19th Feb. 2013,

External Review

@ CCS, University of Tsukuba

Computational Bioscience with Supercomputers

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Collaborators

Univ. Tsukuba

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Katsumasa Kamiya(Assist.Prof)
Kenji Shiraishi (Prof.)
Boku Taisuke (Prof.)
Mitsuhisa Sato (Prof.)
Masayuki Umemura (Prof.)
Kazuhiro Yabana(Prof.)
Tetsuo Hashimoto(Prof.)

Acknowledgements

T2K-Tsukuba, CCS, Univ. Tsukuba
HECToR, EPCC, Univ. Edinburgh

Outline

1. Overview of research fields

2. Recent results of Quantum Mechanics/ Molecular Mechanics (QM/MM)

3. Performance Benchmarks for First Principle Calculations in Supercomputers (T2K-Tsukuba..)

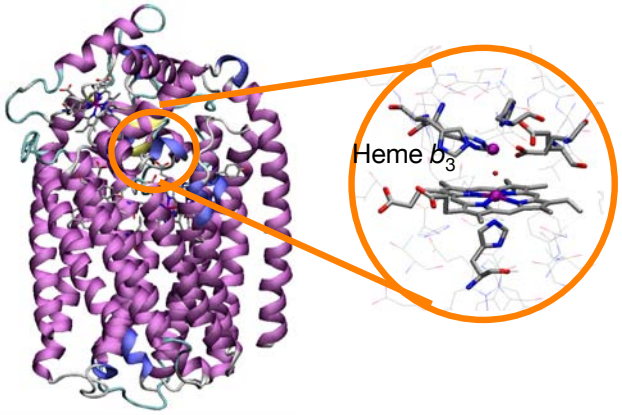
(4. GPU acceleration for Hartree-Fock (HF) calculation)

(5. Recent results for Molecular Dynamics and astrobiology)

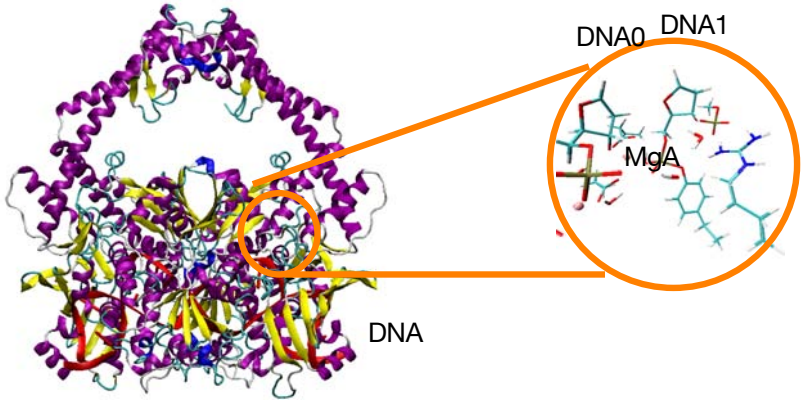
1. Overview of research fields

– Quantum Mechanics/Molecular Mechanics (QM/MM) method
– Molecular Dynamics (MD) simulations
– Astrobiology
– *In silico* structural modeling of proteins

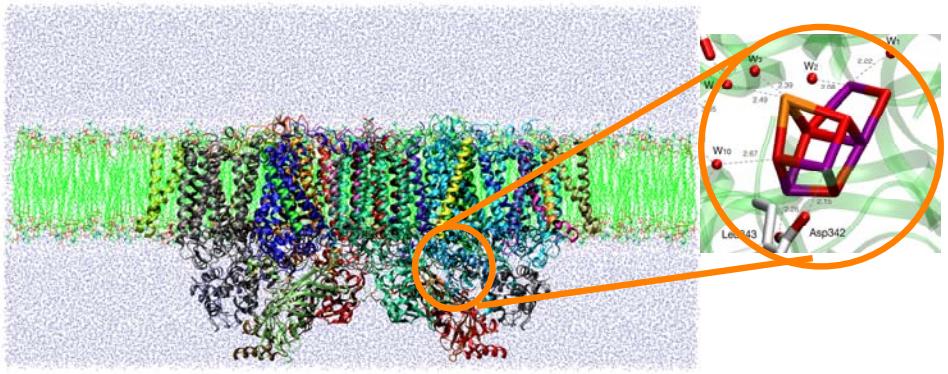
• **Quantum Mechanics/Molecular Mechanics (QM/MM) method**



