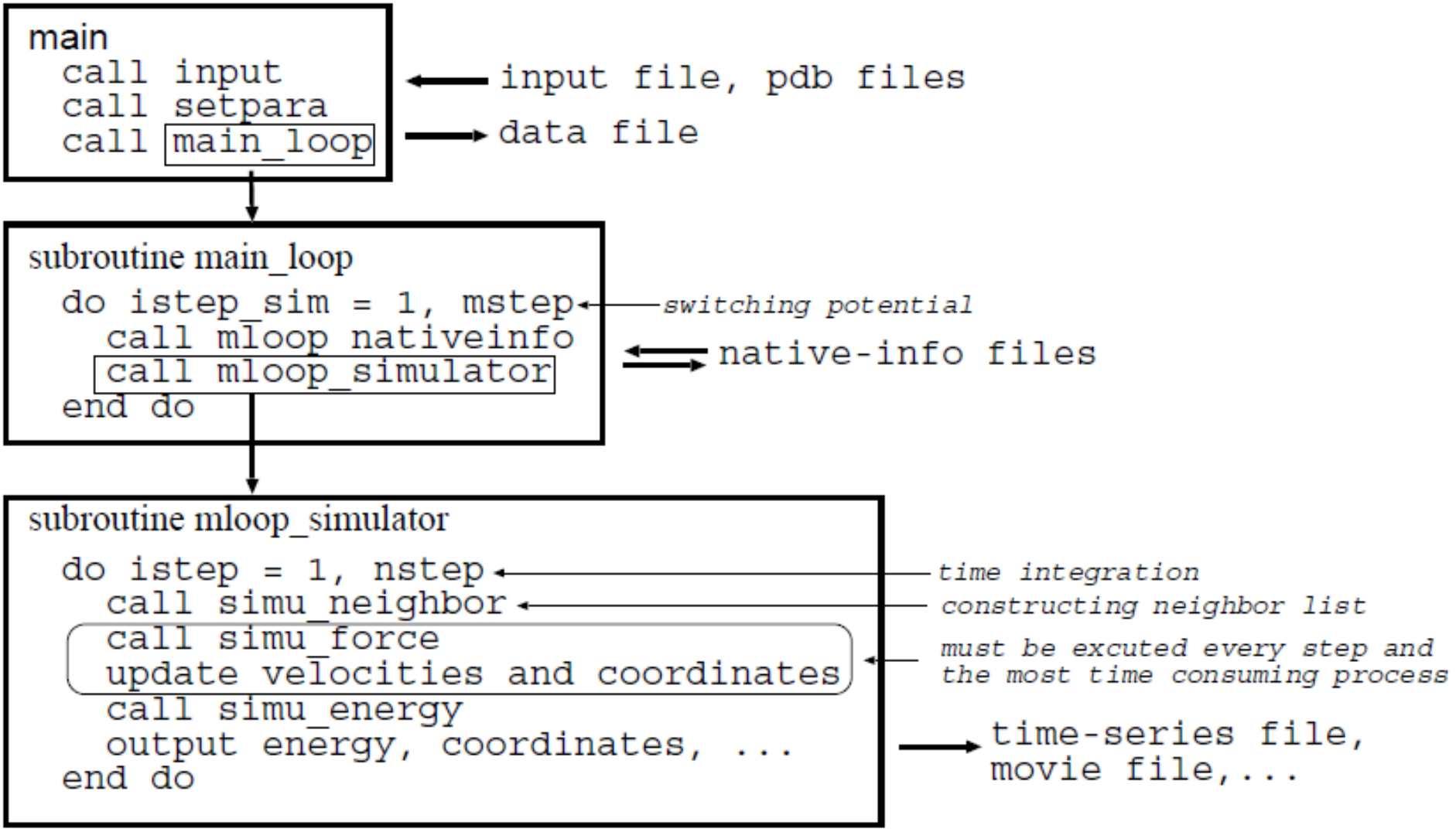


- fix: fix some particles or units

FIX_UNIT($unit_{ini}$-$unit_{las}$)

FIX_MP(mp_{ini}-mp_{las})

