分野横断型研究会「アルゴリズムによる計算科学の融合と発展」
筑波大学計算科学研究センター、つくば、2009年4月22-23日

拡張アンサンブル法：
状態空間の効率的なサンプリング

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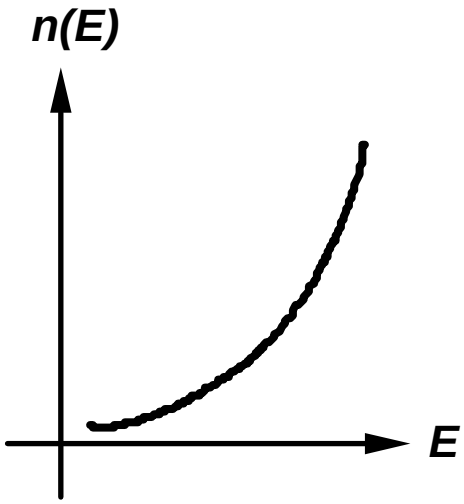
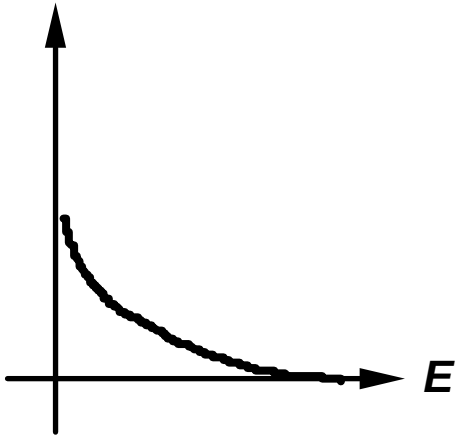
URL: http://jegog.phys.nagoya-u.ac.jp/tb/

Canonical Ensemble at Temperature T



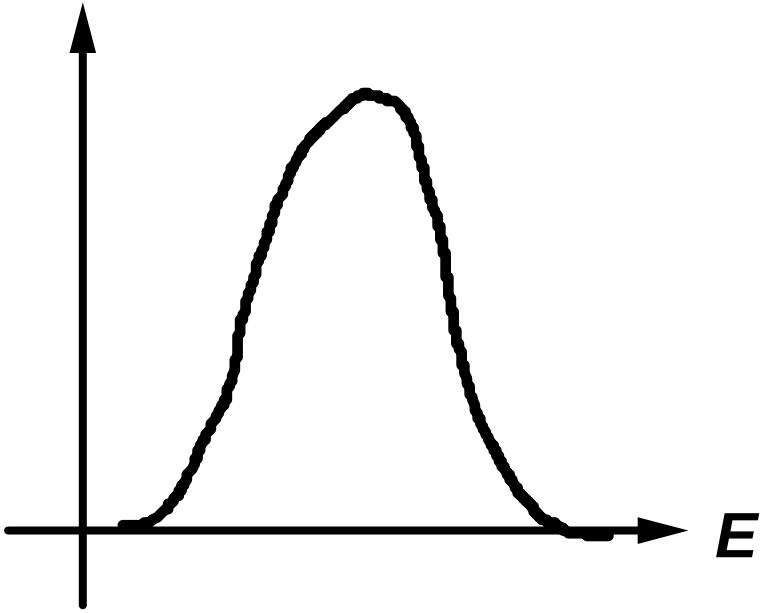
Density of States

$W_B(E) = \exp(-\beta E)$



Boltzmann Factor

$P_B(E) = n(E)W_B(E)$



Canonical Probability Distribution

Generalized-Ensemble Algorithm
（拡張アンサンブル法）

- **Simulation Methods that Do Not Get Trapped in States of Local Energy Minima**

  [e.g., **Multicanonical Algorithm, Simulated Tempering, Replica-Exchange Method**, **Tsallis Statistics**, etc.]
- **Based on Non-Boltzmann Weight Factor**

  Realize random walks in potential energy space
- **Histogram Reweighting Techniques**

  Can obtain thermodynamic quantities for a wide range of temperature from a single simulation run

REVIEWS: **U.H.E. Hansmann & Y.O., *Curr. Opin. Struct. Biol.* 9, 177 (1999);**

A. Mitsutake, Y. Sugita, & Y.O., *Biopolymers* 60, 96 (2001);

Y.O., *J. Mol. Graphics Modell.* 22, 425 (2004);

S.G. Itoh, H. Okumura, & Y.O., *Mol. Sim*. 33, 47 (2007);

Y. Sugita, A. Mitsutake, & Y.O., in *Lecture Notes in Physics*, W. Janke (ed.) (Springer-Verlag, 2008) pp. 369-407.

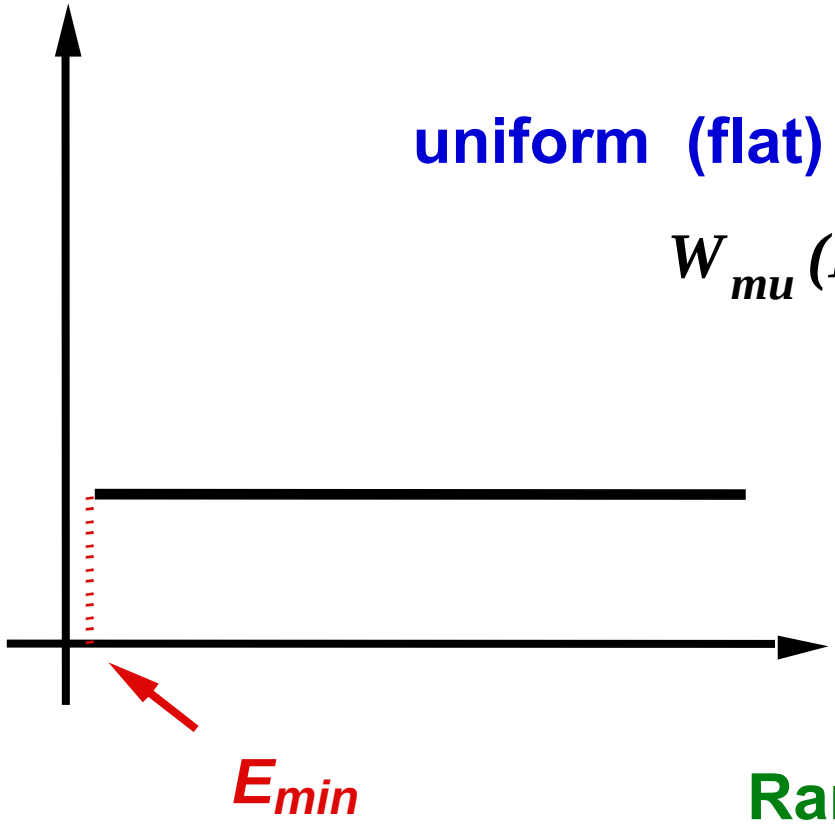
岡崎進・岡本祐幸 編 化学フロンティア NO.8（化学同人, 2002).

Multicanonical Algorithm

B. Berg & T. Neuhaus, *Phys. Lett.* **B267**, 249 (1991).

B. Berg & T. Neuhaus, *Phys. Rev. Lett.* **68**, 9 (1992).

$$P_{mu}(E) = n(E)W_{mu}(E) = \text{const}$$



uniform (flat) distribution in energy

$$W_{mu}(E) = n(E)^{-1}$$

Random Walk in Energy Space

Canonical Ensemble

MC version:

$$W_B(x;T) = \mathrm{e}^{-\beta E(x)}$$

$$w(x \to x') = \min\left(1, \frac{W_B(E';T)}{W_B(E;T)}\right) = \min\left(1, \mathrm{e}^{-\beta \Delta E}\right)$$

Multicanonical Ensemble

$$W_{mu}(E) = \frac{1}{n(E)}$$

MC version:

$$w(x \to x') = \min\left(1, \frac{W_{mu}(E')}{W_{mu}(E)}\right) = \min\left(1, \frac{n(E)}{n(E')}\right)$$

Generalized-Ensemble Algorithms have been developed in MC algorithms

Canonical Ensemble

MD version:

$$\begin{cases} m\ddot{\boldsymbol{q}}_i = -\dfrac{\partial E}{\partial \boldsymbol{q}_i} - \dfrac{\dot{s}}{s} m\dot{\boldsymbol{q}}_i = \boldsymbol{f}_i - \dfrac{\dot{s}}{s} m\dot{\boldsymbol{q}}_i \\ Q\ddot{s} = s\left[\sum_i m\dot{\boldsymbol{q}}_i^2 - 3Nk_BT\right] + Q\dfrac{\dot{s}^2}{s} \end{cases}$$

$$W_B(x;T) = \mathrm{e}^{-\beta E(x)}$$

Multicanonical Ensemble

MD version:

$$\begin{cases} m\ddot{\boldsymbol{q}}_i = -\dfrac{\partial E_{mu}}{\partial \boldsymbol{q}_i} - \dfrac{\dot{s}}{s} m\dot{\boldsymbol{q}}_i = \dfrac{\partial E_{mu}}{\partial E}\boldsymbol{f}_i - \dfrac{\dot{s}}{s} m\dot{\boldsymbol{q}}_i \\ Q\ddot{s} = s\left[\sum_i m\dot{\boldsymbol{q}}_i^2 - 3Nk_BT_0\right] + Q\dfrac{\dot{s}^2}{s} \end{cases}$$

$$W_{mu}(E) = \frac{1}{n(E)} = \exp(-\beta_0 E_{mu}(E))$$

U. Hansmann, Y.O. & F. Eisenmenger, *Chem. Phys. Lett.* **259**, 321 (1996);
N. Nakajima, H. Nakamura & A. Kidera, *J. Phys. Chem. B* **101**, 817 (1997).

MULTICANONICAL ALGORITHM

B. Berg & T. Neuhaus, *Phys. Lett.* **B267**, 249 (1991).

B. Berg & T. Neuhaus, *Phys. Rev. Lett.* **68**, 9 (1992).

Step 1: Iterations of Short Preliminary Runs to Determine the Multicanonical Weight Factor $W_{mu}(E)$

Step 2: One Long Production Run

Step 3: Analyze the Data to Obtain:

* Global-Minimum Energy Configuration

* Thermodynamic Quantities for Desired Temperatures (by Ferrenberg-Swendsen Single-Histogram Reweighting Techniques)

$$P_C(E;T) \propto P_{mu}(E) \frac{W_B(E;T)}{W_{mu}(E)}$$

Single-Histogram Reweighting Techniques

A. Ferrenberg & R. Swendsen, *Phys. Rev. Lett.* **61**, 2635 (1988).

$$< A >_T = \frac{\sum_E A(E) P_C\left(E;T\right)}{\sum_E P_C\left(E;T\right)} = \frac{\sum_E A(E) n\left(E\right) e^{-\beta E}}{\sum_E n\left(E\right) e^{-\beta E}}$$

Here, the density of states $n(E)$ is obtained from the histogram of the energy distribution $N_{mu}(E)$ that was obtained from the production run of the multicanonical simulation:

$$n\left(E\right) = \frac{N_{mu}(E)}{W_{mu}(E)}, \quad \text{where} \quad N_{mu}(E) = n\left(E\right) W_{mu}(E) \ .$$

MULTICANONICAL ALGORITHM

Step 1: Determination of Multicanonical Weight Factor

Wmu (E)

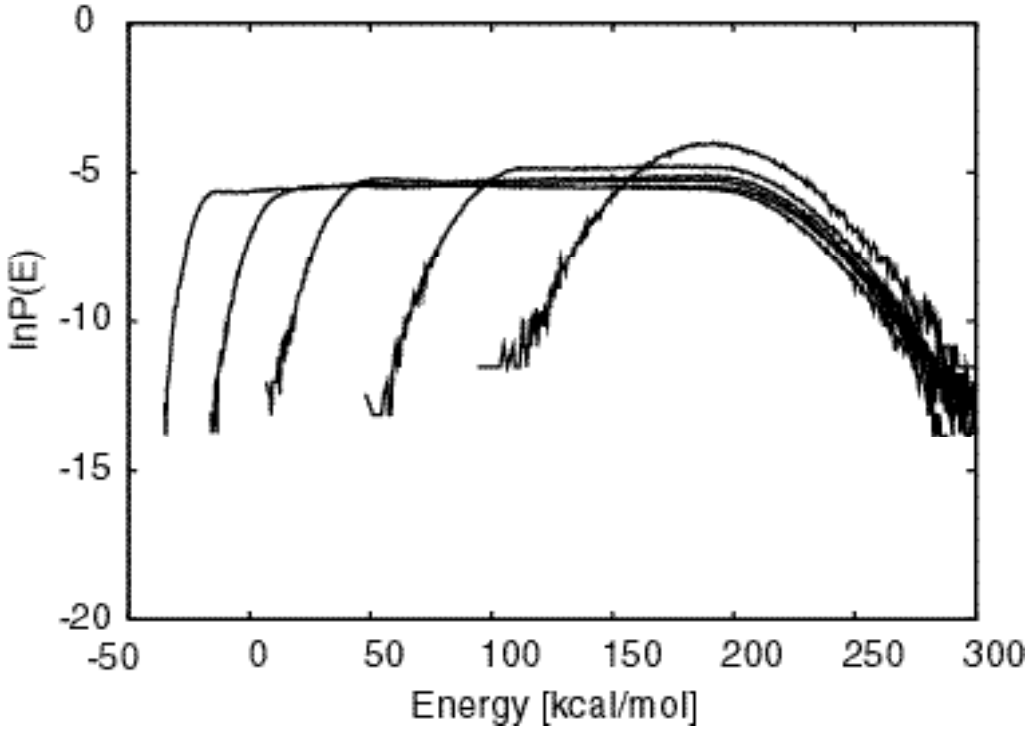
$$W(E) = \ln n(E) = \beta_0 E + \ln P_c(E, \beta_0)$$

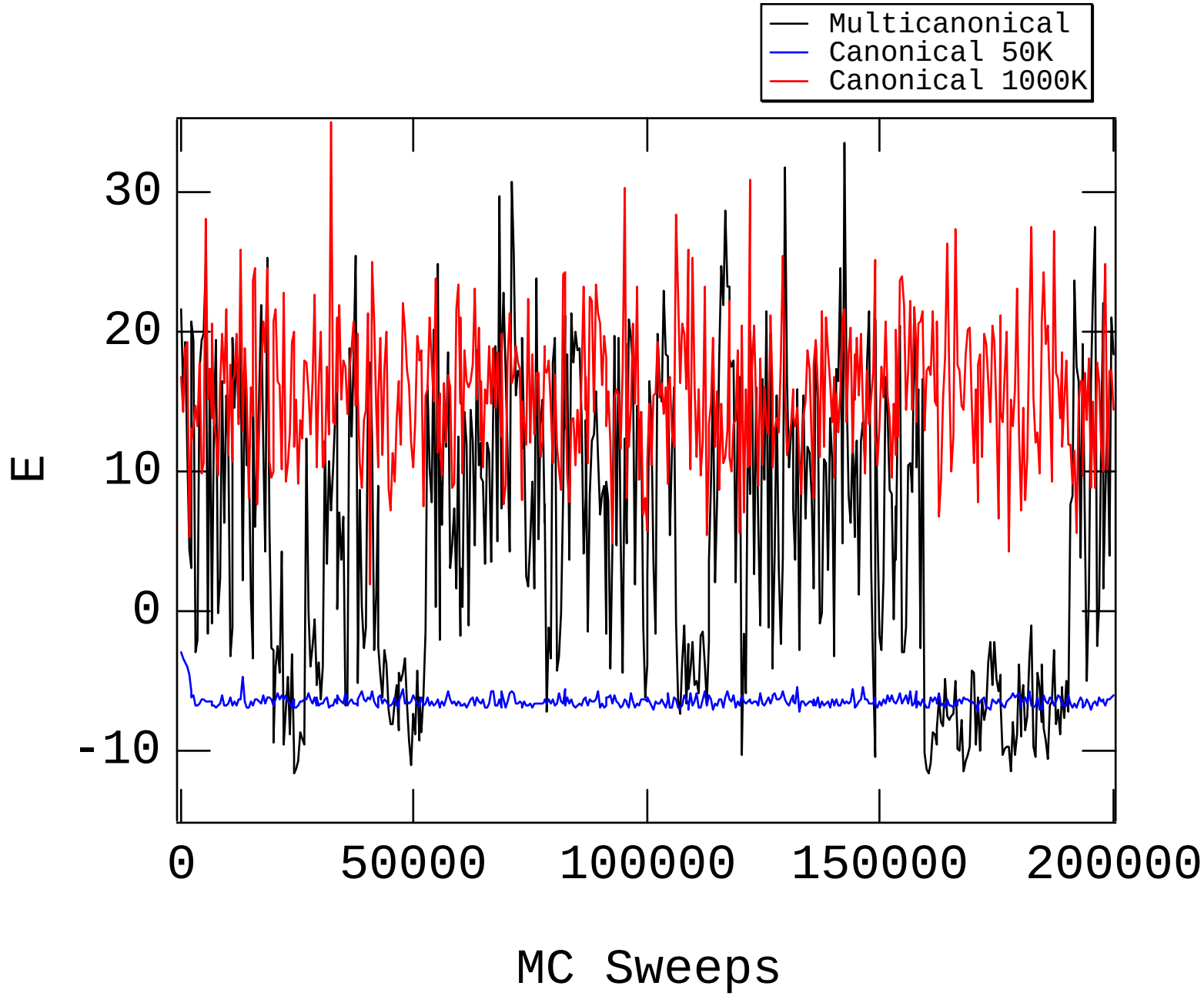
$$W^{i+1}(E) = W^i(E) + \ln P^i_{mc}(E)$$

This step becomes non-trivial as the system becomes complex.

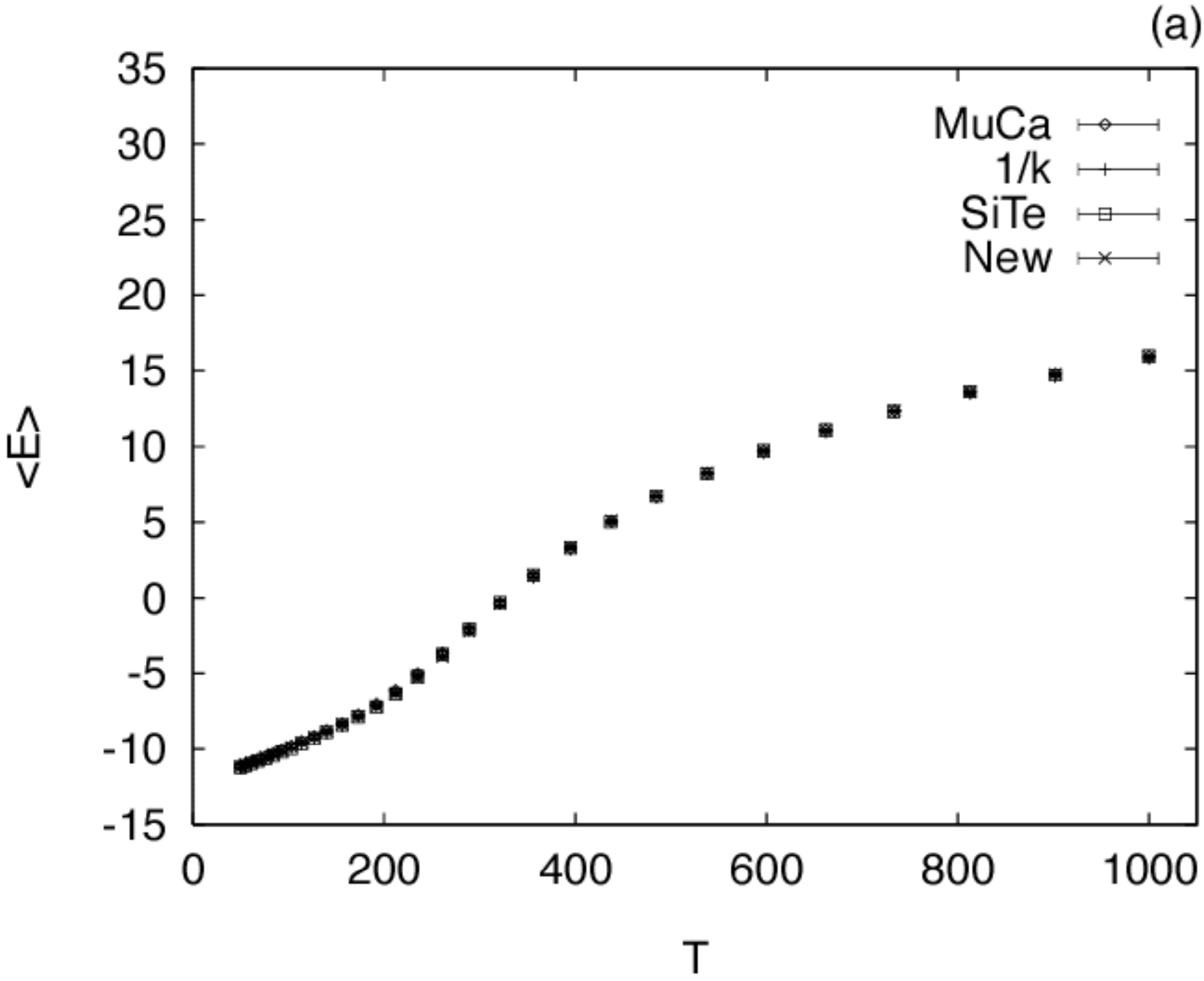
Wang-Landau method is very efficient for this step.

F. Wang & D.P. Landau, *Phys. Rev. Lett.* **86**, 2050 (2001).

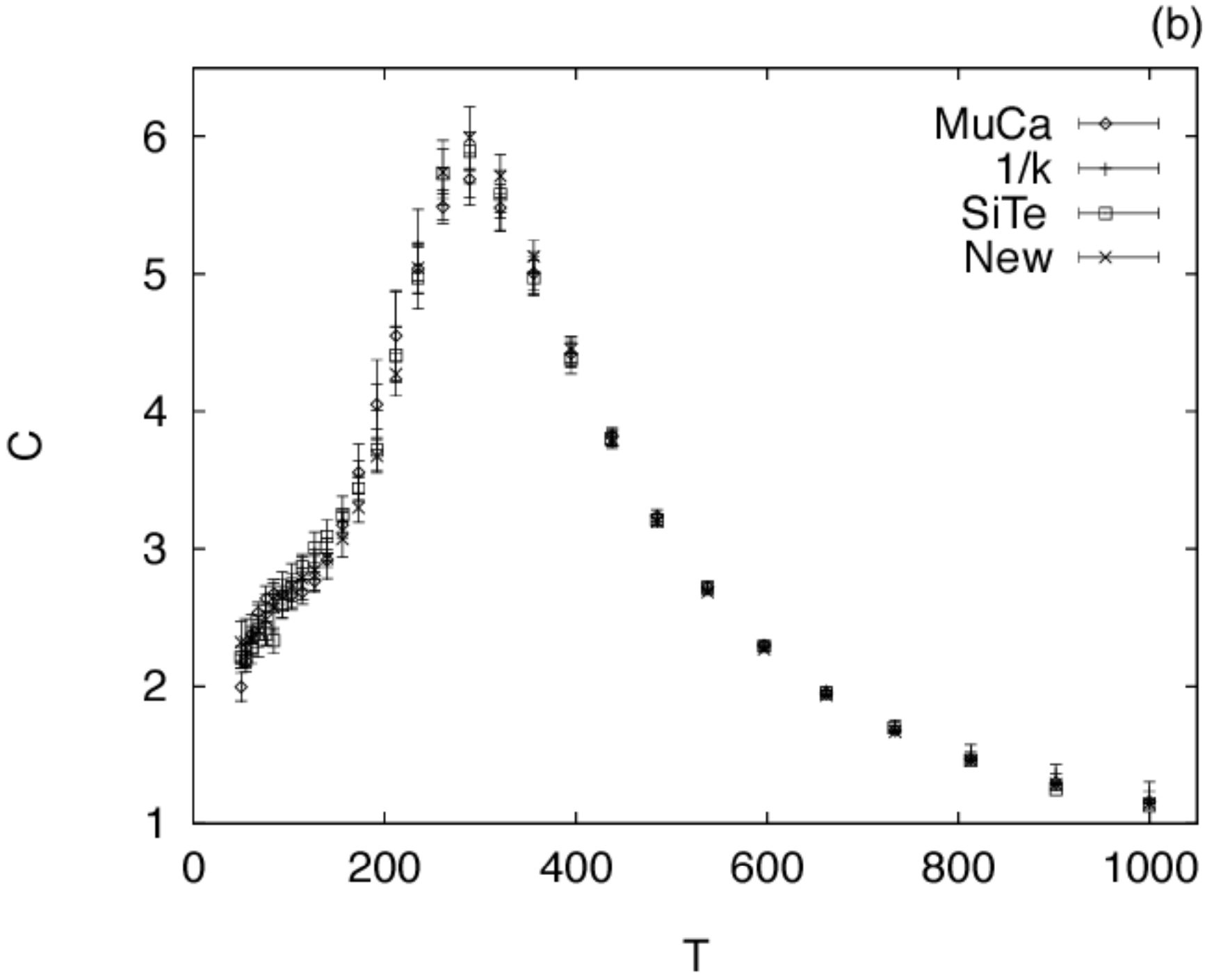



Multicanonical
Canonical 50K
Canonical 1000K
E
30
20
10
0
-10
0
50000
100000
150000
200000
MC Sweeps

Enk

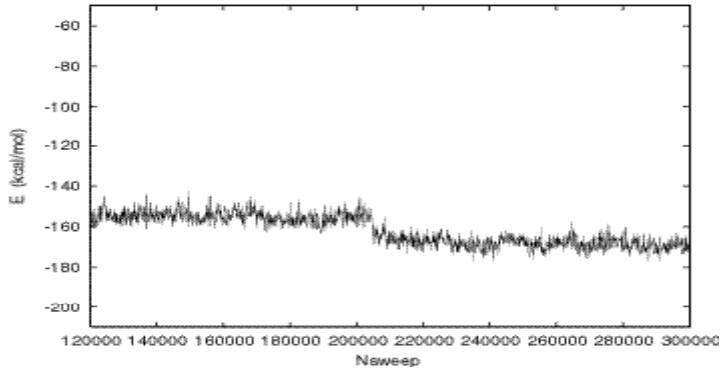

(a)
MuCa
1/k
SiTe
New
<E>
T
35
30
25
20
15
10
5
0
-5
-10
-15
0
200
400
600
800
1000

Enk-s

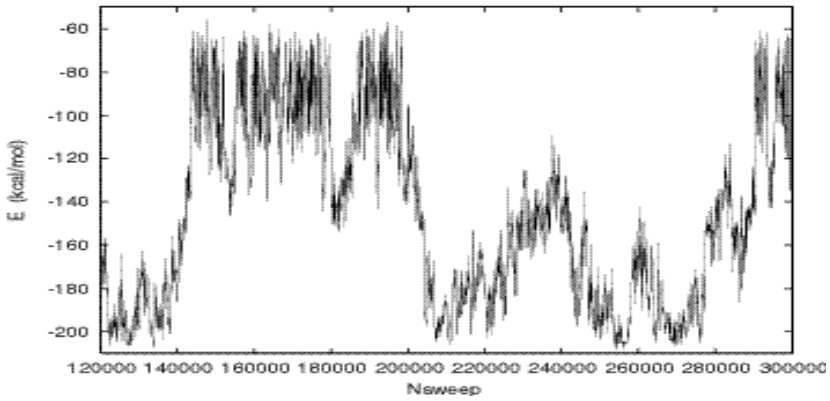


17-Residue Helical Peptide (120000-300000 MC Sweeps)

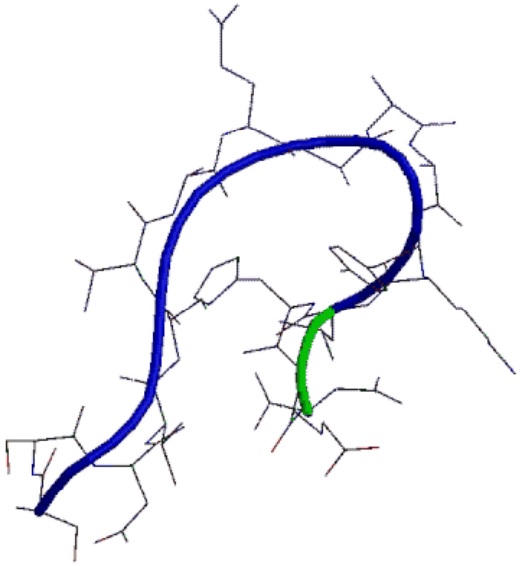
Simulation and movie by A. Mitsutake

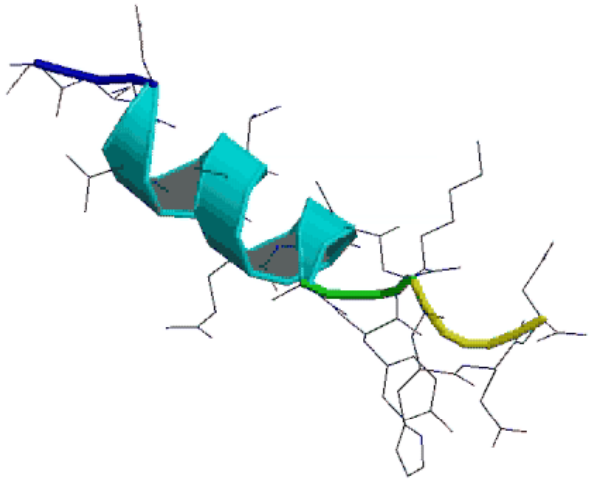


Canonical MC: T = 200 K



Multicanonical MC





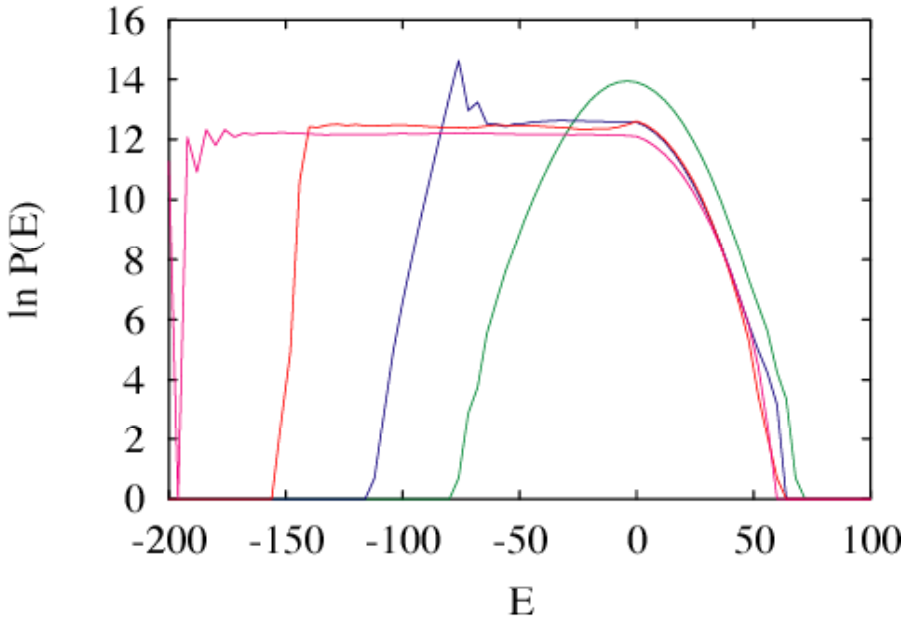
2D Ising Model

$$E = -J \sum_{<i,j>} S_i S_j \qquad \text{where } S_i = \pm 1$$

Simulation by A. Mitsutake

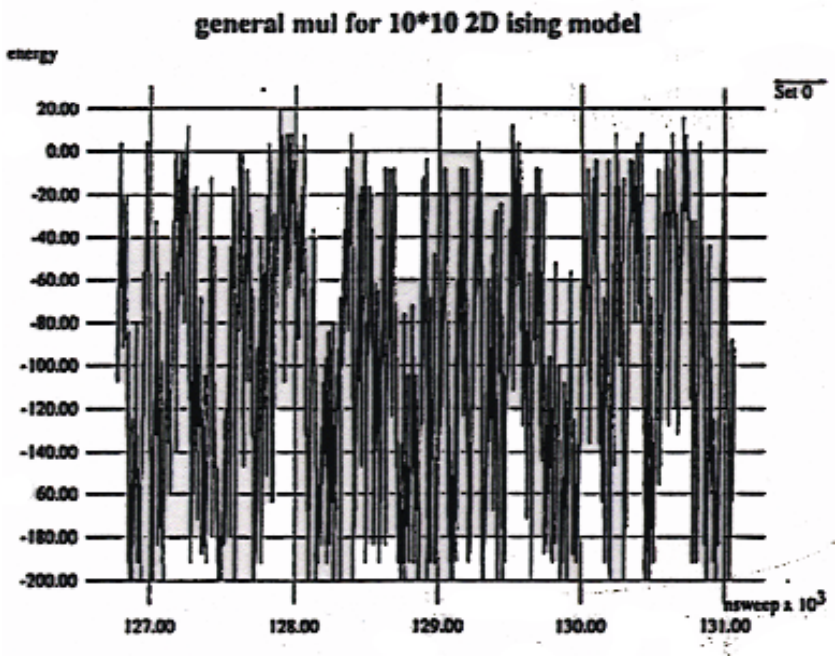
1. Determination of Multicanonical Weight