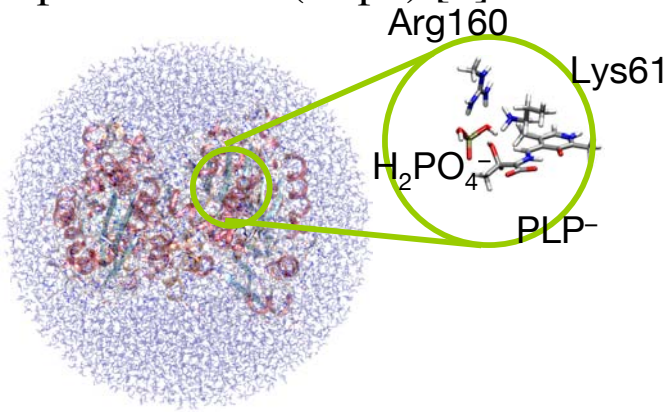
Nitric oxide reductase (NOR) [1]



Topoisomerase (Topo) [2]



Oxygen Evolving Complex in Photosystem II



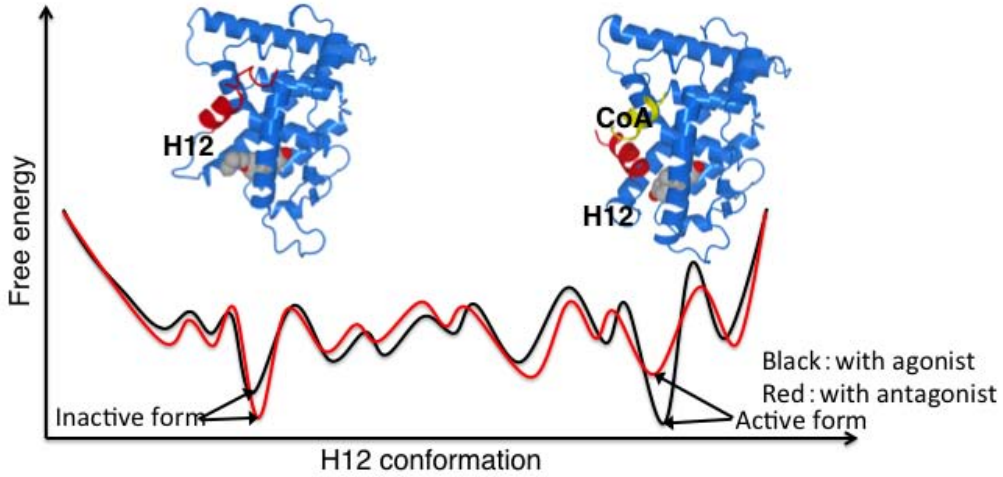
Threonine Synthase

Theoretical study on a calculation method of electron transfer coupling matrix (*T*) [3]

[1] M. Shoji et al, Mol. Phys. Accepted 2013.
[2] K. Hanaoka et al, J. Bio. Struct. & Dyn., Accepted 2013.
[3] M. Shoji et al, Int. J. Quantum Chem., 113, 342 (2013).
[4] M. Shoji, et al, Catal.Sci.Technol,3,1831.
[5] M. Shoji et al., submitted

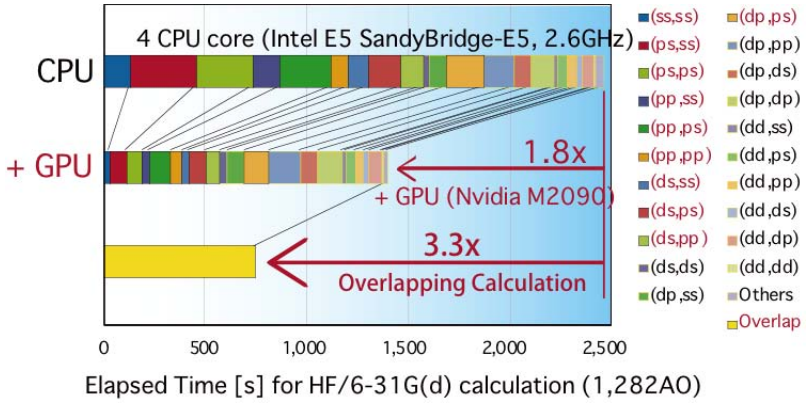
- **Molecular Dynamics (MD) simulations**