CafeMol code



CafeMol code parallization

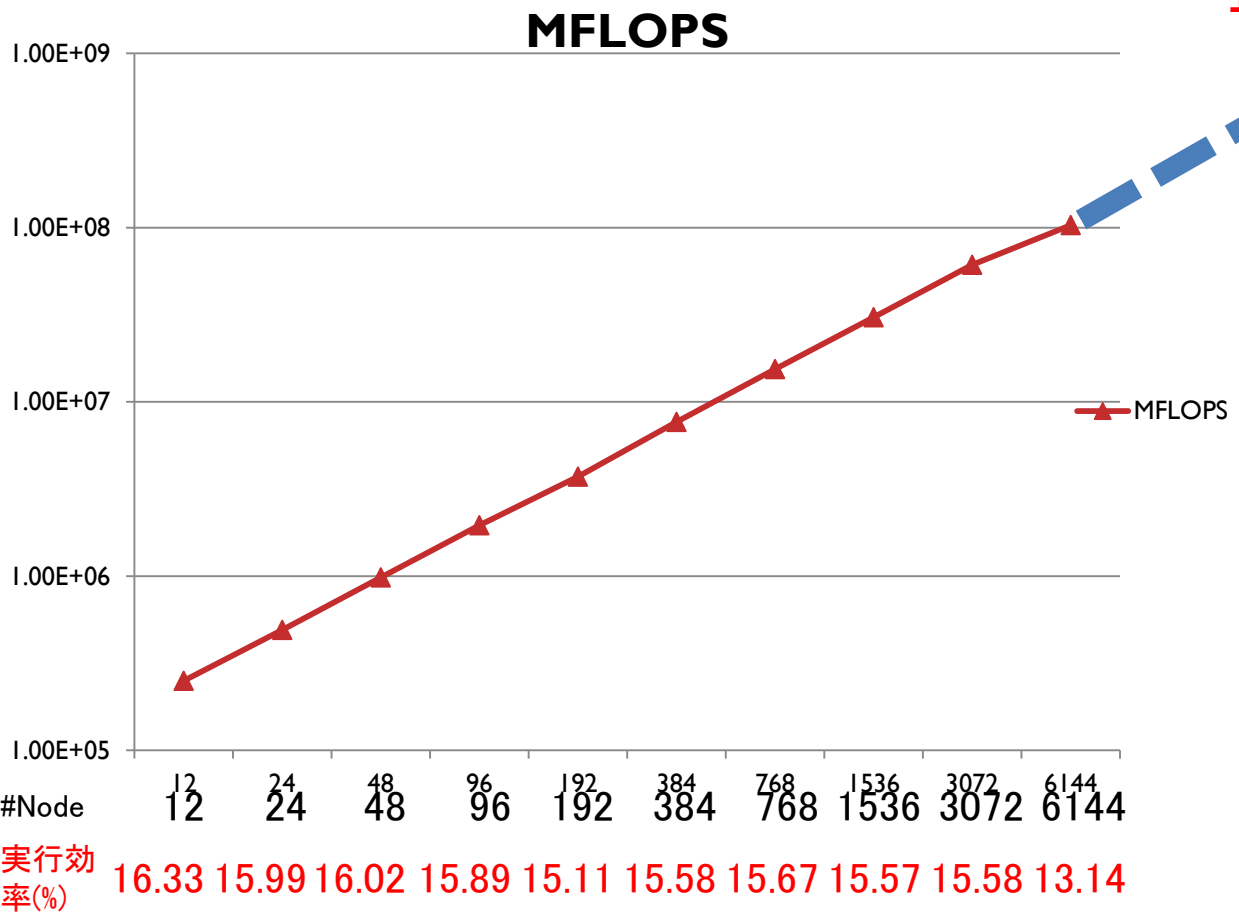
- Time integral(MPI+OpenMP)
  - neighboring list
    - each node calculates distances between assigned pairs and makes neighboring list
  - force, energy
    - each node calculates force or energy including their neighboring list
    - these calculations are parallelized by OpenMP
- Temperature/Hamiltonian REMD(MPI)
  - replica_1, replica_2, …. , replica_n

Performance of parallelization at K Computer

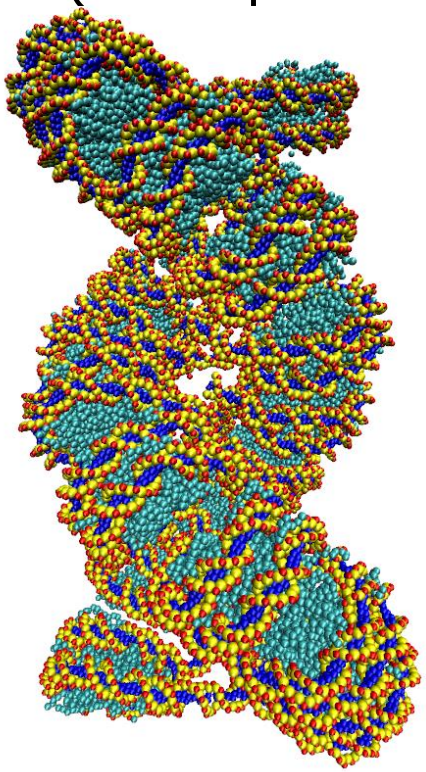
Before 2010
RICC at Riken (MPI+Open MP)
After 2011
at K-computer (SIMD)

