蛋白研セミナー05Mar2011

*Platypus*によるhybrid-QM/MDとDFTによる超並列計算

阪大蛋白研: 米澤 康滋
阪大理学部: 山中 秀介
NEC: 中田 一人

Ab initio QM/MD連成計算プログラム（*platypus*）の開発

PLATform for dYnamic Protein Unified Simulation

【特徴】

1) オリジナルなコードによって超並列を実現する***ab initio*** **QM（RHF, UHF, R-DFT, U-DFT, MR-DFT, CASCI, MRCI)**と、古典力学による**MD**（分子動力学）との連成計算

2) 周期境界系に対して、**PME**法に替わる**Wolf**型長距離相互作用計算手法を導入。

3) **Multicanonical MD**や**Umbrella Sampling**法等の手法による ***ab initio*** **QM/MD** による自由エネルギー計算。

4) **Chain-of-State** 法による、超多重 – 高並列 最小自由エネルギー経路探索。

Wolf型Potential

特徴： Cutoff型Potentialで、超並列による高速化に適している。
Ewald法に匹敵する精度を実現できる。
Ewald法に固有のartifactが無い。

Charge neutrality

J. Chem. Phys., Vol. 110, No. 17, 1 May 1999

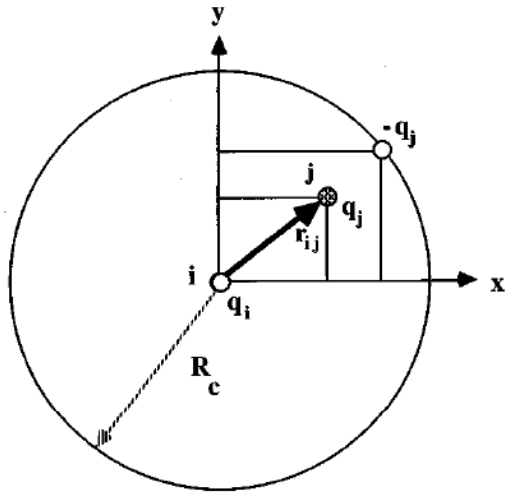
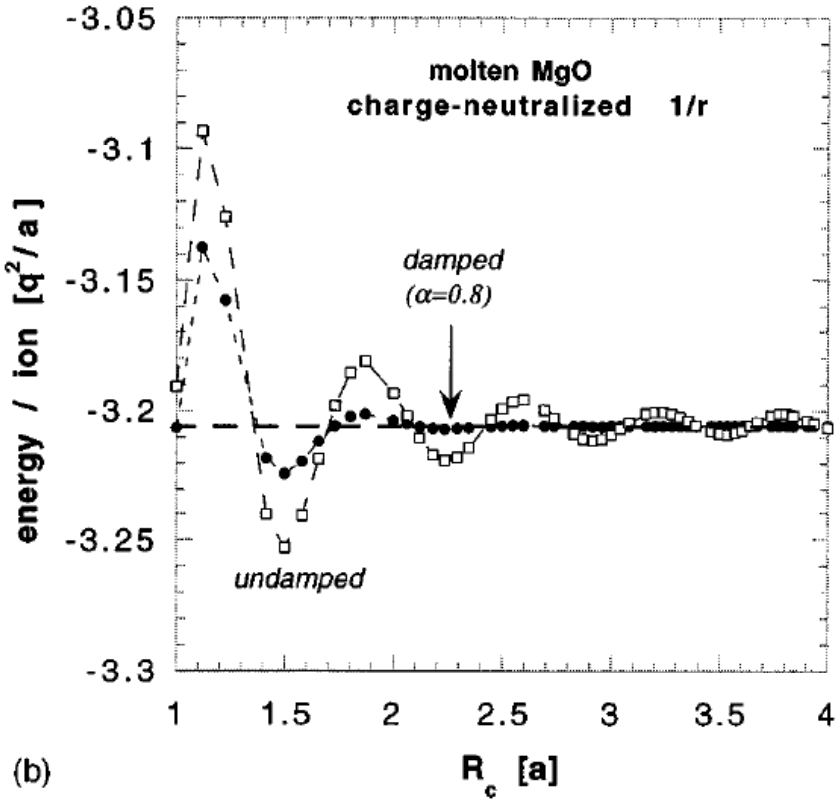


FIG. 11. An interpretation of Eqs. (3.10) and (3.11) is that for every charge q_j at distance r_{ij} from some central ion i, an image charge of opposite sign is projected onto the truncation sphere at R_c, such that ion i effectively interacts only with neutral pairs.

Damping potential



Potential とForce の誤差評価

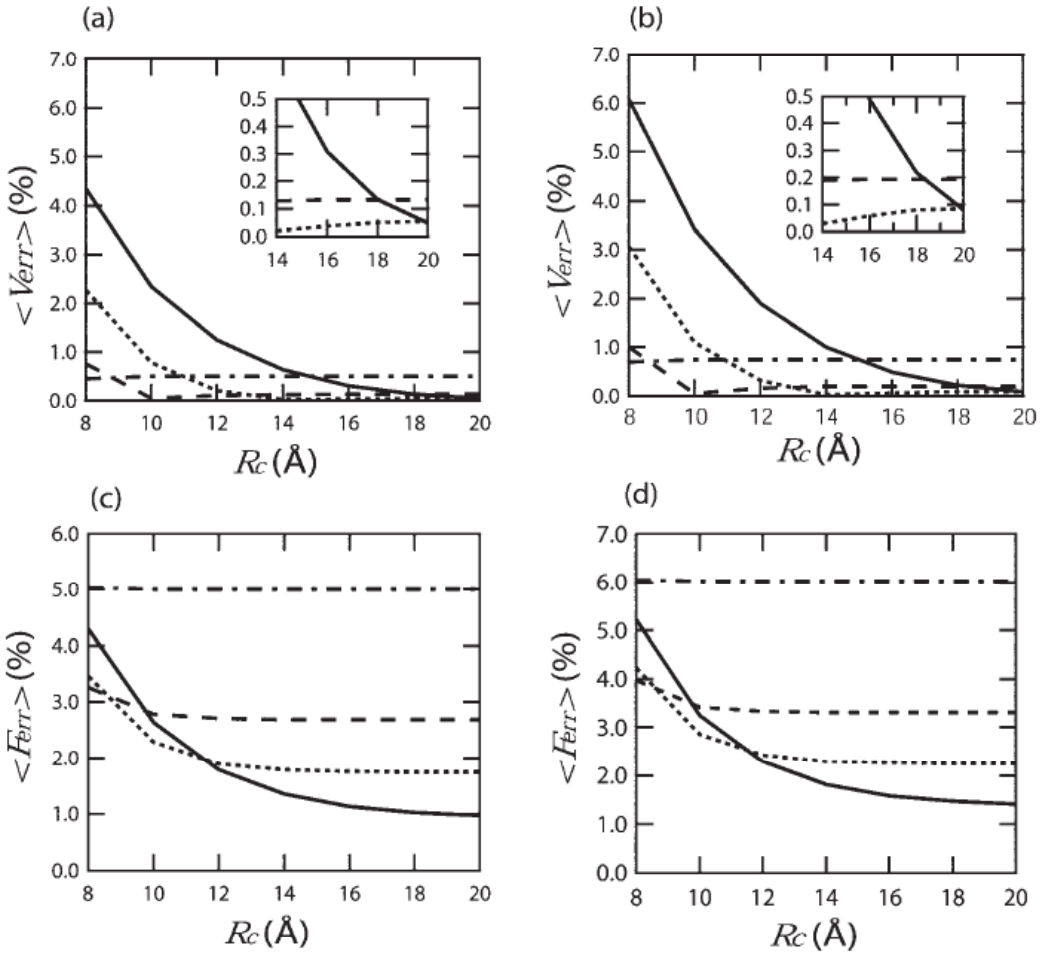


Figure 1. Upper two panels: Dependence of the electrostatic potential error, $\langle V_{err} \rangle$ in eq. (5), on α and cutoff distance R_c in the Fennell method with respect to the potential of the PME method (a) for the BPTI simulations, and (b) for the MAOA simulations. Insets are the magnified views at large R_c. Lower two panels: Dependence of the force vector error, $\langle F_{err} \rangle$ in eq. (6), on α and cutoff distance R_c in the Fennell method with respect to the PME method (c) for the BPTI simulations, and (d) for the MAOA simulations. Solid line, dotted line, dashed line and dotted-dashed line present with $\alpha = 0.1$, 0.15, 0.2, and 0.3 $Å^{-1}$, respectively.