Long time (64 μ s) simulations for a Nuclear Receptor (Vitamin D) [3]



- **Development of GPU codes (○Umeda,Hanawa,Shoji,Boku)**

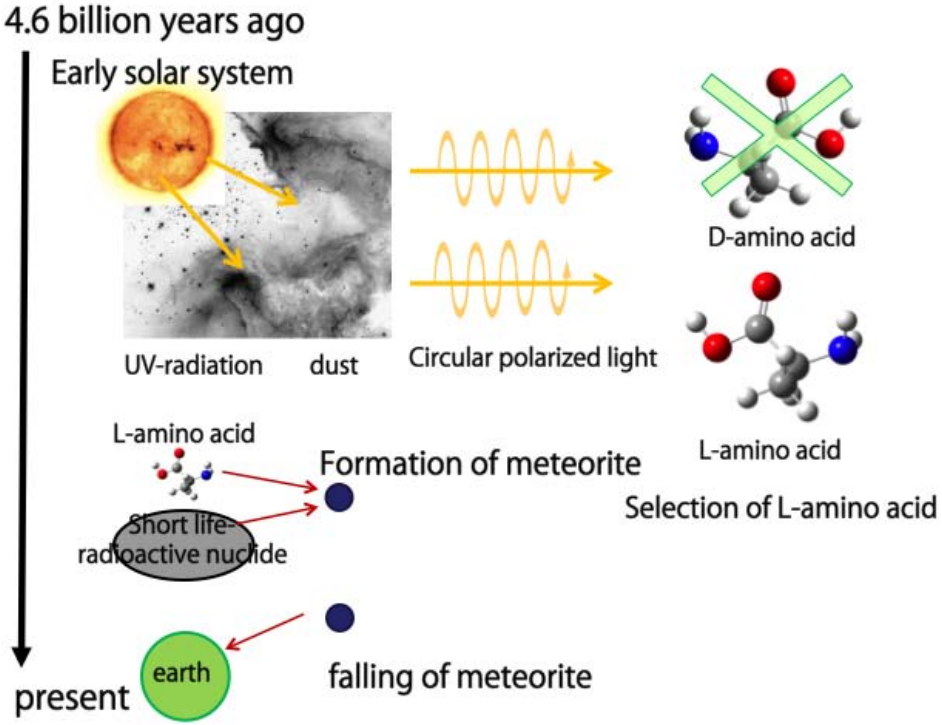
GPU code for HF calculation in openFMO [4]

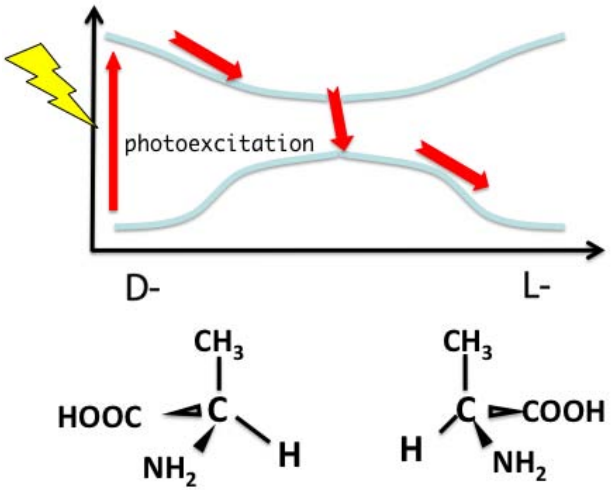


[6] K. Hanaoka et al, submitted
[7] Umeda et al, the Information Processing Society of Japan, 6,4, 26-37 (2013).