Efficiency of parallelization:
99.996%

#node ~73,000 ⇒
~1PFLOPS !?



20 nucleosomes
(35918 particles)



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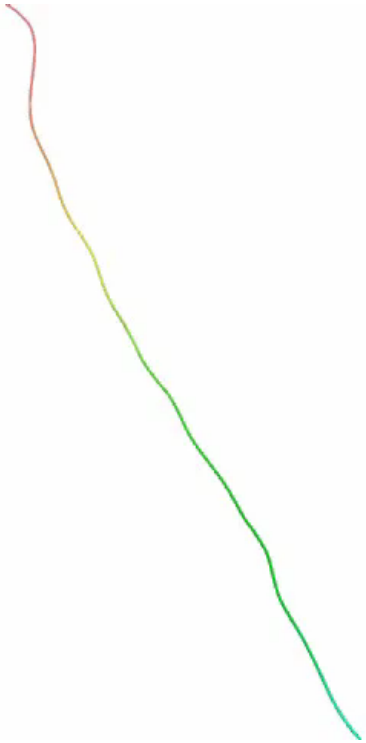
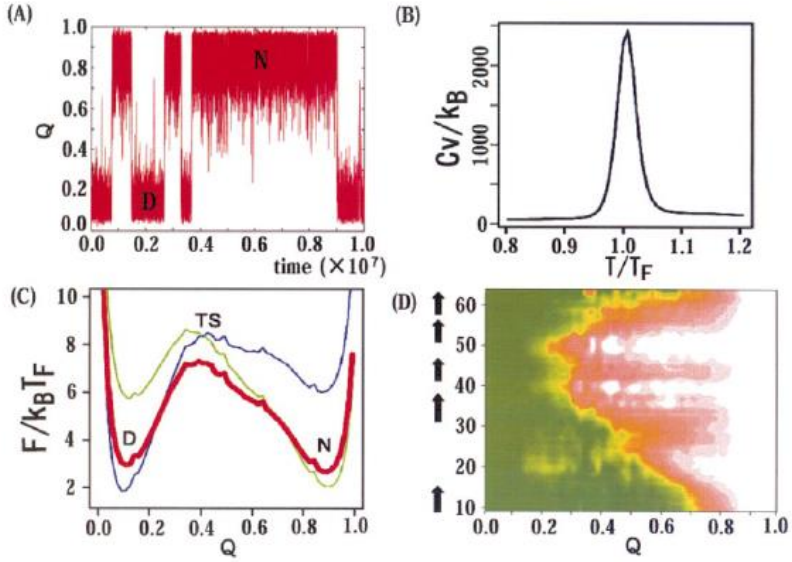
Folding simulation of src SH3 domain