Dynamicsの誤差評価

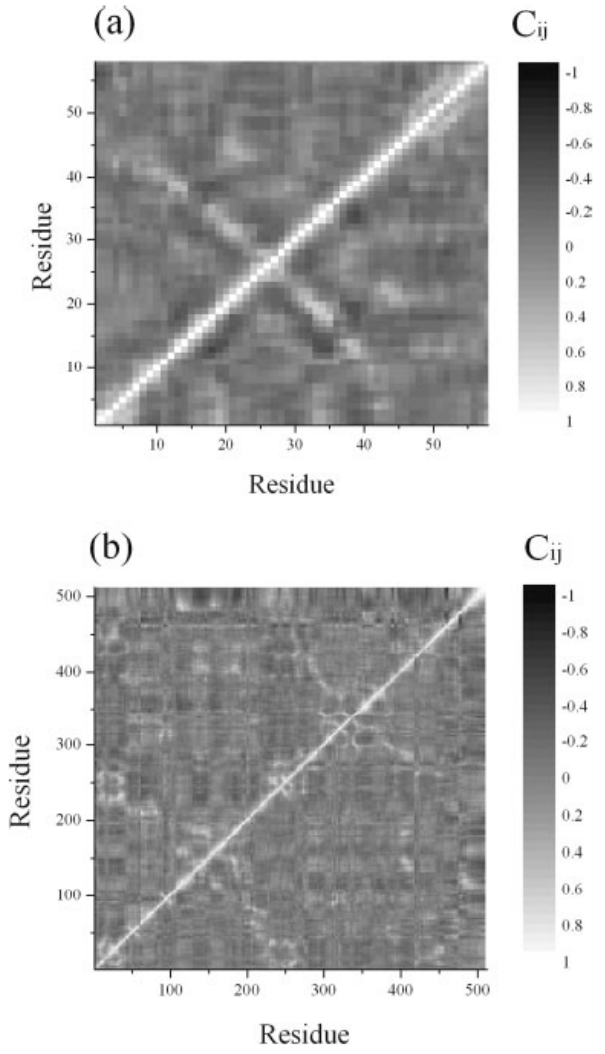


Figure 4. Time averaged cross-correlation matrix obtained by the Fennell method with $\alpha = 0.1$ $Å^{-1}$ and $R_c = 16$ Å (upper left triangle part of the matrix) and the PME method (lower right triangle part of the matrix), (a) for the BPTI simulations and (b) for the MAOA simulations.

Kikugawa G.; Apostolov R.; Kamiya N.; Himeno R.;Taiji M.; Nakamura H.; Yonezawa Y, JCC vol.30, 110-118, 2009

Improved Wolf Type Potential

Wolf type potential: Ewald法のFourier計算部分をtruncateしつつ、精度を保つ手法。

オリジナル法にはEnergy-Forceのinconsistencyがあったため、それを解決した。

$$\mathcal{E}(x) \equiv \frac{1}{2}\sum_{i\in\mathcal{N}}\sum_{j\in\mathcal{N}_i} q_i q_j \tilde{V}(r_{ij}) + \left(\frac{c}{2} - \frac{\alpha}{\sqrt{\pi}}\right)\sum_{i\in\mathcal{N}} q_i^2 .$$

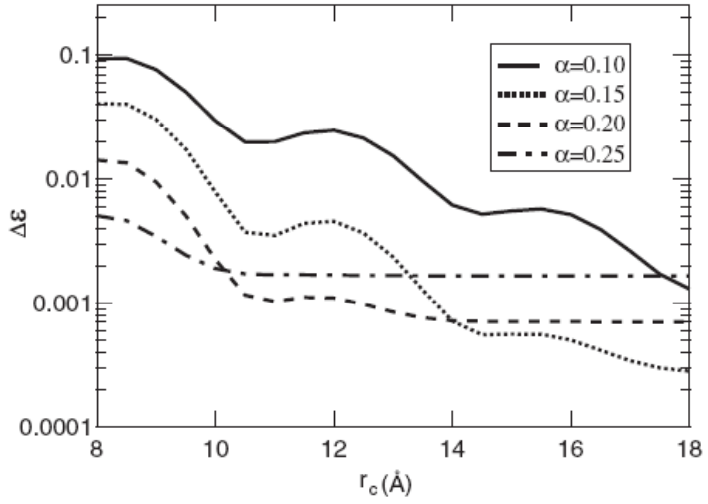


Fig. 1. Total coulombic energy difference $\Delta\mathcal{E}$ (dimensionless) between current and Ewald methods in NaCl liquid system. Differences are shown for each value of the current method parameter: cutoff length r_c (Å) and damping parameter α (Å^{-1}).

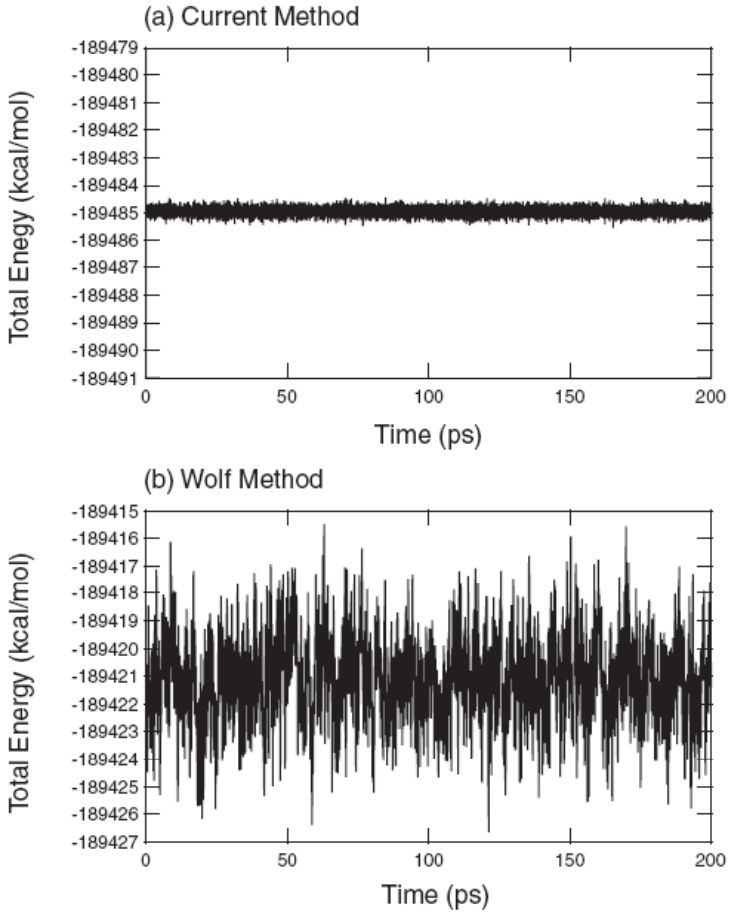
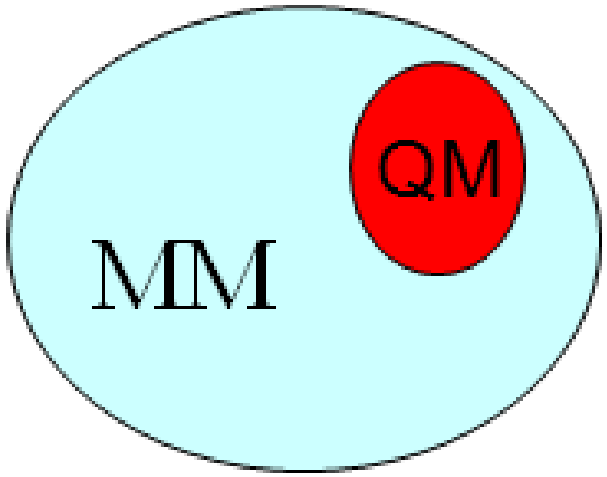


Fig. 2. Energy trajectory in *NEV* simulation of NaCl system, obtained by (a) current method with $r_c = 12$ Å and $\alpha = 0.2$ Å^{-1} and by (b) original Wolf method with same parameter values.

(I. Fukuda, Y. Yonezawa, H. Nakamura (2008) J. Phys. Soc. Jpn. 77, 114301)

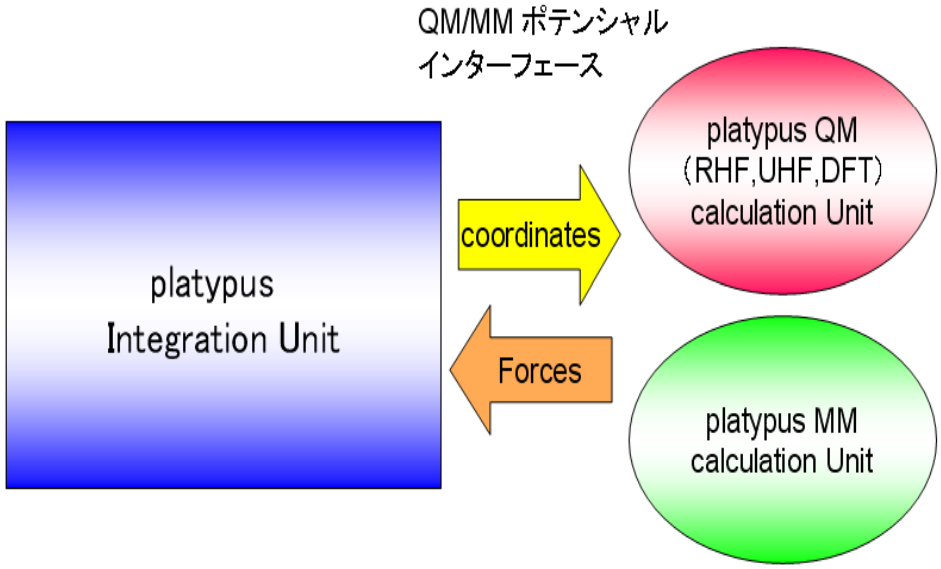
QM/MD:
Quantum/Classical Multi Level Molecular Dynamics Simulations