•Astrobiology

•Chirality formation of amino acids in the early solar system
•Amino acid formation on interstellar dusts



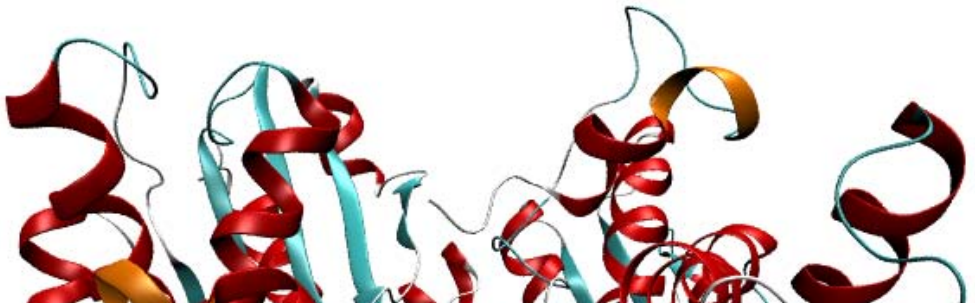


•*In silico* structural modeling of proteins

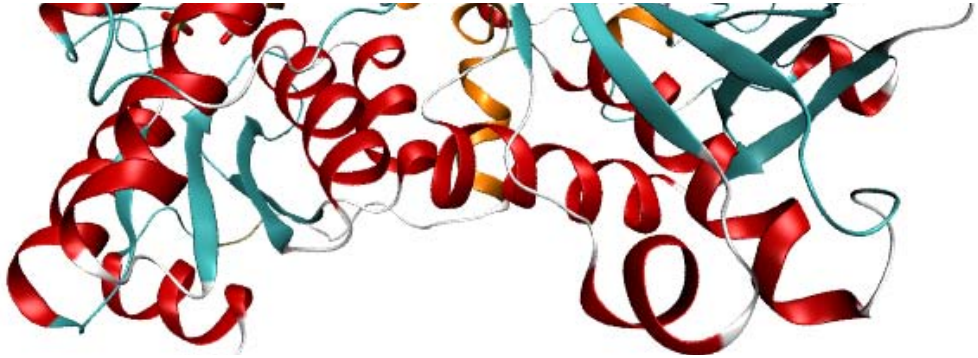
•Collaboration with Hashimoto and Inagaki group.

1. Recent results of Quantum Mechanics/ Molecular Mechanics (QM/MM)

- **Threonine Synthase**
- **Photosystem II - oxygen evolving complex**



Theoretical elucidation on the reaction control mechanism in Threonine Synthase



Mitsuo Shoji*[1], K. Hanaoka[1], Y. Ujiie[1], W. Tanaka[1], M. Kayanuma[1],
H. Umeda[1], Y. Machida[2], T. Murakawa[2], H. Hayashi[2]
[1]University of Tsukuba, [2]Osaka Medical College

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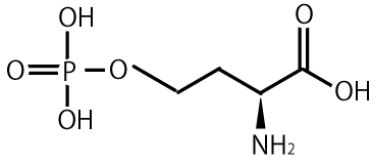
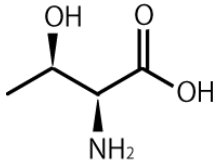
Threonine Synthase (TS)