iterations of short simulations



Global Minimum = -200

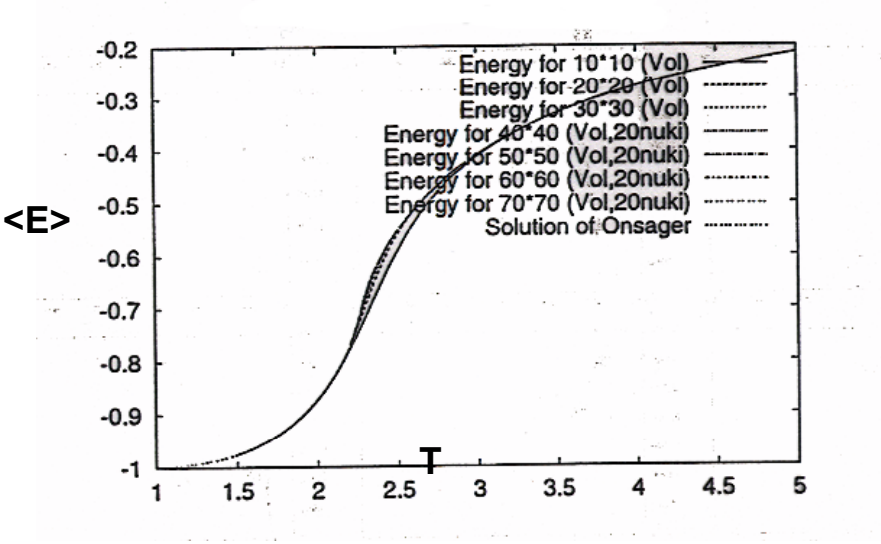
2. Long Production Run



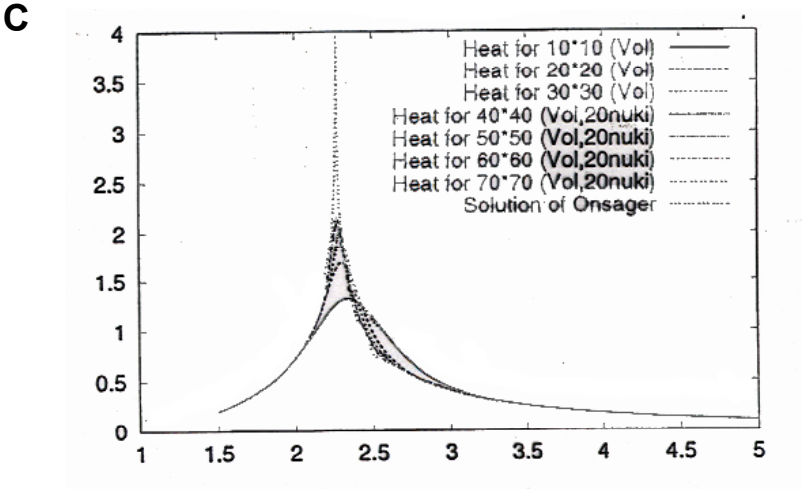
E

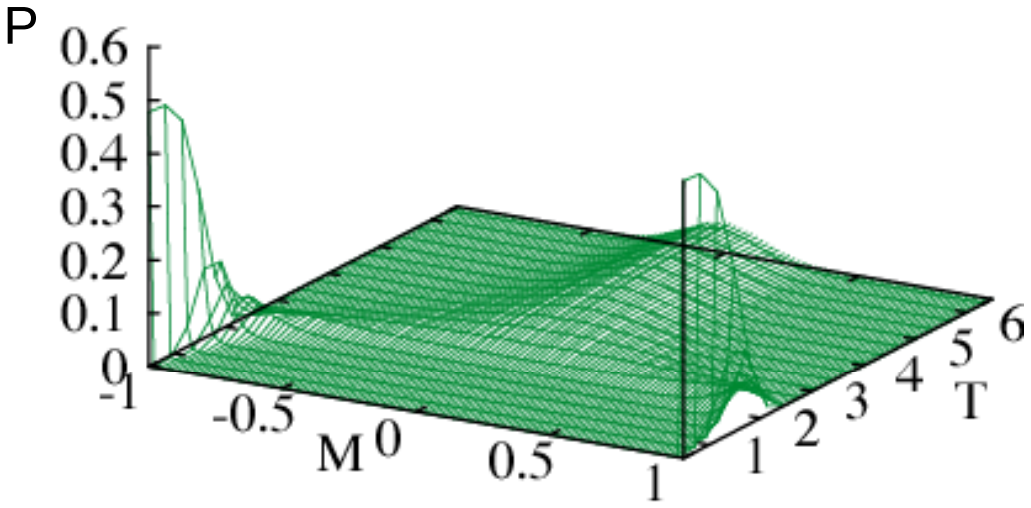
MC sweeps

Simulation by A. Mitsutake



From a single production run, one can calculated thermodynamic quantities such as internal energy, specific heat, magnetization, etc. as a function of temperature





q-state Potts Model (*q*=10)

Energy:

34 X 34 Lattice

$$E = -\sum_{<i,j>} \delta_{s_i s_j}$$

$$S_i = 0, 1, \ldots, q\text{-}1$$

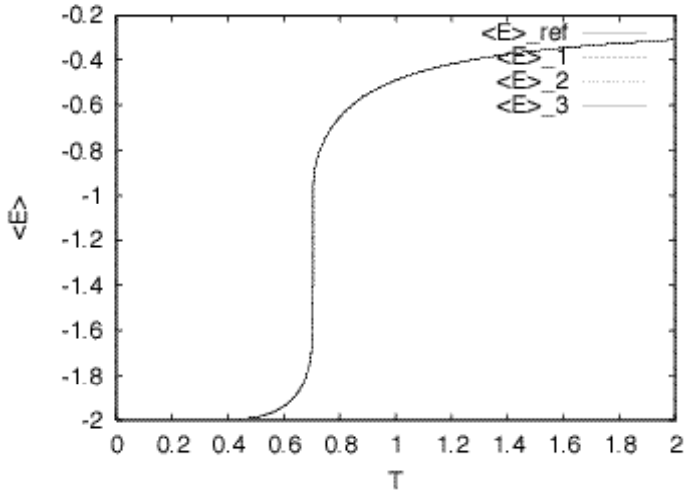
First-Order Phase Transition for $q > 4$ in 2D

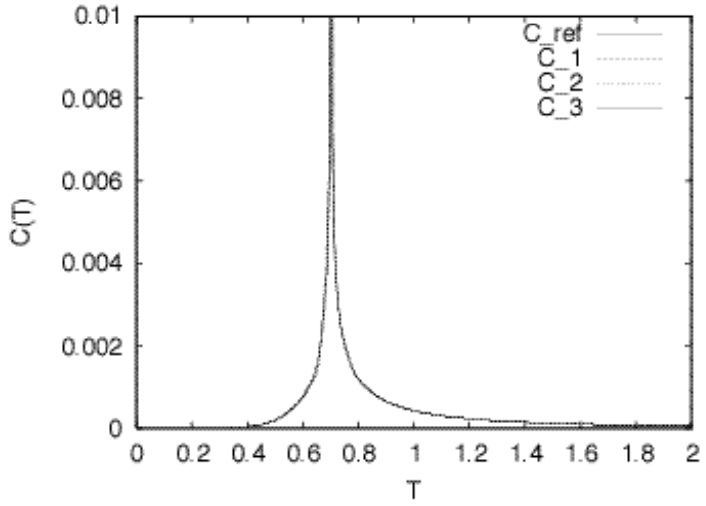
(Baxter, *J. Phys. C* **6**, L445 (1973))

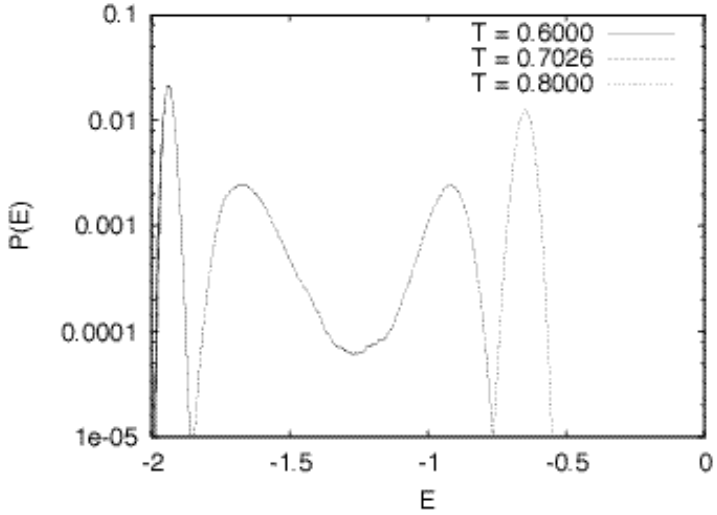
Thus, replica-exchange method cannot be applied.

q-state Potts Model (*q*=10)

T. Nagasima, Y. Sugita, A. Mitsutake, and Y. O., unpublished.







Calculation of residual entropy of ice by multicanonical simulations

B.A. Berg, C. Muguruma & Y.O., *Phys. Rev. B* **75**, 092202 (2007);
C. Muguruma, Y.O. & B.A. Berg, *Phys. Rev. E* **78**, 041113 (2008).

$S_0^{\text{experiment}} = 0.82(5)$ cal/deg/mole

W.F. Giauque and M. Ashley, *Phys. Rev.* **43** 81 (1933).

O. Haida, T. Matsuo, H. Suga, and S. Seki,
J. Chem. Thermodynamics **6**, 815 (1977).

$S_0 = k \ln(W)$ where $W = (W_1)^N$

$S_0^{\text{Pauling}} = 0.80574...$ cal/deg/mole $\qquad W_1^{\text{Pauling}} = \frac{3}{2}$

L. Pauling, *J. Am. Chem. Soc.* **57** 2680 (1935).

Onsager pointed out this is just a lower bound.

L. Onsager and M. Dupuis, *J. Rend. Sc. Inst. Fis. "Enrico Fermi"* **10**, 294 (1960).

$S_0^{\text{Nagle}} = 0.81480\ (20)$ cal/deg/mole $\qquad W_1^{\text{Nagle}} = 1.50685\ (15)$

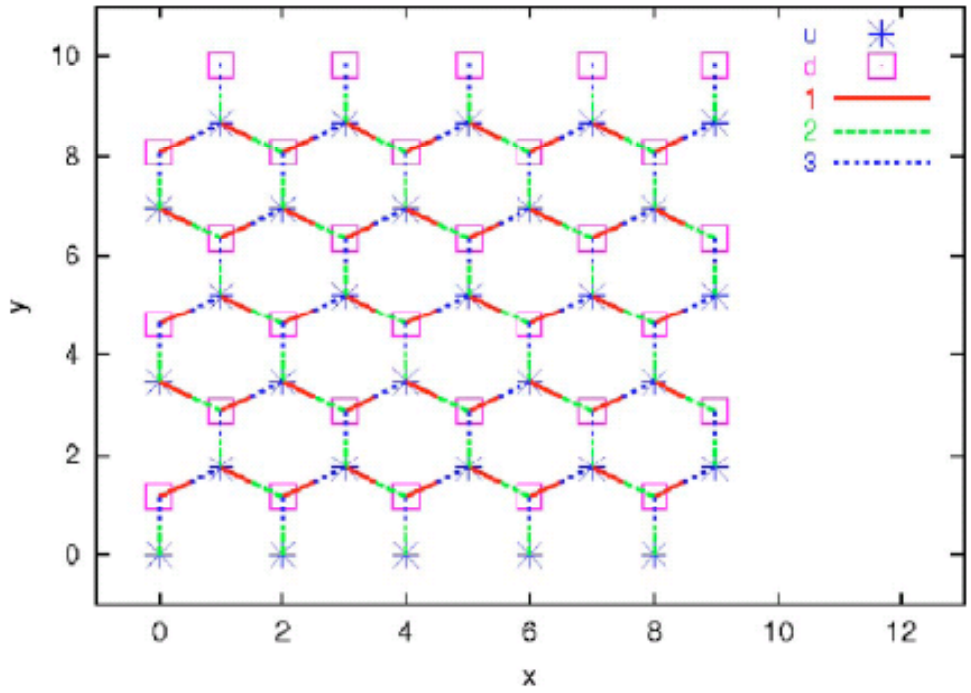
J.F. Nagle, *J. Mat. Phys.* **7**, 1484 (1966).

$S_0^{\text{MUCA}} = 0.81550(21)$ cal/deg/mole $\qquad W_1^{\text{MUCA}} = 1.50738(16)$

B.A. Berg, C. Muguruma & Y.O., *Phys. Rev. B* **75**, 092202 (2007);
C. Muguruma, Y.O. & B.A. Berg, *Phys. Rev. E* **78**, 041113 (2008).

Ice Rules

1. There is one hydrogen atom on each bond
   (then called hydrogen bond)
2. There are two hydrogen atoms near each oxygen atom
   (these constitute a water molecule)



Lattice structure of one layer of ice I

B.A. Berg, C. Muguruma & Y.O., *Phys. Rev. B* **75**, 092202 (2007).

We proposed the following two Hamiltonians in which only the groundstate satisfies both of the Ice Rules.

$$E = -\sum_b h(b, s_b^1, s_b^2)$$

6-state H_2O molecule model

[Ice Rule (2) is always enforced]

where $$h(b, s_b^1, s_b^2) = \begin{cases} 1, & \text{for H-bond} \\ 0, & \text{otherwise} \end{cases}$$

$$E = -\sum_s f(s, b_s^1, b_s^2, b_s^3, b_s^4)$$

2-state H-bond model

[Ice Rule (1) is always enforced]

where

$$f(s, b_s^1, b_s^2, b_s^3, b_s^4) = \begin{cases} 2, & \text{for 2 H nuclei close to } s \\ 1, & \text{for 1 or 3 H nuclei close to } s \\ 0, & \text{for 0 or 4 H nuclei close to } s \end{cases}$$

Single-Histogram Reweighting Techniques

A. Ferrenberg & R. Swendsen, *Phys. Rev. Lett.* **61**, 2635 (1988).

The number of states *n(E)* is obtained from the histogram of the energy distribution $N_{mu}(E)$ that was obtained from the production run of the multicanonical simulation:

$$n(E) = \frac{N_{mu}(E)}{W_{mu}(E)}, \quad \text{where} \quad N_{mu}(E) = n(E) W_{mu}(E) \ .$$

Then the residual entropy is obtained by

$$S_0 = k \ln(n(E_0)), \quad \text{where } E_0 \text{ is the energy of the groundstate}$$

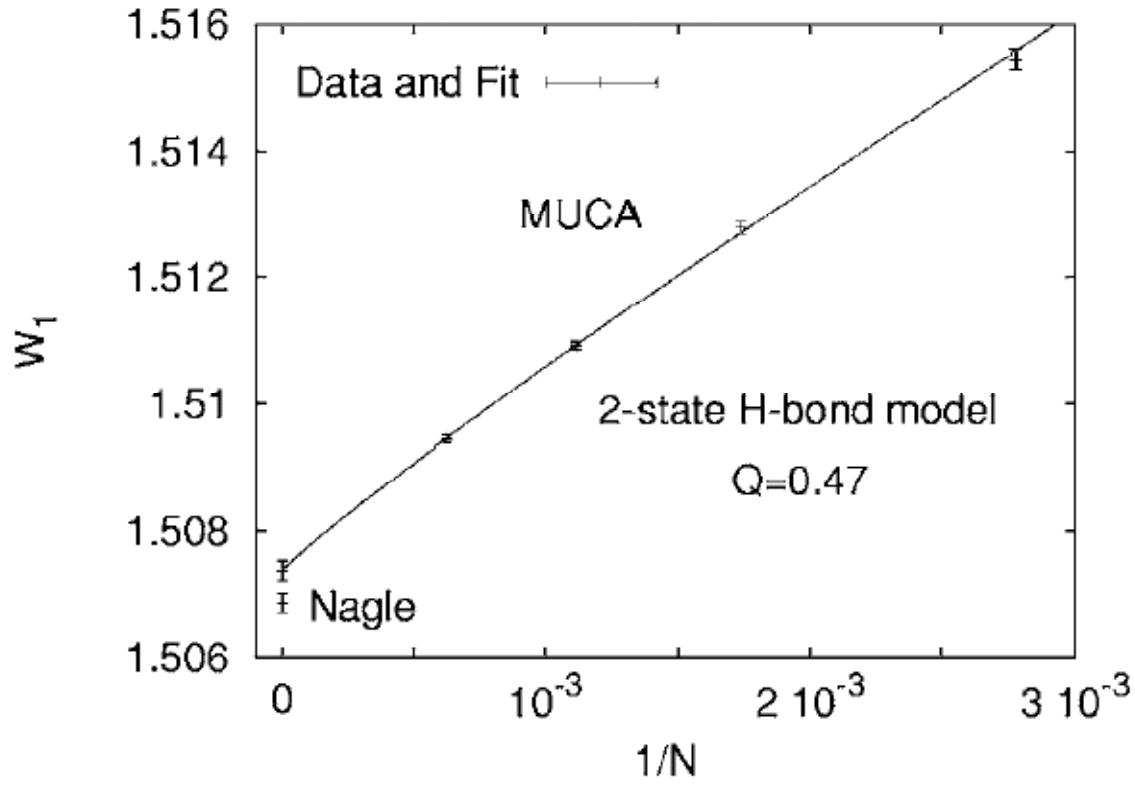
where the normalization for *n(E)* is set by

$$n(E) = \begin{cases} 6^N & \text{for the 6-state model} \\ 2^{2N} & \text{for the 2-state model} \end{cases} \qquad \text{at } \beta = 0$$

B.A. Berg, C. Muguruma & Y.O., *Phys. Rev. B* **75**, 092202 (2007).

$S_0 = k \ln(W)$ where $W = (W_1)^N$

$S_0^{\mathrm{MUCA}} = 0.81550(21)$ cal/deg/mole $W_1^{\mathrm{MUCA}} = 1.50738(16)$



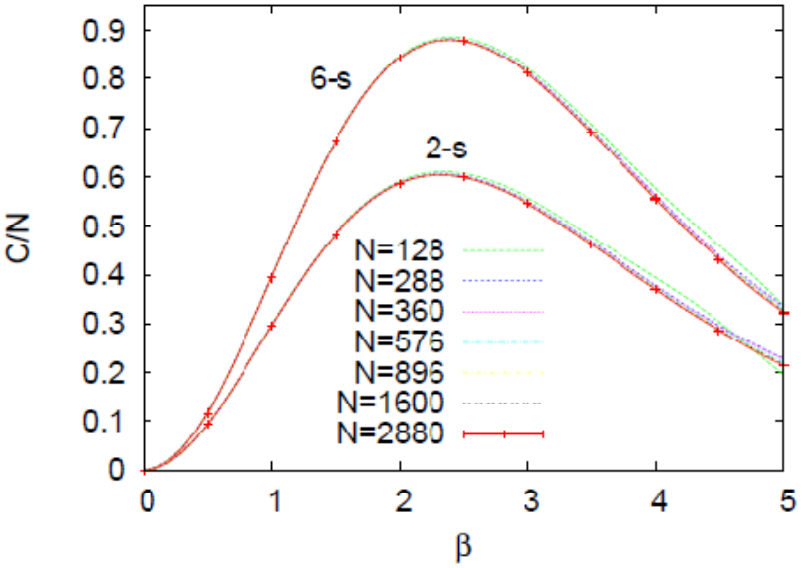


FIG. 3: Specific heat per site for the 6-s and 2-s models.

C. Muguruma, Y.O. & B.A. Berg,

Phys. Rev. E **78**, 041113 (2008).

No order-disorder phase transitions in our models!

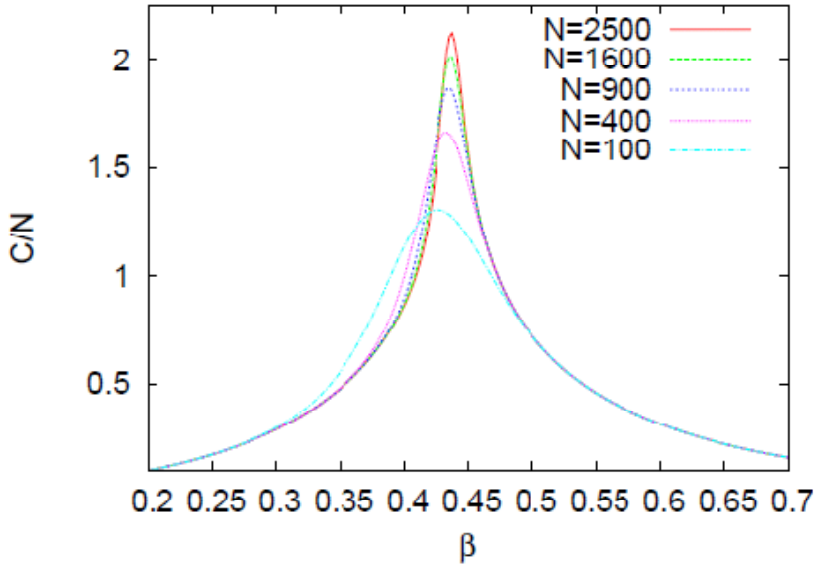


FIG. 4: Specific heat per site for the 2D Ising model on $N = L^2$ lattices.

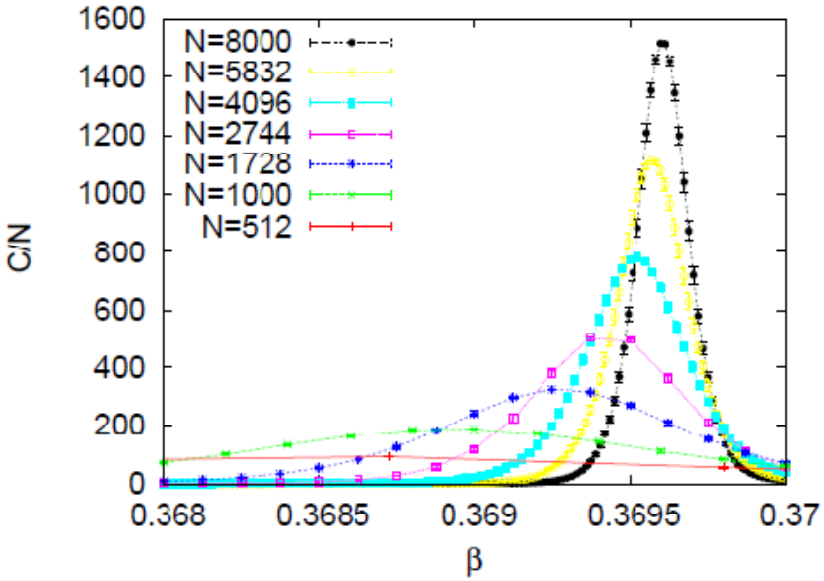


FIG. 5: Specific heat per site for the 3D 6-state Potts model on $N = L^3$ lattices.

分子動力学シミュレーション（Molecular Dynamics）

ニュートン方程式を数値的に解く

$$v(t) = \frac{dq}{dt}(t) = \lim_{\Delta t \to 0} \frac{q(t+\Delta t) - q(t)}{\Delta t} = \frac{q(t+\Delta t) - q(t)}{\Delta t}$$

$$a(t) = \frac{d^2 q}{dt^2} = \lim_{\Delta t \to 0} \frac{v(t+\Delta t) - v(t)}{\Delta t} = \frac{q(t+2\Delta t) - 2q(t+\Delta t) + q(t)}{(\Delta t)^2}$$

ニュートンの運動方程式の数値解

$$m\frac{d^2 q}{dt^2} = -\frac{\partial E}{\partial q} = f$$

$$q(t+2\Delta t) = 2q(t+\Delta t) - q(t) + (\Delta t)^2 \frac{f(t)}{m}$$

（速度）ベルレ法などいろいろな数値解（積分法）がある

調和振動子

$$f(t) = -m\omega^2 q(t)$$

$$q(t+\Delta t) = q(t) + \Delta t v(t)$$

$$v(t+\Delta t) = v(t) + \Delta t a(t) = v(t) + \Delta t \frac{f(t)}{m} = v(t) - \Delta t \omega^2 q(t)$$

$$\eta(t) = \begin{pmatrix} q(t) \\ v(t) \end{pmatrix} \rightarrow \eta(t+\Delta t) = M\eta(t) = \begin{pmatrix} 1 & \Delta t \\ -\omega^2 \Delta t & 1 \end{pmatrix} \eta(t)$$

$$\det M = 1 + \omega^2 (\Delta t)^2$$

だんだん発散

$$q(t+\Delta t) = q(t) + \Delta t v(t+\Delta t)$$

$$v(t+\Delta t) = v(t) - \Delta t \omega^2 q(t)$$

$$M = \begin{pmatrix} 1 - \omega^2 (\Delta t)^2 & \Delta t \\ -\omega^2 \Delta t & 1 \end{pmatrix}$$

$$\det M = 1$$

安定な周期運動

$$\boldsymbol{J} = \begin{pmatrix} \mathbf{0} & \mathbf{1} \\ \mathbf{-1} & \mathbf{0} \end{pmatrix}$$

- シンプレクティック条件

  $\boldsymbol{M}\boldsymbol{J}\boldsymbol{M}^{\mathrm{T}} = \boldsymbol{J}$

$\Rightarrow$

位相空間体積保存

$\det \boldsymbol{M} = 1$

1. 剛体分子の定温シンプレクティック分子動力学シミュレーション法の開発

H. Okumura, S.G. Itoh & Y.O., *J. Chem. Phys.* **126**, 084103 (17 pages) (2007).

能勢・Poincaré熱浴＋シンプレクティック剛体MD

分子動力学シミュレーションの時間ステップを
$\Delta t = 4$ fsec ぐらいまで大きく取れる。

カノニカルMD、剛体分子MDの発展

	カノニカル	剛体分子
非シンプレクテック 位相空間体積非保存	能勢の熱浴（1984） 予測子・修正子法 能勢・Hoover熱浴 Martynaら（1996）	４元数 予測子・修正子法
非シンプレクテック 位相空間体積保存	――	４元数 松林、中原（1999）
シンプレクテック 位相空間体積保存	能勢・Poincaré熱浴 Bondら(陰的1999) 能勢（陽的2001）	４元数 Millerら（2002）

本研究　能勢・Poincaré熱浴
Millerらの剛体MD　} 組み合わせ　初めて

能勢・Poincaré熱浴＋シンプレクティック剛体MD

ハミルトニアン

$$H = s\left[\sum_i \frac{\boldsymbol{p}'^2_i}{2m_i s^2} + \sum_i \frac{1}{8s^2}\boldsymbol{\pi}'^{\mathrm{T}}_i \boldsymbol{S}(\boldsymbol{q}_i)\boldsymbol{D}_i\boldsymbol{S}^{\mathrm{T}}(\boldsymbol{q}_i)\boldsymbol{\pi}'_i + E(\boldsymbol{r},\boldsymbol{q}) + \frac{P_S^{\,2}}{2Q} + gkT_0 \ln s - H_0\right]$$

運動方程式

$$\dot{\boldsymbol{r}}_i = \frac{\boldsymbol{p}_i}{m} \qquad \dot{\boldsymbol{p}}_i = \boldsymbol{F}_i - \frac{\dot{s}}{s}\boldsymbol{p}_i$$

$$\dot{\boldsymbol{q}}_i = \frac{1}{2}\boldsymbol{S}(\boldsymbol{q}_i)\boldsymbol{\omega}_i^{(4)} \qquad I_i\dot{\omega}_i = \boldsymbol{N}_i - \omega_i \times \left(I_i\omega_i\right) - \frac{\dot{s}}{s}I_i\boldsymbol{\omega}_i$$

$$\dot{s} = s\frac{P_s}{Q} \qquad \dot{P}_s = \sum_i \frac{\boldsymbol{p}_i^2}{m} + \sum_i \boldsymbol{\omega}_i^{\mathrm{T}} I_\iota \boldsymbol{\omega}_i - gkT_0$$

能勢・Poincaré熱浴＋シンプレクティック剛体MD

ハミルトニアンの分割

$$H = \underbrace{s\left[\sum_i \frac{\boldsymbol{p}'^2_i}{2ms^2} + \sum_i \frac{1}{8I_1 s^2}\left(\boldsymbol{\pi}'^{\mathrm{T}}_i \mathbf{P}_1 \boldsymbol{q}_i\right)^2 + gkT_0 \ln s - H_0\right]}_{H_1}$$
$$+ \underbrace{\sum_i \frac{1}{8I_2 s}\left(\boldsymbol{\pi}'^{\mathrm{T}}_i \mathbf{P}_2 \boldsymbol{q}_i\right)^2}_{H_2} + \underbrace{\sum_i \frac{1}{8I_3 s}\left(\boldsymbol{\pi}'^{\mathrm{T}}_i \mathbf{P}_3 \boldsymbol{q}_i\right)^2}_{H_3} + \underbrace{sE(\boldsymbol{r},\boldsymbol{q})}_{H_4} + \underbrace{\frac{sP_s^2}{2Q}}_{H_5}$$

時間発展演算子の分割

$$\exp\left[D_H \Delta t\right] = \exp\left[D_{H5}\frac{\Delta t}{2}\right]\exp\left[D_{H4}\frac{\Delta t}{2}\right]\exp\left[D_{H3}\frac{\Delta t}{2}\right]\exp\left[D_{H2}\frac{\Delta t}{2}\right]\exp\left[D_{H1}\Delta t\right]$$
$$\times \exp\left[D_{H2}\frac{\Delta t}{2}\right]\exp\left[D_{H3}\frac{\Delta t}{2}\right]\exp\left[D_{H4}\frac{\Delta t}{2}\right]\exp\left[D_{H5}\frac{\Delta t}{2}\right] + O\left(\Delta t^3\right)$$