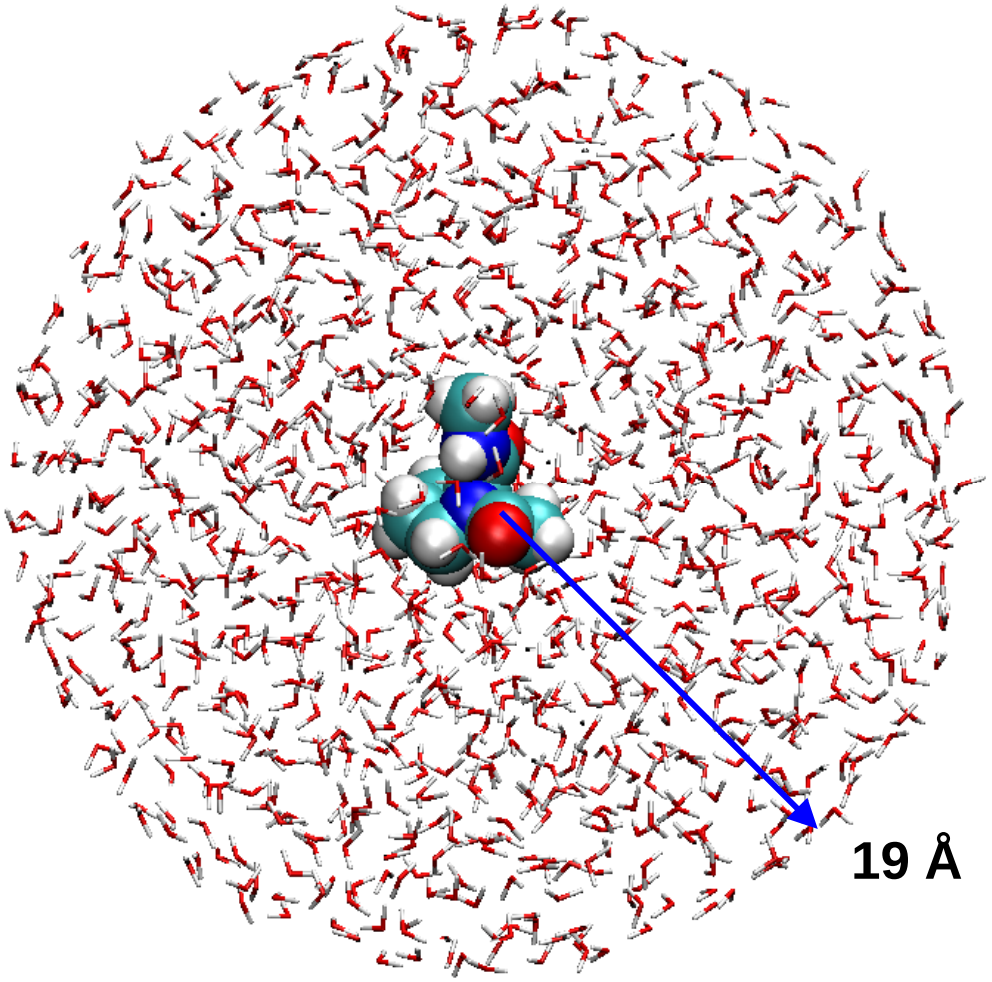
$$E_{tot} = E_{QM} + E_{MM} + E_{QM/MM}$$

$$E_{QM/MM} = E_{vdW} + E_{ele}$$

The QM/MM simulation system



Cis-trans isomerization process of a solvated Proline dipeptide



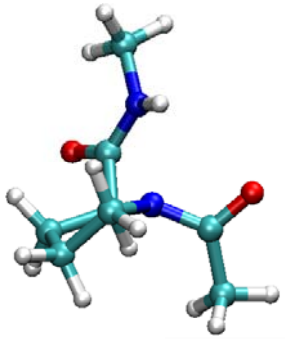
Simulation system

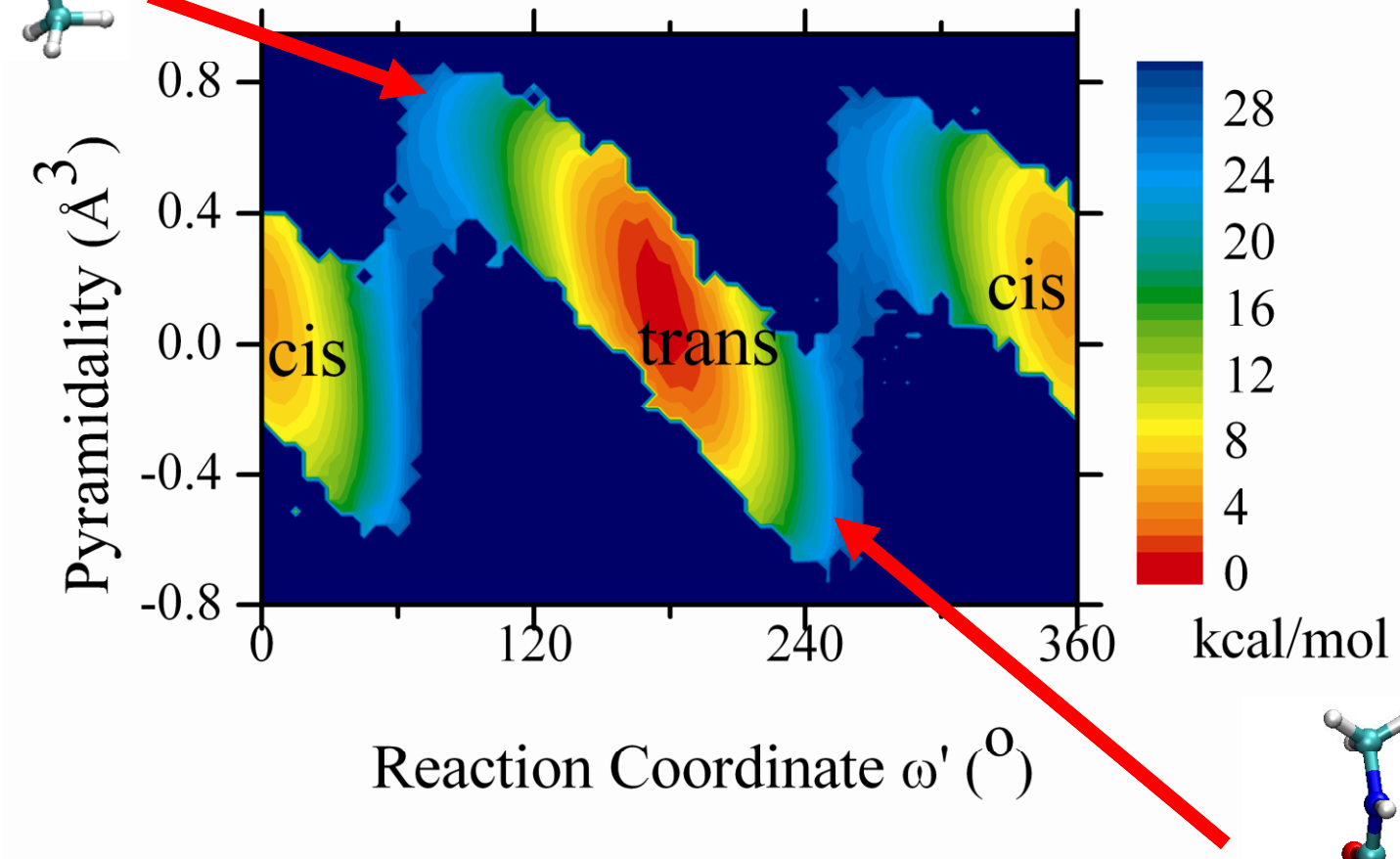
Ace-Pro-NMe in TIP3P 1354
Basis Set 4-31G
Δt = 2 fsec
Cutoff = 12 Å 300K
Umbrella sampling/Umbrella integration methods

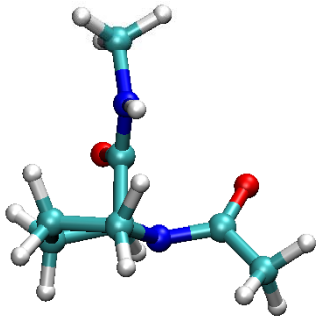
Computation with *Platypus* program

Free energy landscape of the pyramidality

(Yonezawa et al (2009) J. Ame. Chem. Soc.)