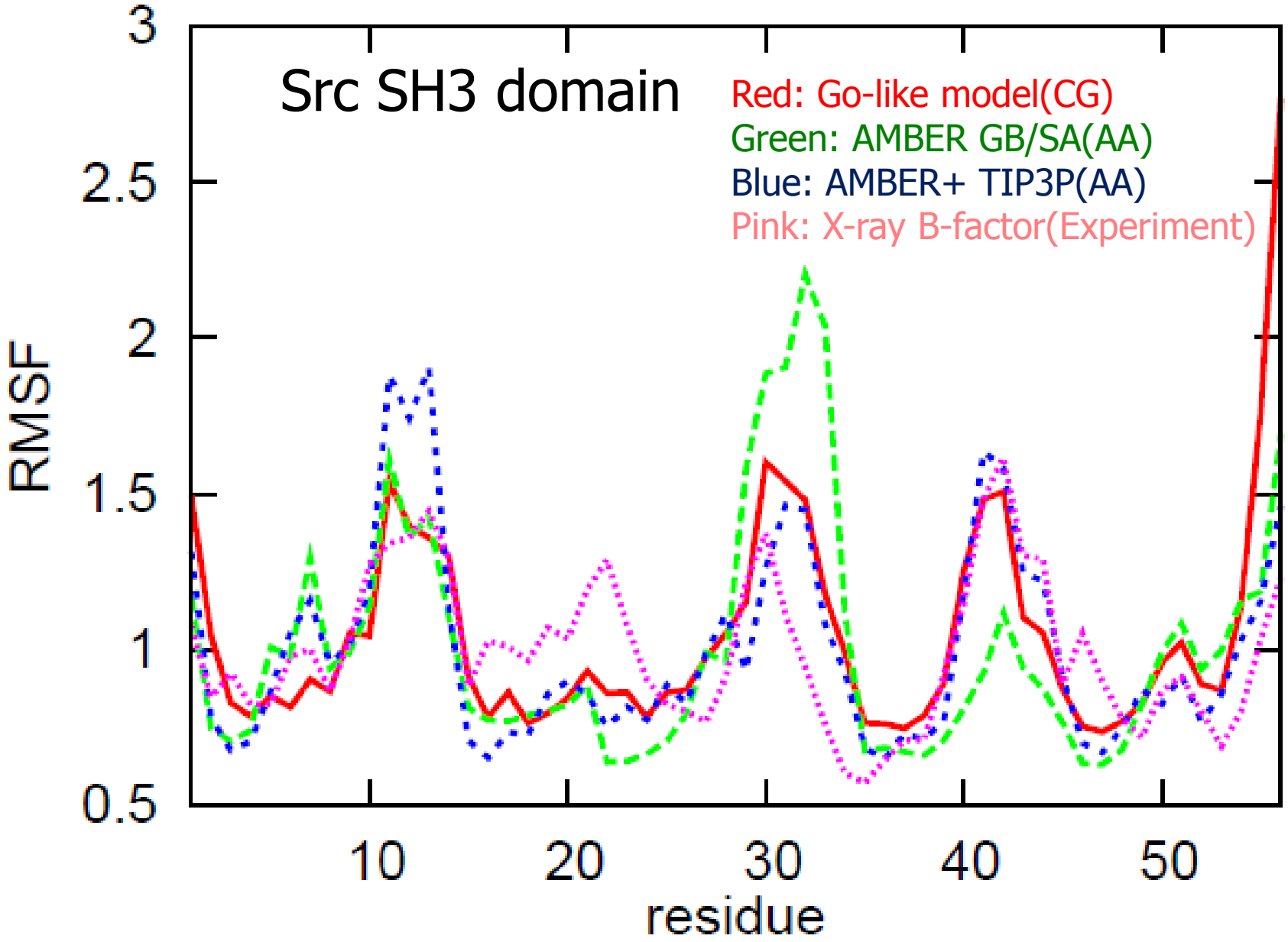


N. Koga, and S. Takada, J. Mol. Biol. (2001)

computed ϕ–values experimental ϕ–values



Native fluctuation by Go-like model



Folding temperature of src SH3 (Auto-search of Tf)

Bi-section method

```
<<<< job_cntl
i_run_mode = 4
i_simulate_type = 1
i_initial_state = 1
>>>>
<<<< searching_tf
tempk_upper = 500.0
tempk_lower = 100.0
>>>>
```

```
**********************************
tf_out   tempk n_state d_state p_trans
tf_out 300.000     995       5       1
**********************************
tf_out   tempk n_state d_state p_trans
tf_out 400.000       1    1000       0
**********************************
tf_out   tempk n_state d_state p_trans
tf_out 350.000     166     835      78
**********************************
tf_out   tempk n_state d_state p_trans
tf_out 325.000     953      48      19
**********************************
...
...
**********************************
tf_out   tempk n_state d_state p_trans
tf_out 341.406     638     363      98
**********************************
```

Folding temperature of some proteins

Protein	Number of amino acid	Folding temperature(K)
albumin binding domain	53	380.4
src SH3 domain	56	342.9
protein G	56	338.2
α-spectrin SH3 domain	57	360.1
Sso7d	64	332.0
protein L	78	374.2
Im9	86	382.0
cytochrom B562	106	352.2

“Switching” simulation

```
<<<< native_info_sim1
NINFO(1/1) 1      Intra-mol 1
...
NINFO(3/6) 13     Inter-mol 3/6
1= f1atp_alpha_E.ninfo
...
13= f1atp_alphDP_betaDP.ninfo
>>>>
```

switching

```
<<<< native_info_sim2
NINFO(1/1) 1
...
NINFO(3/6) 13
1= f1atp_alpha_TP.ninfo
...
13= f1atp_alphE_betaE.ninfo
>>>>
```