3. 水分子系への応用

水分子: 80分子、TIP3Pモデル
温度: 300 K, 密度: 0.997 g/cm^3
周期境界条件
静電力の計算: Ewald法
計算時間: 1.5ns
時間ステップ: Δt = 2fs, 3fs, 4fs, 5fs

a) 能勢・Poincaré熱浴＋シンプレクティック剛体MD
(Miller et al. (2002))

b) 能勢・Poincaré熱浴＋非シンプレクティック剛体MD
(Matubayasi & Nakahara (1999))

c) 能勢・Hoover熱浴＋シンプレクティック剛体MD

d) 能勢・Hoover熱浴＋非シンプレクティック剛体MD

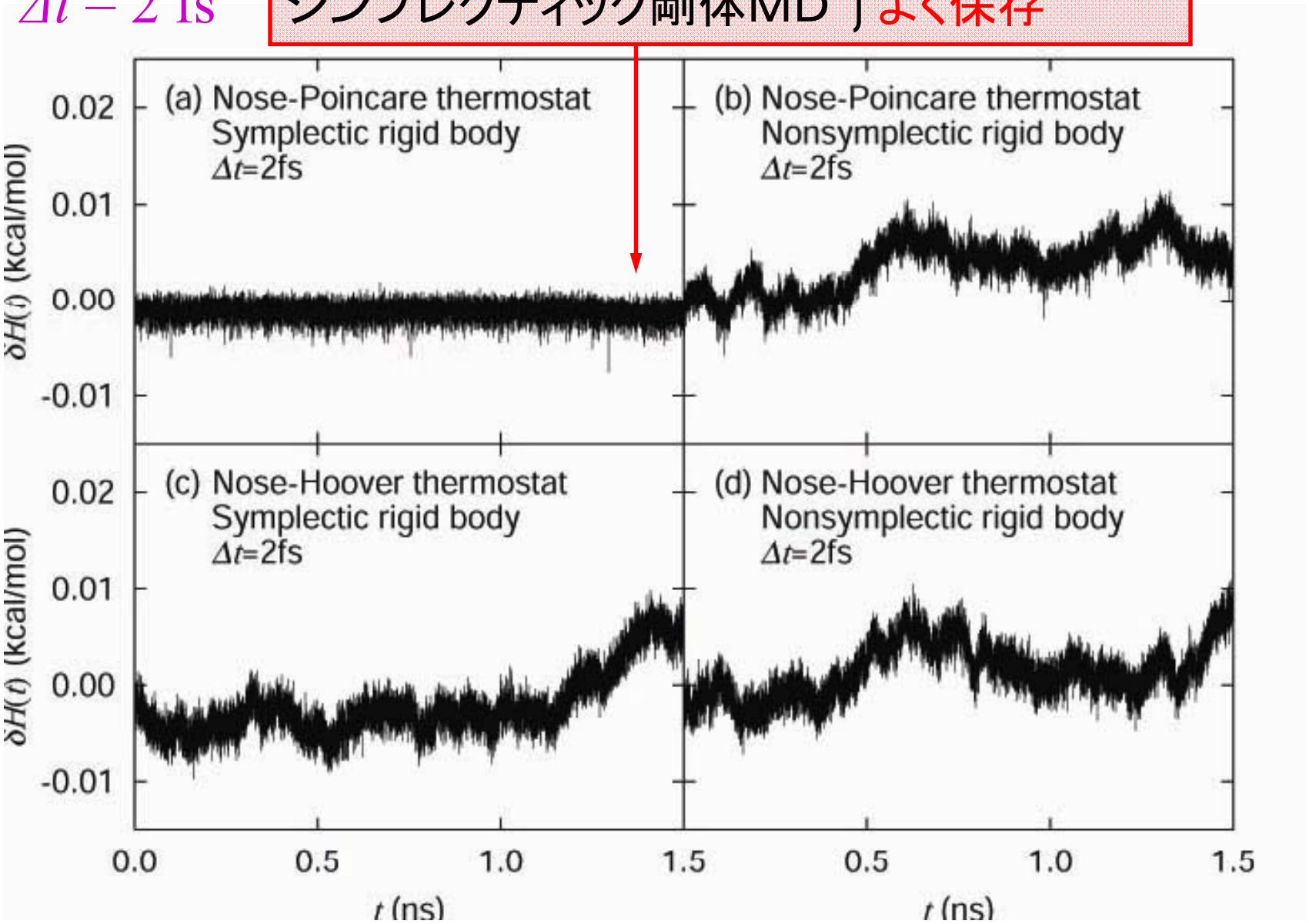
結果

$\Delta t = 2$ fs

能勢・Poincaré熱浴＋シンプレクティック剛体MD } ハミルトニアンよく保存

シンプレクティック　非シンプレクティック

熱浴



剛体　　シンプレクティック　　非シンプレクティック

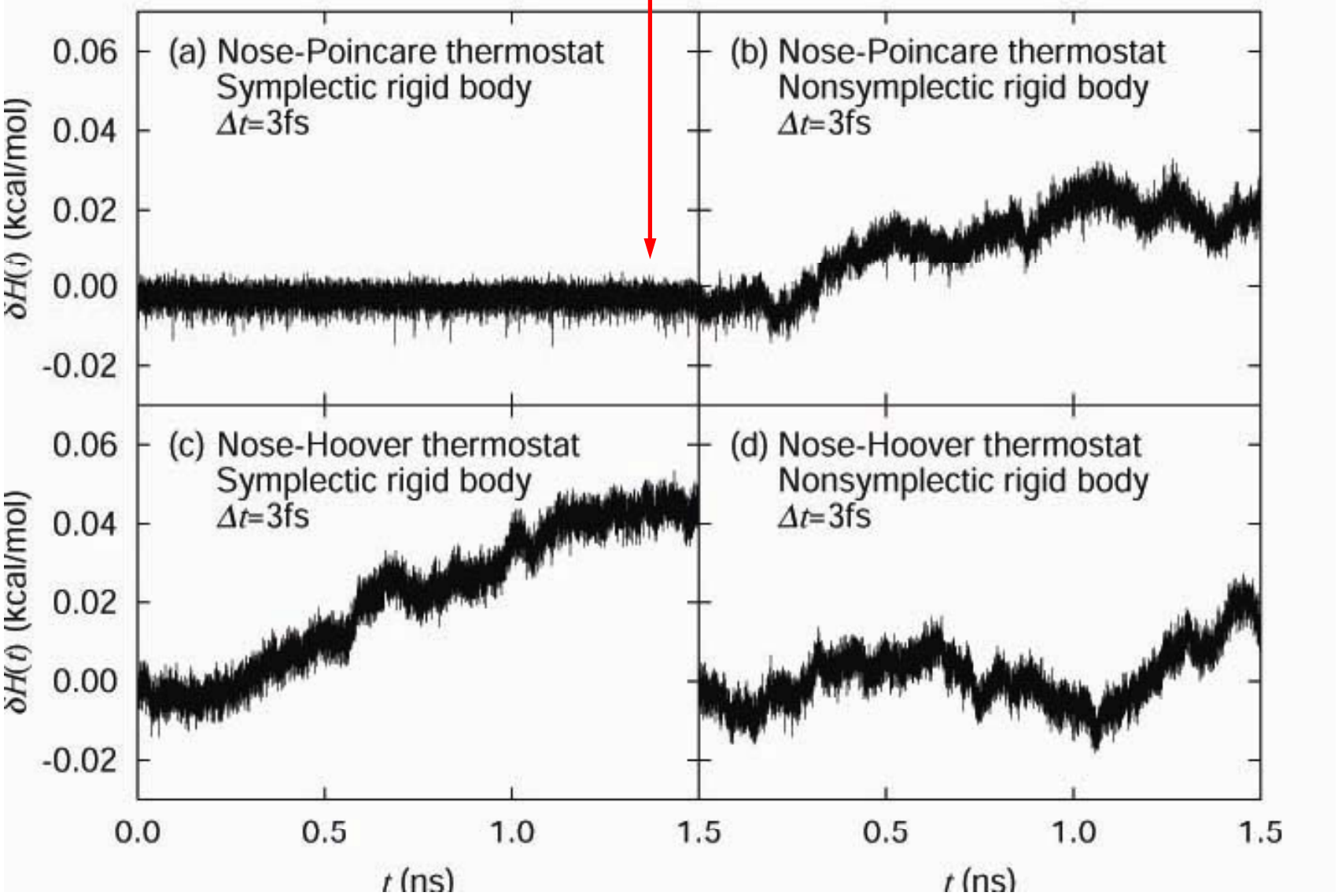
結果

$\Delta t = 3$ fs

能勢・Poincaré熱浴＋シンプレクティック剛体MD } ハミルトニアンよく保存

シンプレクティック　非シンプレクティック

熱浴



剛体　　シンプレクティック　　非シンプレクティック

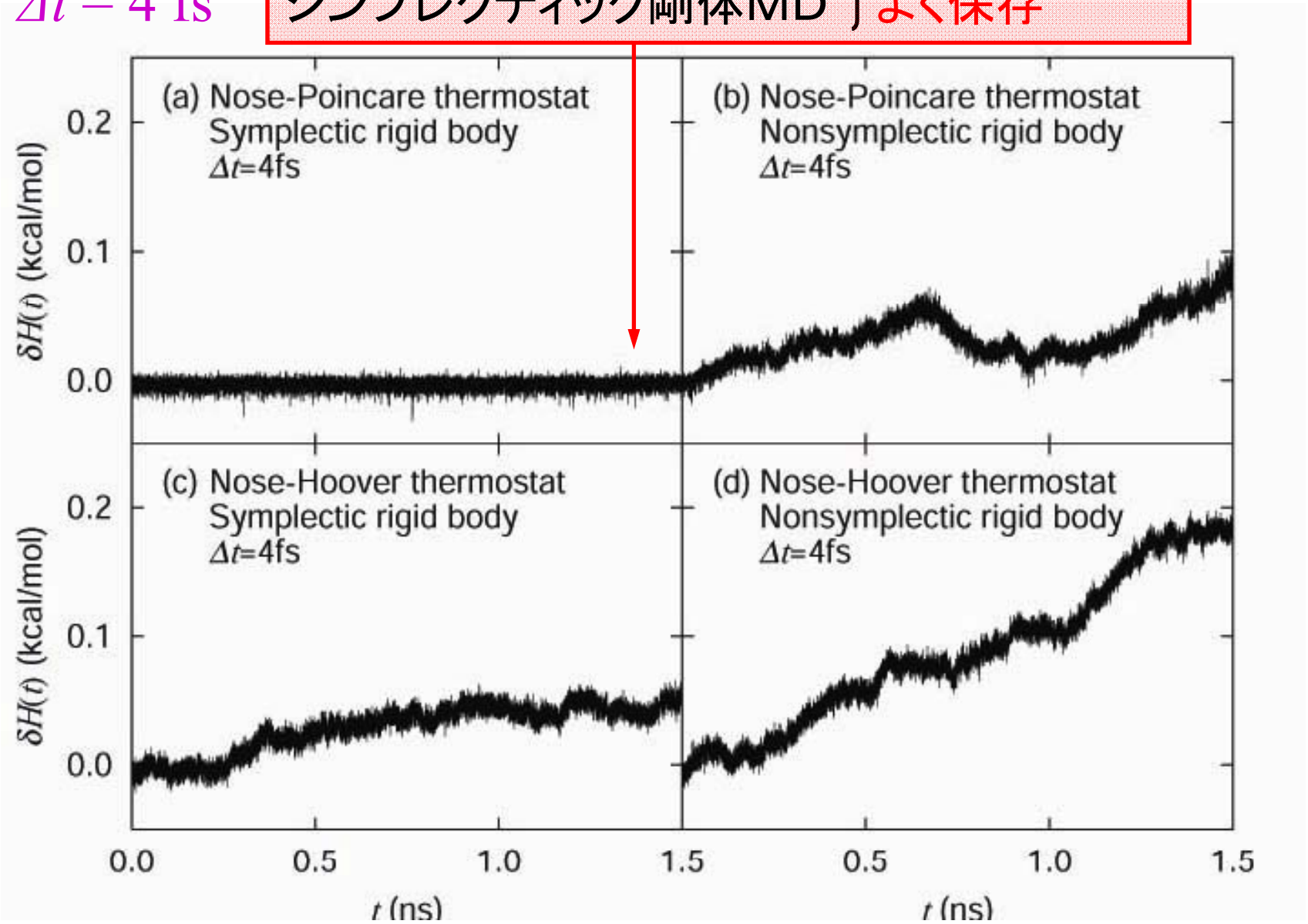
結果

$\Delta t = 4$ fs

能勢・Poincaré熱浴＋シンプレクティック剛体MD } ハミルトニアンよく保存

シンプレクティック　非シンプレクティック

熱浴



剛体　　シンプレクティック　　非シンプレクティック

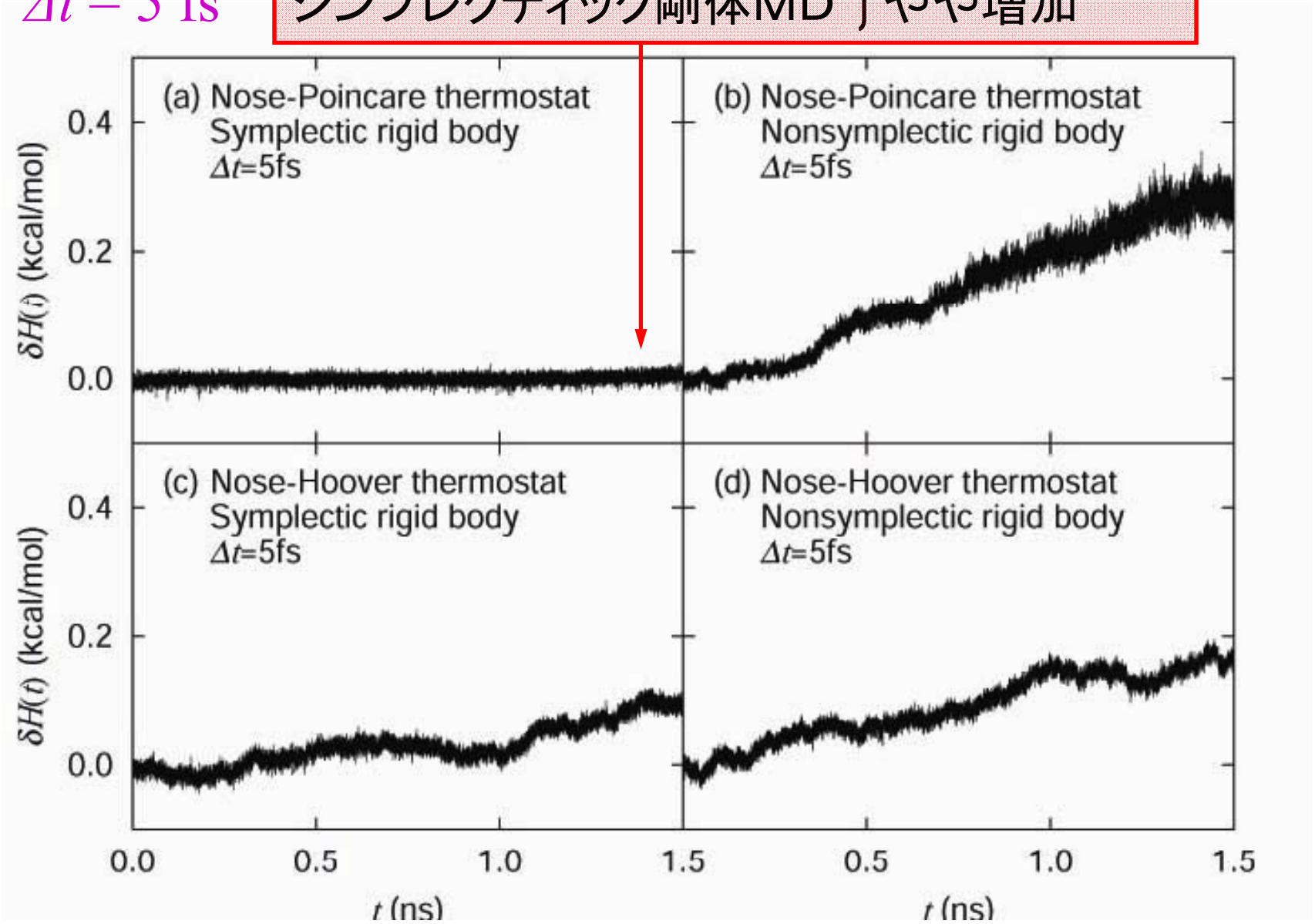
結果

$\Delta t = 5$ fs

能勢・Poincaré熱浴＋シンプレクティック剛体MD ｝ハミルトニアンやや増加

シンプレクティック　非シンプレクティック

熱浴



剛体　　シンプレクティック　　非シンプレクティック

剛体系のシンプレクティック法のまとめ

- カノニカル(NVT)アンサンブルにおける
  剛体分子の陽的シンプレクティックMD

- 能勢・Poincaré熱浴＋シンプレクティック剛体MD
  初めて

- シンプレクティックMDの利点
  ハミルトニアンに近い保存量が存在
  ハミルトニアンよく保存：$\Delta t = 4$ fs までO.K.

- 従来の非シンプレクティックな方法
  典型的な時間ステップ $\Delta t = 0.5 \sim 2$ fs

- ＋Andersenの定圧法→定温定圧アンサンブルでも可

H. Okumura, S.G. Itoh, and Y.O., *J. Chem. Phys.* **126**, 084103 (2007)

REPLICA-EXCHANGE METHOD（レプリカ交換法）

K. Hukushima & K. Nemoto, *J. Phys. Soc. Jpn.* **65**, 1604 (1996).

(EXCHANGE MONTE CARLO)

K. Hukushima, H. Takayama & K. Nemoto, *Int. J. Mod. Phys. C* **7**, 337 (1996).

(REPLICA-EXCHANGE METHOD)

For MD version, see

Y. Sugita & Y.O., *Chem. Phys. Lett*. **314**, 141 (1999).

(Replica-Exchange Molecular Dynamics: REMD)

See also:

- M. Tesi, E. van Rensburg, E. Orlandini & S. Whittington, *J. Stat. Phys*. **82**, 155 (1996). (MULTIPLE MARKOV CHAIN METHOD)
- E. Marinari, G. Parisi & J. Ruiz-Lorenzo, in *Spin Glasses and Random Fields*

  A. Young (ed) (1998) 59. (PARALLEL TEMPERING)

Replica-Exchange Method

MC: K. Hukushima & K. Nemoto, *J. Phys. Soc. Jpn*. **65**, 1604 (1996).
MD: Y. Sugita & Y.O., *Chem. Phys. Lett*. **314**, 141 (1999).

1. System

M *Non-Interacting* Replicas of the Original System at M Different Temperatures

2. Replica-Exchange

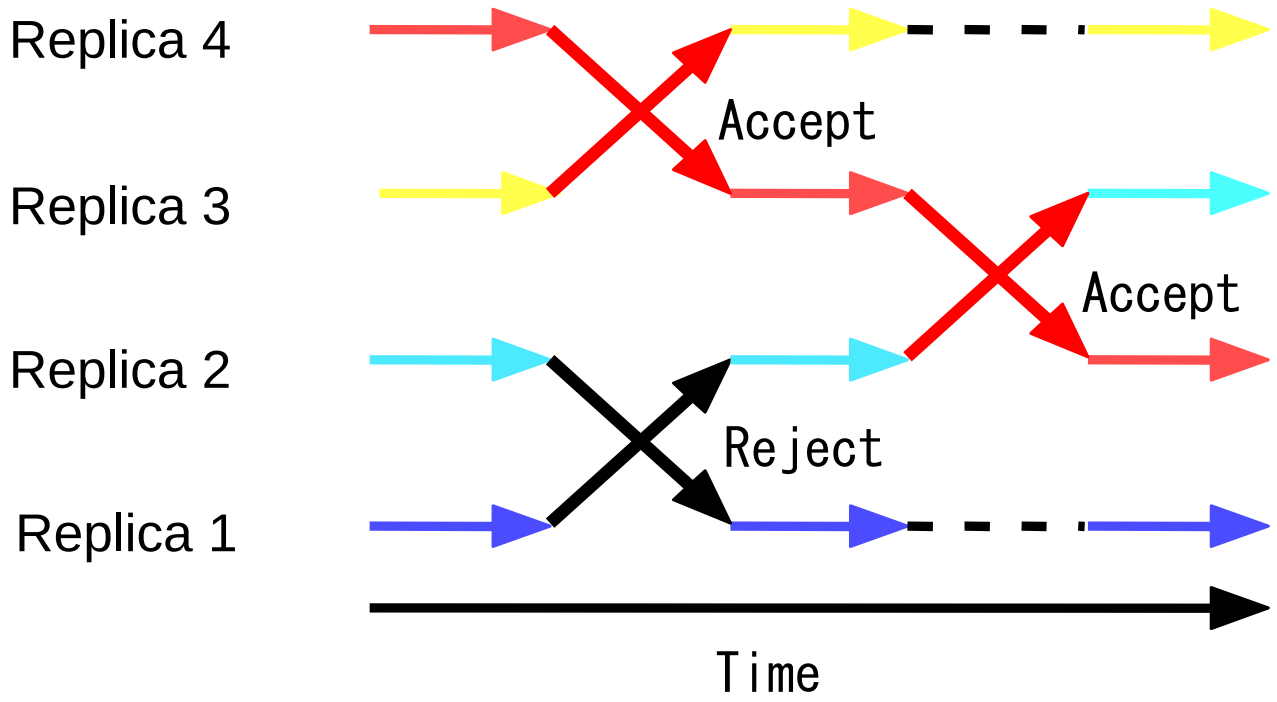
- Step 1: Independent Canonical Simulations Performed for Each Replica
- Step 2: A Pair of Replicas Corresponding to Neighboring Temperatures are Exchanged *a la* Metropolis

Repeat These 2 Steps

3. Canonical Distribution at Any Temperature

by Multiple Histogram Reweighting Techniques (WHAM)

Replica-Exchange Method (Parallel Tempering)



Particularly Suitable for Parallel Computers

Multiple-Histogram Reweighting Techniques (Weighted Histogram Analysis Method: WHAM)

A. Ferrenberg & R. Swendsen, *Phys. Rev. Lett.* **63**, 1195 (1989).
S. Kumar, D. Bouzida, R. Swendsen, P. Kollman & J. Rosenberg, *J. Comput. Chem.* **13**, 1011 (1992).

$$< A >_T = \frac{\sum_E A(E) n(E) e^{-\beta E}}{\sum_E n(E) e^{-\beta E}}$$

Given *M* set of histograms *Nm(E)*, the following WHAM equations are solved iteratively for density of states *n(E)* and dimensionless Helmholtz free energy *fm* :

$$n(E) = \frac{\sum_{m=1}^{M} N_m(E)}{\sum_{m=1}^{M} n_m e^{f_m - \beta_m E}}, \text{ where } e^{-f_m} = \sum_E n(E) e^{-\beta_m E}.$$

Multidimensional Replica-Exchange Method

Y. Sugita, A. Kitao & Y.O., *J. Chem. Phys.* **113**, 6042 (2000).

1. System

M *Non-Interacting* Replicas of the Original System at M Different Sets of Temperatures and Parameters

2. Replica-Exchange

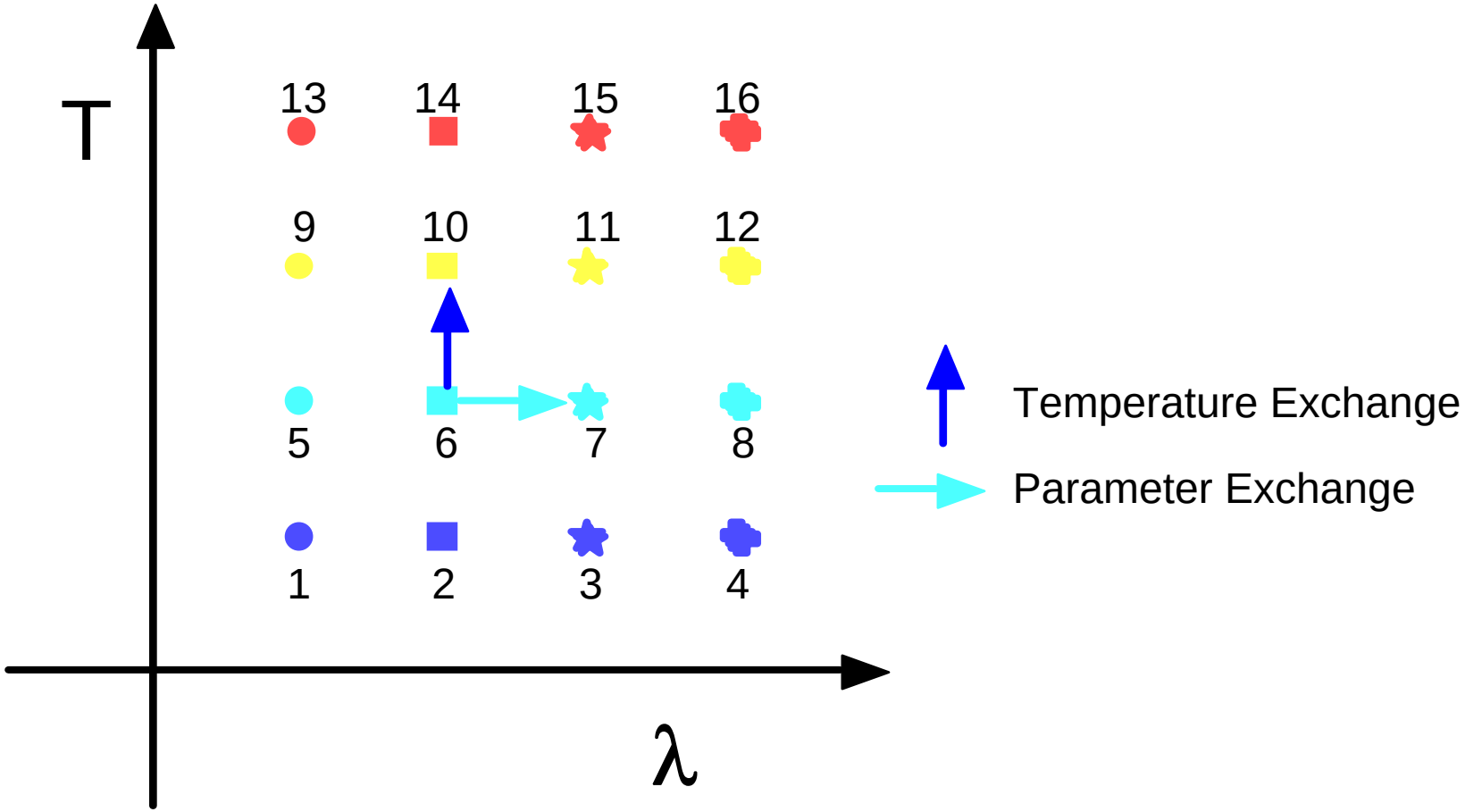
- Independent Canonical Simulations Performed for Each Replica
- A Pair of Replicas Corresponding to Neighboring Temperatures or Parameters are Exchanged

Repeat These 2 Steps

3. Canonical Distribution at Any Temperature

by Multiple Histogram Reweighting Techniques (WHAM)

Multidimensional Replica-Exchange Method



Multidimensional Replica-Exchange Method

Y. Sugita, A. Kitao & Y.O., *J. Chem. Phys.* **113**, 6042 (2000).

Special Cases of MREM:

parameter exchange without *temperature* exchange

Generalized Parallel Sampling (*q*-exchange in Tsallis)

T.W. Whitfield, L. Bu & J.E. Straub, *Physica A* **305**, 157 (2002).

Hamiltonian Replica-Exchange

H. Fukunishi, O. Watanabe & S. Takada, *J. Chem. Phys.* **116**, 9058 (2002).

Replica-Exchange Method Using the Generalized Effective Potential

S. Jang, S. Shin & Y. Pak, *Phys. Rev. Lett.* **91**, 058305 (2003).

Model Hopping

W. Kwak & U.H.E. Hansmann, *Phys.Rev. Lett.* **95**, 138102 (2005).

Development of New Generalized-Ensemble Algorithms

REVIEWS: A. Mitsutake, Y. Sugita, & Y.O., *Biopolymers* **60**, 96 (2001);
Y.O., *J. Mol. Graphics Modell.* **22**, 425 (2004);
Y. Sugita, A. Mitsutake, & Y.O., in *Lecture Notes in Physics*,
W. Janke (ed.) (Springer-Verlag, 2008) pp. 369-407.

Combination of Replica-Exchange Method (REM) and
Multicanonical Algorithm (MUCA)

1. **Replica-Exchange Multicanonical Algorithm (REMUCA)**

Y. Sugita & Y.O., *Chem. Phys. Lett.* 329, 261 (2000).

A. Mitsutake, Y. Sugita, & Y.O., *J. Chem. Phys.* 118, 6664; 6676 (2003).

- Multicanonical weight factor is determined from a short REM simulation by multiple histogram techniques

2. **Multicanonical Replica-Exchange Method (MUCAREM)**

Y. Sugita & Y.O., *Chem. Phys. Lett.* 329, 261 (2000).

A. Mitsutake, Y. Sugita, & Y.O., *J. Chem. Phys.* 118, 6664; 6676 (2003).

- Multicanonical simulations are performed for each replica and a pair of replicas are exchanged

Development of New Generalized-Ensemble Algorithms

REVIEWS: A. Mitsutake, Y. Sugita, & Y.O., *Biopolymers* **60**, 96 (2001);
Y.O., *J. Mol. Graphics Modell.* **22**, 425 (2004);
Y. Sugita, A. Mitsutake, & Y.O., in *Lecture Notes in Physics*,
W. Janke (ed.) (Springer-Verlag, 2008) pp. 369-407.

Combination of Replica-Exchange Method (REM) and
Simulated Tempering (ST)

3. **Replica-Exchange Simulated Tempering (REST)**

A. Mitsutake & Y.O., *Chem. Phys. Lett.* 332, 131 (2000).

- Simulated tempering weight factor is determined from a short REM simulation by multiple histogram techniques

4. **Simulated Tempering Replica-Exchange Method (STREM)**

A. Mitsutake & Y.O., *J. Chem. Phys.* 121, 2491 (2004).

- Simulated tempering simulations are performed for each replica and a pair of replicas are exchanged

See also:

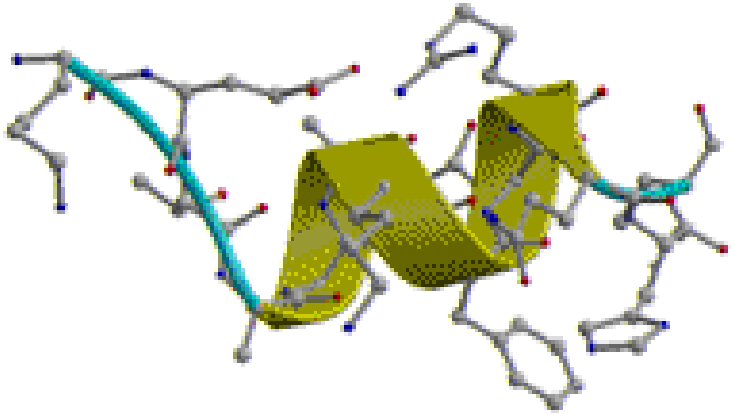
M.K. Fenwick & F.A. Escobedo, *J. Chem. Phys.* 119, 11998 (2003).

KEY ELEMENT: Multiple-Histogram Reweighting Techniques (WHAM)

Given *M* set of histograms *Nm(E)*, the following WHAM equations are solved iteratively for density of states *n(E)* and dimensionless Helmholtz free energy f_m (the former gives the multicanonical weight factor and the latter gives the simulated tempering weight factor):

$$n(E) = \frac{\sum_{m=1}^{M} N_m(E)}{\sum_{m=1}^{M} n_m e^{f_m - \beta_m E}}, \text{ where } e^{-f_m} = \sum_E n(E) e^{-\beta_m E}.$$

C-Peptide (N = 13): X-Ray



C-Peptide of Ribonuclease A

Amino-Acid Sequence:

Lys-Glu-Thr-Ala-Ala-Ala-Lys-Phe-Glu-Arg-

Gln-His-Met

C-Peptide of Ribonuclease A (N=13) in Water (Level 3)

Amino-Acid Sequence:

ACE-Ala-Glu-Thr-Ala-Ala-Ala-Lys-Phe-Leu-Arg-Ala-His-Ala-NME

AMBER 99 Force Field (peptide)
TIP3P (water)

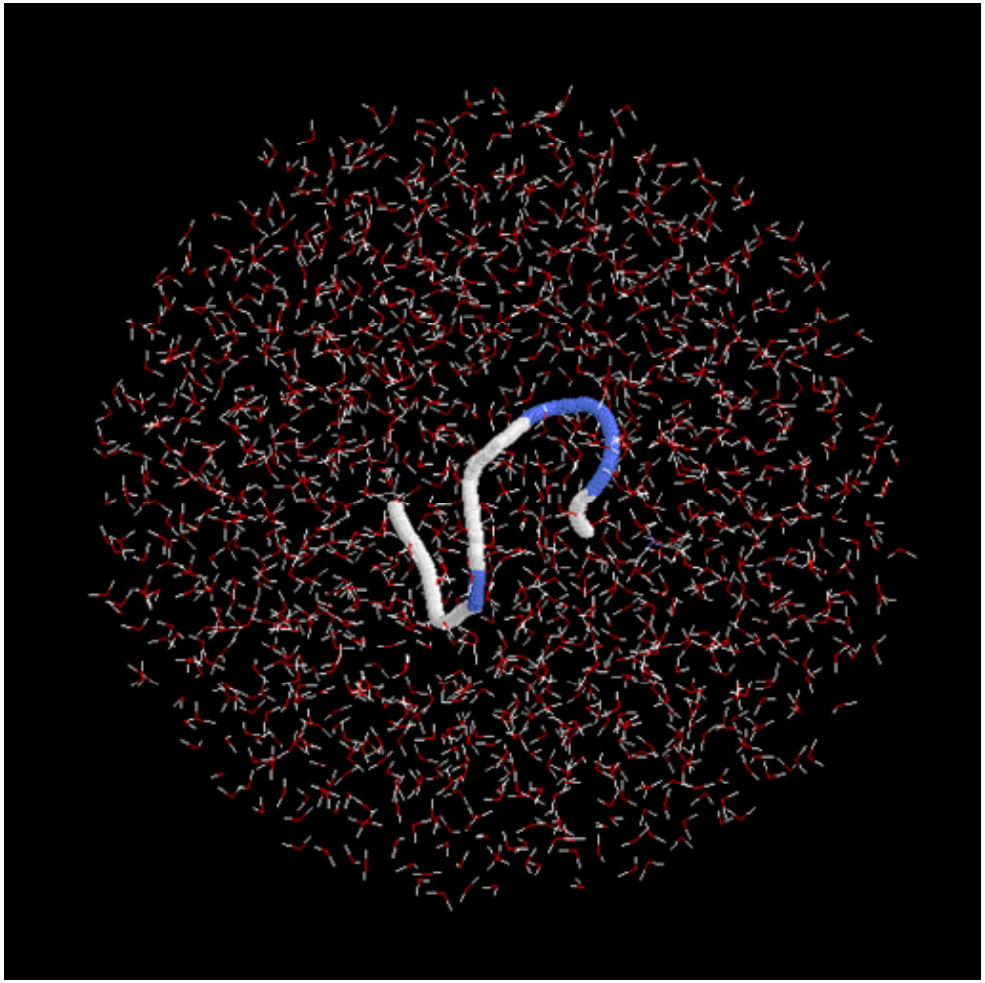
13 residue peptide

1387 Water Molecules

(R = 22 Å)

Total 4365 atoms

Initial Configuration



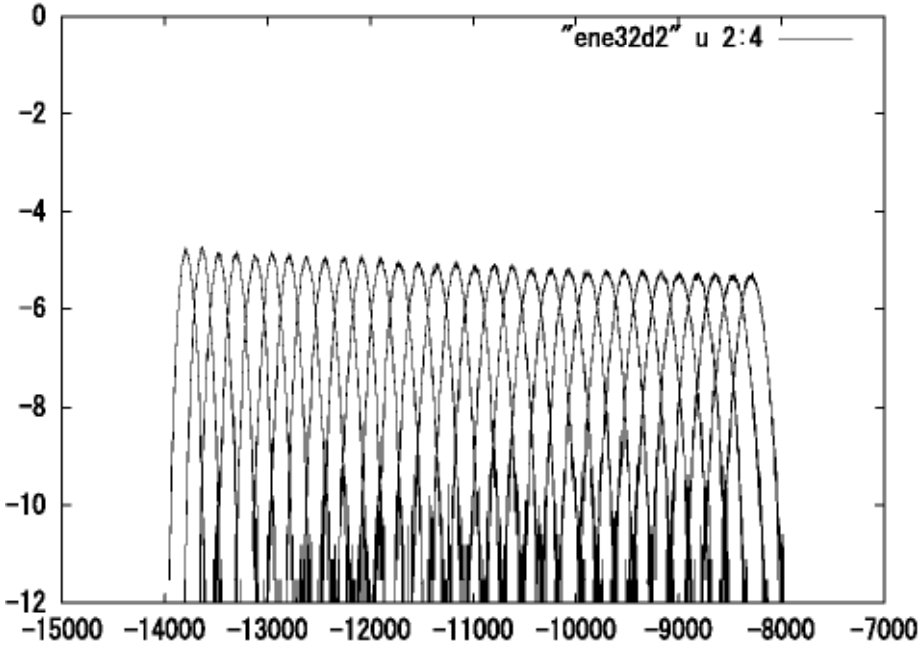
NMR Studies (Osterhout 1988)

- 50-60% helix in solution
- First three residues are distorted
- Formation of a salt bridge between Glu2 and Arg10

C-Peptide of Ribonuclease A (N=13) in Water

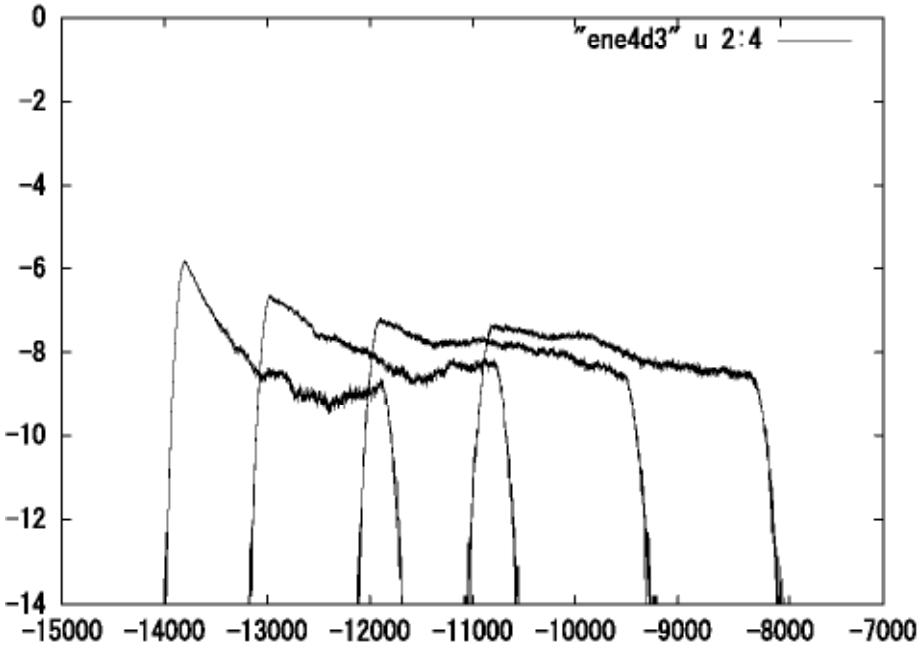
Y. Sugita & Y. O., *Biophys. J.* 88, 3180 (2005).