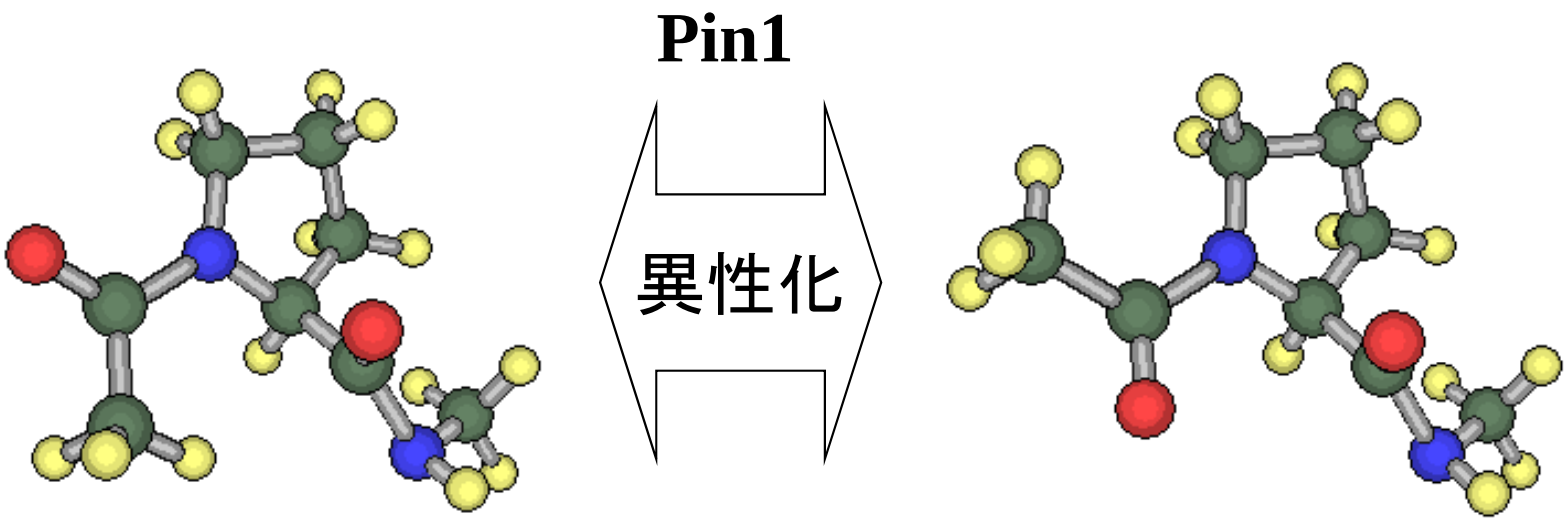




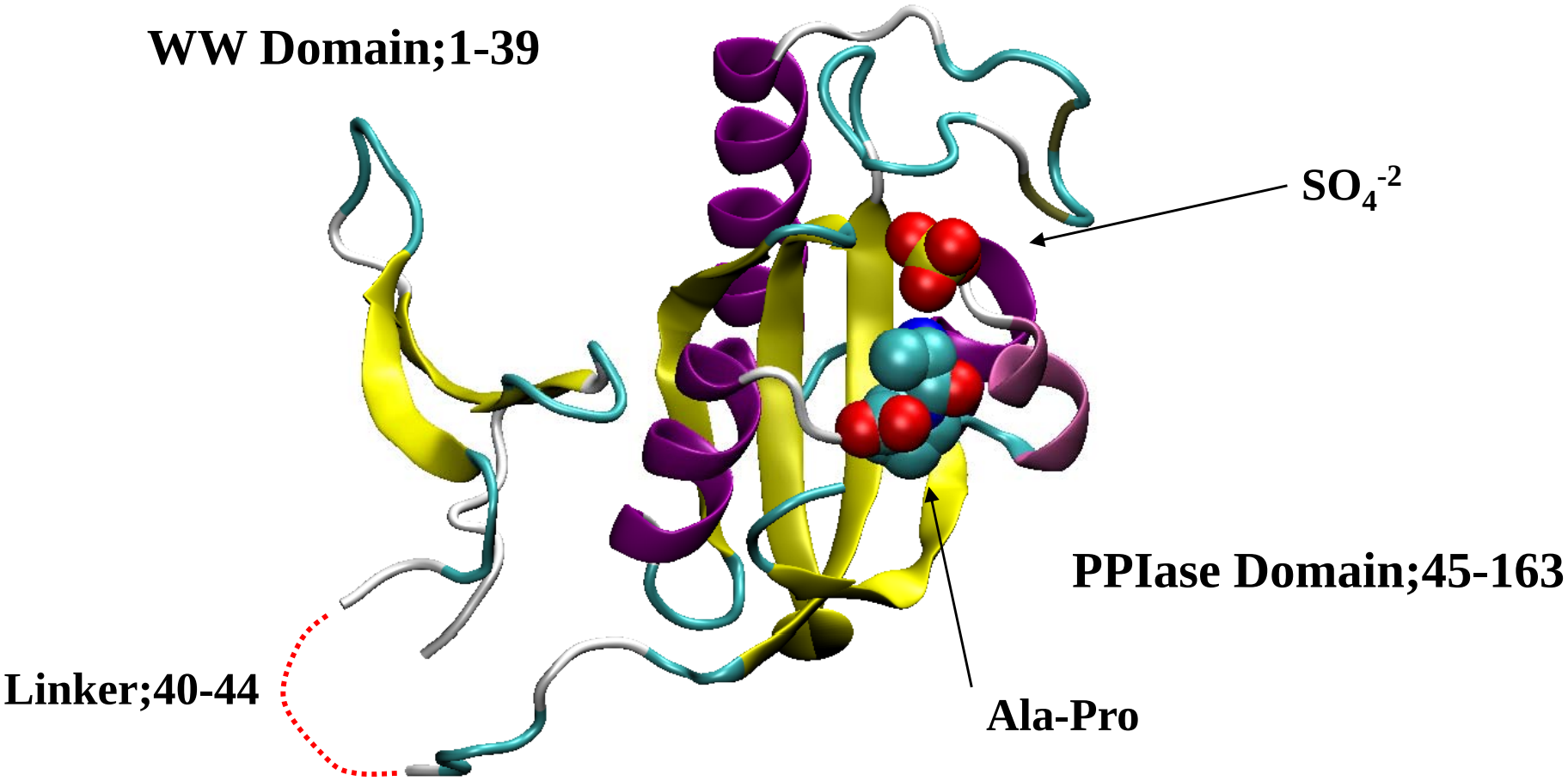
The pyramidal conformations is confirmed as the transition state, reducing the barrier height.

Pin1によるプロリン異性化反応

Pin1, one of the peptidyl-prolyl isomerases (PPIase), catalyzes the isomerization of the peptide bond between pSer/Thr-Pro in proteins, thereby regulating their biological functions which include protein assembly, folding, intracellular transport, intracellular signaling, transcription, cell cycle progression and apoptosis.



Xray Structure of Pin1 (PDB Code: 1PIN)

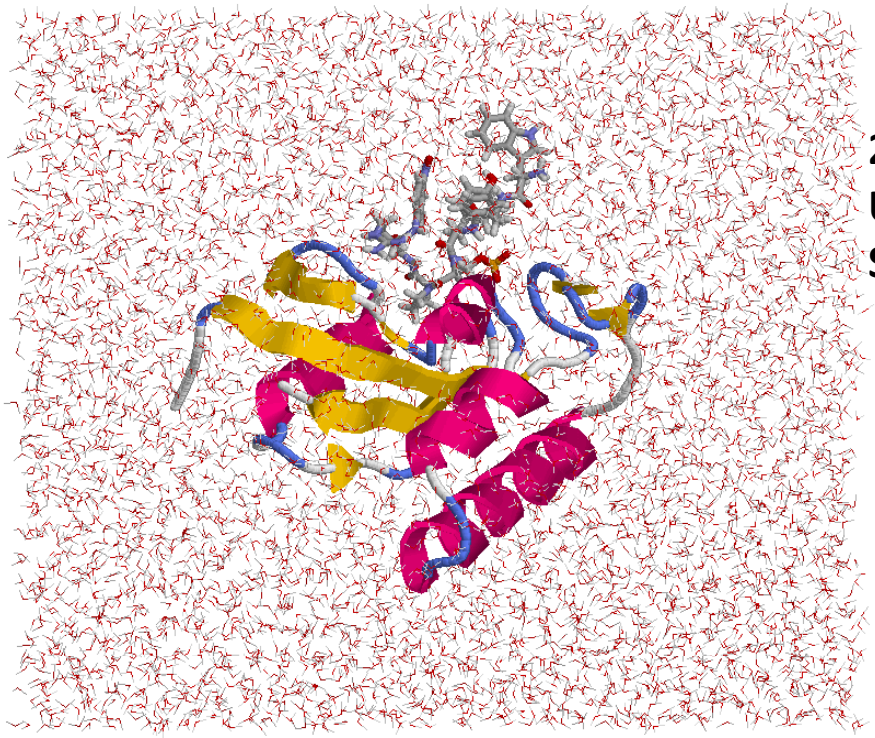


Structural and Functional Analysis of the Mitotic Rotamase Pin1 Suggests Substrate Recognition Is Phosphorylation Dependent

Rama Ranganathan, Kun Ping Lu, Tony Hunter, and Joseph P. Noel

Cell,Volume 89, Issue 6, 13 June 1997, Pages 875-886

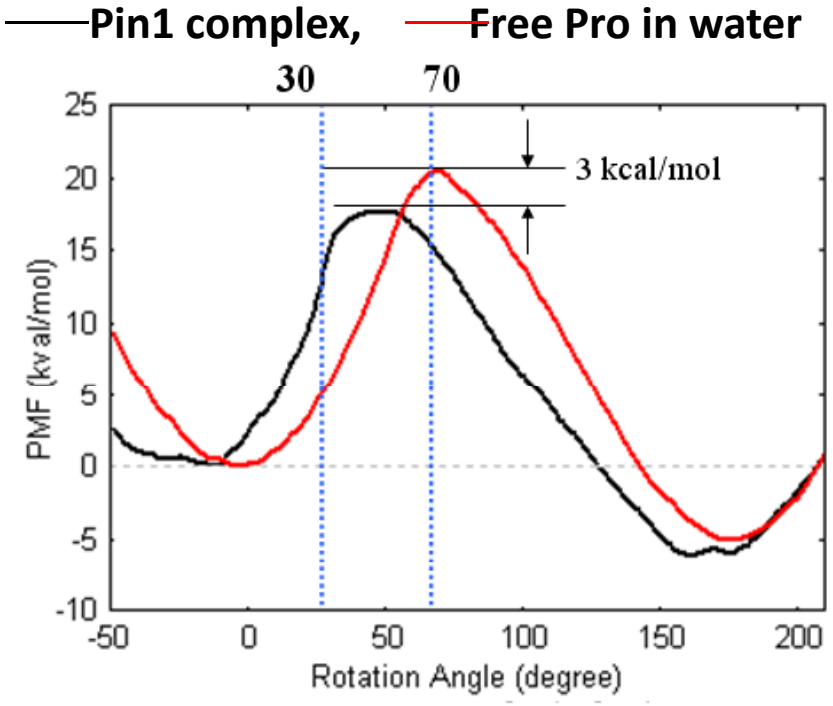
Ab initio QM/MD連成シミュレーションによる Prolyl Peptidyl Isomerase (PPIase) Pin1 Enzyme の研究