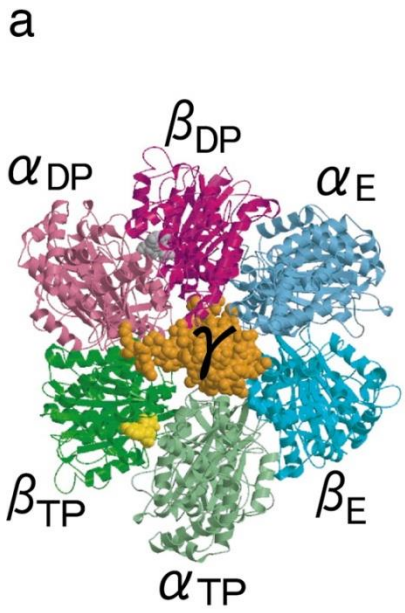
native-info file *(alpha_E subunit)*

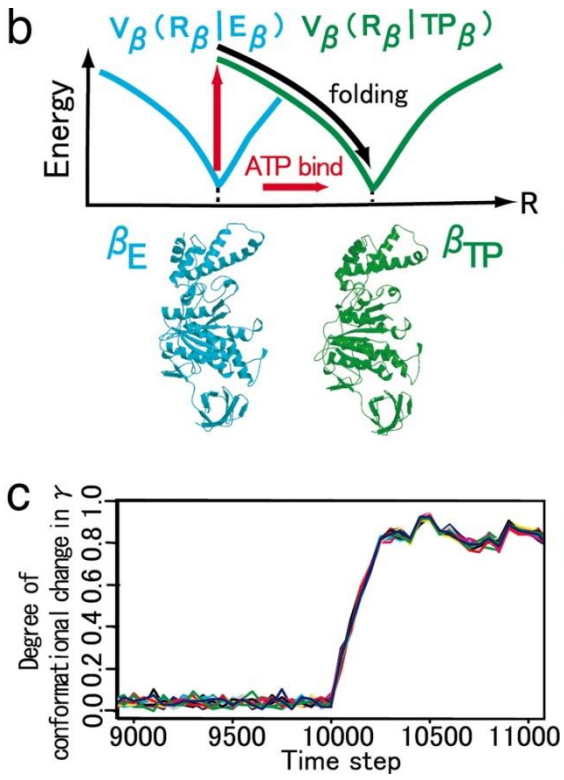
```
bond  1  1  1  1  2  1  2   3.8132   1.0000   1.0000   100.0000
...
angl  1  1  1  1  2  3  1  2  3  93.2170   1.0000   1.0000   20.0000
...
dihd   1  1  1  1  2  3  4  1  2  3  4  67.0855  1.0000  1.0000  1.0000
...
contact  1  1  1  1  5  1  5  5.9973  1.0000   1  0.3000
...
```

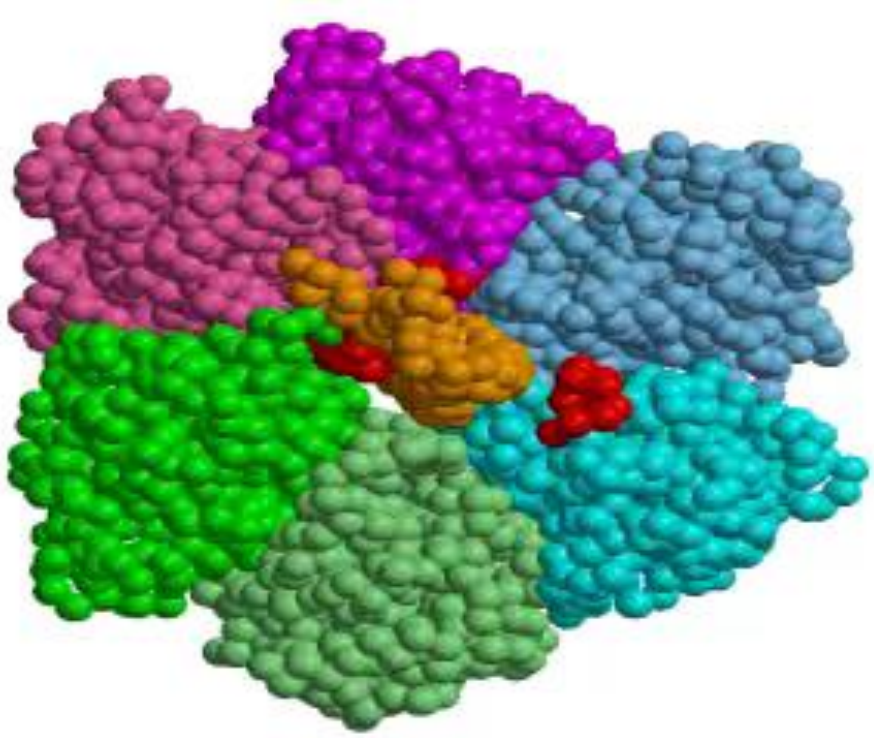
pair ij *nat- distance* *coefficient contact interaction*