1. REM (32 replicas)
   100 ps X 32



# of tunneling events = 0
(-12850, -8250)

2. MUCAREM (4 replicas)
   1 ns X 4



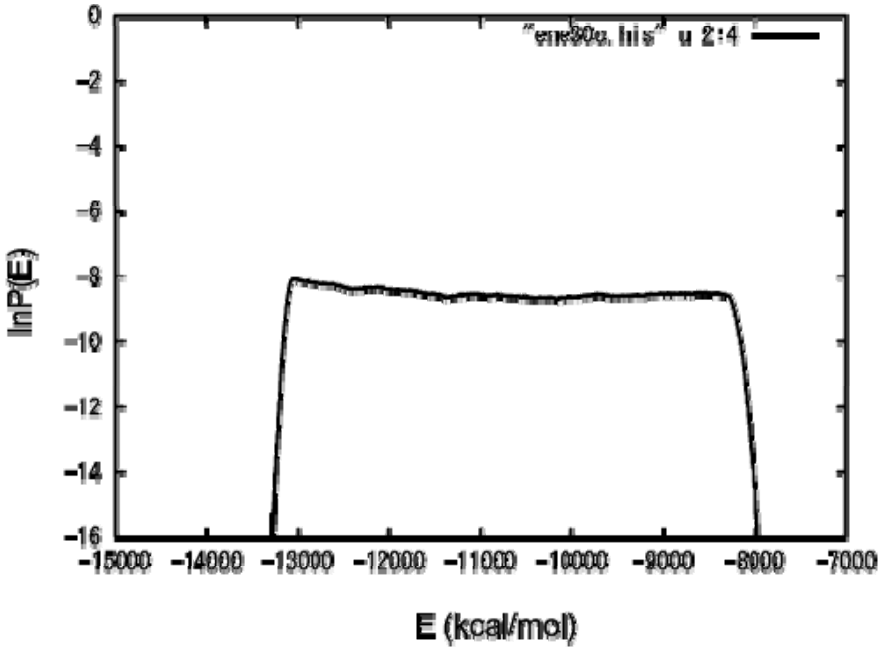
# of tunneling events = 5
(-12850, -8250)

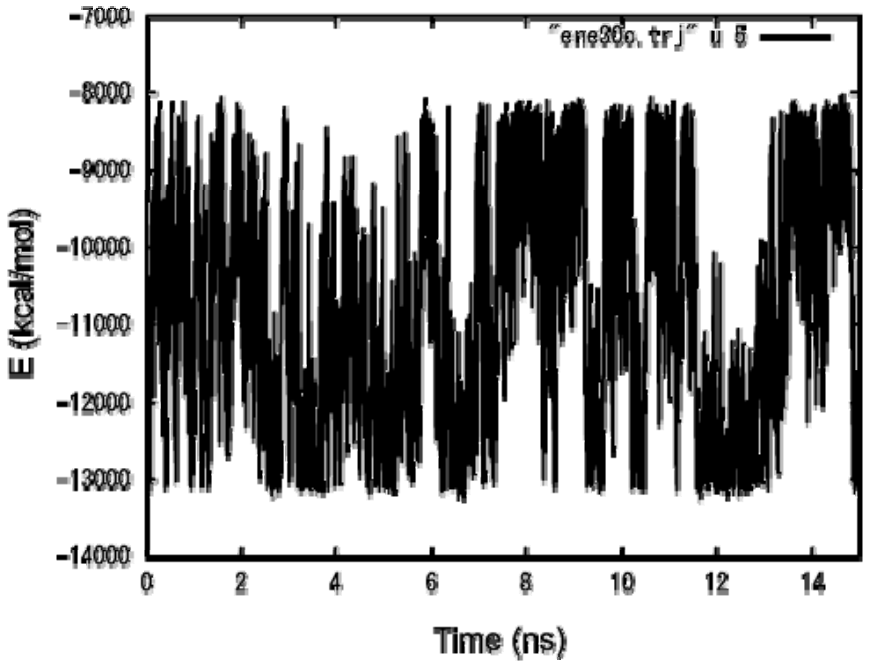
C-Peptide of Ribonuclease A (N=13) in Water

Y. Sugita & Y. O., *Biophys. J.* 88, 3180 (2005).

3. REMUCA (1 replica)
   15 ns

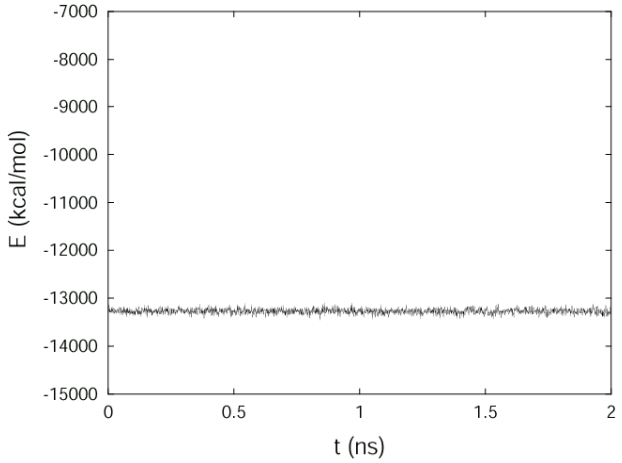
Time series of potential energy

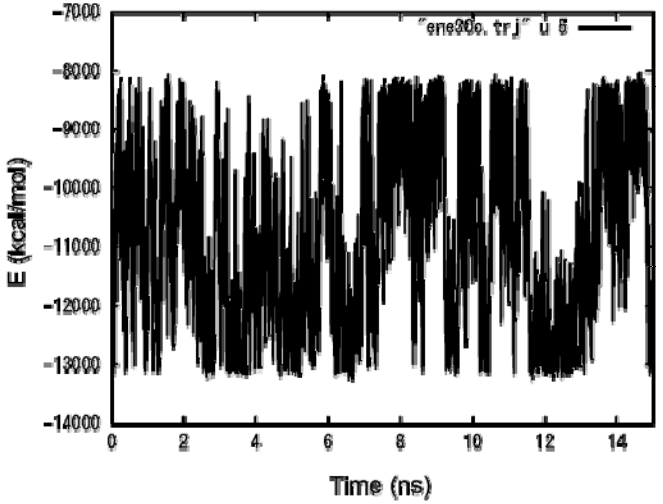




# of tunneling events = 46
(-12850, -8250)

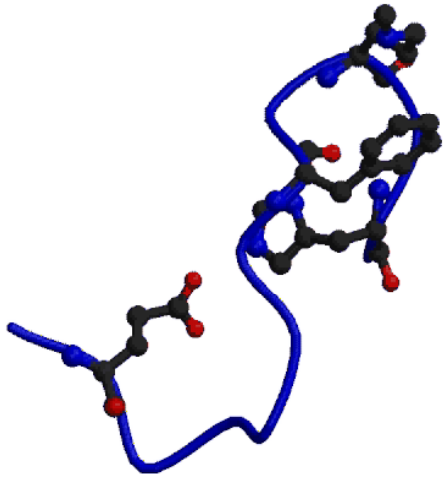
C-Peptide of Ribonuclease A (N=13) in Water

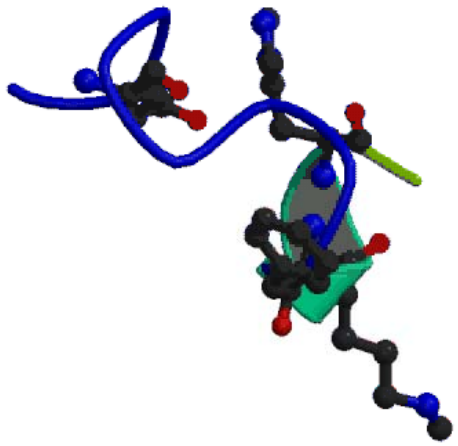




Canonical (T = 275 K)

REMUCA

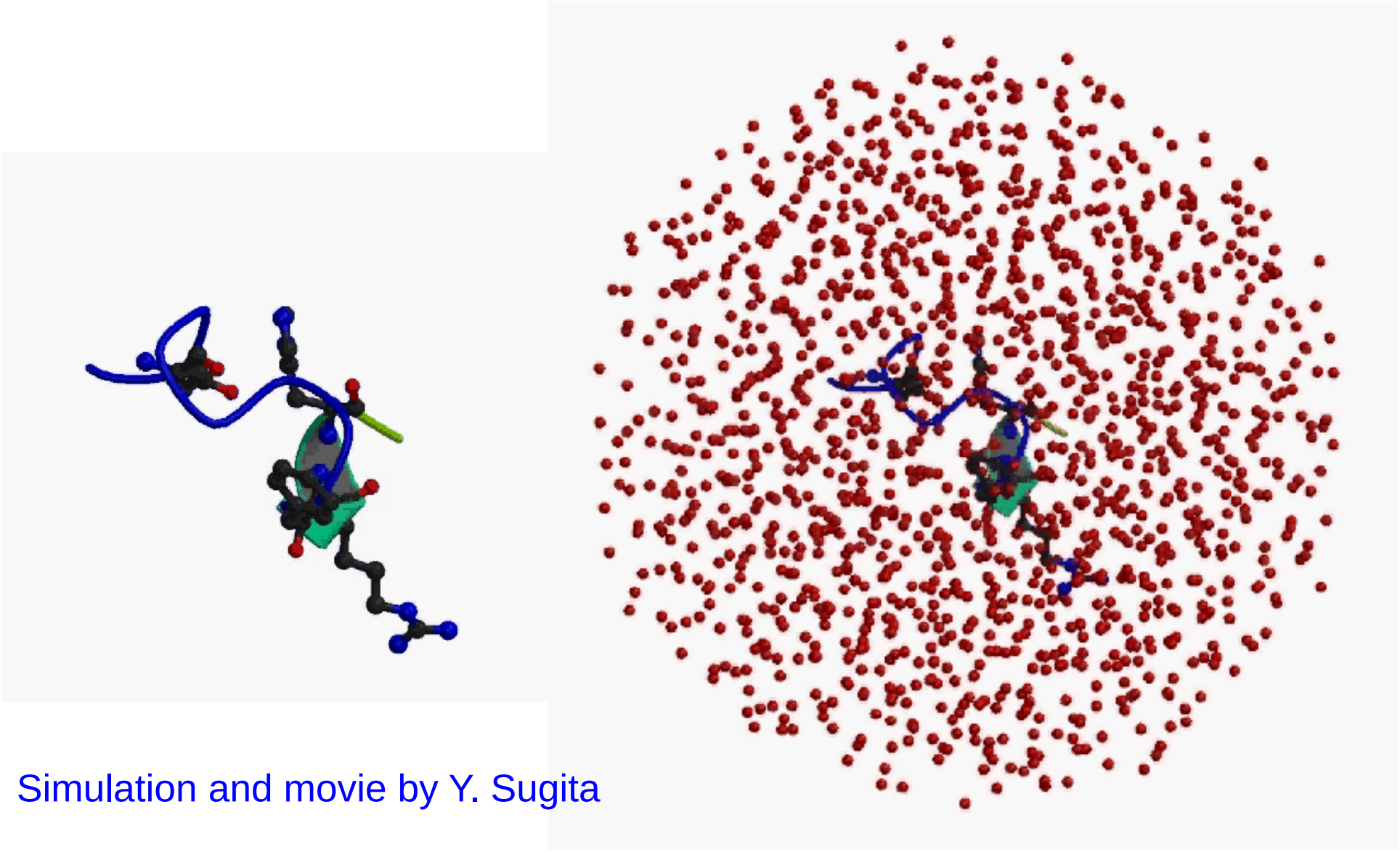




Simulation and movie by Y. Sugita

C-Peptide of Ribonuclease A (N=13) in Water

REMUCA Simulation with AMBER (parm99)



Simulation and movie by Y. Sugita

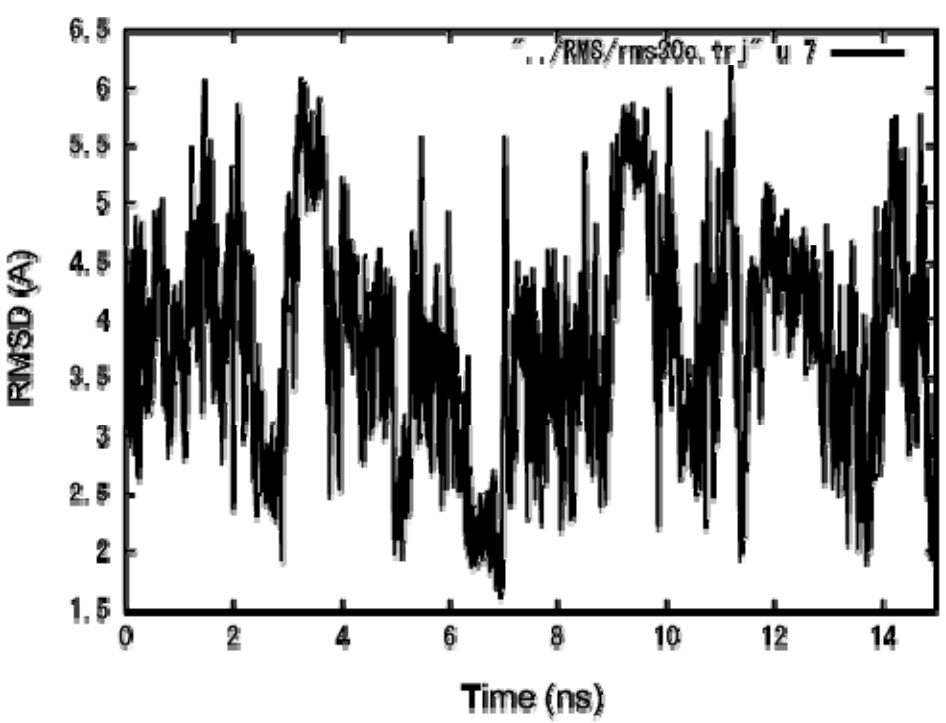
C-Peptide of Ribonuclease A (N=13) in Water

Y. Sugita & Y. O., *Biophys. J.* 88, 3180 (2005).

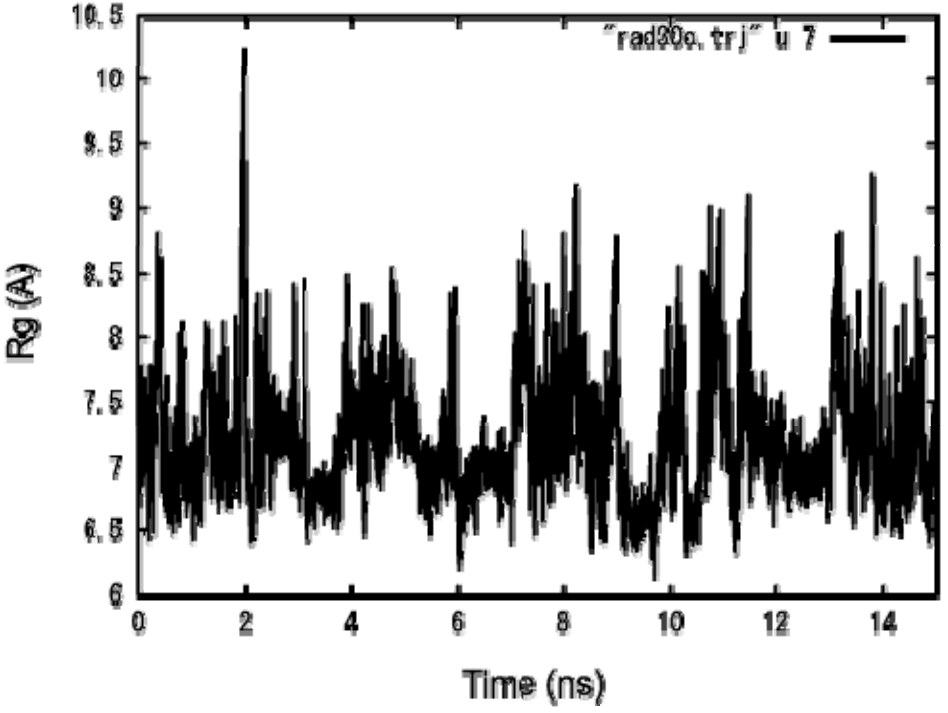
RMSD from “native structure”

Rg: radius of gyration

Time Series of RMSD

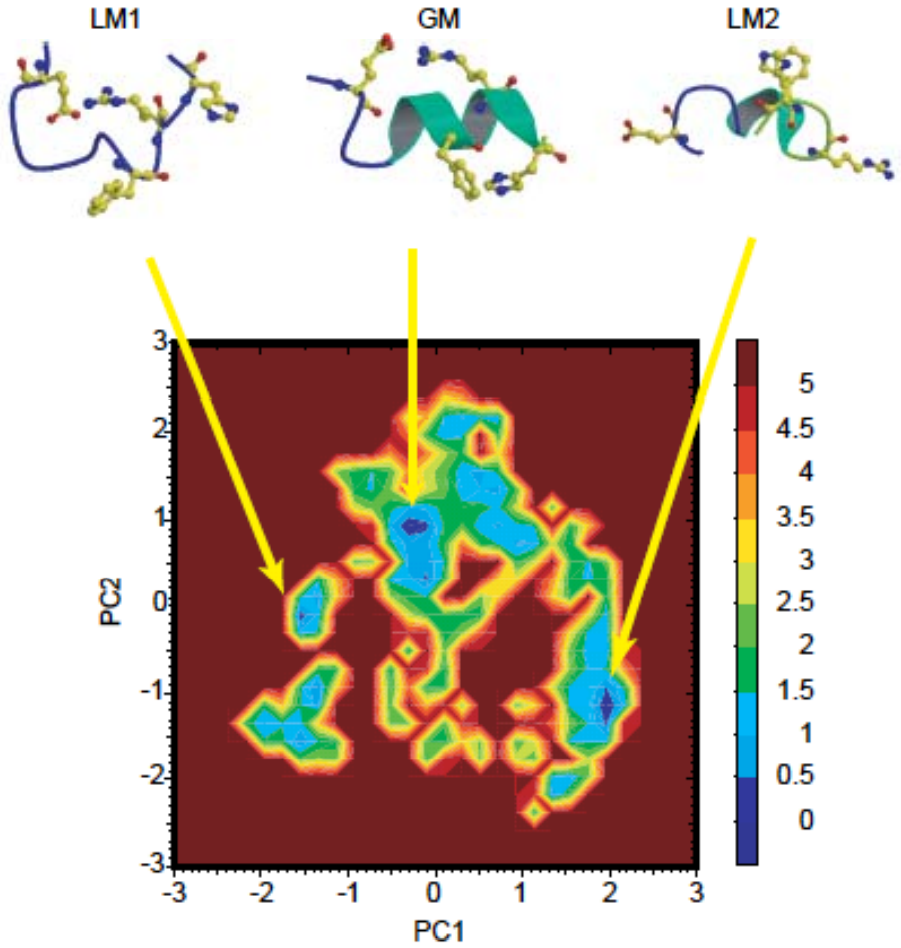


Time Series of Rg



Free Energy Landscape (C-peptide)

T = 300 K



At T = 300 K, 3 characteristic structural groups exist, among which the group of native-like structure with Glu2-Arg10 salt bridge is the global minimum in free energy.

Y. Sugita & Y. O., *Biophys. J.* 88, 3180 (2005).

G-Peptide (N=16) of Protein G in Water

Amino-Acid Sequence:

Gly-Glu-Trp-Thr-Tyr-Asp-Asp-Ala-Thr-Lys-Thr-Phe-Thr-Val-Thr-Glu

16 residue peptide

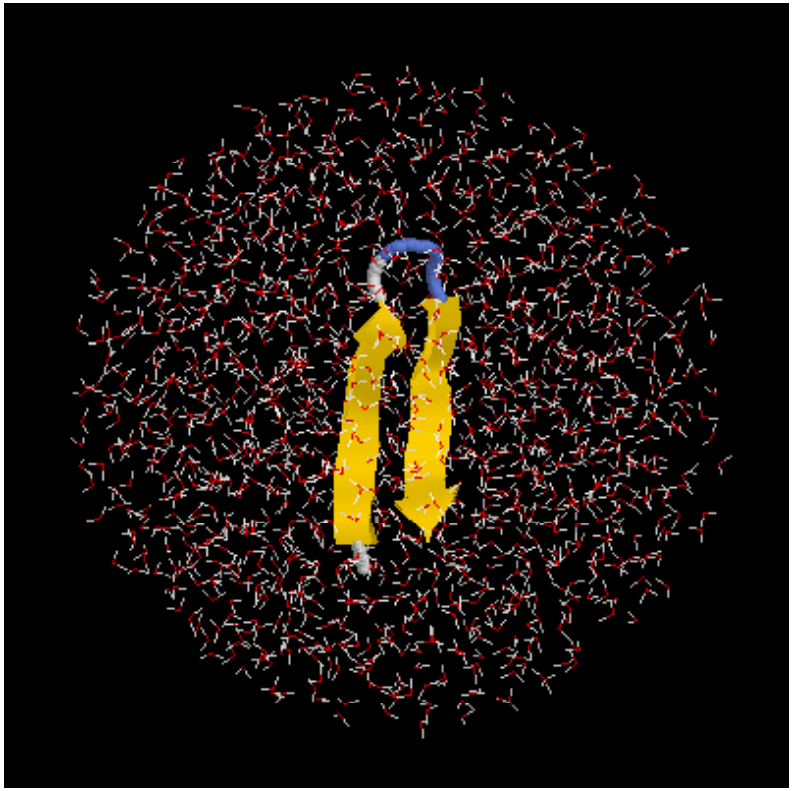
2328 TIP3P water molecules

(R = 26 Å)

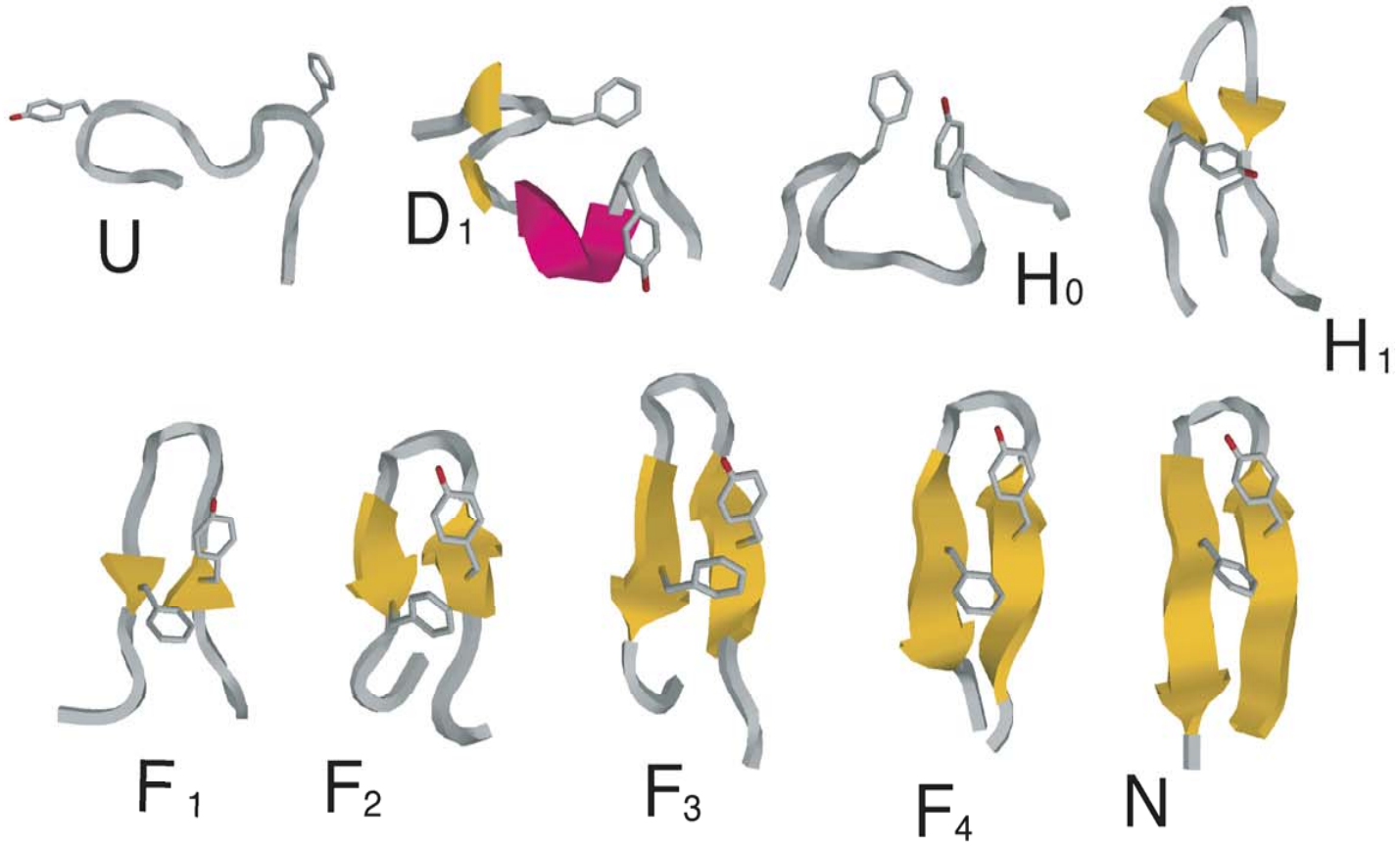
Total: 7231 atoms

- G-peptide is a C-terminal fragment (41-56 residues) of protein G B1 domain.
- This β-hairpin structure is stable in aqueous solution (F. Blanco, G. Rivas & L. Serrano, *Nature Struct. Biol.* **1**, 584 (1994); N. Kobayashi, S. Honda, H. Yoshii, H. Uedaira & E. Munekata, *FEBS Lett*. **366**, 99 (1995)).

"Native Structure" of G-Peptide



Snap-shot Structures of G-peptide observed in the Simulation



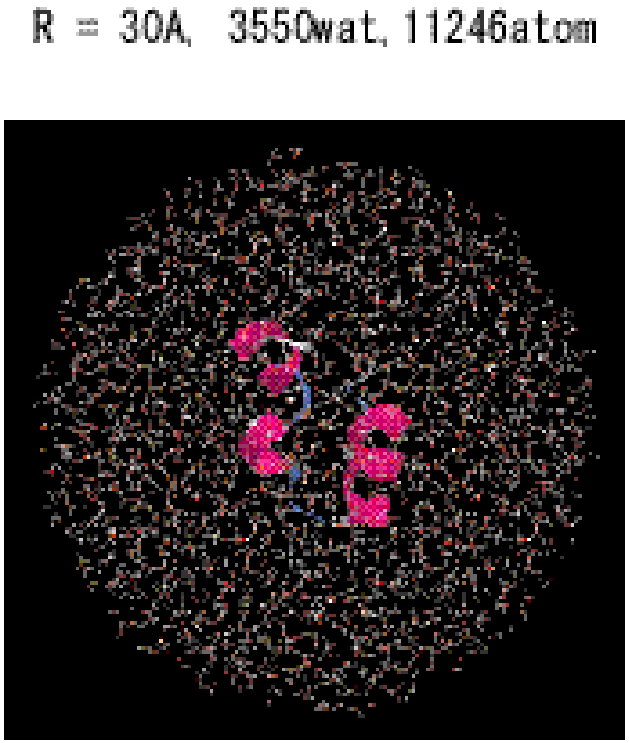
T. Yoda, Y. Sugita & Y.O., *Proteins* **66**, 846 (2007).