- TS catalyzes last step of the L-threonine biosynthesis

  O-phospho-L-homoserine + H_2O -> L-threonine + phosphate



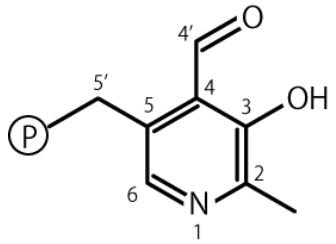


- TS is not found in mammals

- TS belongs to PLP-dependent enzymes

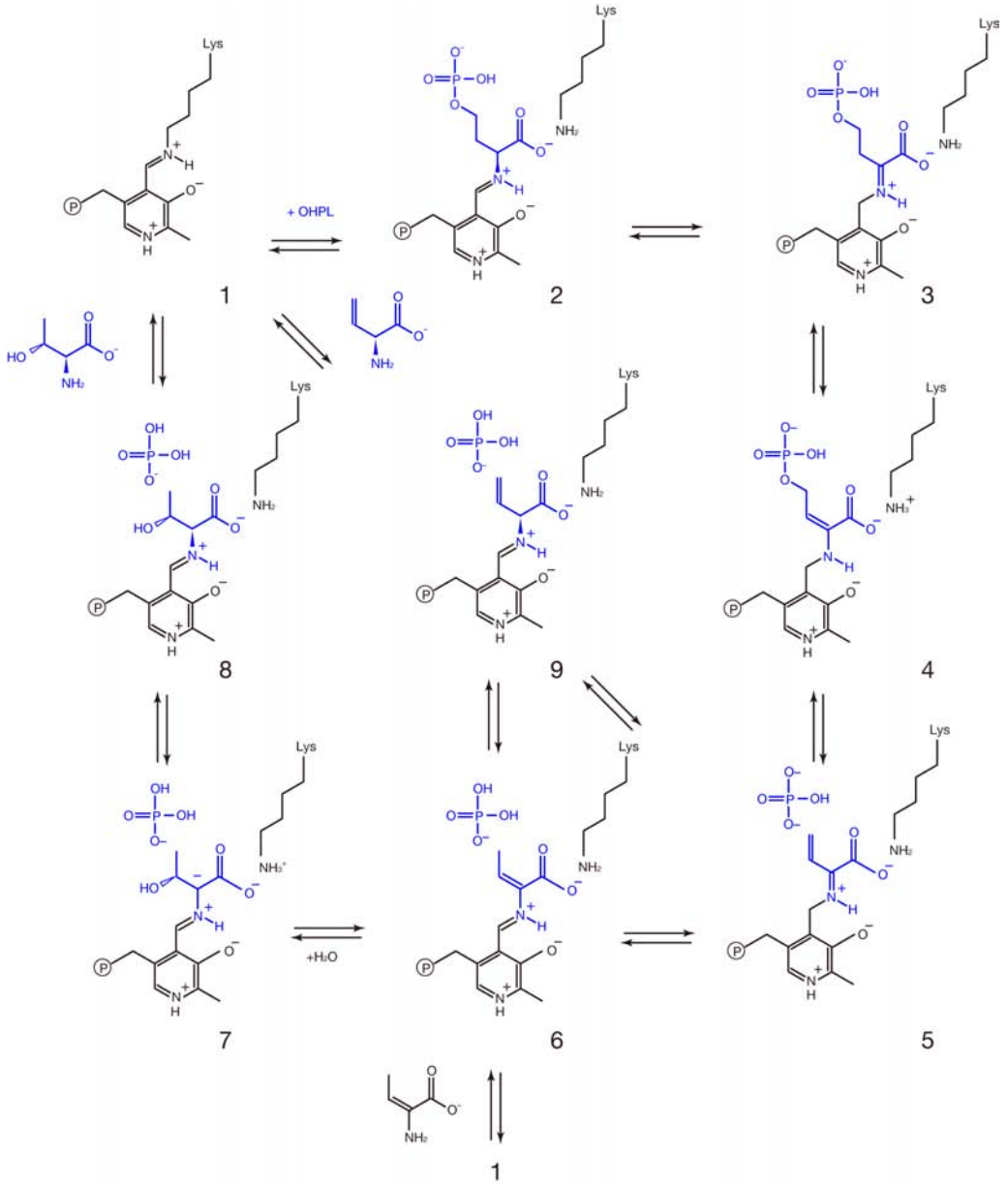
- Reaction mechanism is most complicated
  (regiospecific and stereospecific)

- All the types of intermediates are formed



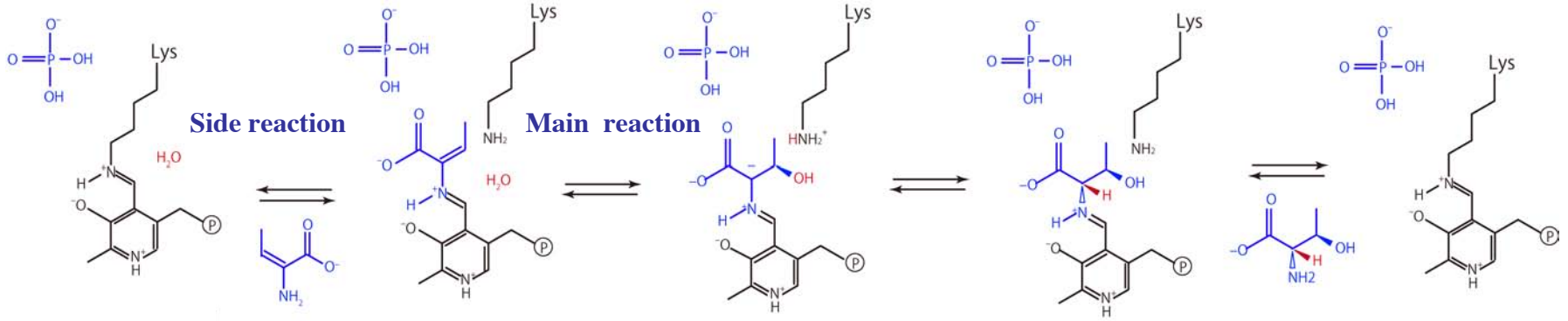
pyridoxal 5'–phosphate
(PLP)