Rotation mechanism of F_1-ATPase by switching Go model

N. Koga, and S. Takada, PNAS (2006)

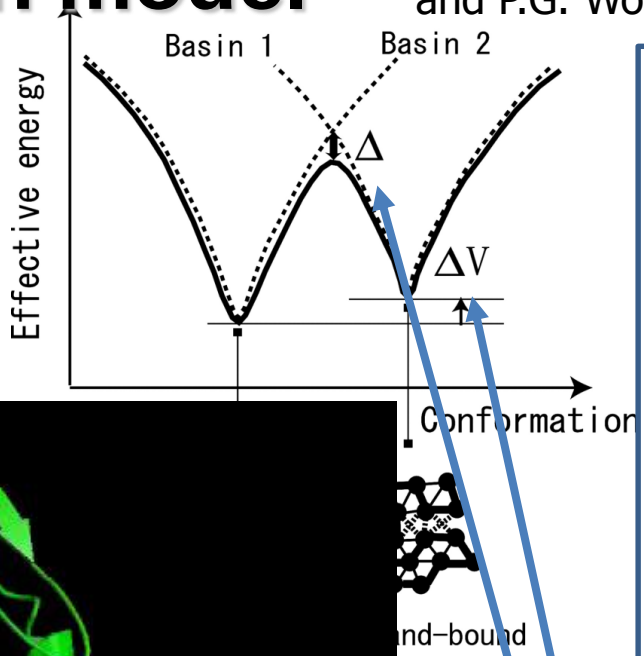






Conformational change by Multi-basin model

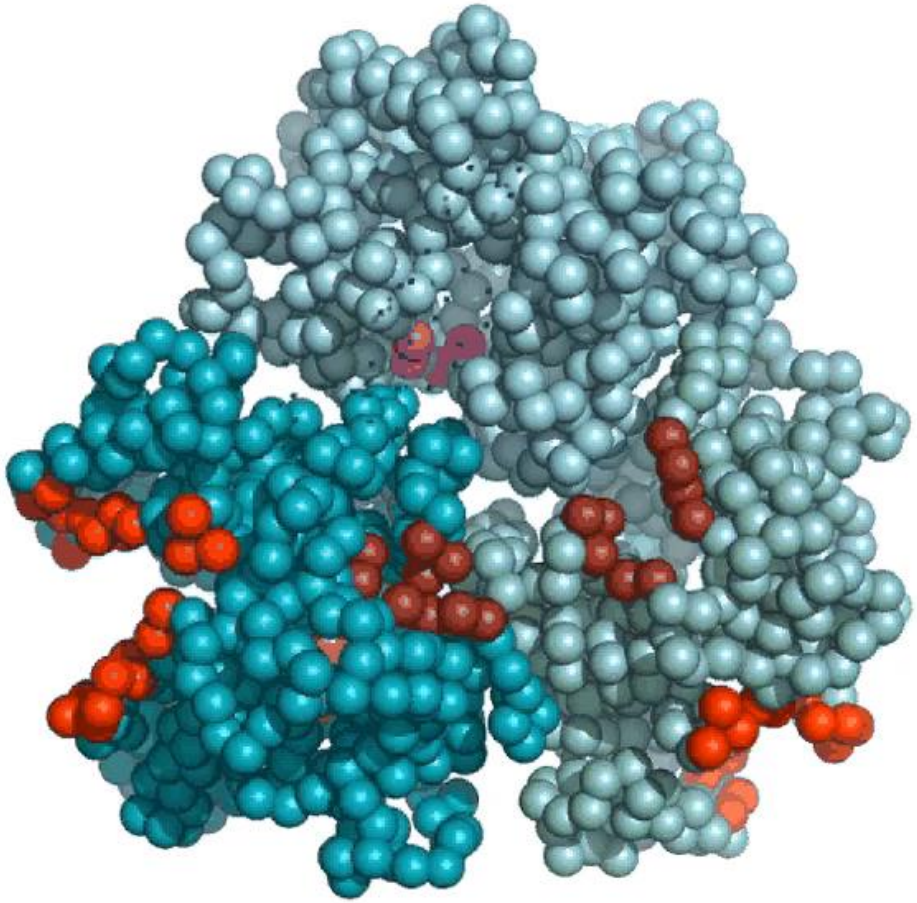
K. Okazaki, N. Koga, S. Takada, J.N. Onuchic, and P.G. Wolynes, PNAS (2006)



```
<<<< unit_and_state
i_seq_read_style = 1
i_go_native_read_style = 1
1a  protein  1GGG_2.pdb
1b  protein  1WDN_2.pdb
>>>>
<<<< energy_function
NLOCAL(1a/1a)    GO EXV
NLOCAL(1b/1b)    GO EXV
MULTIGO_SYSTEM(1a)  1a/1a
MULTIGO_SYSTEM(1b)  1b/1b
>>>>
<<<< multiple_go
bdemax_mgo = 100.0
baemax_mgo = 1.0
dihemax_mgo = 0.5
ENEGAP(1)(1)  0.0   -1.8
DELTA(1ab)    28.0
>>>>
```