Structure Predictions of a Small Globular Protein

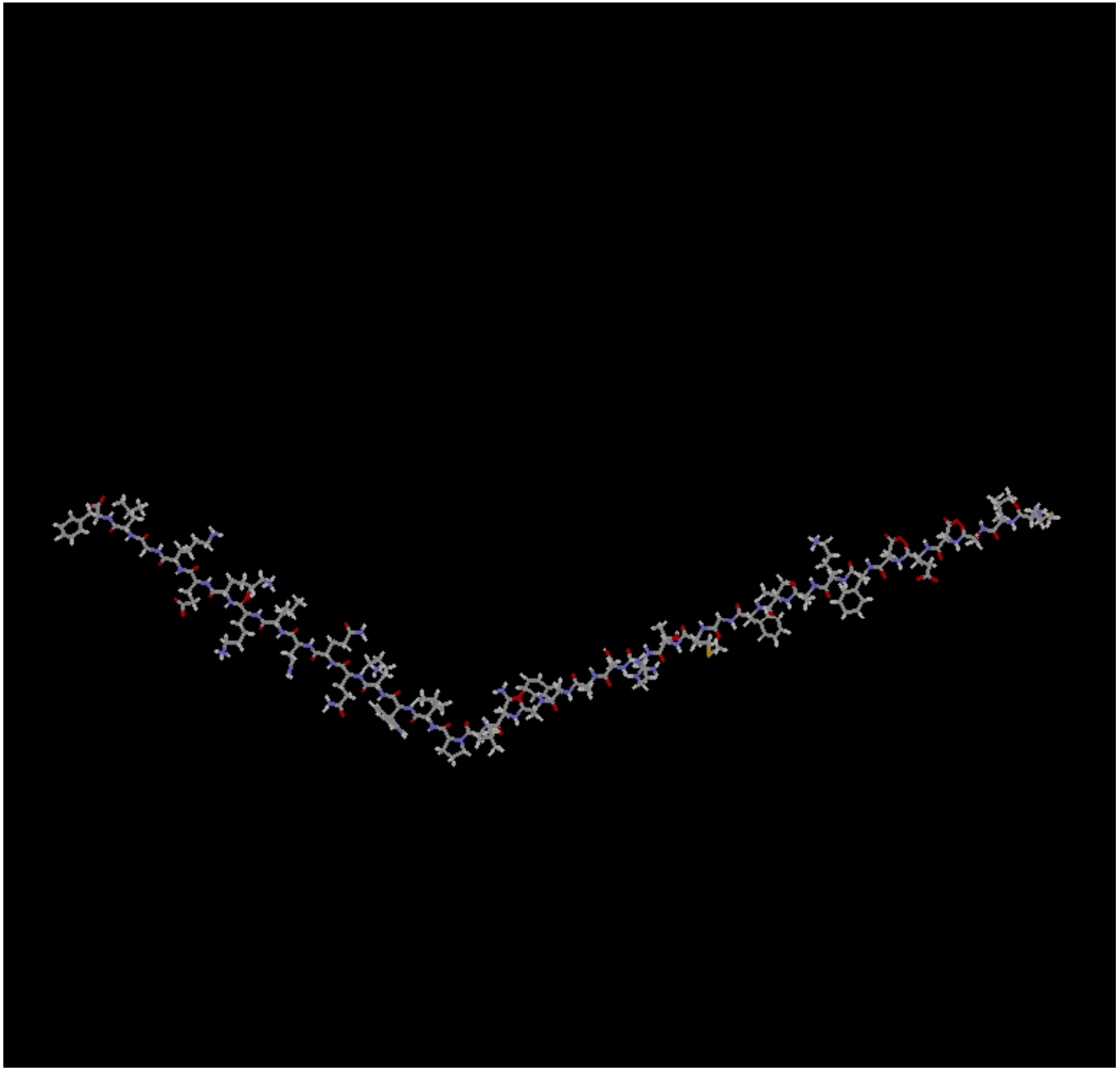
T. Yoda, Y. Sugita & Y.O., in preparation.

Challenge the prediction of the 3-dimensional structure of a small protein by MUCAREM.

Villin headpiece subdomain
(36 amino acids; 596 atoms)
sphere of water with radius 30 Å
(3513 water molecules);
Total number of atoms = 11,135



Initial Conformation

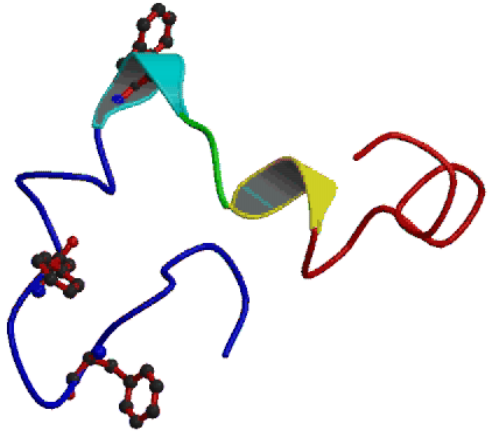


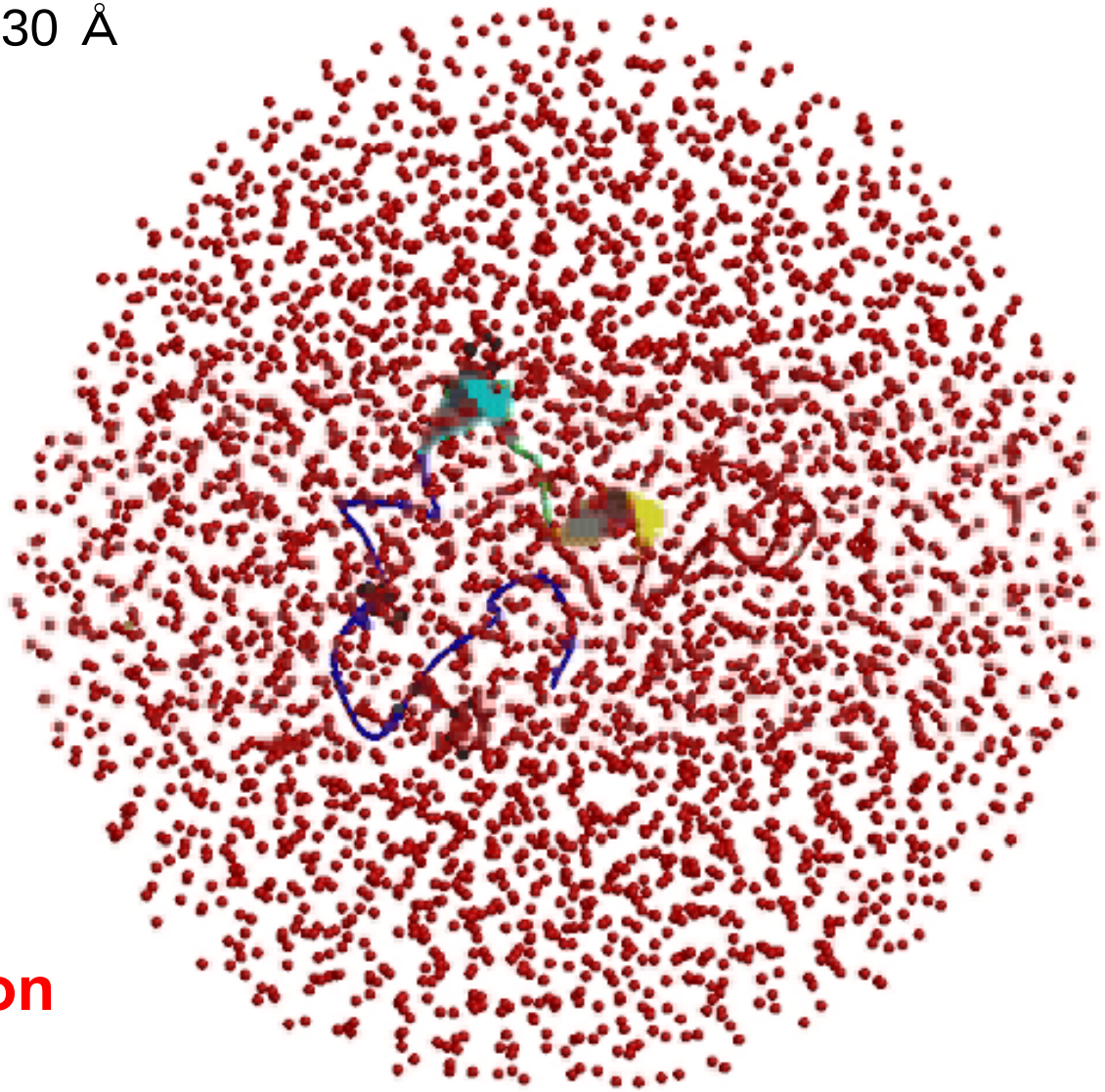
First REMD in gas phase with 96 replicas

Then REMD in water with 96 replicas

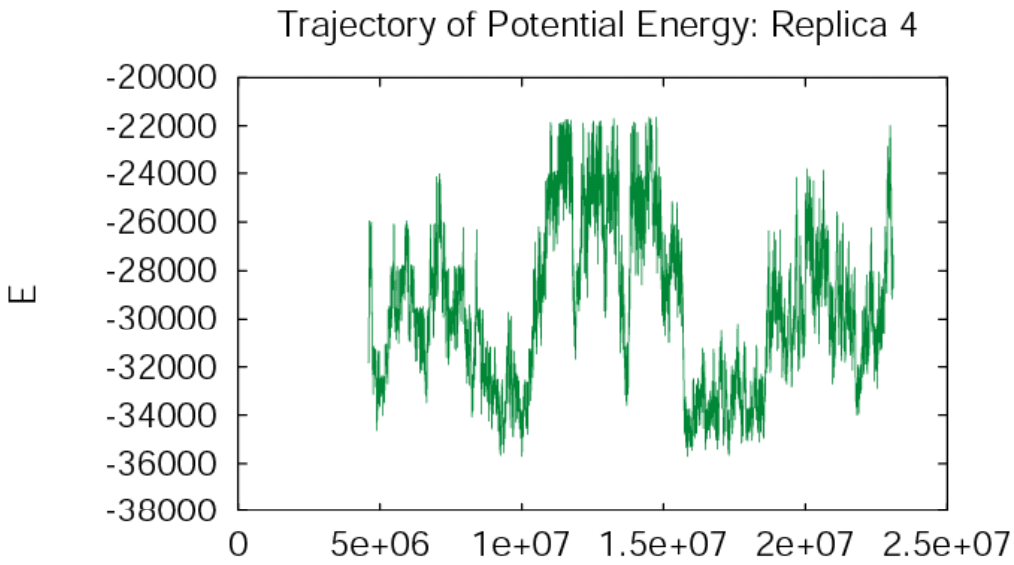
Then MUCAREM in water with 8 replicas

Villin headpiece subdomain
(36 amino acids; 596 atoms)
in sphere of water of radius 30 Å
(3513 water molecules);
altogether 11,135 atoms

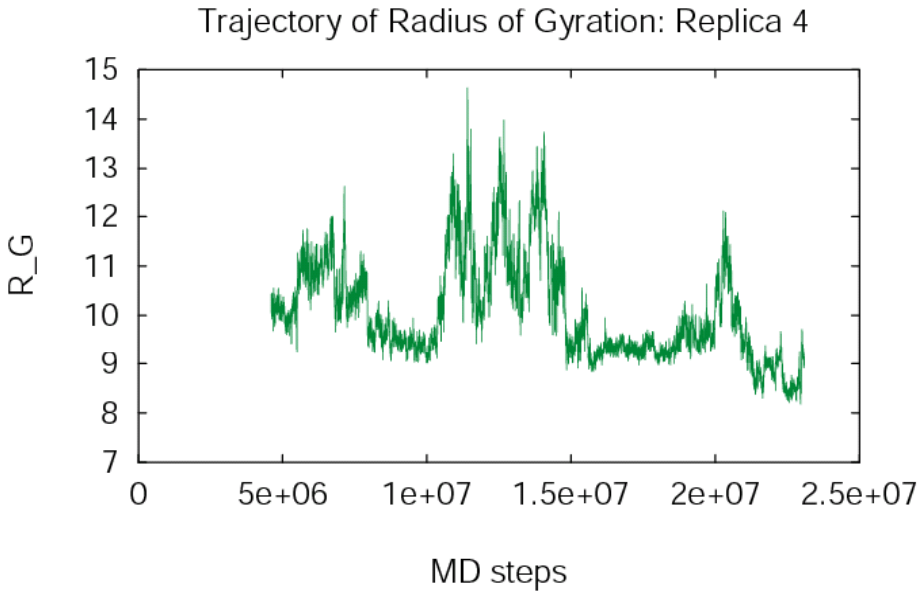


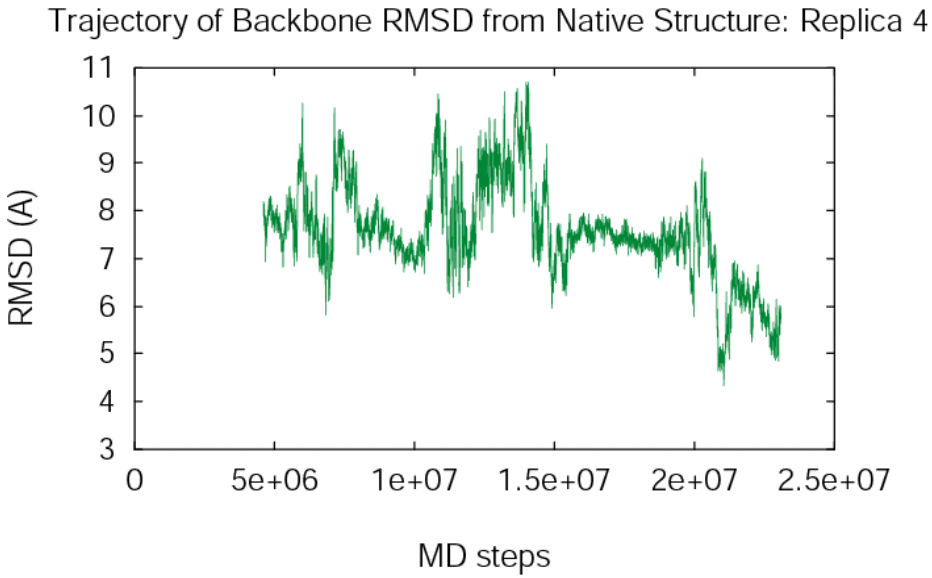


MUCAREM simulation



R_G (native) = 8.56 A





T. Yoda, Y. Sugita & Y.O., in preparation.

Native Helices:

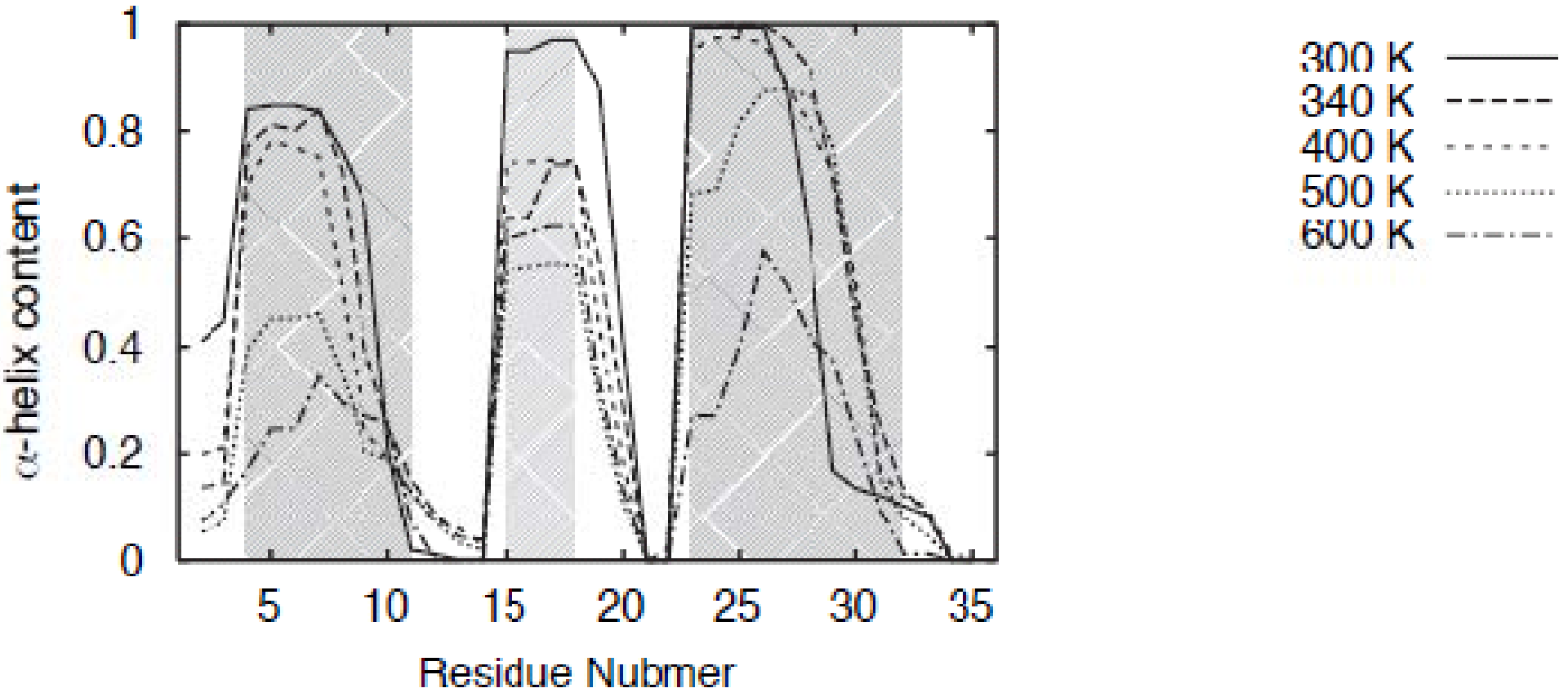
Helix 1: Res. No. 4 ～ 8

Helix 2: Res. No. 15 ～ 18

Helix 3: Res. No. 23 ～ 32

(CHARMM22 with Cmap)

（140 ns/replicas ×8 replicas = 1.12 μs）

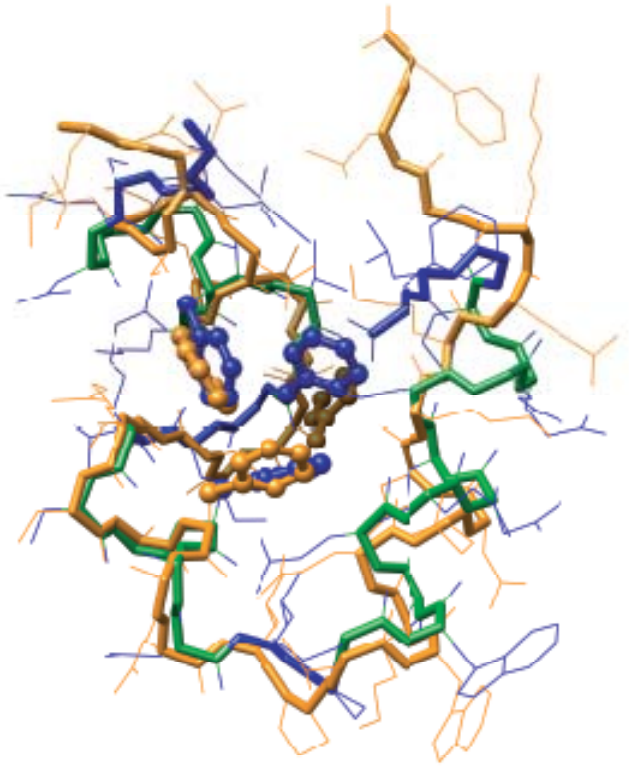


T. Yoda, Y. Sugita & Y.O., in preparation.

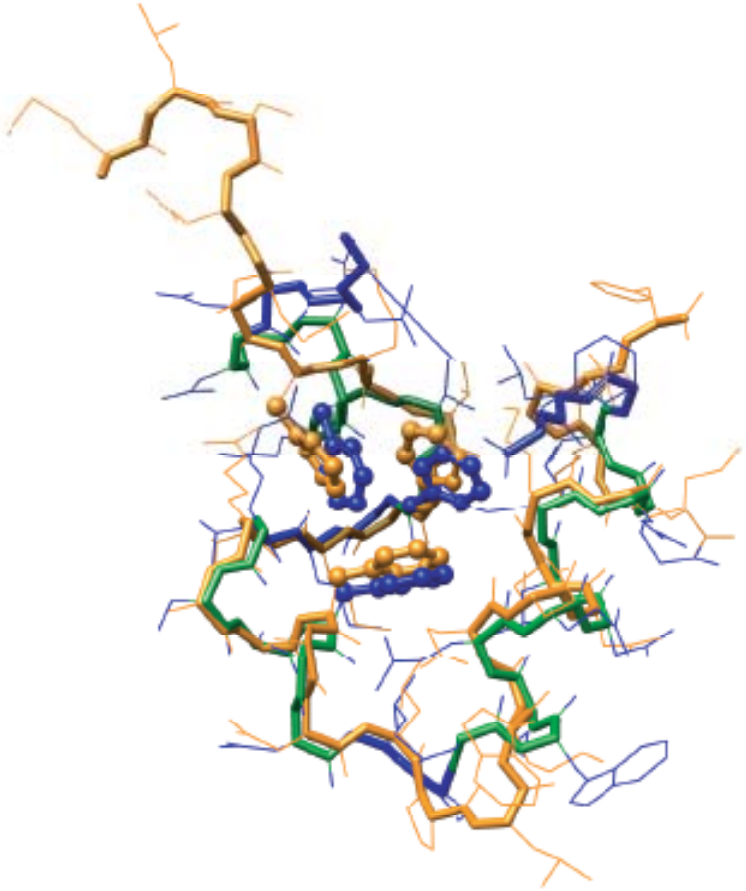
Villin headpiece subdomain (36 amino acids; 596 atoms)
Lowest RMSD structures superimposed with the native structure
(CHARMM22 with Cmap)（140 ns/replicas × 8 replicas = 1.12 μs）

T. Yoda, Y. Sugita & Y.O., in preparation.

(a) **Structure with the least RMSD (1.1 Å) of backbone 2-35**



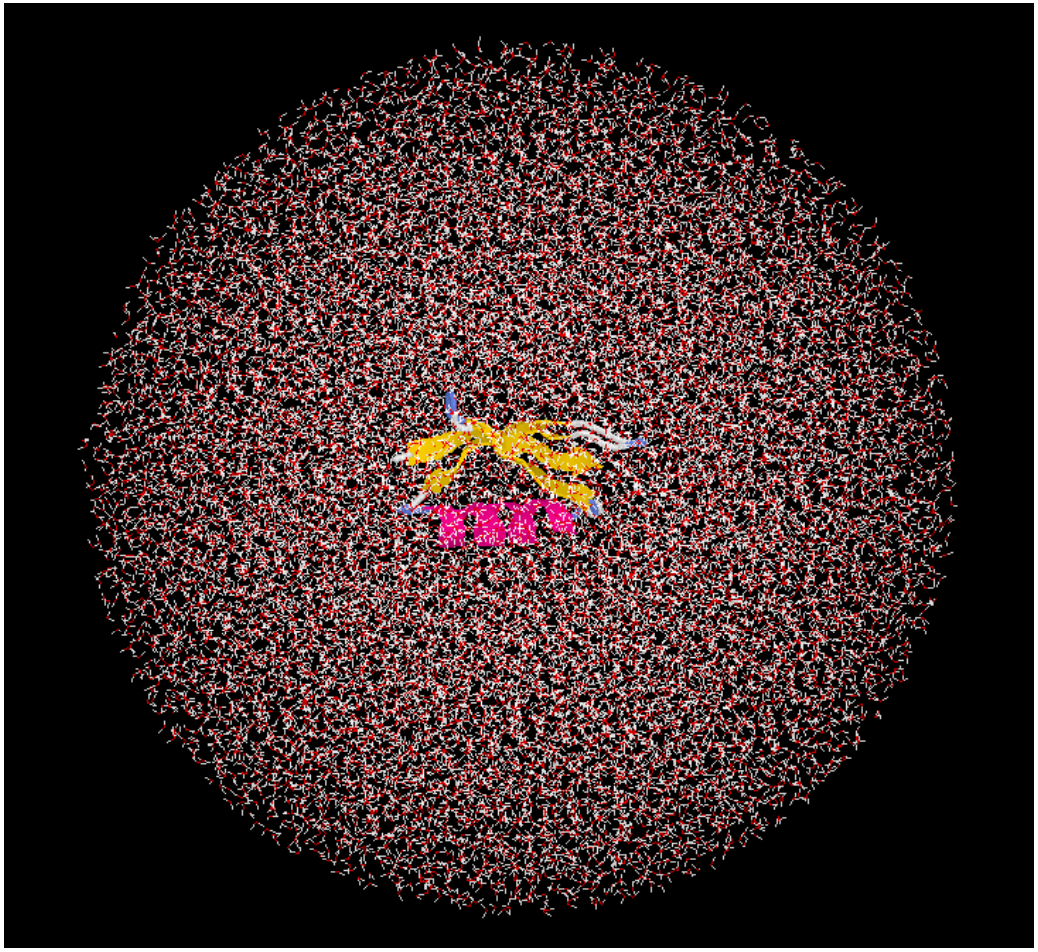
(b) **Structure with the least RMSD (1.2 Å) of backbone 9-32**



Folding of Protein G (56 Amino Acids)

A. Mitsutake, Y. Sugita, T. Yoda, T. Nishikawa, Y. Sakae & Y.O., in preparation.

B1 Domain of Streptococcal Protein G (56 amino acids; 855 atoms)
in sphere of water of radius 50 Å (17,063 water molecules);
altogether 52,044 atoms

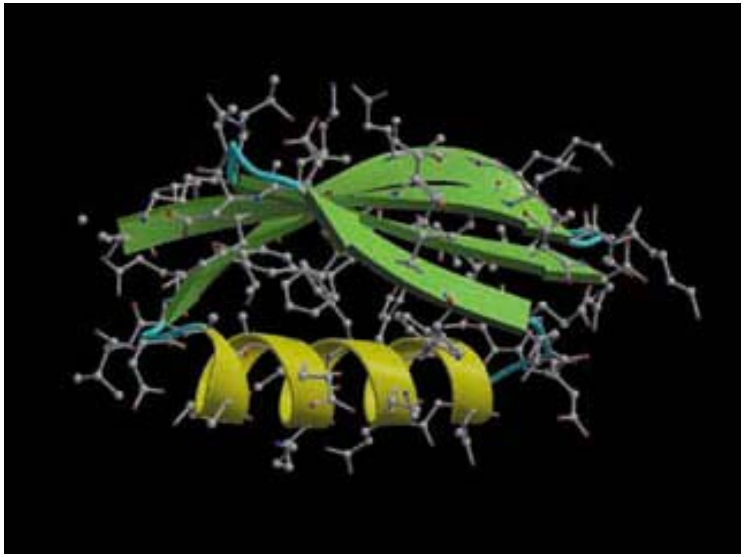


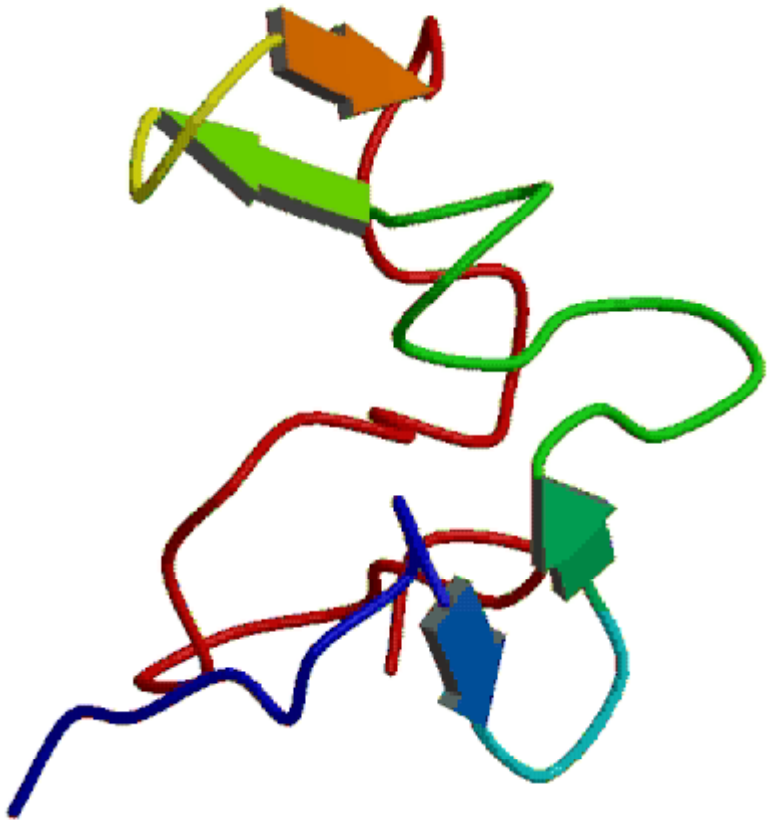
Folding of Protein G

REMD Simulation (17,063 Water Molecules) with 224 Replicas
(Used 112 nodes of the Earth Simulator)

Initial Structure : Fully Extended

Goal: X-ray Structure
(Green is β-sheet; Yellow is α-helix)

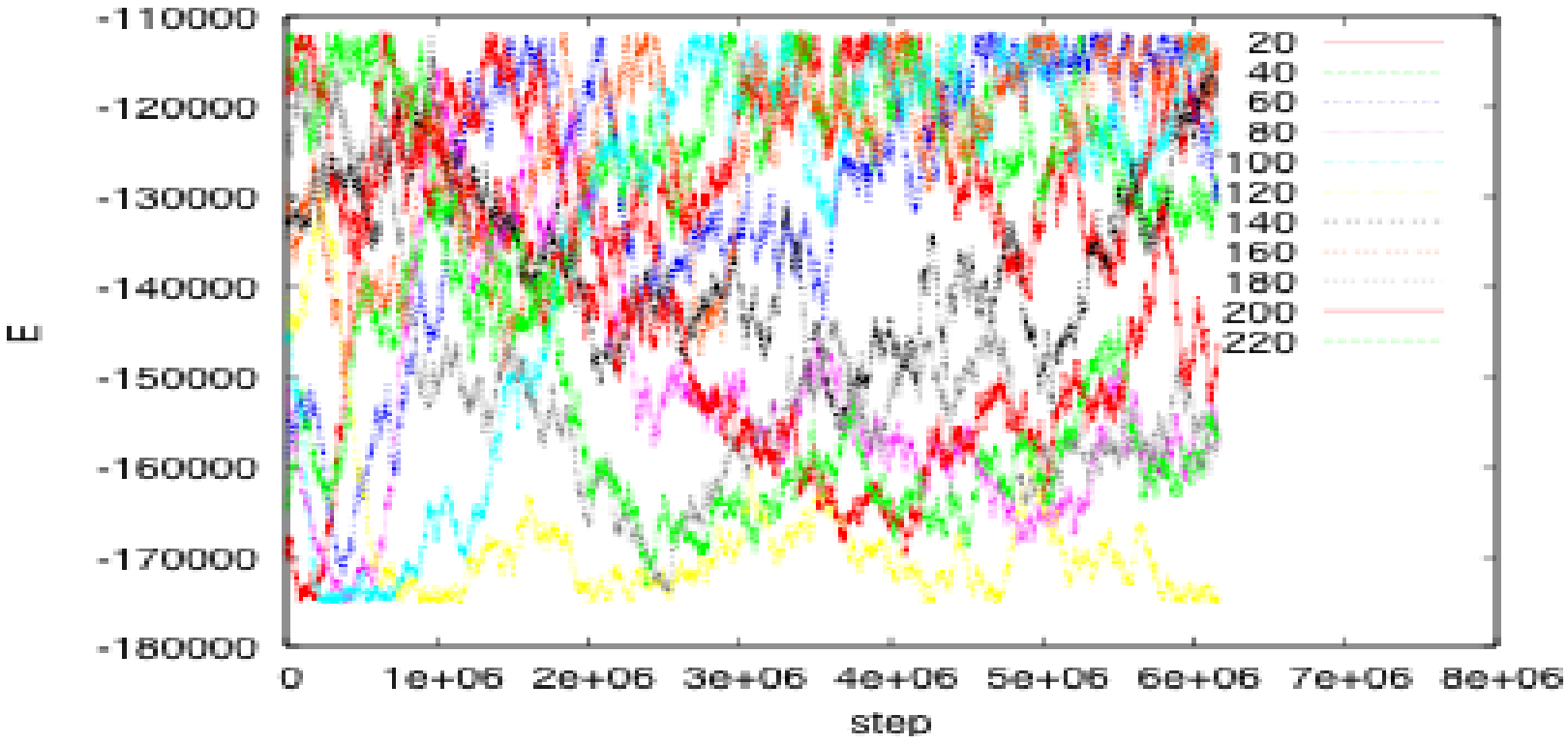




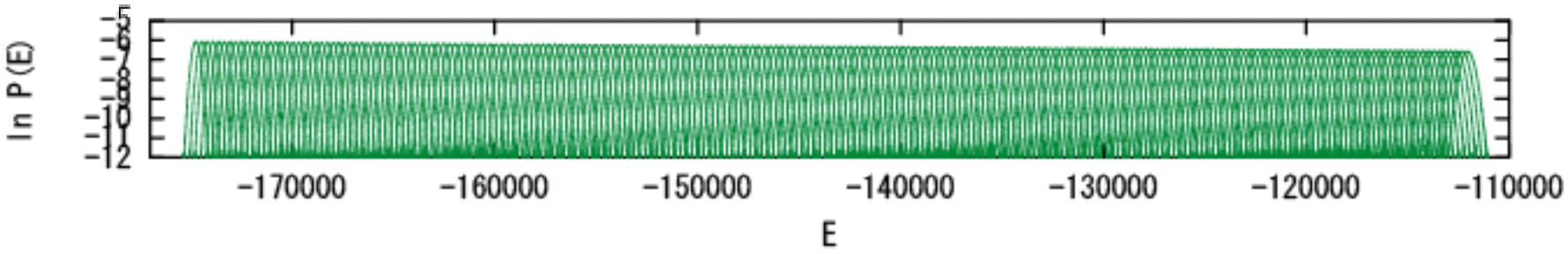
Simulation and movie by A. Mitsutake

Folding of Protein G

Random Walk in Potential Energy Space is Realized.