26 QM/MD-Umbrella Simulations

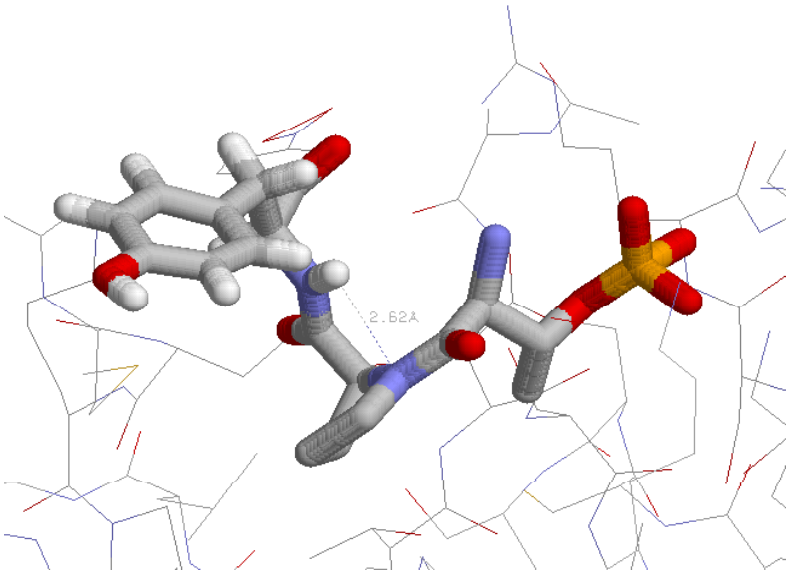
with Xeon 3.16GHz 172Core (10days)

Free energy landscape of proline binding to Pin1

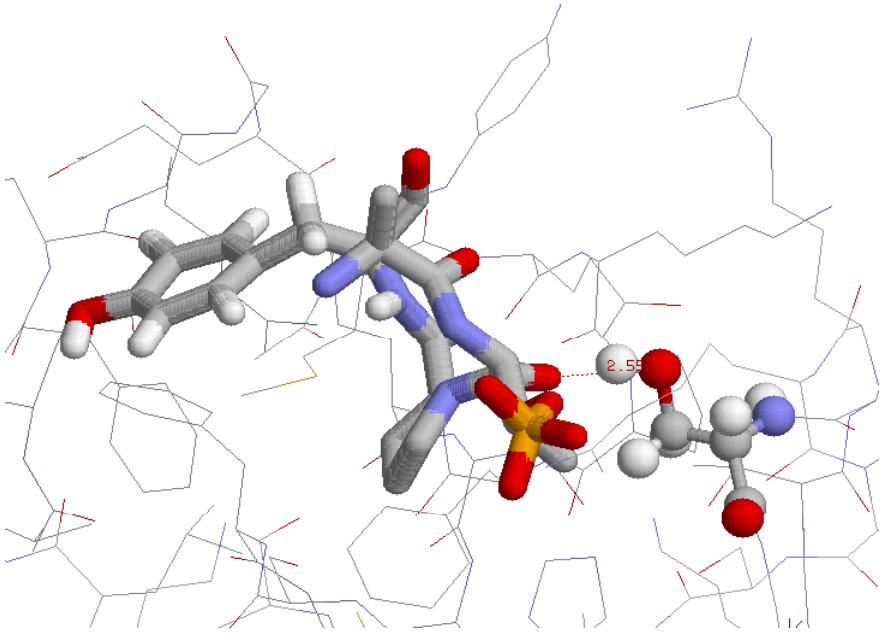


Total atoms: 21957 (QM atoms:26)
Periodic Boundary Condition with a cell: 54 x 70 x 60 Å^3
Basis set: 4-31G

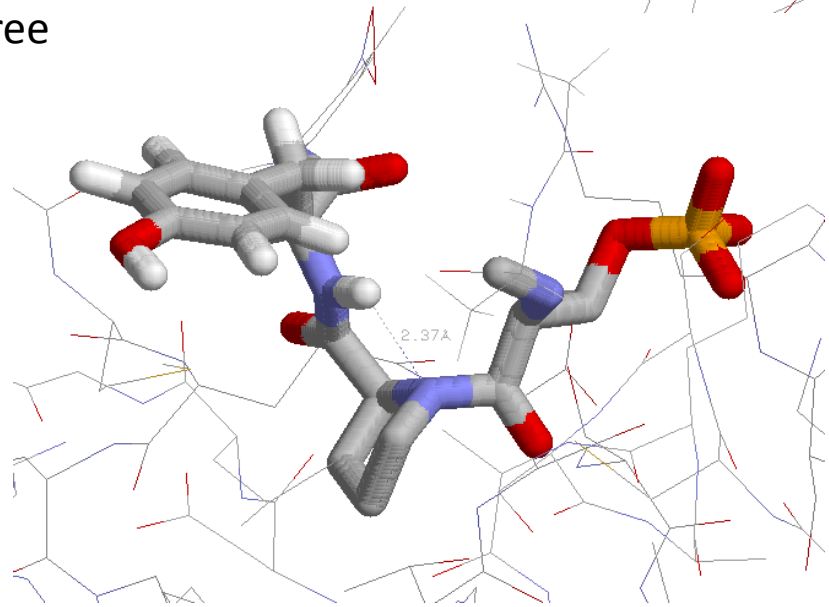
Umbrella Integration 法により、高精度で **Pin1 PPIase** における**Pro**の***cis-trans***異性化反応の自由エネルギー地形を決定。