Conformational change using 3-state multi-basin model

X. Yao, H. Kenzaki, S. Murakami, and S. Takada, *Nature Comm.* (2010)



Multidrug transporter AcrB

- Largely responsible for multidrug resistance
- Asymmetric homo-trimer structure

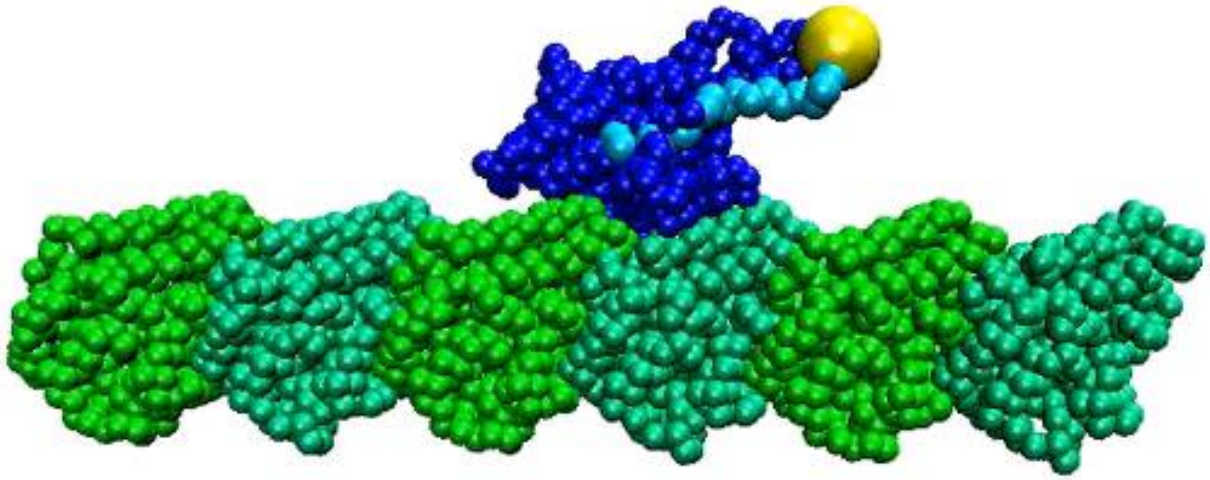
Suggesting mechanism of drug exportation and functional rotation!