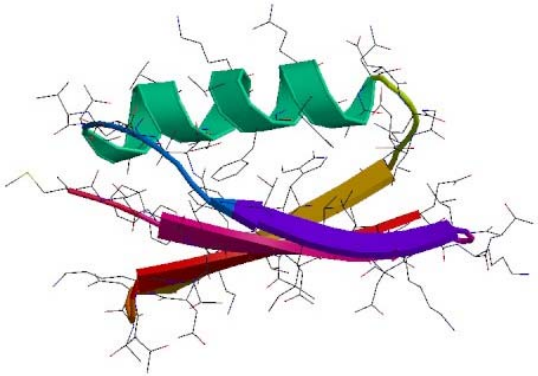


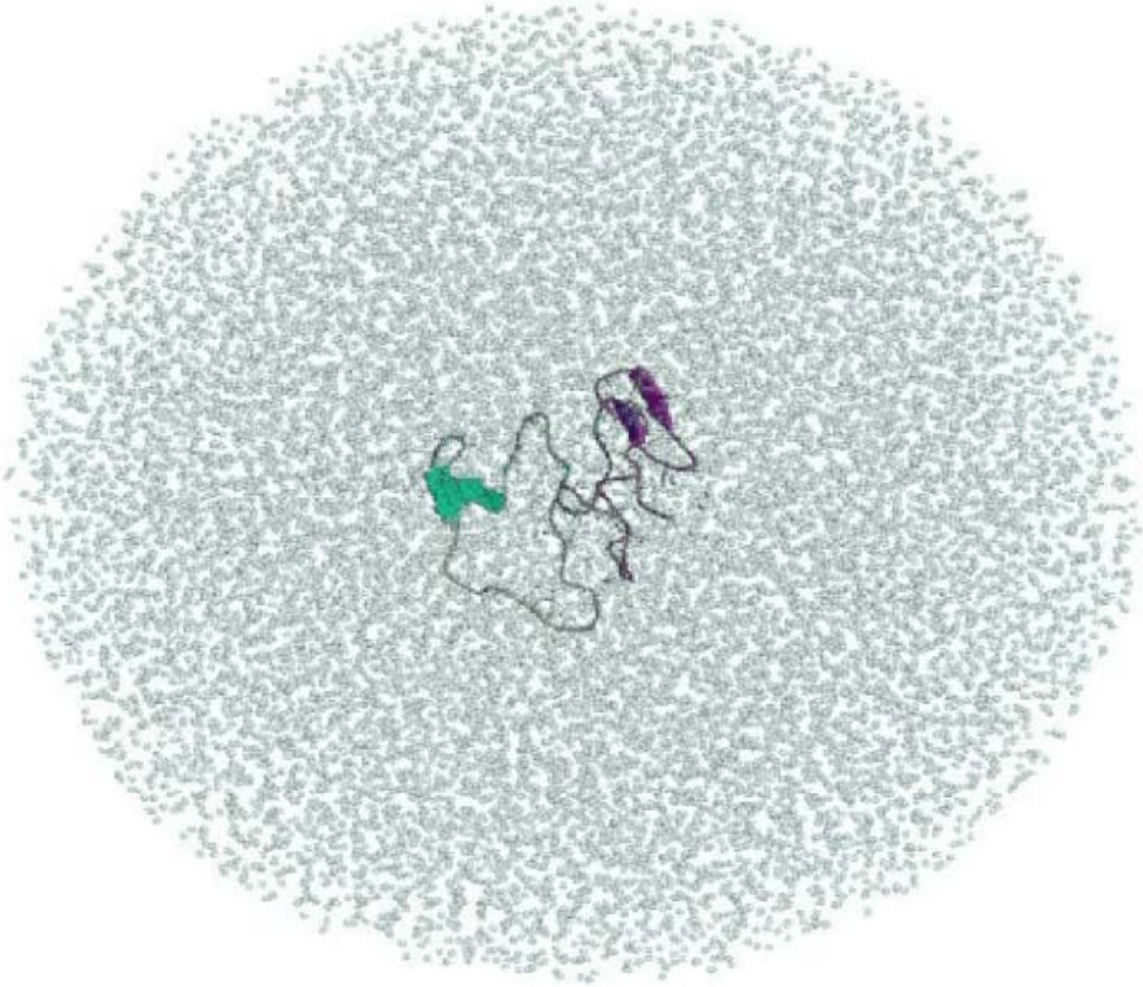
224 Distributions of Potential Energy at 224 Temperatures Obtained from the REMD Simulation (using 112 nodes of the Earth Simulator)

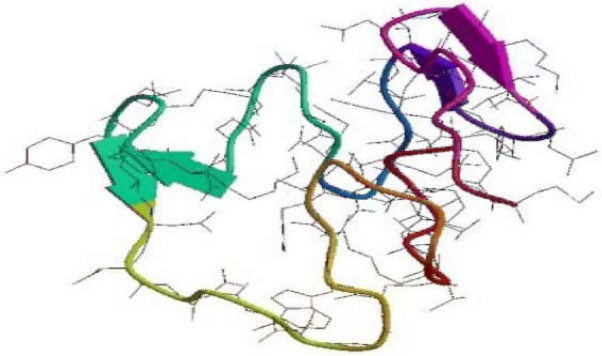


A. Mitsutake, Y. Sugita, T. Yoda, T. Nishikawa, Y. Sakae & Y.O., in preparation.

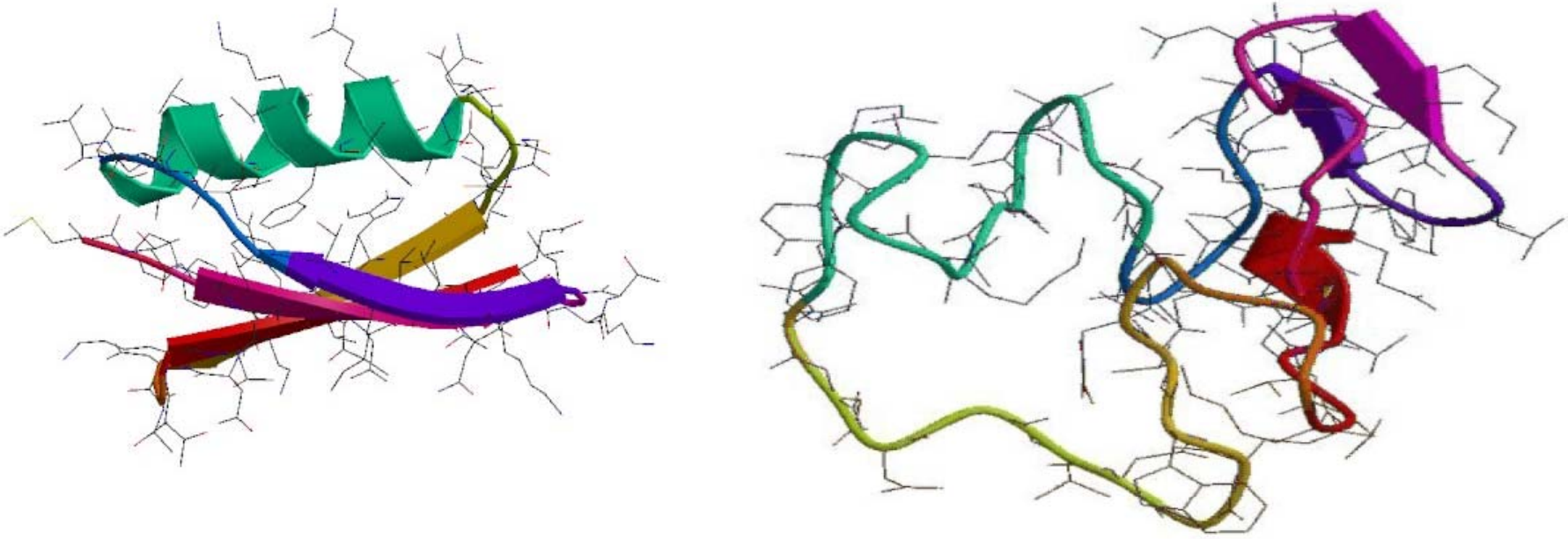
REMD Simulation with 224 Replicas
5 nsec for each replica (i.e., **1.12 μsec**) in total.
(used 112 nodes of the Earth Simulator)





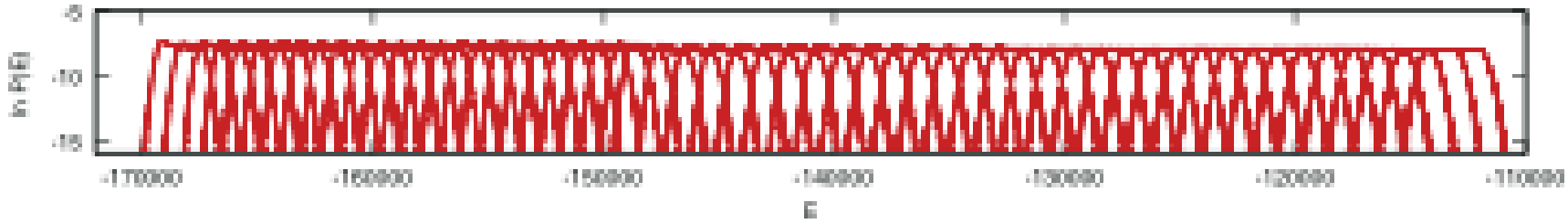


Simulation and movie by A. Mitsutake



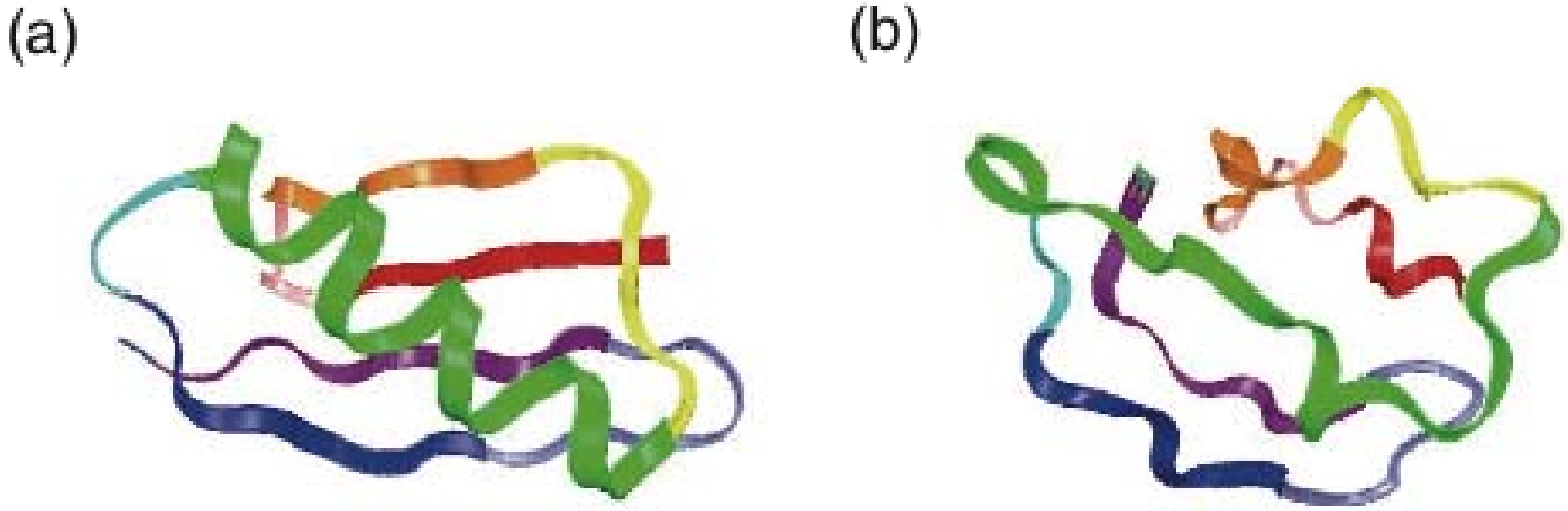
Simulation and movie by A. Mitsutake

54 Distributions of Potential Energy for 54 MUCA Ensembles Obtained from the MUCAREM Simulation (using 112 nodes of the Earth Simulator)



A. Mitsutake, Y. Sugita, T. Yoda, T. Nishikawa, Y. Sakae & Y.O., in preparation.

Protein G:
the native structure (a) and
the present simulation result (b)



A. Mitsutake, Y. Sugita, T. Yoda, T. Nishikawa, Y. Sakae & Y.O., in preparation.

Generalizations of Multicanonical Algorithm to NPT Ensemble: Multibaric-Multithermal Algorithm (MUBATH)

H. Okumura & Y.O., *Chem. Phys. Lett*. **383**, 391 (2004). (MC version)
H. Okumura & Y.O., *Chem. Phys. Lett*. **391**, 248 (2004). (MD version)
H. Okumura & Y.O., *Phys. Rev*. *E* **70**, 026702 (2004).
H. Okumura & Y.O., *J. Phys. Soc. Jpn.* **73**, 3304 (2004).
H. Okumura & Y.O., *J. Comput. Chem*. **27**, 379 (2006).
H. Okumura & Y.O., *Bull. Chem. Soc. Jpn*. **80**, 1114 (2007).
H. Okumura & Y.O., *J. Phys. Chem*. *B* **112**, 12038 (2008).

Suitable for studies of pressure-induced denaturations of proteins.

Multibaric-Multithermal Algorithm (MUBATH)

H. Okumura & Y.O., *Chem. Phys. Lett*. **383**, 403 (2004).

Prob. Distr. of ***E, V***

$$p_{mNPT}(E,V) = n(E,V)\, W_{mNPT}(E,V) \equiv const$$

Reweighting

$$p_{NPT}(E,V) = \frac{p_{mNPT}(E,V)\, W_{mNPT}^{-1}(E,V)\, \mathrm{e}^{-\beta(E+PV)}}{\int dV \int dE\; p_{mNPT}(E,V)\, W_{mNPT}^{-1}(E,V)\, \mathrm{e}^{-\beta(E+PV)}}$$

Expect. Value of Phys. Quanti. ***A***

$$< A >_{NPT} = \int dV \int dE\; A(E,V)\, p_{NPT}(E,V;T,P)$$

W_{mNPT}
Determined iteratively

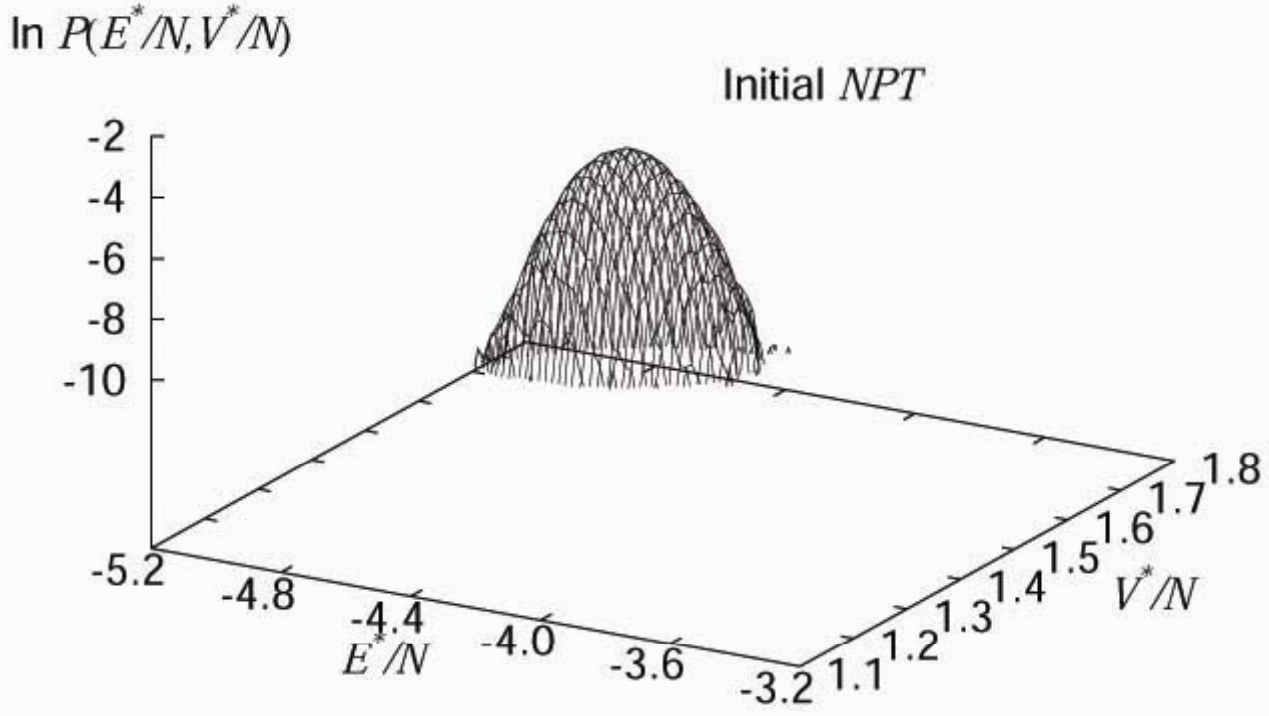
$$\begin{cases} H_{mNPT}^{(1)}(E,V) = E + PV \\ W_{mNPT}^{(1)}(E,V) = e^{-\beta_0 H_{mNPT}^{(1)}} \end{cases}$$

$$\begin{cases} H_{mNPT}^{(i+1)}(E,V) = H_{mNPT}^{(i)}(E,V) + k_B T_0 \ln p_{mNPT}^{(i)}(E,V) \\ W_{mNPT}^{(i+1)}(E,V) = e^{-\beta_0 H_{mNPT}^{(i+1)}} \end{cases}$$

Simulations

Lennard-Jones 12-6 system, N=500, P_0^*=3.0, T_0^*=2.0

distribution $p(E,V)$ of E, P

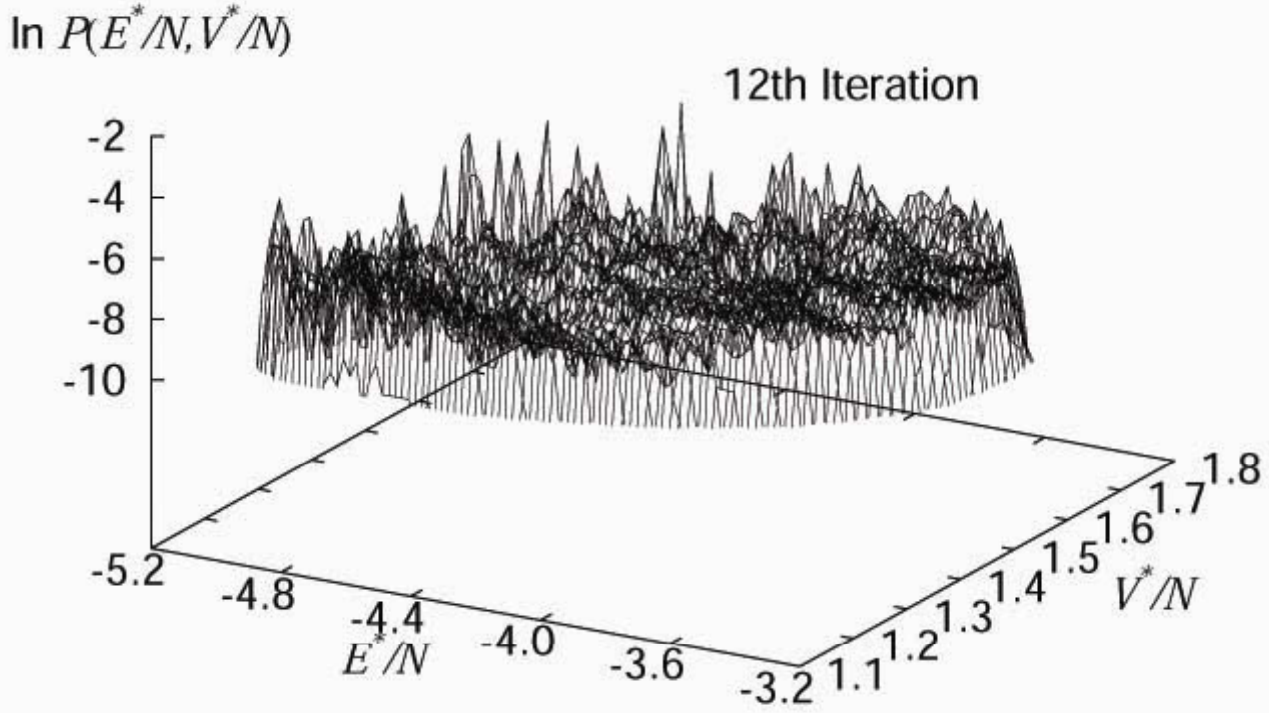


1. Convent. NPT
   10^5 Sweeps
2. MUMATH
   iteration (12-th)
   10^5 Sweeps
3. MUBATH
   production
   4×10^5 Sweeps
4. reweighting

Simulations

Lennard-Jones 12-6 system, N=500, P_0^*=3.0, T_0^*=2.0

distribution $p(E,V)$ of E, P

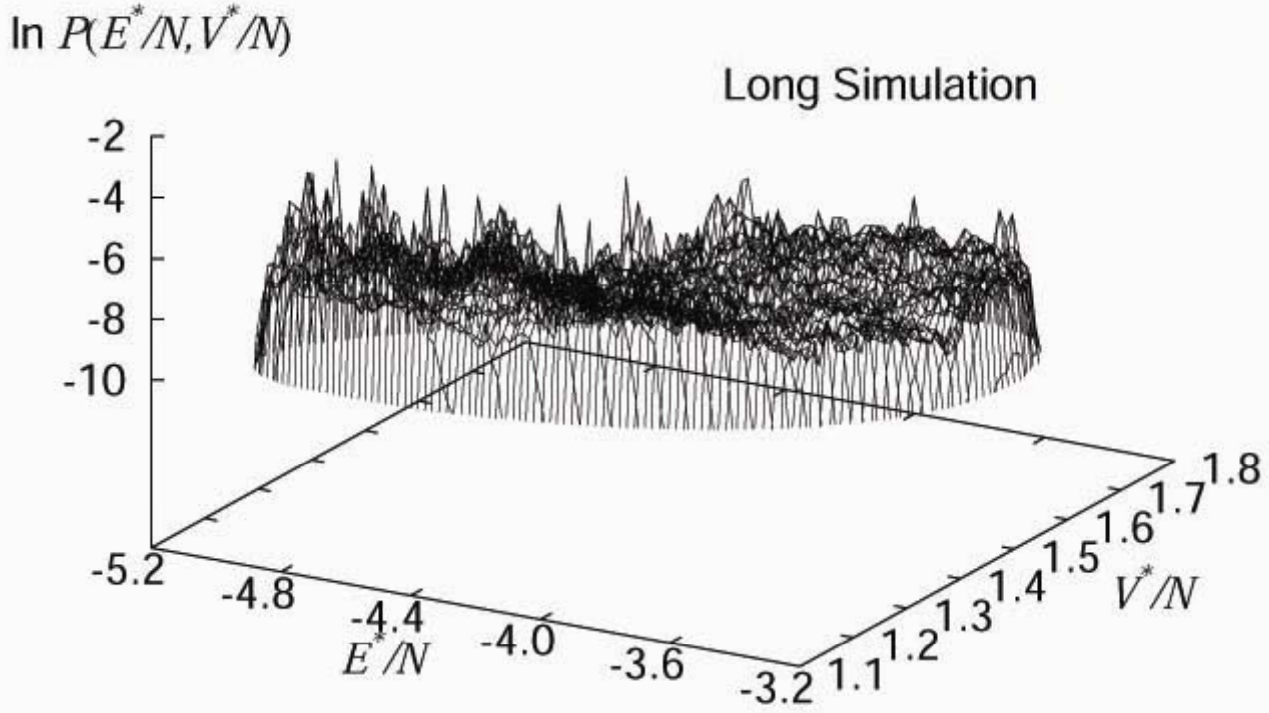


1. Convent. *NPT*
   10^5 Sweeps
2. MUMATH
   iteration (12-th)
   10^5 Sweeps
3. MUBATH
   production
   4×10^5 Sweeps
4. reweighting

Simulations

Lennard-Jones 12-6 system, N=500, P_0^*=3.0, T_0^*=2.0

distribution $p(E,V)$ of E, P

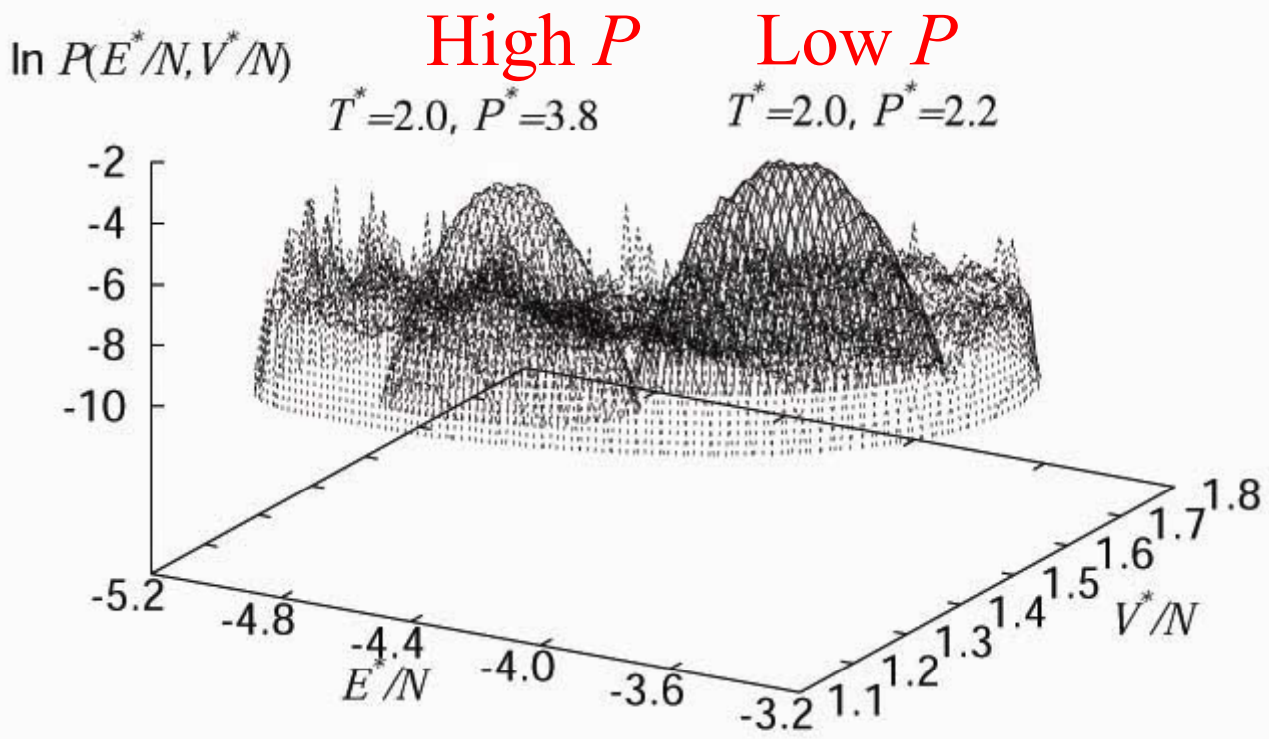


1. Convent. *NPT*
   10^5 Sweeps
2. MUMATH
   iteration (12-th)
   10^5 Sweeps
3. MUBATH
   production
   4×10^5 Sweeps
4. reweighting

Equations of States

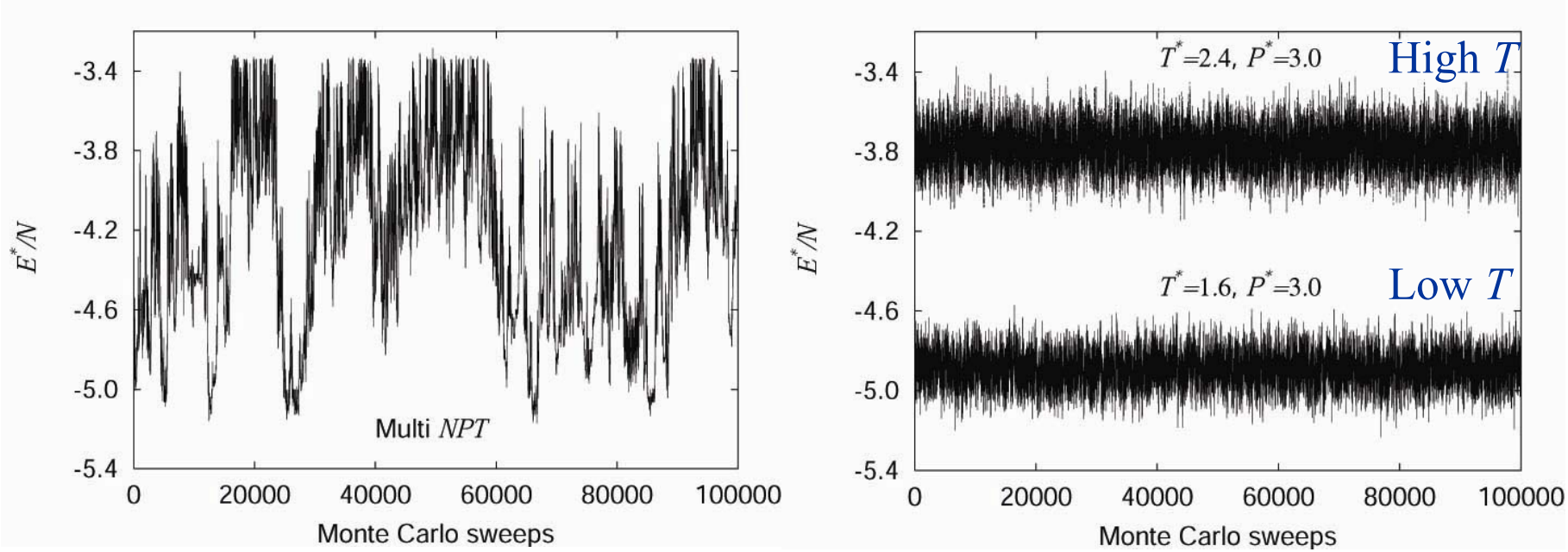
Lennard-Jones 12-6 system, N=500, P_0^*=3.0, T_0^*=2.0

distribution $p(E,V)$ of E, P



1. Convent. *NPT*
   10^5 Sweeps
2. MUMATH
   iteration (12-th)
   10^5 Sweeps
3. MUBATH
   production
   4×10^5 Sweeps
4. reweighting