Cis : ω = 0 degree



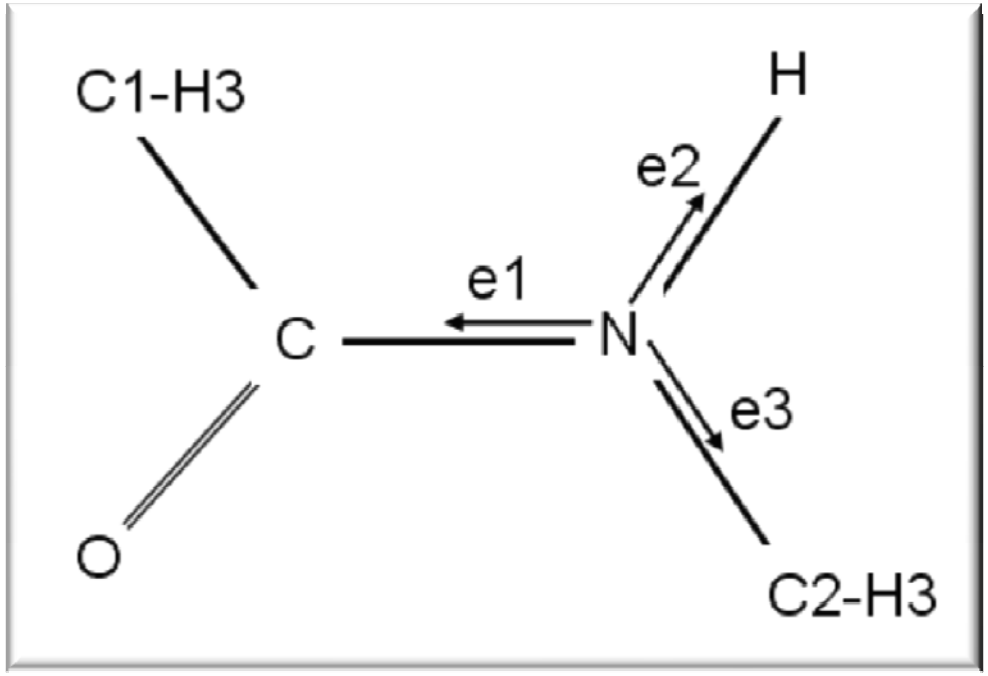
Trans : Ser144 と水素結合
ω = 150 degree



TS: Pyramidal conformation ω = 60 degree

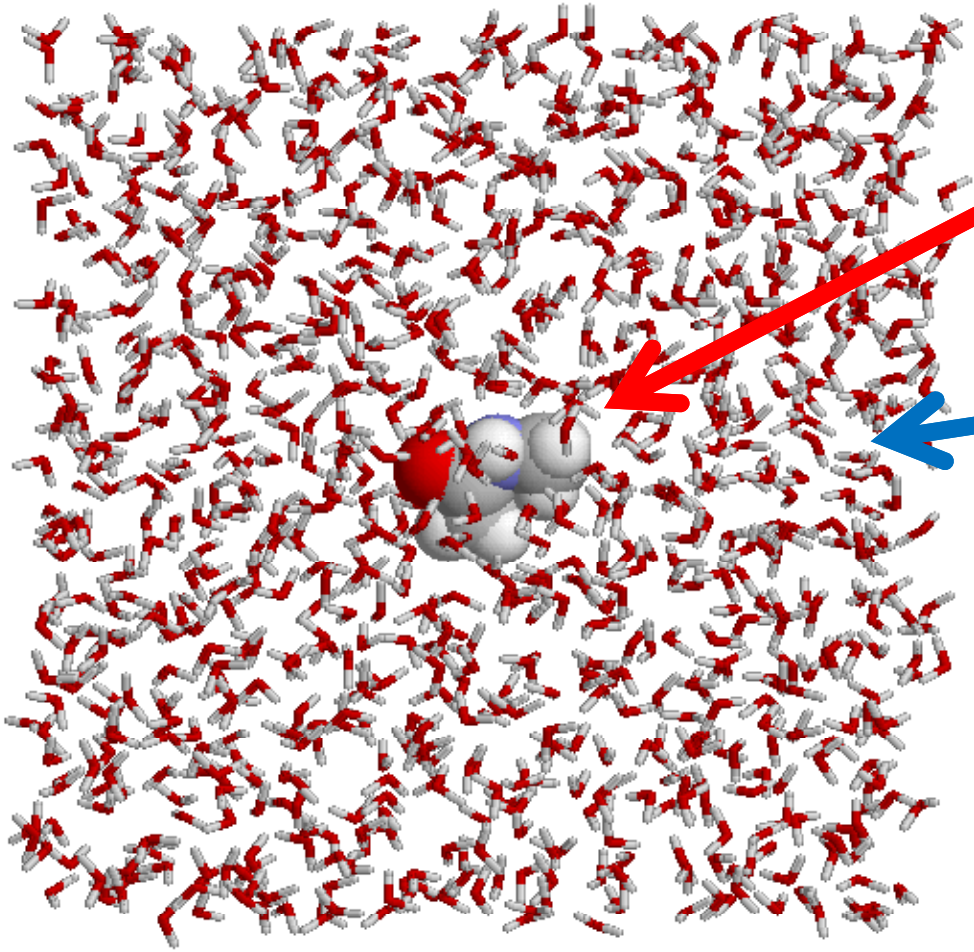
,

A transition state in the isomerization: Pyramidal Comformation



N-methylacetamide and unit vectors **e1**, **e2**, and **e3** in the above equation .

$$\text{Pyramidality} = \det\left|\mathbf{e1}, \mathbf{e2}, \mathbf{e3}\right|$$



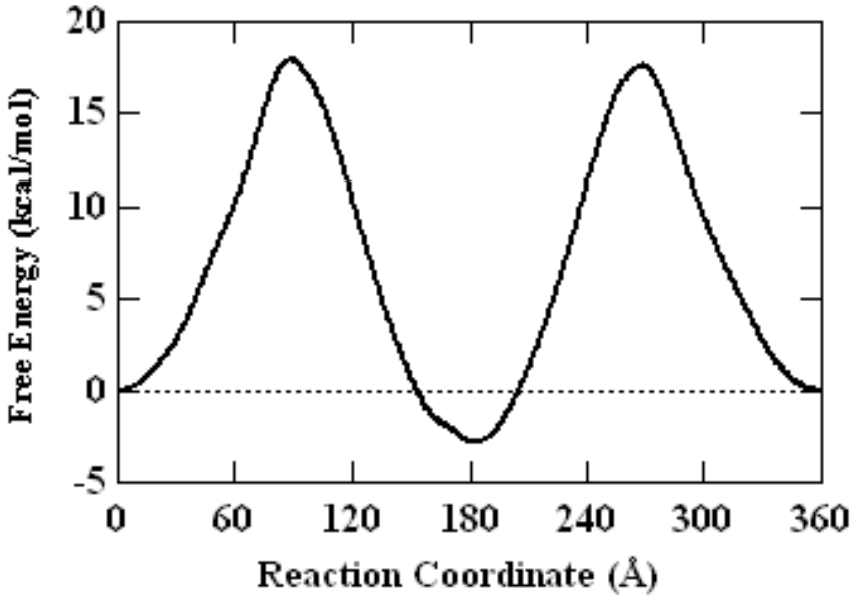
The system:

N-Methylacetamide
RHF 6-31G Basis Set

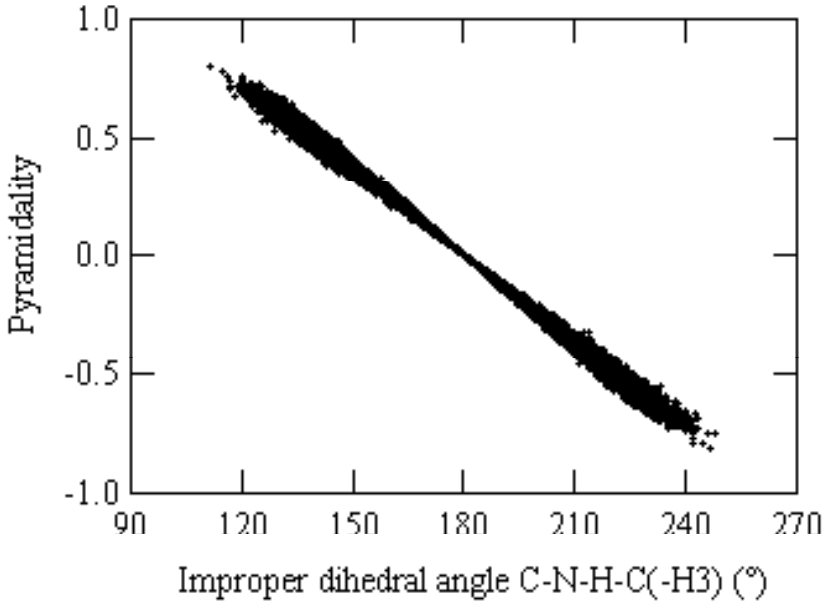
Water TIP3P model
893 molecules

Total 2691 atoms in the system

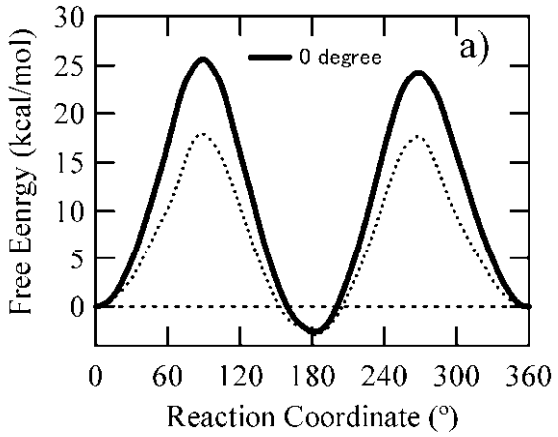
NVT ensemble
Periodic Boundary Conditions
30x30x30 $Å^3$

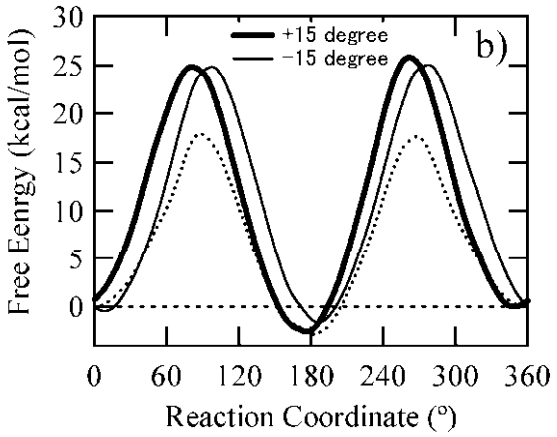


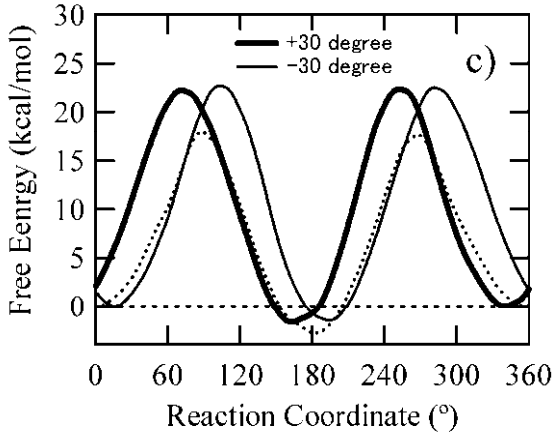
The potential of mean force of the cis-trans isomerization of NMA with respect to the reaction coordinate （Chem.Phys.Lett. 503,2011,p139-144）