Sliding movement of KIF1A

R. Kanada, T. Kuwata, H.Kenzaki, S.Takada, PLOS Comput. Biol. (2013)

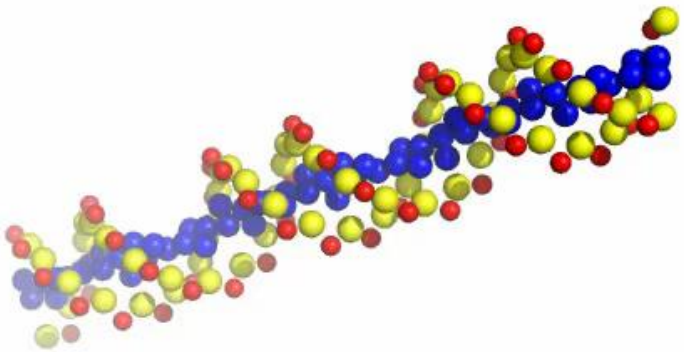
1 phase: multiple-basin (T, D)
2 phase: go(D)
3 phase: multiple-basin(D, phi)
4 phase: go(phi)
5 phase: go(T)

KIF1A:blue
tubulin:green
cargo:yellow



CG DNA simulation

- 30 bp DNA duplex
- Langevin dynamics (300K)
- $[Na^+]$ = 69mM
- cutoff length $20\kappa_D$(Debye length)



```
<<<< unit_and_state
i_seq_read_style = 2
i_go_native_read_style = 3
1-2    dna     sequence
>>>>
<<<< energy_function
LOCAL(1-2)  L_BDNA
NLOCAL(1-2/1-2)  DNA ELE
>>>>
<<<< electrostatic
cutoff_ele = 20.0
ionic_strength = 0.069
diele_water = 78.0
>>>>
<<<< in_box
xbox = 120.0
ybox = 120.0
zbox = 120.0
boxsigma = 4.0
>>>>
```

DH

3SPN.1

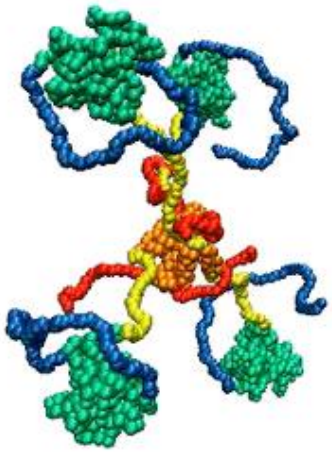
Intra mol 1,2

Inter mol 1-2

Diffusional search of p53 on DNA

T. Terakawa, H. Kenzaki, and S. Takada, JACS, (2012)

- Tumor suppressor
- Transcription factor
  1. Nonspecific diffusional search on DNA
  2. Specific binding



protein:AICG and FLP model
DNA:CG DNA model
protein-DNA:
excluded and electrostatic interaction

Core domain hopping
C-terminal domain sliding

Simulation of nucleosome

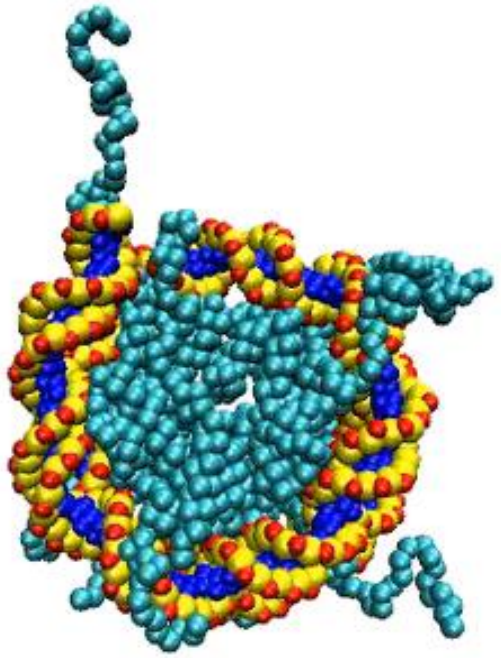
1KX5.pdb

- Electrostatic interaction + Go potential

$\varepsilon_{go}^{\text{pro-dna}} = 0.8\varepsilon_{go}^{\text{pro}}$
$[Na^+]$ = 200mM

$\varepsilon_{go}^{\text{pro-dna}}$:coefficient of protein-DNA Go potential

```
<<<< energy_function
LOCAL(1-2) L_BDNA
LOCAL(3-10) L_GO
NLOCAL(1-2/1-2) ELE DNA
NLOCAL(1-2/3-10)  GO EXV ELE
NLOCAL(3-10/3-10)  GO EXV
>>>>
<<<< electrostatic
cutoff_ele = 5.0
ionic_strength = 0.2
diele_water = 78.0
>>>>
```



H. Kenzaki, et al unpublished data

Acknowledgement

CafeMol development has been supported by Research and Development of the Next-Generation Integrated Simulation of Living Matter, a part of the Development and Use of the Next-Generation Supercomputer Project of the Ministry of Education, Culture, Sports, Science and Technology.