Time Series of Potential Energy

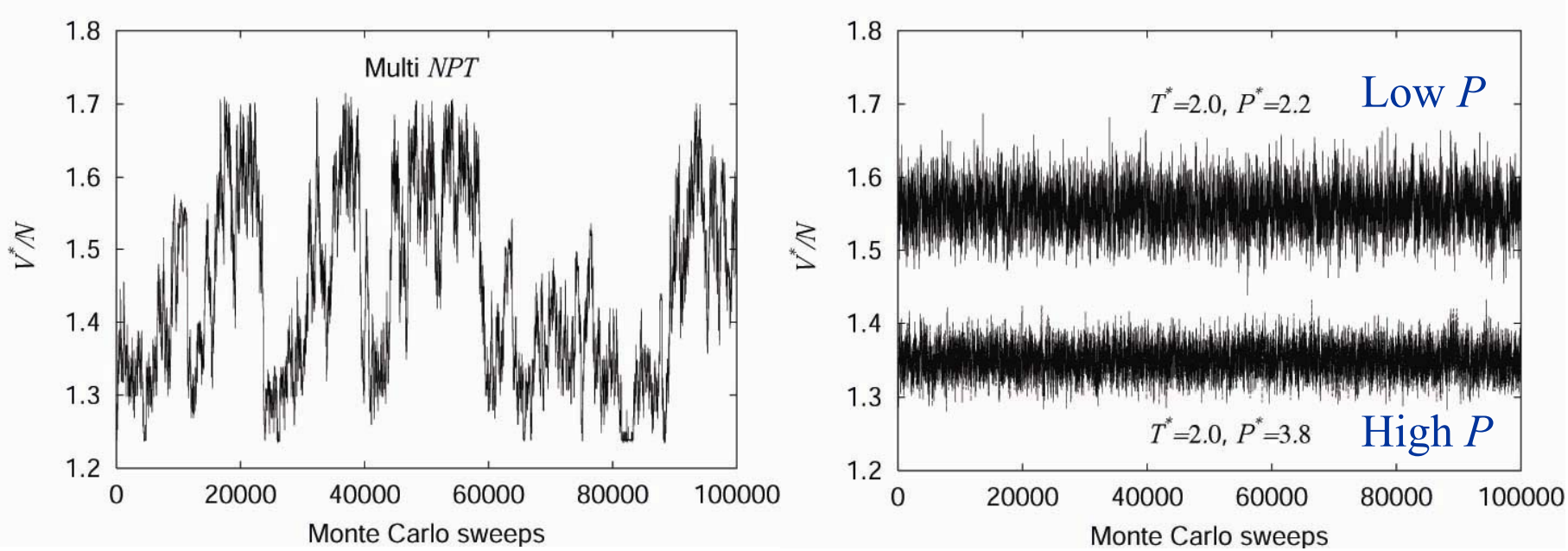


MUBATH

Conventional *NPT*

Random Walk in Energy Space

Time Series of Volume



MUBATH

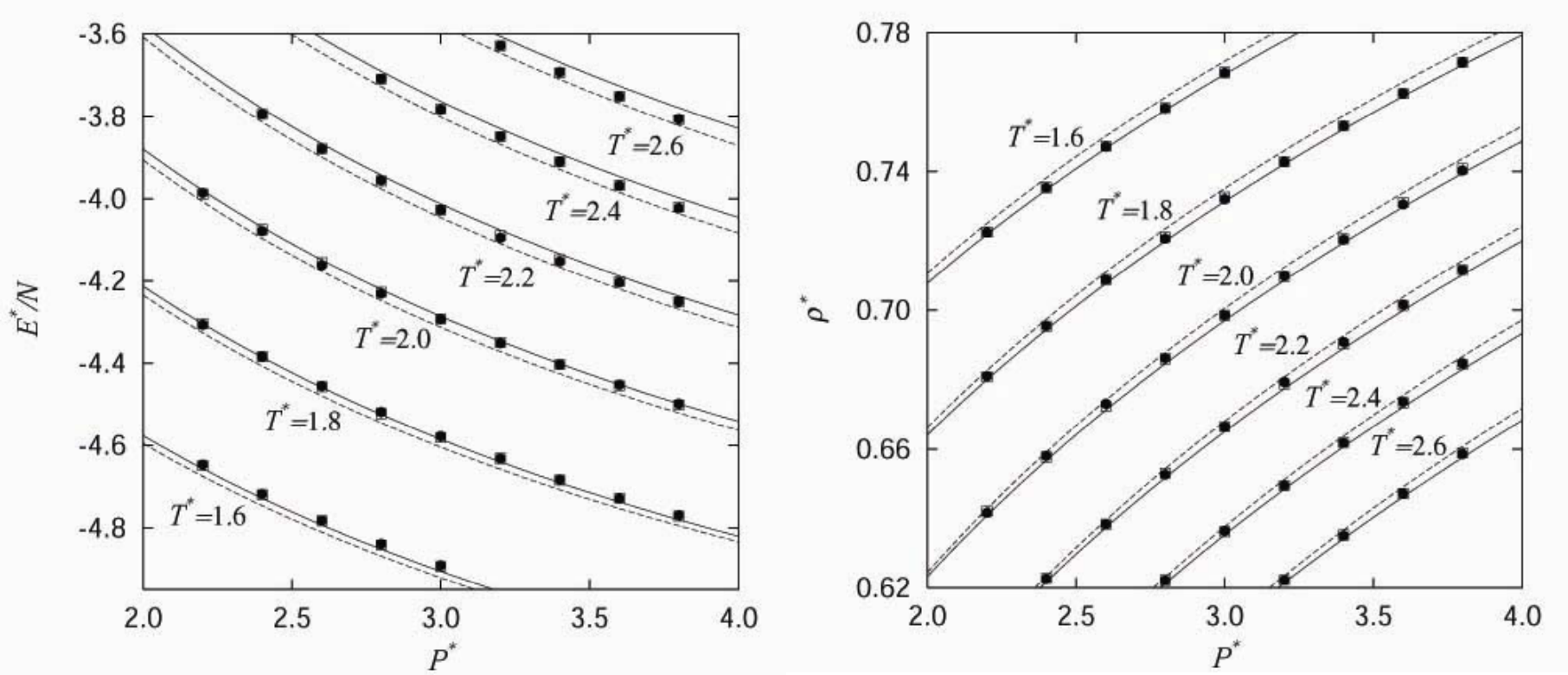
Conventional *NPT*

Random Walk in Volume Space

H. Okumura & Y.O., *Chem. Phys. Lett.* **383**, 403 (2004).

Expectation Values

Energy <*E*>, Density <ρ>



MUBATH

Good agreement w/ prev. results

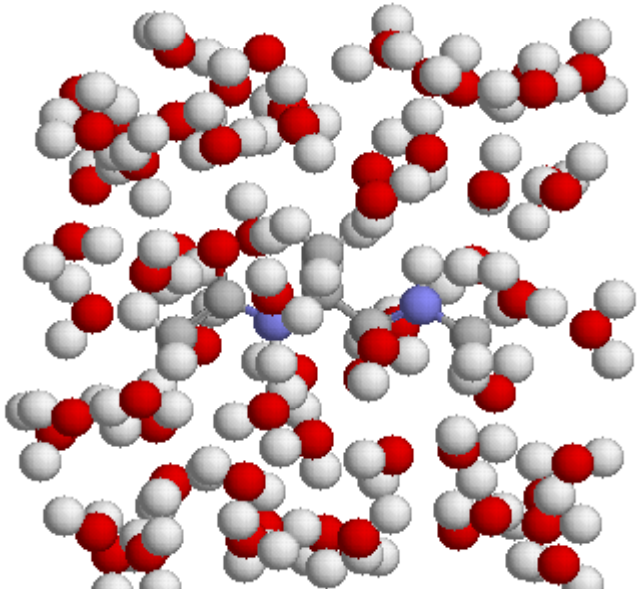
- ● MUBATH
- ▫ Conventional *NPT*
- —— Eqn. of States (Johnson et al.)
- ----- Eqn. os States (Sun et al.)

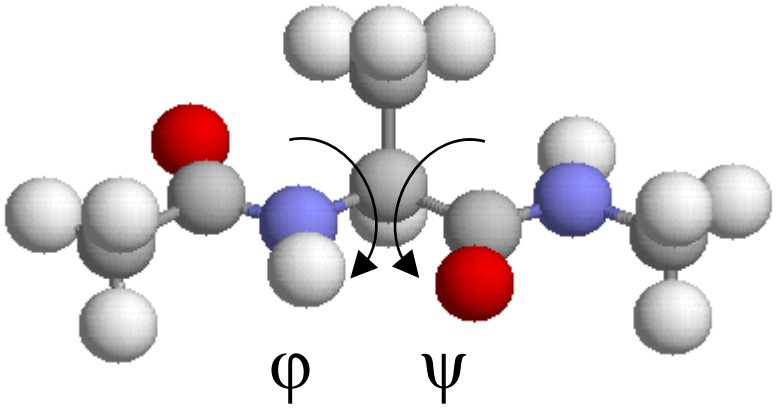
Application of MUBATH to Alanine Dipeptide in Water

H. Okumura & Y.O., *Bull. Chem. Soc. Jpn*. **80**, 1114 (2007);
H. Okumura & Y.O., *J. Phys. Chem*. *B* **112**, 12038 (2008).

Ace-Ala-Nme + 63 H_2O
Peptide: AMBER96 & AMBER99
Water: TIP3P

Periodic boundary condition
Coulomb force: Ewald method
T-control: Nose
P-control: Andersen

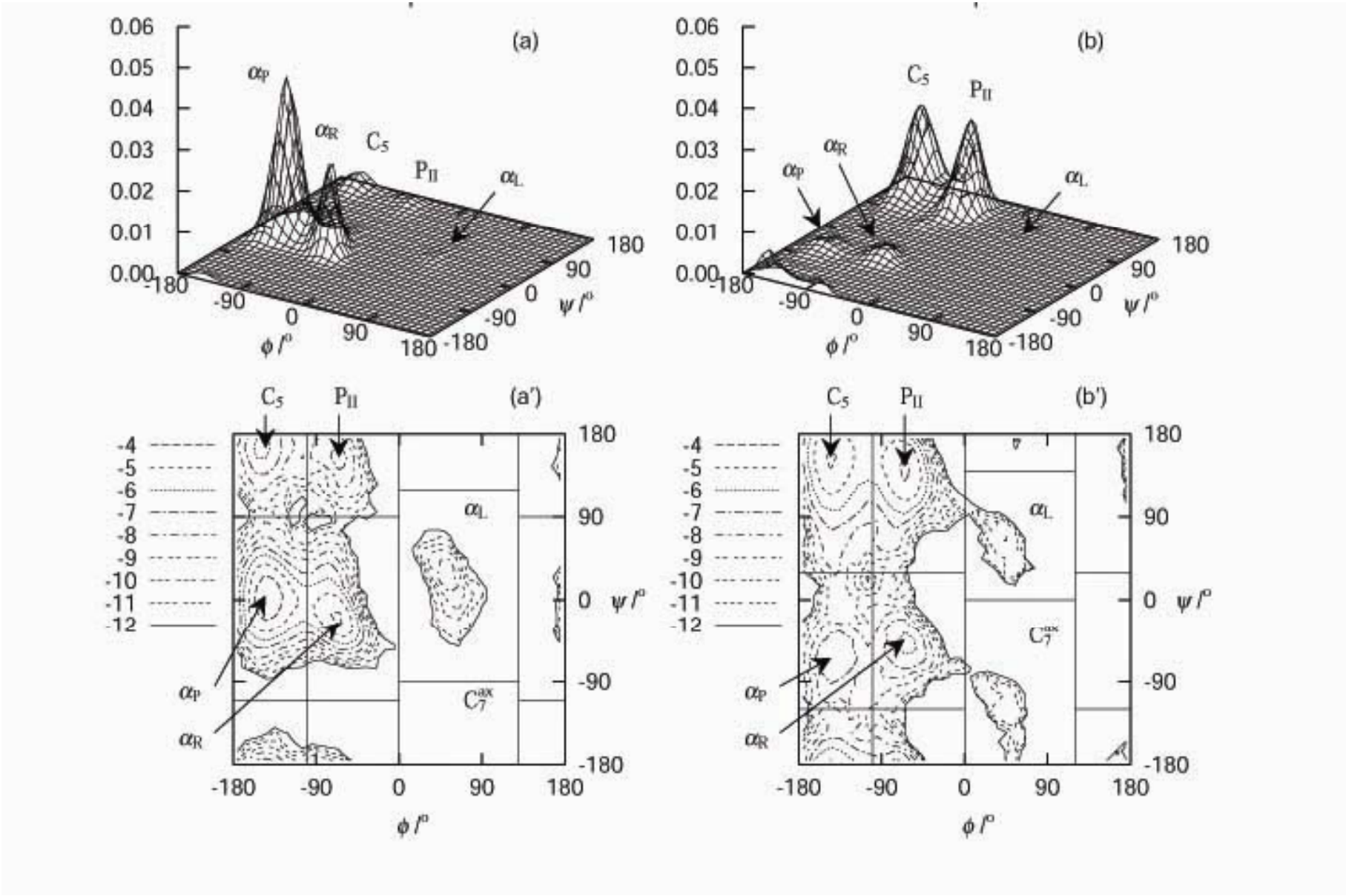




Force field dependence: Amber 99 vs. Amber 96 $T = 298$ K $P = 0.1$ MPa

Amber 99

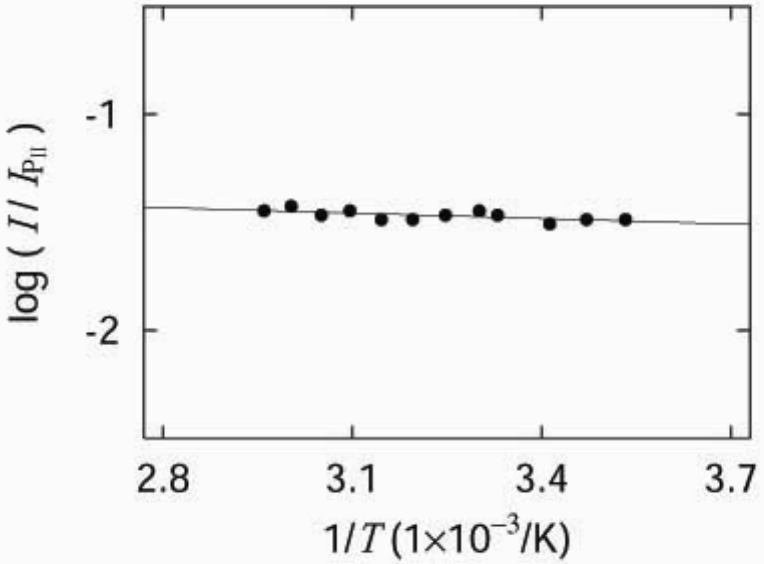
Amber 96



Temperature dependence at $P = 0.1$ MPa

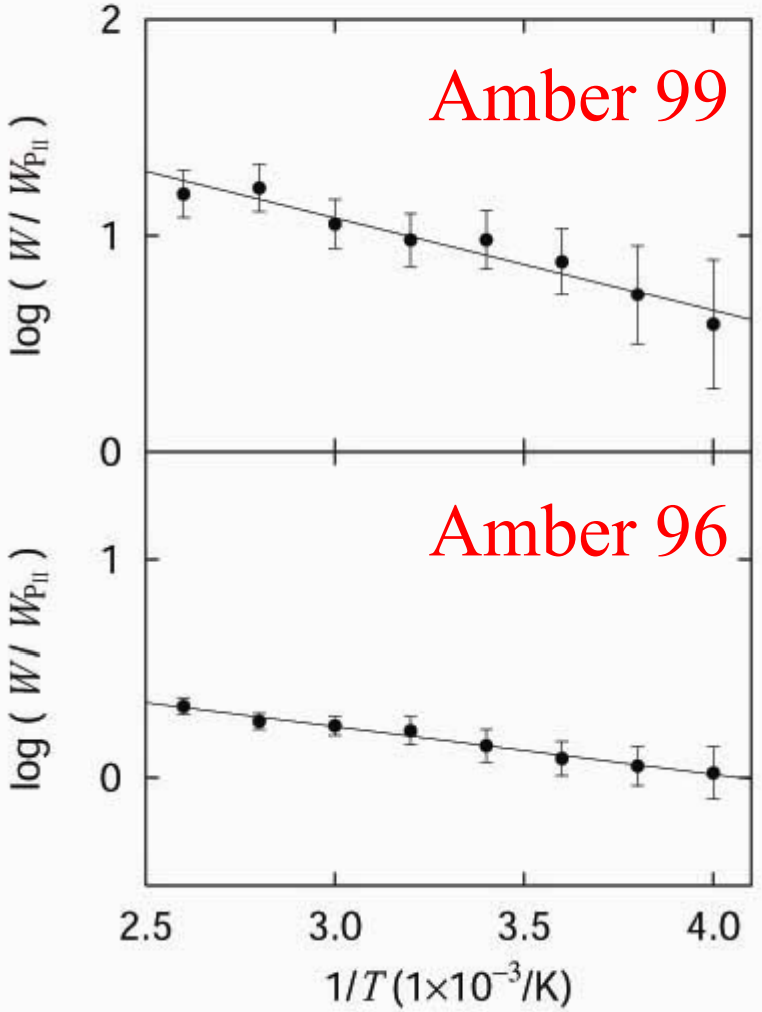
C_5/P_{II}

Exp. Raman scattering



T. Takekiyo, T. Imai,
M. Kato, Y. Taniguchi
Biopolymers **73** 283 (2004)

MUBATH MD

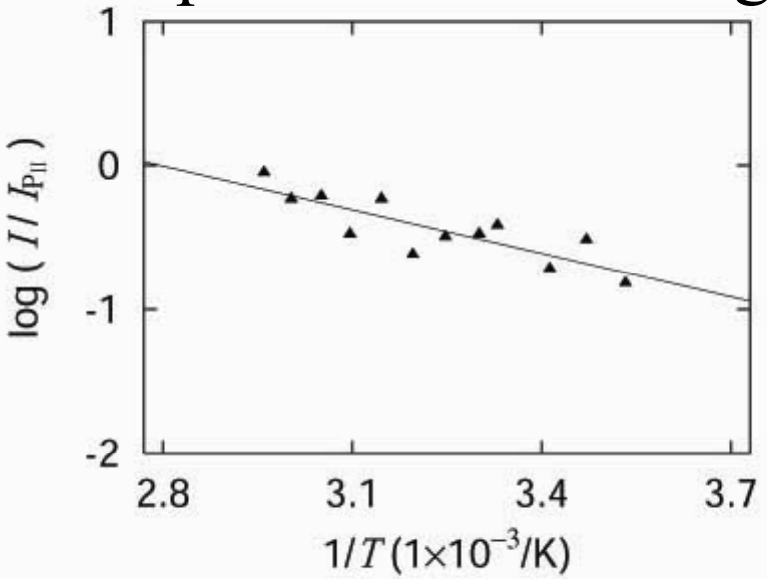


First work to calculate
the temperature dependence

Temperature dependence at $P = 0.1$ MPa

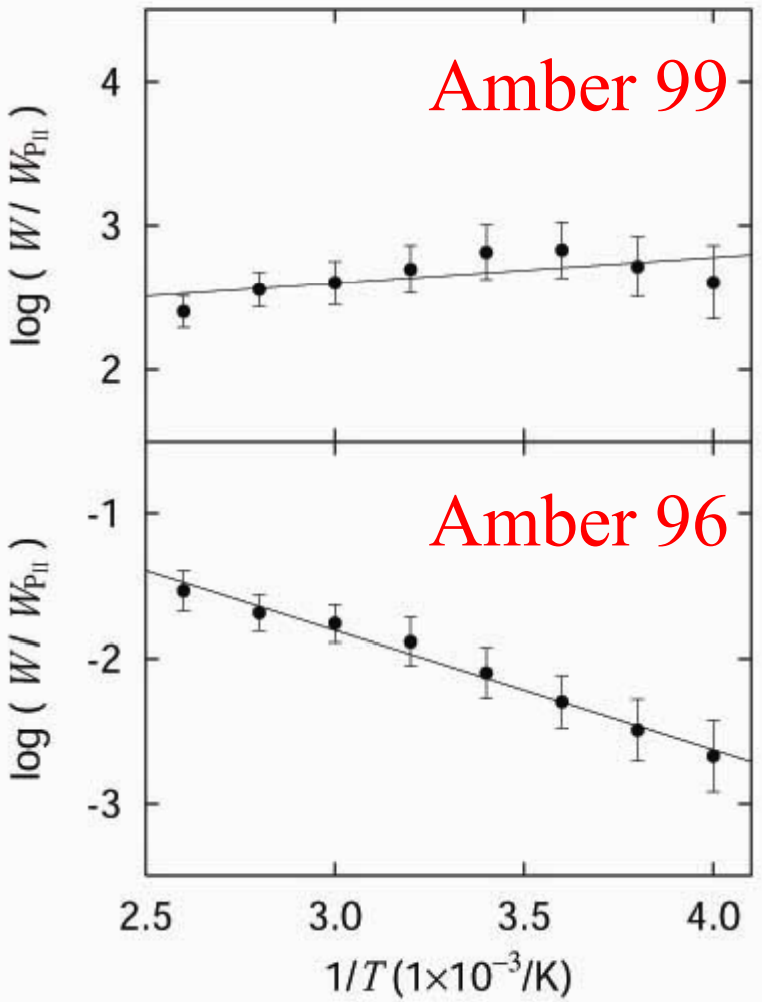
α_R / P_{II}

Exp. Raman scattering



T. Takekiyo, T. Imai,
M. Kato, Y. Taniguchi
Biopolymers **73** 283 (2004)

MUBATH MD



First work to calculate
the temperature dependence

Partial molar enthalpy difference ΔH from the P_{II} state

$$\Delta H = -R\left[\frac{\partial \ln\left(W / W_{P_{II}}\right)}{\partial\left(1/T\right)}\right]_P$$

R : gas constant

kJ/mol

ΔH	Raman*	MUBATH Amber 99	MUBATH Amber 96	RISM-KB*
C_5	2.5 ±0.3	3.6±2.2	1.8±0.8	—
α_R	4.4 ±1.5	-1.5±2.0	6.8±1.9	—

($P = 0.1$ MPa)

Multibaric-Multithermal MD

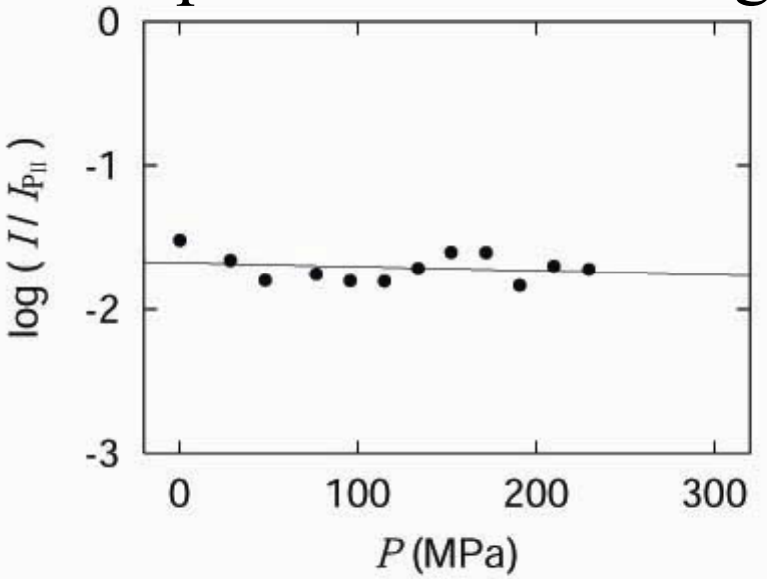
First work to calculate partial molar enthalpy

*T. Takekiyo, T. Imai, M. Kato, Y. Taniguchi, Biopolymers **73** 283 (2004)

Pressure dependence at $T = 298$ K

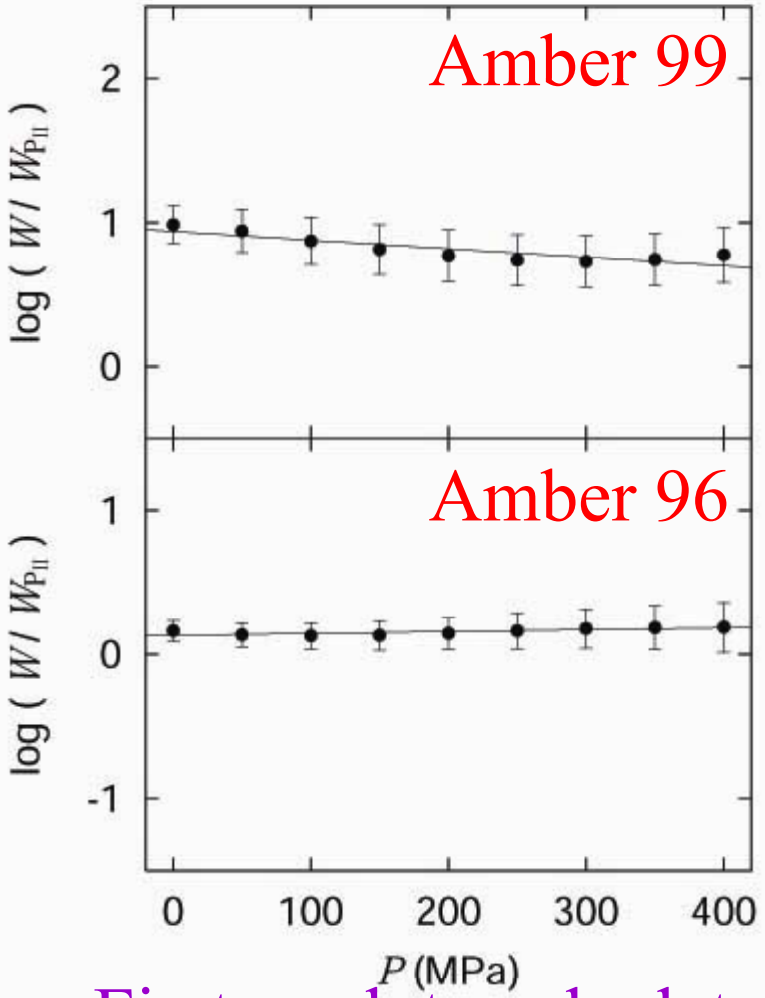
C_5/P_{II}

Exp. Raman scattering



T. Takekiyo, T. Imai,
M. Kato, Y. Taniguchi
Biopolymers **73** 283 (2004)

MUBATH MD

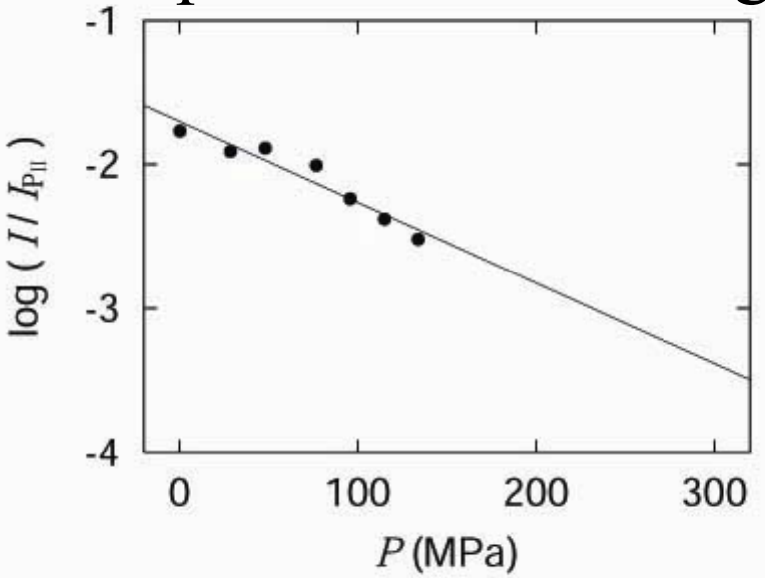


First work to calculate
the pressure dependence

Pressure dependence at $T = 298$ K

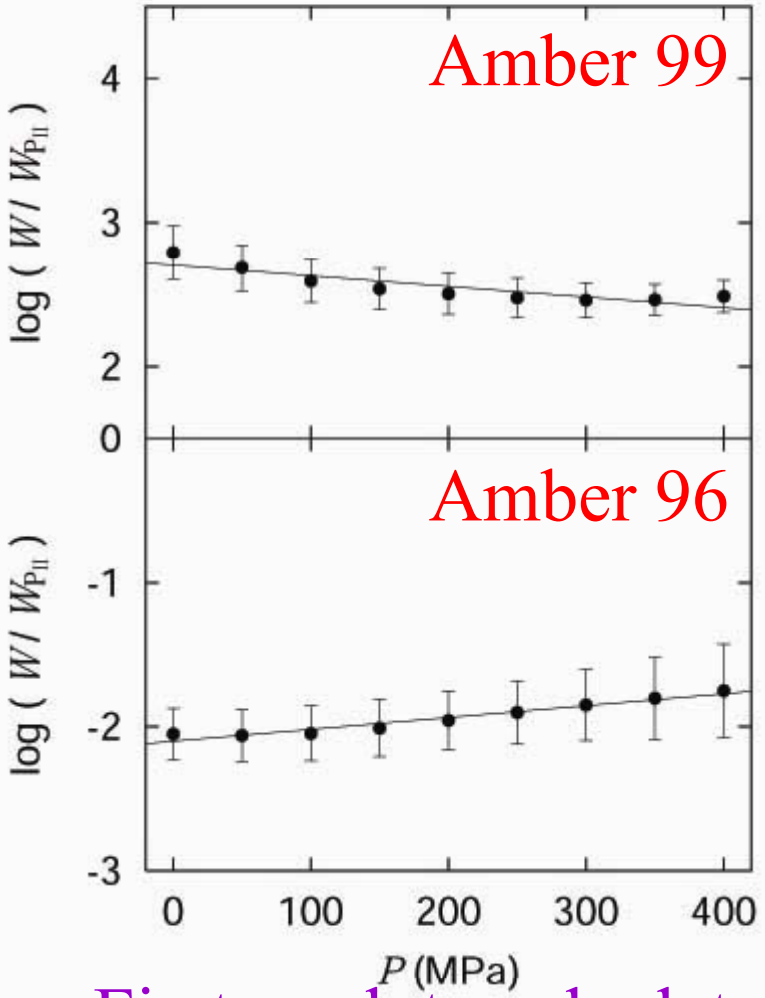
α_R / P_{II}

Exp. Raman scattering



T. Takekiyo, T. Imai,
M. Kato, Y. Taniguchi
Biopolymers **73** 283 (2004)

MUBATH MD



First work to calculate
the pressure dependence

Partial molar volume difference ΔV from the P_{II} state

H. Okumura & Y.O., *Bull. Chem. Soc. Jpn*. **80**, 1114 (2007);

H. Okumura & Y.O., *J. Phys. Chem. B* **112**, 12038 (2008).

$$\Delta V = -RT\left[\frac{\partial \ln\left(W / W_{P_{II}}\right)}{\partial P}\right]_T \qquad R: \text{gas constant}$$

cm^3/mol

ΔV	Raman*	MUBATH Amber 99	MUBATH Amber 96	RISM-KB*
C_5	0.1 ± 0.3	1.5 ± 0.9	-0.3 ± 0.9	-1.8
α_R	1.1 ± 0.2	1.8 ± 0.8	-2.0 ± 2.0	-1.2

Multibaric-Multithermal MD ($T = 298$ K)

Agreement with the experiment

*T. Takekiyo, T. Imai, M. Kato, Y. Taniguchi, *Biopolymers* **73**, 283 (2004).

Multicanonical-Multioverlap Simulatioin of Amyloid-β peptide Aβ(29-42) dimer

S.G. Itoh & Y.O., *J. Phys. Chem. B* **112**, 2767 (2008).

Multioverlap Algorithm

MC: B. A. Berg, H. Noguchi and Y.O., *Phys. Rev. E* **68**, 036126 (2003).

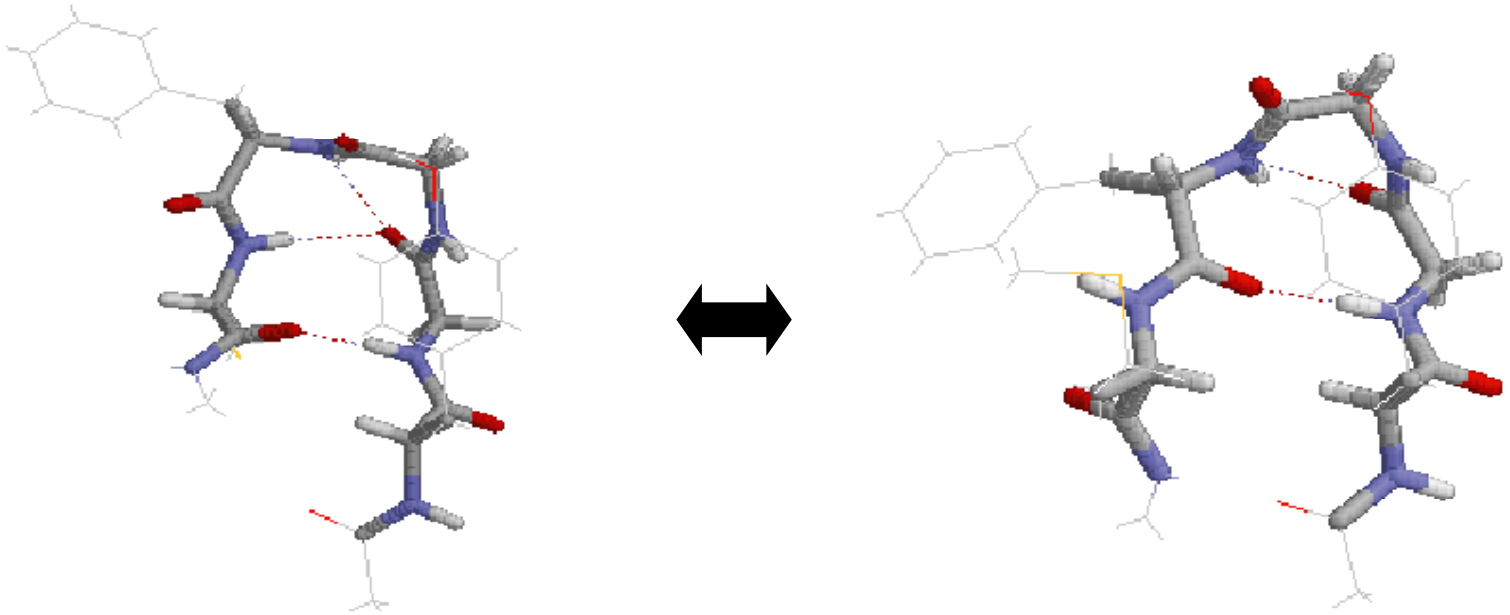
MD: S. G. Itoh and Y.O., *Chem. Phys. Lett*. **400**, 308 (2004);

J. Chem. Phys. **124**, 104103 (2006).

Multicanonical-Multioverlap Algorithm

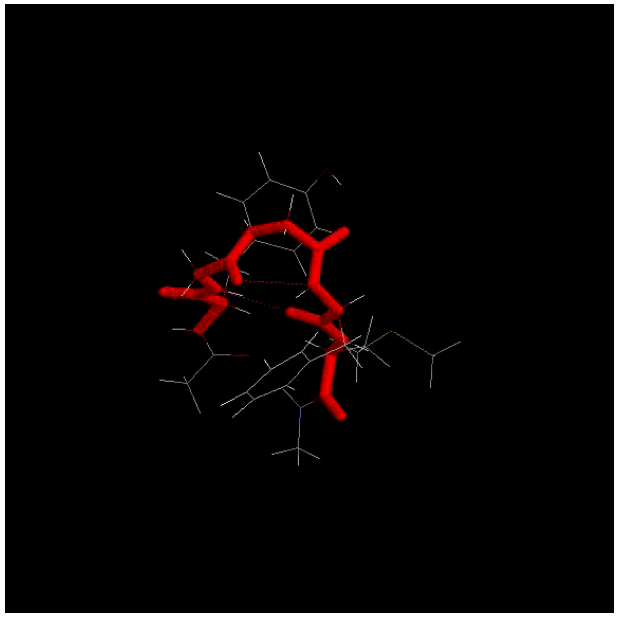
S. G. Itoh and Y.O., *Phys. Rev. E* **76**, 026705 (2007).