Proposed Reaction Mechanism of TS

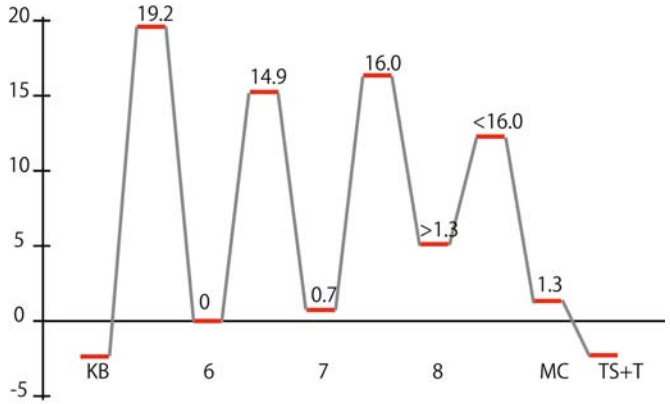


[1] T. Murakawa, Y. Machida, H.Hayashi, J.Bio. Chem.,286, 2774(2001).

A proposed reaction mechanism from α-ketobutyrate to L-threonine



α-ketobutyrate formation	Hydroxylation of Cβ	protonation of Cα	L-threonine formation
1	**6**	**7**	**8**	**1**
Aldimine	AC (PLP-α-aminocrotonate aldimine)	quinonoid	Aldimine	Aldimine



Free energy profile of the TS catalytic reaction determined by stopped-flow spectroscopy [1:T. Murakawa et al.].

Purpose

- Elucidation of the detailed TS reaction mechanism by using high-accurate QM/MM methodology
- Determine the reaction pathway and intermediate states
- Characterization of the intermediate states with direct comparison with experimental UV spectrum

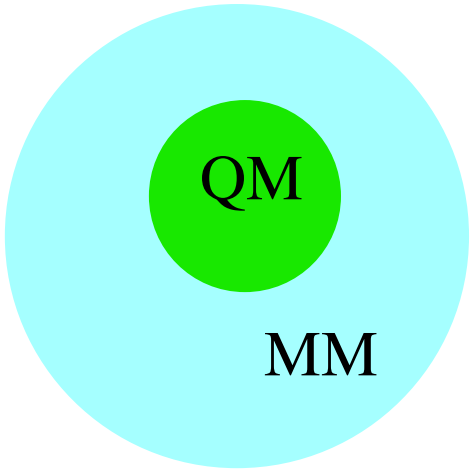
QM/MM method

$$H_{\text{system}} = H_{\text{QM}} + H_{\text{QM/MM}} + H_{\text{MM}}$$

$$H_{QM} = \sum_{i}^{e} \frac{1}{2}\nabla_{ri}^{2} + \sum_{\langle i,j \rangle}^{N_e,N_e} \frac{1}{r_{i,j}} - \sum_{i,a}^{e,N_{QM}} \frac{Z_a}{r_{i,a}} - \sum_{i,q}^{e,N_{MM}} \frac{Z_q}{r_{i,q}} + \sum_{<a,b>}^{N_{QM}N_{QM+MM}} \frac{Z_a Z_b}{r_{a,b}}$$

$$H_{QM/MM} = V_{QM/MM}^{bonded} + V_{QM/MM}^{vdW}$$

$$H_{MM} = T_{MM} + V_{MM}^{bonded} + V_{MM}^{coulomb} + V_{MM}^{vdW}$$



Purpose

- Elucidation of the detailed TS reaction mechanism by using high-accurate QM/MM methodology
- Determine the reaction pathway and intermediate states
- Characterization of the intermediate states with direct comparison with experimental UV spectrum