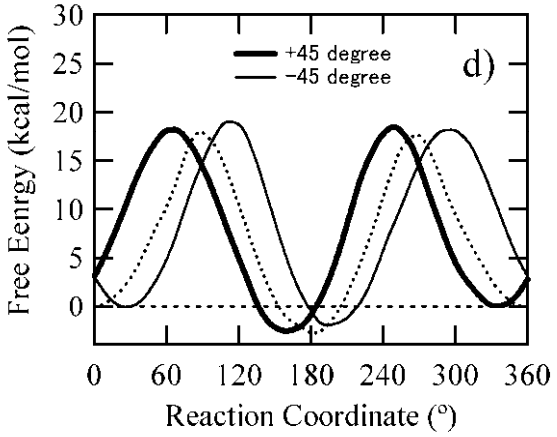


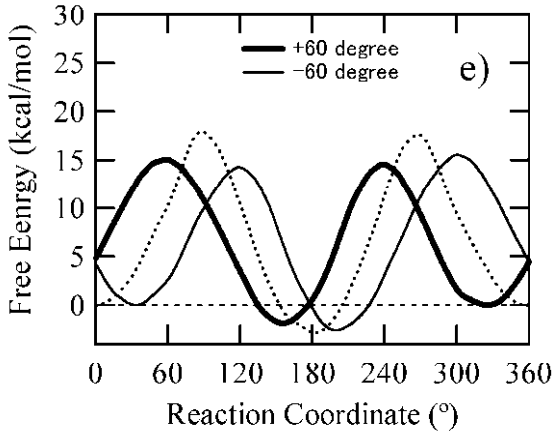
Pyramidality of the NMA conformations as functions of the improper dihedral angle C-N-H-C(-H3)
（Chem.Phys.Lett. 503,2011,p139-144）

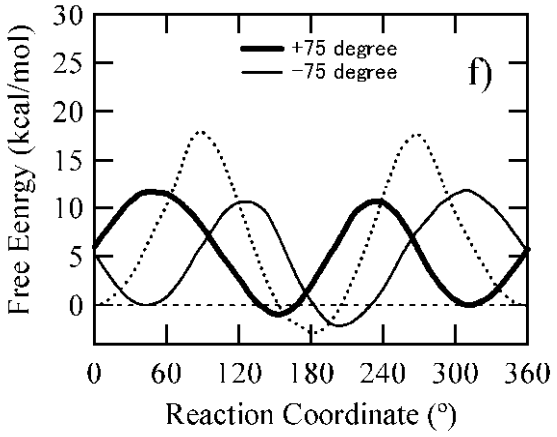






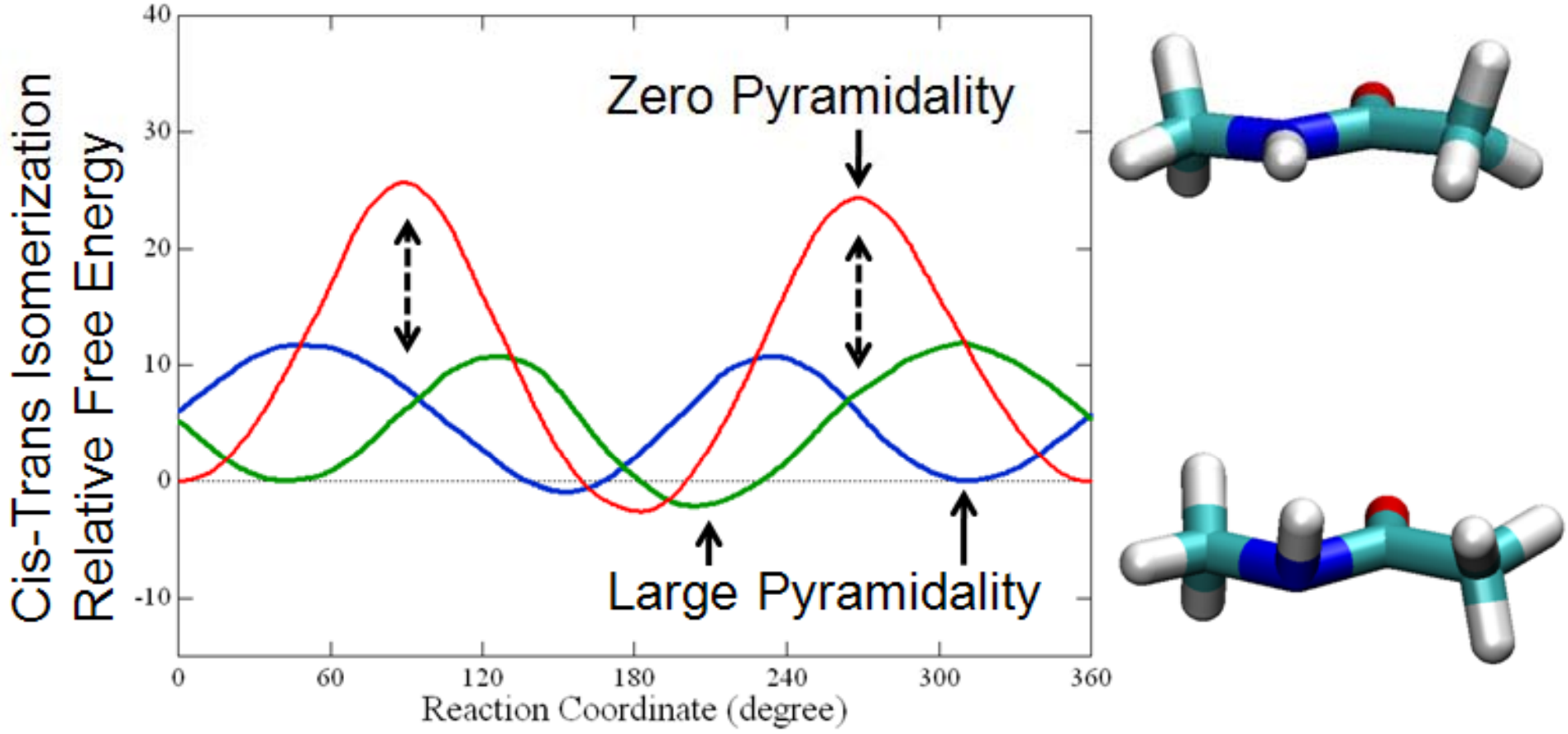






Free energy landscape of NMA with various restraining value of the improper dihedral angle in the cis-trans isomerizations. a) the value of the improper dihedral angle restraining to 0 degree, b) +15° and -15°, c) +30° and -30°, d) +45° and -45°, e) +60° and -60°, f) +75° and -75°.

（Chem.Phys.Lett. 503,2011,p139-144）



（Chem.Phys.Lett. 503,2011,p139-144）

Platypus_qm

生体高分子の大規模超並列分子軌道理論計算:
RHF、DFT、CASSCF、CIS-DFT
数百～数千原子（中田、山中）

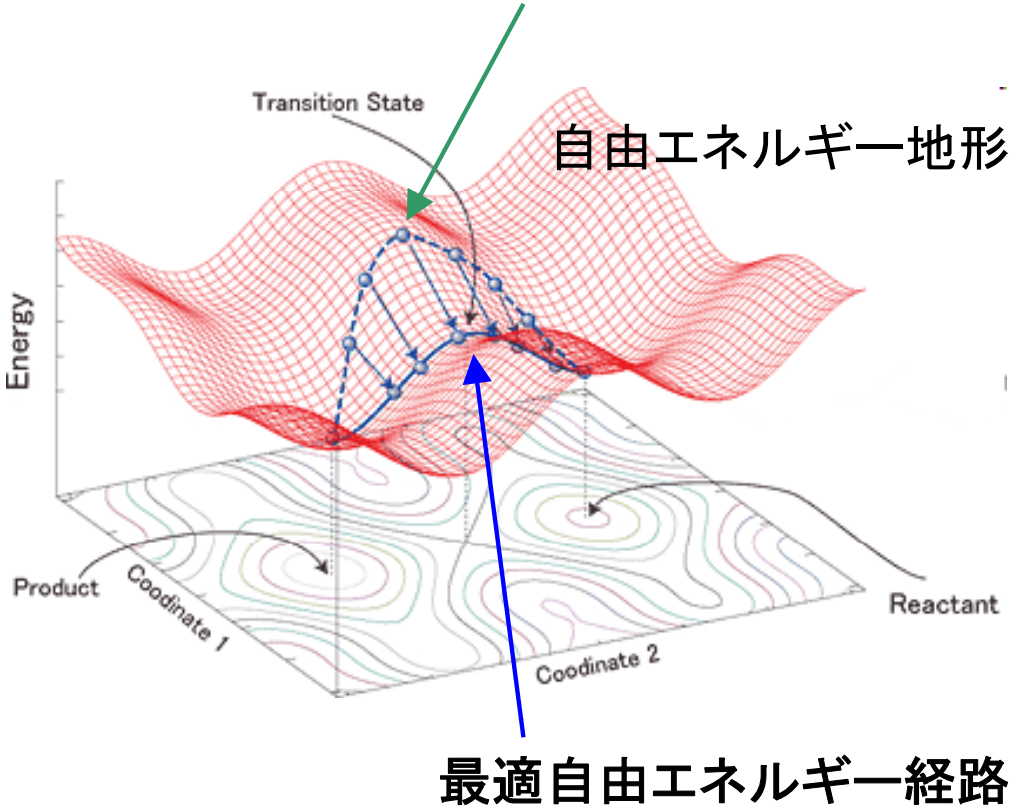
Platypus_qmmm

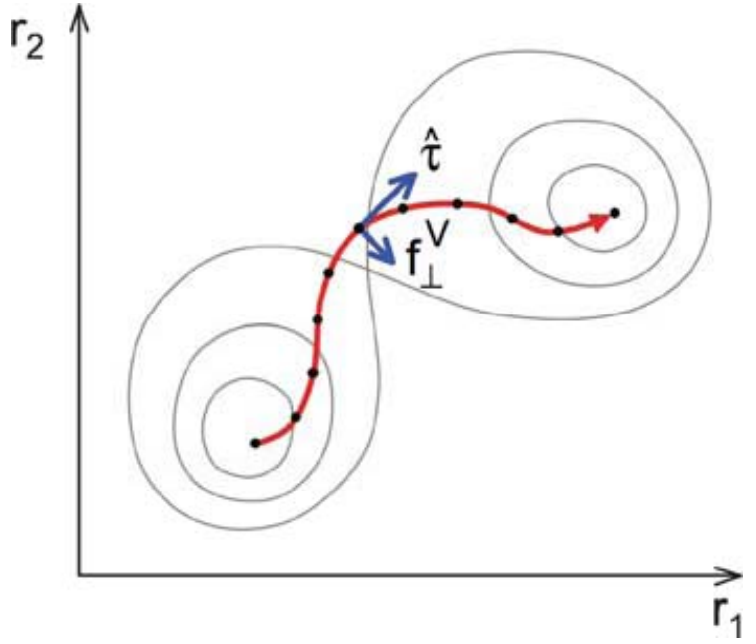
生体高分子の効率的な自由エネルギー地形:

Chain-of-State 法;
QM/MDの粗結合による並行連成シミュレーション
数十～百QM原子＋数万MM原子

Chain-of-State（String Method）と hybrid-QM/MDを利用した酵素反応機構研究

各点（～100点）で、QM/MD連成計算（～1000並列）を実行する。



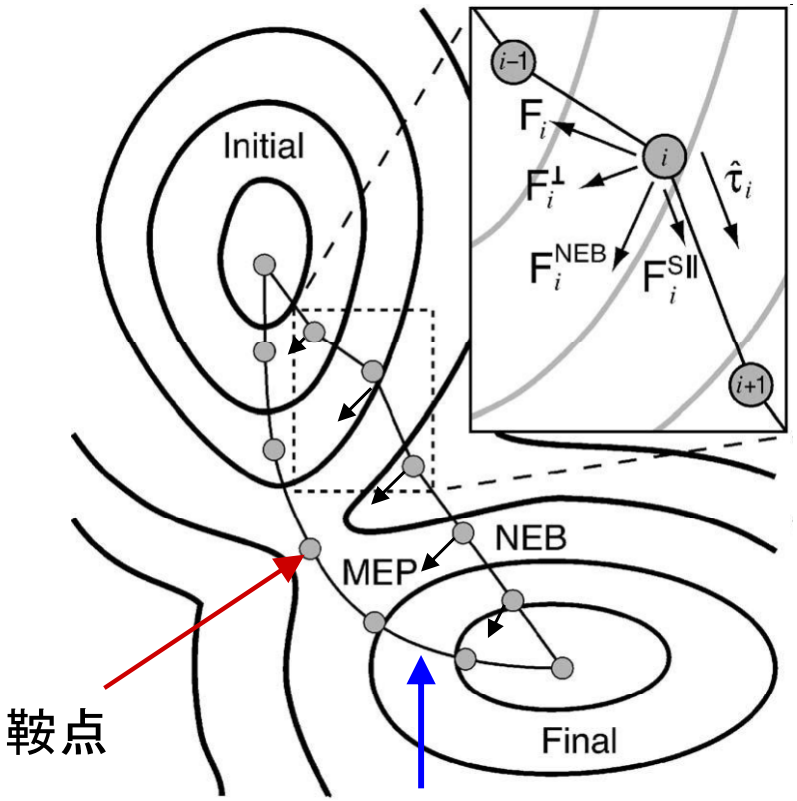


String or Nudged Elastic Band

酵素機構の解明

Chain-of-State Method

最小エネルギー経路、最小自由エネルギー経路を探索する方法。



最適経路

D. Sheppard, R. Terrell, and G. Henkelman, *J. Chem. Phys.* **128**, 134106 (2008).

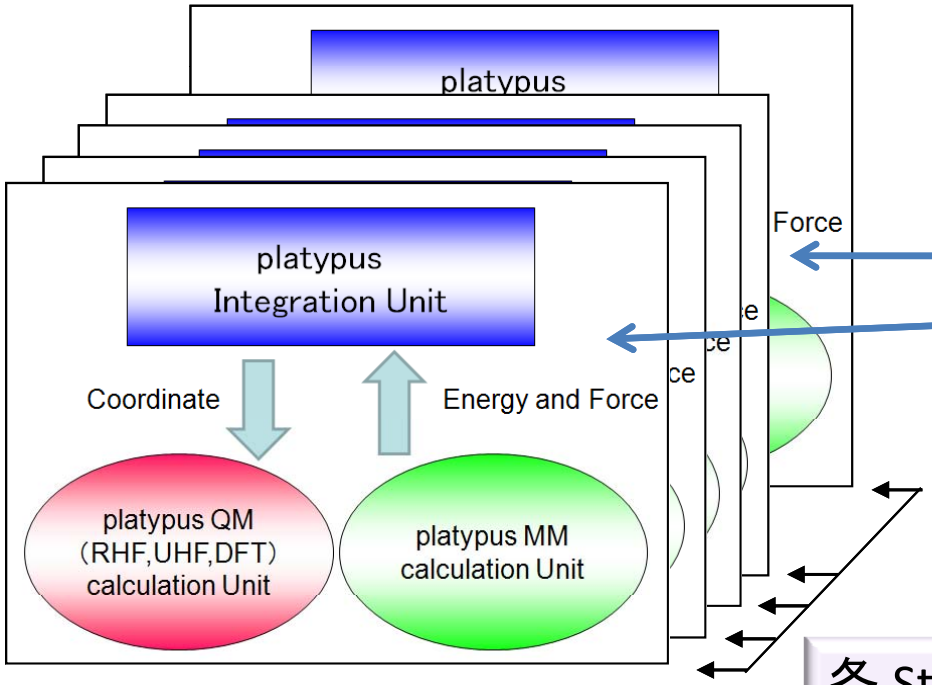
始状態と終状態を結ぶ、いくつかの
位相空間点を位相空間でエネルギー最小化
もしくは自由エネルギー最小化して、
位相空間点が均一に並ぶ位相空間経路
（＝最適経路）を決定する方法。

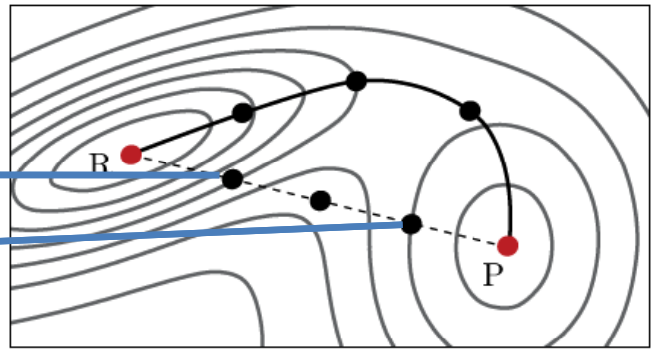
鞍点＝遷移状態
も得られる。

酵素反応経路や蛋白質の大きなコンフォメーション変化経路を、
（粗結合による超高並列）で決定できる。

粗結合MPI通信による“超多重 - 並列 ”QM/MD の実現

MPI分割による、QM/MD複製 （初期化、
各々のUmbrella Potential Setting）





各 State 間のデータ通信、
共有及びQM/MD のUpdate

Umbrella Integration Method → Potential of mean force

$$\Delta A_{a\to b} = \int_{\xi_a}^{\xi_b} \left\langle \frac{\partial E}{\partial \xi} \right\rangle_{\xi'} d\xi' = \int_{\xi_a}^{\xi_b} \langle F_c \rangle_{\xi'} d\xi'$$ Thermodynamic Integration

$$\omega_i(\xi) = \frac{1}{2} K (\xi - \xi_i)^2$$

$$A_i^u(\xi) = -\frac{1}{\beta} \ln P_i^b(\xi) - \omega_i(\xi) + F_i$$ Umbrella Simulation

$$\frac{\partial A_i^u}{\partial \xi} = \frac{\partial A_i^b}{\partial \xi} - \frac{d\omega_i}{d\xi} = -\frac{1}{\beta} \frac{\ln P_i^b(\xi)}{\partial \xi} - \frac{d\omega_i}{d\xi} \quad P_i^b(\xi) = \frac{1}{\sigma_i^b \sqrt{2\pi}} \exp\left[-\frac{1}{2} \left(\frac{\xi - \bar{\xi}^b{}_i}{\sigma_i^b} \right)^2 \right]$$

$$\frac{\partial A_i^u}{\partial \xi} = \frac{1}{\beta} \frac{\xi - \bar{\xi}^b{}_i}{\partial \xi} - K(\xi - \xi_i)$$ 一つの**Window**

$$P_i(\xi) = \frac{N_i P_i^b(\xi)}{\sum_i N_i P_i^b(\xi)}$$ 全ての**Window**の和

$$\left. \frac{\partial A_i^u}{\partial \xi} \right|_{\xi_{bin}} = \sum_i^{windows} p_i(\xi_{bin}) \left(\frac{\partial A_i^u}{\partial \xi} \right)_{\xi_{bin}}$$ ←

Free Energy の微係数を求めて積分することで**PMF**を求める。

Bridging the gap between thermodynamic integration and umbrella sampling provides a novel analysis method: "Umbrella integration"
Johannes Kästner and Walter Thiel J. Chem. Phys. **123**, 144104 (2005)
(5 pages)