We performed a multi-overlap MD simulation for Met-enkephalin with two reference configurations.

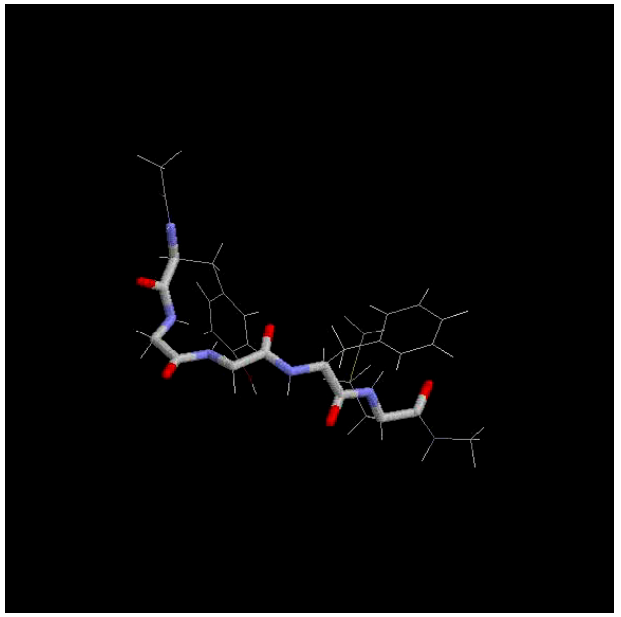


Reference conformation 1

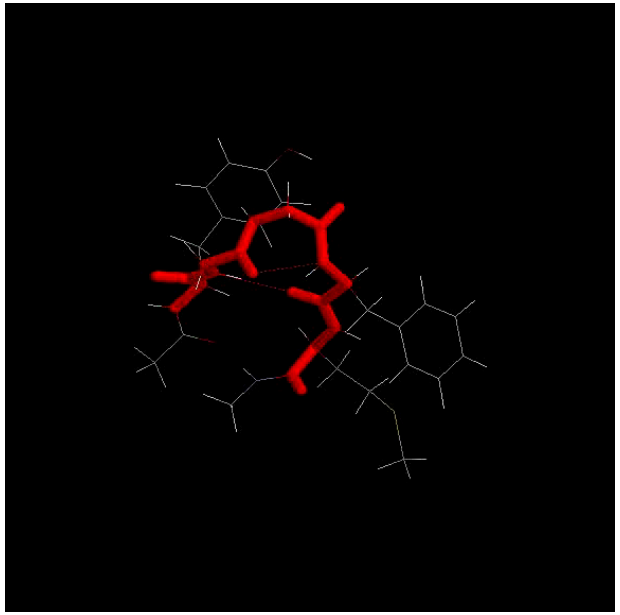
Reference conformation 2



Canonical MD



Multicanonical MD



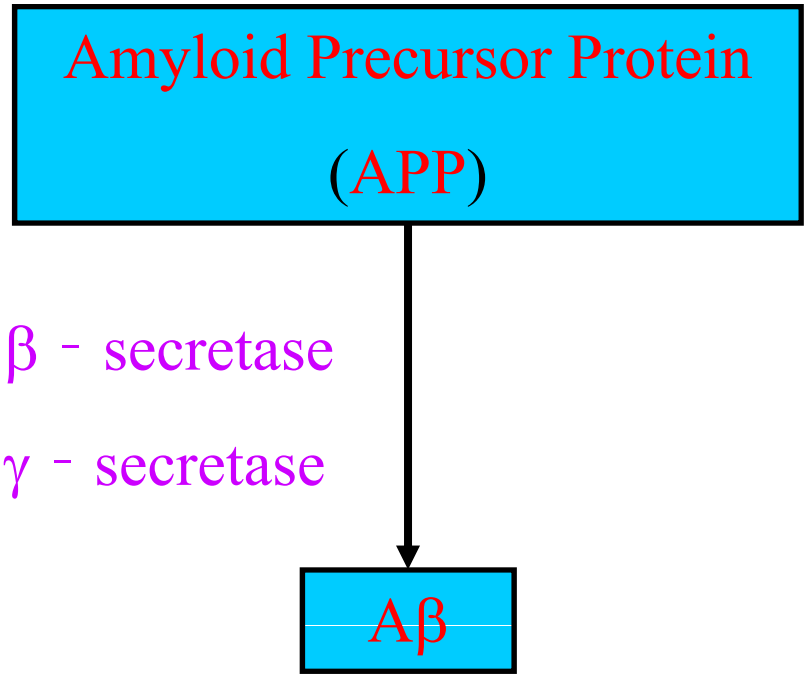
Multioverlap MD

$r_1 < 0.5 \Rightarrow$

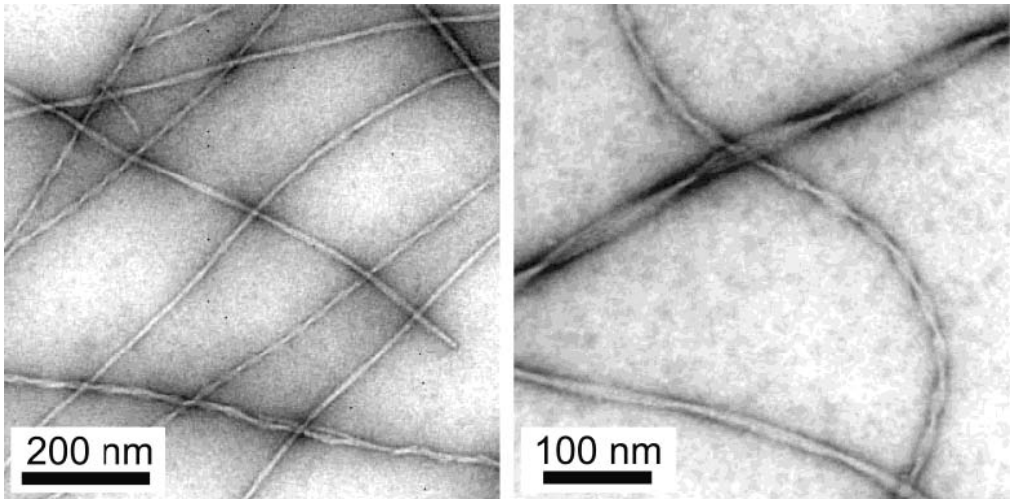
$r_2 < 0.5 \Rightarrow$

- Amyloid β-peptide (Aβ)

Aβ is comprised of 39 to 42 amino-acid residues and has a tendency to form amyloid fibrils, which are associated with Alzheimer's disease.

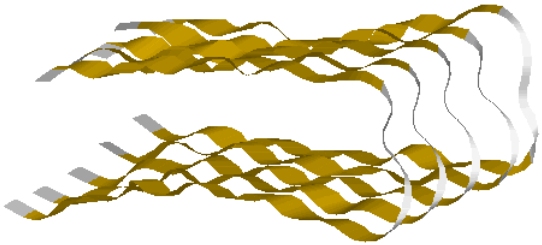


Aβ



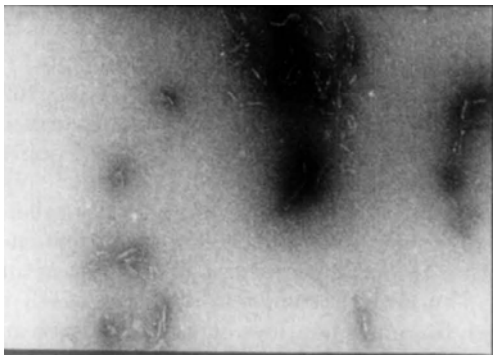
Tycko, *Biochemistry* **42**, 3151

ASP-ALA-GLU-PHE-ARG-HIS-ASP-SER-GLY-TYR-GLU-VAL-HIS-HIS-GLN-LYS-LEU-VAL-PHE-PHE-ALA-GLU-ASP-VAL-GLY-SER-ASN-LYS-GLY-ALA-ILE-ILE-GLY-LEU-MET-VAL-GLY-GLY-VAL-VAL-ILE-ALA



Lührs et al., *Proc. Natl. Acad. Sci. USA* **102**, 17342

Aβ(29-42)

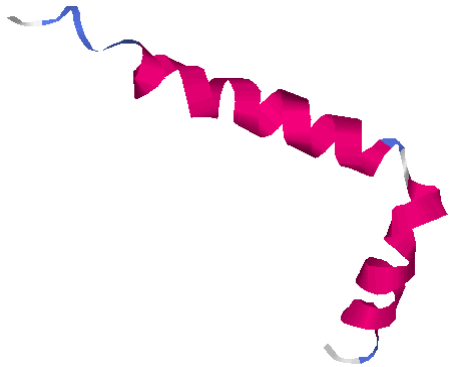


Hilbich et al., *J. Mol. Biol.* **218**, 149

- $A\beta_{42}$

In nonpolar solvent

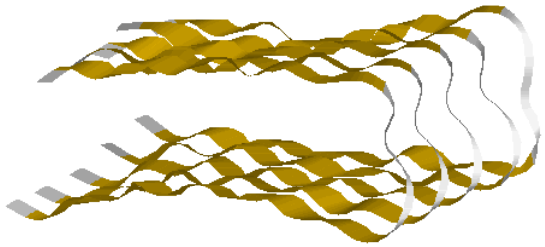
ASP-ALA-GLU-PHE-ARG-HIS-ASP-SER-GLY-TYR-GLU-VAL-HIS-HIS-GLN-LYS-LEU-VAL-PHE-PHE-ALA-GLU-ASP-VAL-GLY-SER-ASN-LYS-GLY-ALA-ILE-ILE-GLY-LEU-MET-VAL-GLY-GLY-VAL-VAL-ILE-ALA



PDB code: 1AML

In aqueous solution

ASP-ALA-GLU-PHE-ARG-HIS-ASP-SER-GLY-TYR-GLU-VAL-HIS-HIS-GLN-LYS-LEU-VAL-PHE-PHE-ALA-GLU-ASP-VAL-GLY-SER-ASN-LYS-GLY-ALA-ILE-ILE-GLY-LEU-MET-VAL-GLY-GLY-VAL-VAL-ILE-ALA



PDB code: 2BEG

- $A\beta(29\text{-}42)$

$A\beta(29\text{-}42)$ is the transmembrane domain of $A\beta_{42}$ and comprised of from the residues 29-42.

Simulation : multicanonical-multioverlap MD simulation

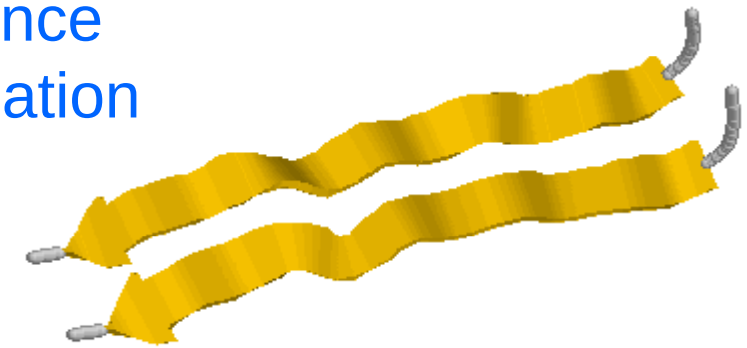
System : Aβ(29-42) dimer with GB/SA model

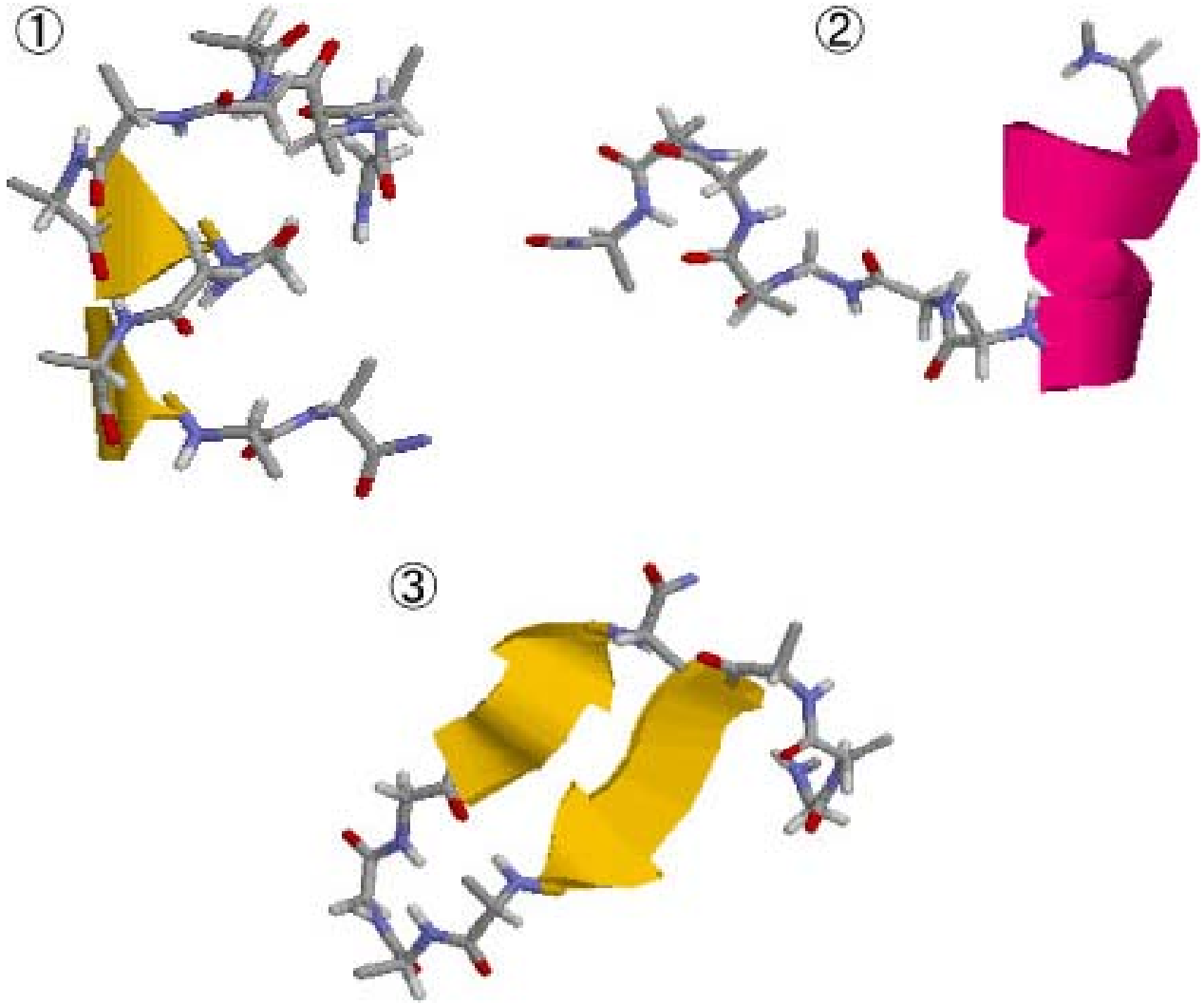
Temperature : 250K

Force field : CHARMM param 22 (all-atom model)

Time step : 0.5fs

Reference conformation

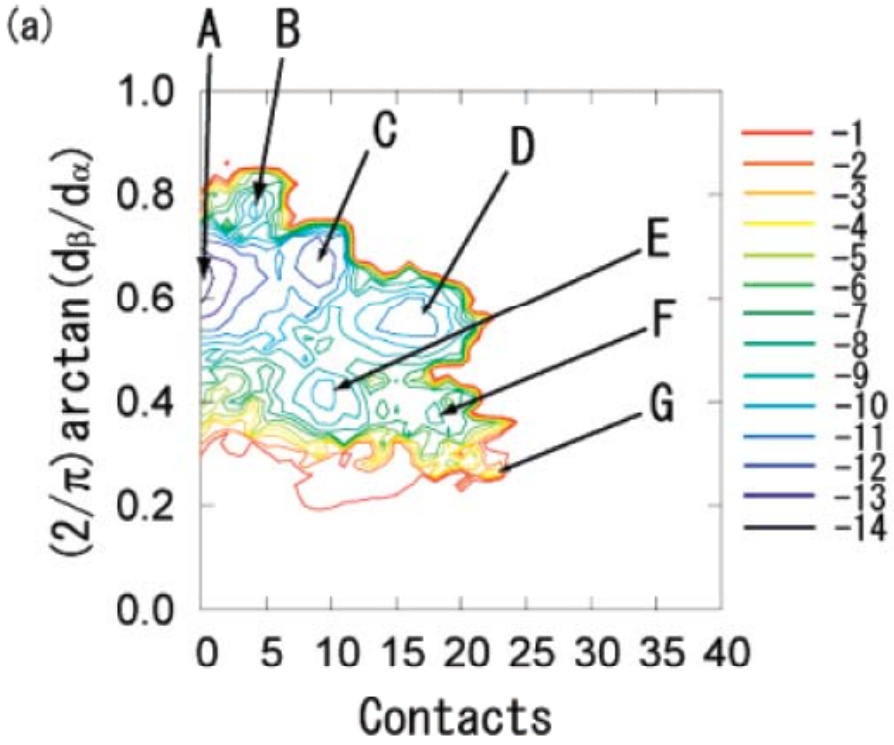


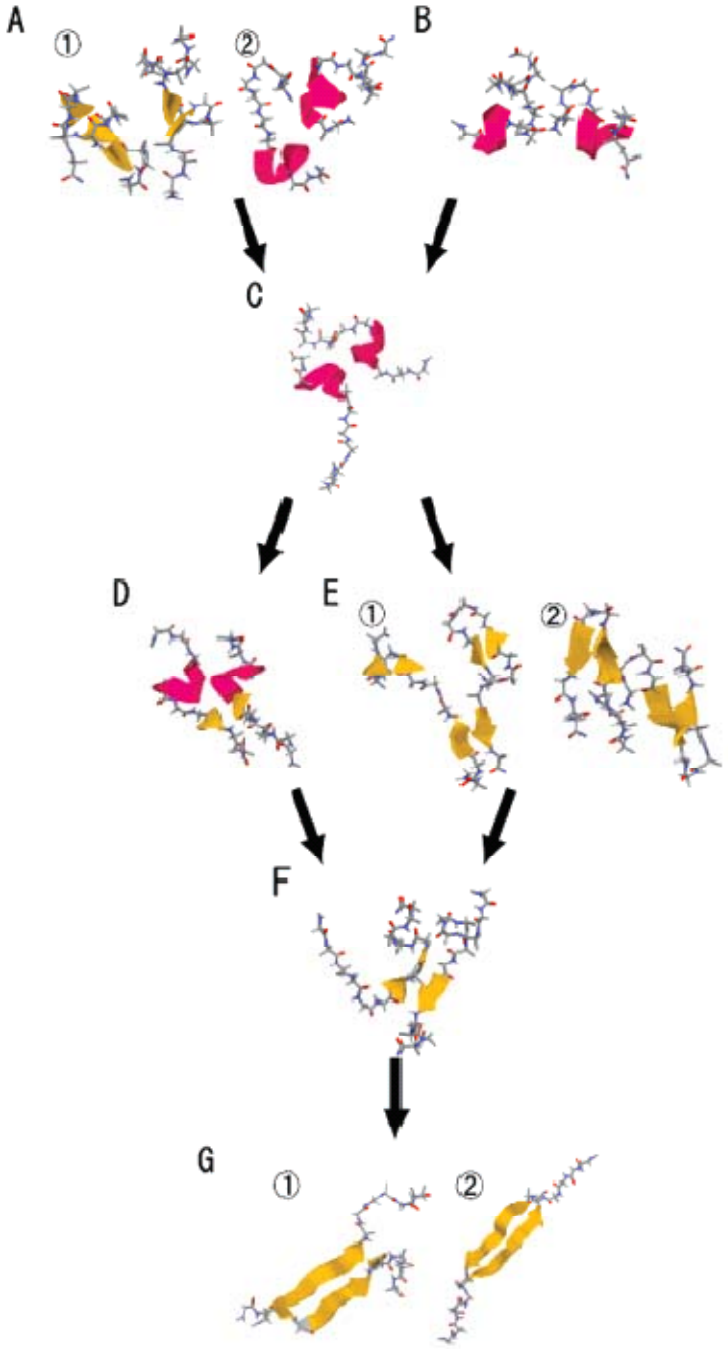


Typical Structures of Monomers

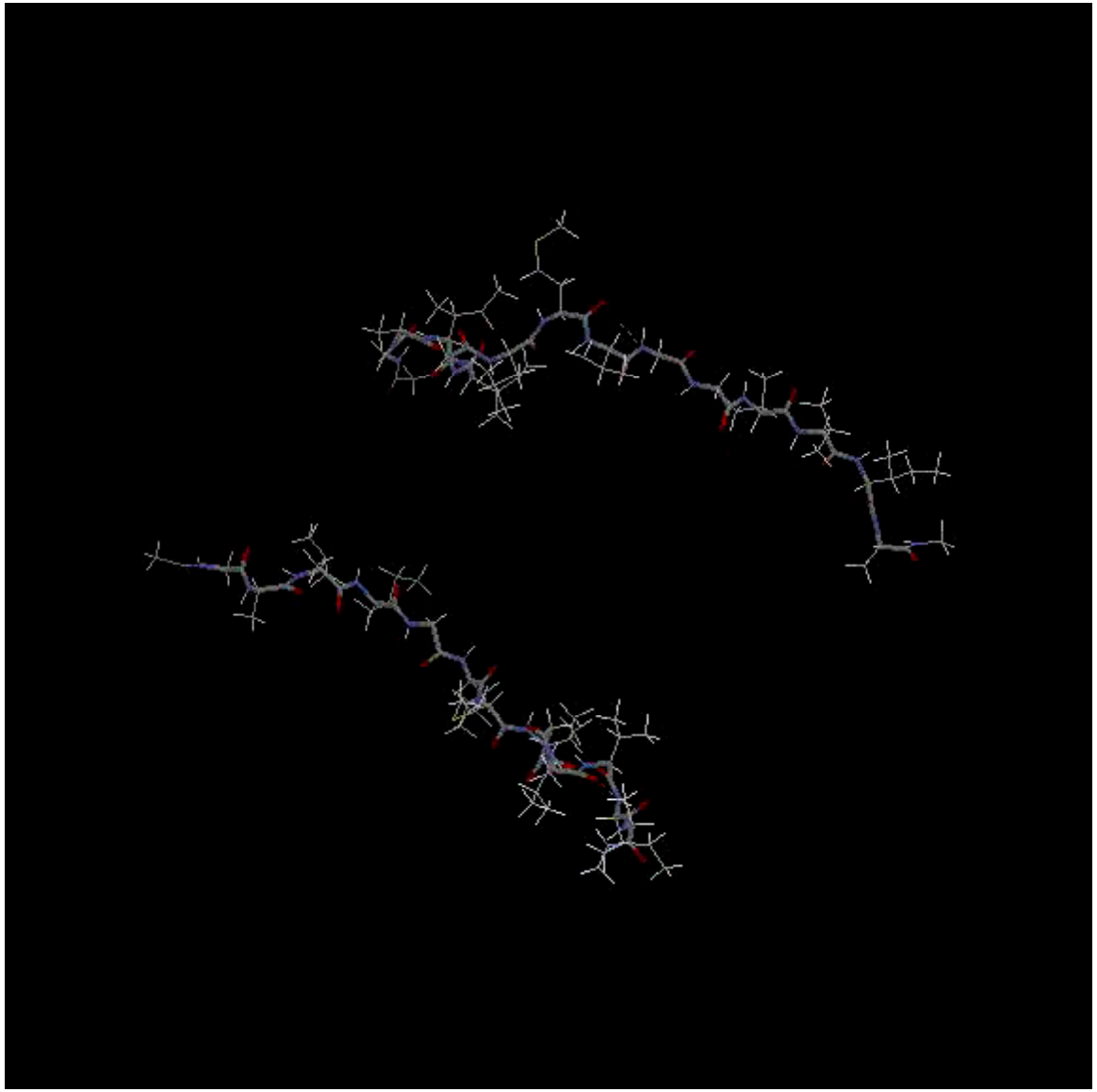
Free-energy landscape

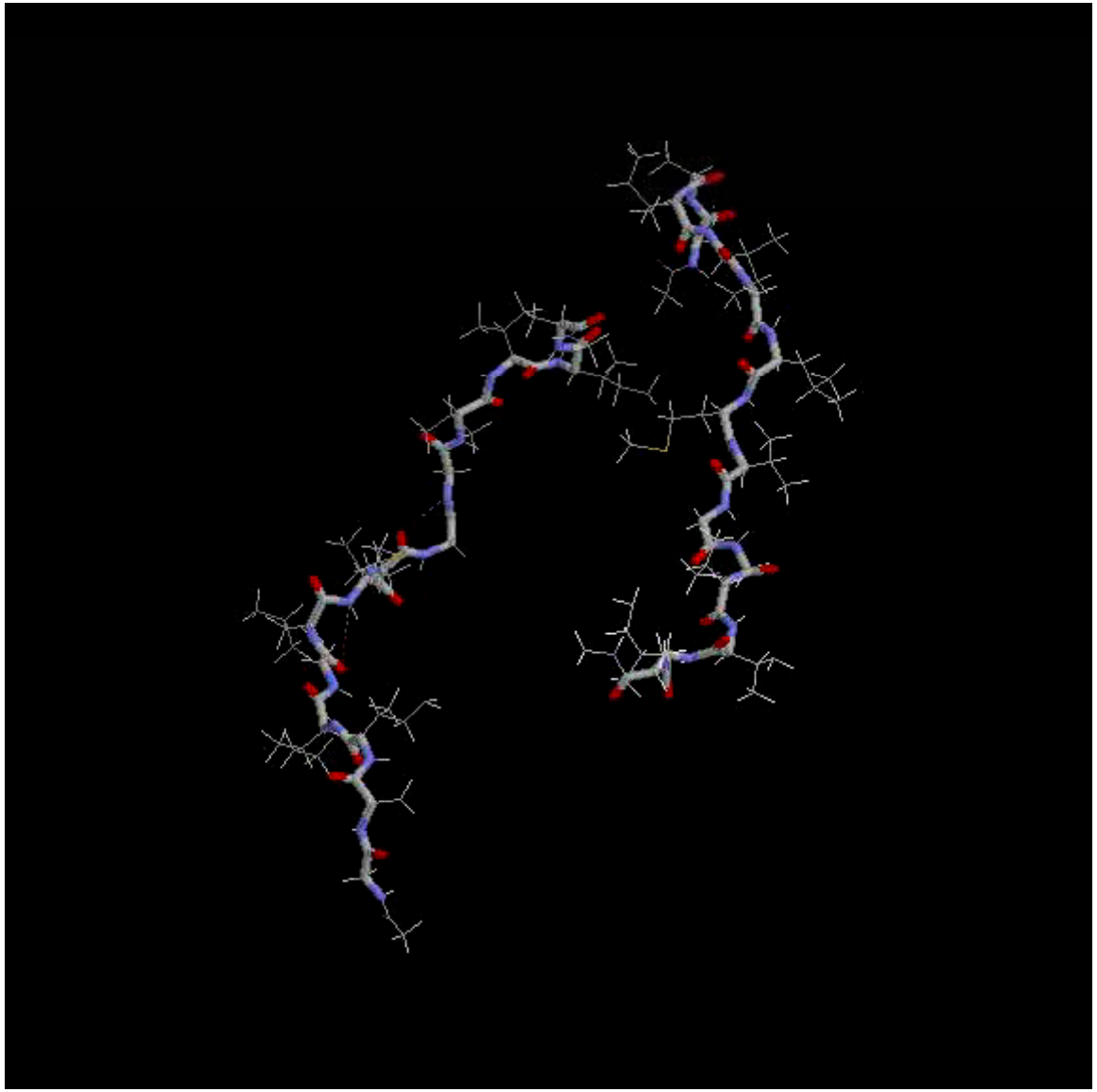
at T = 300 K

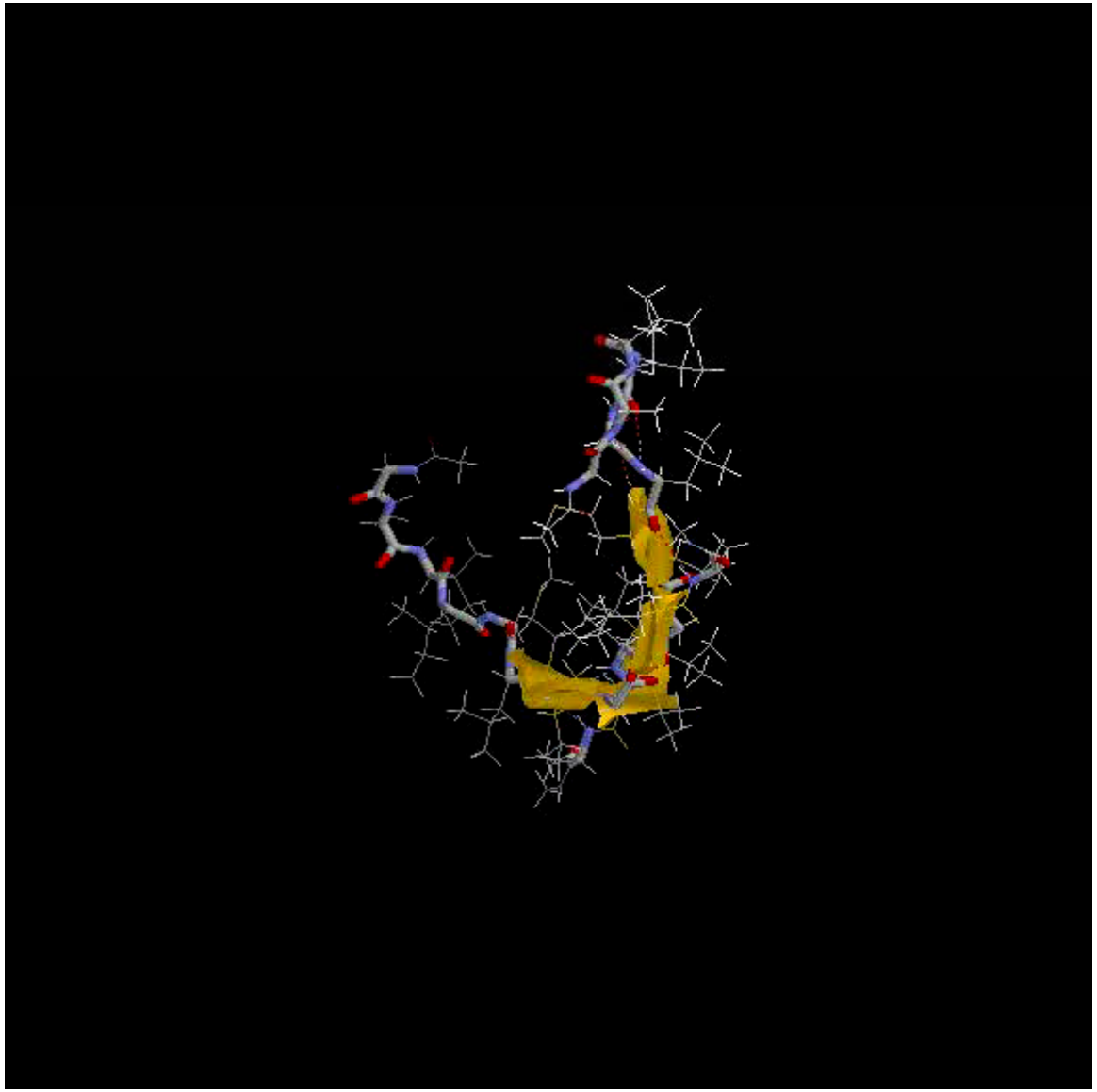




S.G. Itoh & Y.O.,
J. Phys. Chem. B **112**, 2767 (2008).







SUMMARY

We have shown the effectiveness of generalized-ensemble algorithms (such as multicanonical algorithm, replica-exchange method, and their generalizations) in simulations of complex systems such as spin systems and biomolecular systems.

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