QM/MM study on the photosystem II oxygen evolving complex at the S_0-S_2 state

Mitsuo Shoji, [1] **Hiroshi Isobe,** [2] **Shusuke Yamanaka,** [2]
Nobuo Kamiya, [3] **Jian-Ren Shen,** [4] **Kizashi Yamaguchi** [5]

[1] *Graduate School of Pure and Applied Science, University of Tsukuba*
[2] *Graduate School of Science, Osaka University*
[3] *OCARINA, Osaka City University*
[4] *Graduate School of Natural Science and Technology, Okayama University*
[5] *Toyota Physical & Chemical Research Institute*

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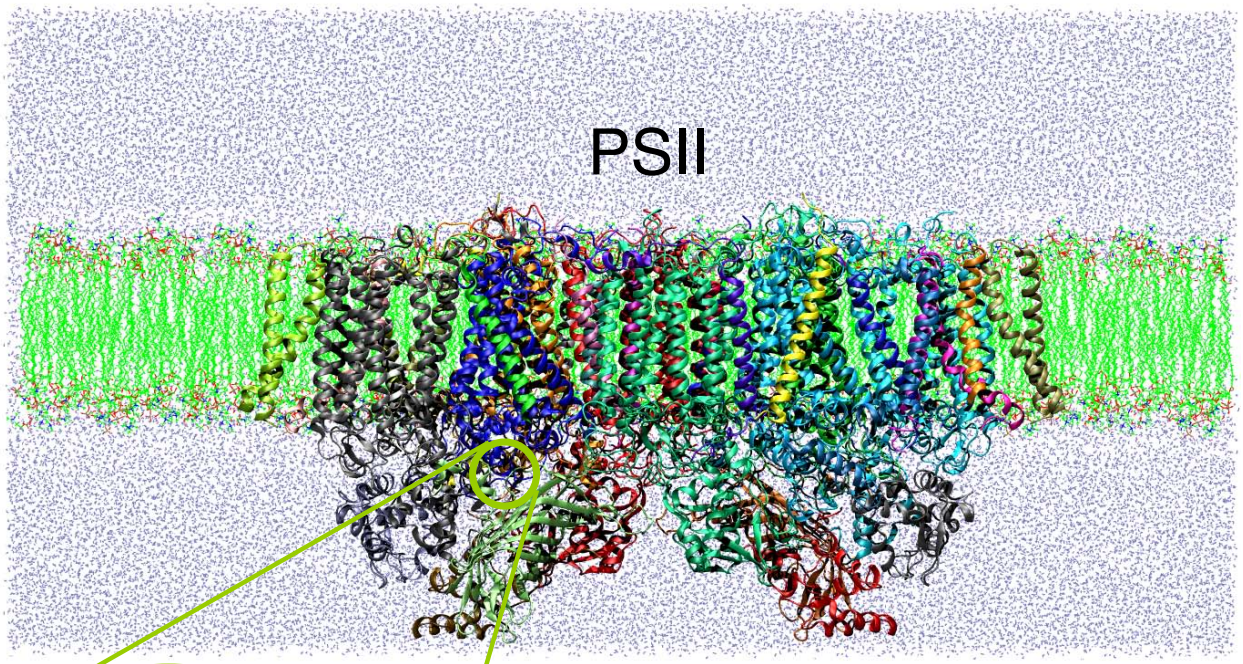
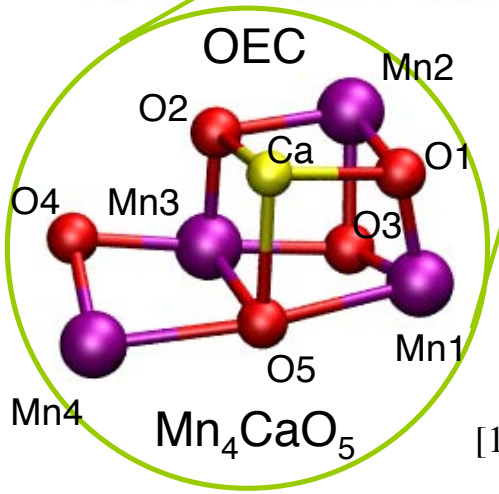
Photosystem II (PSII) and Oxygen-evolving complex (OEC)



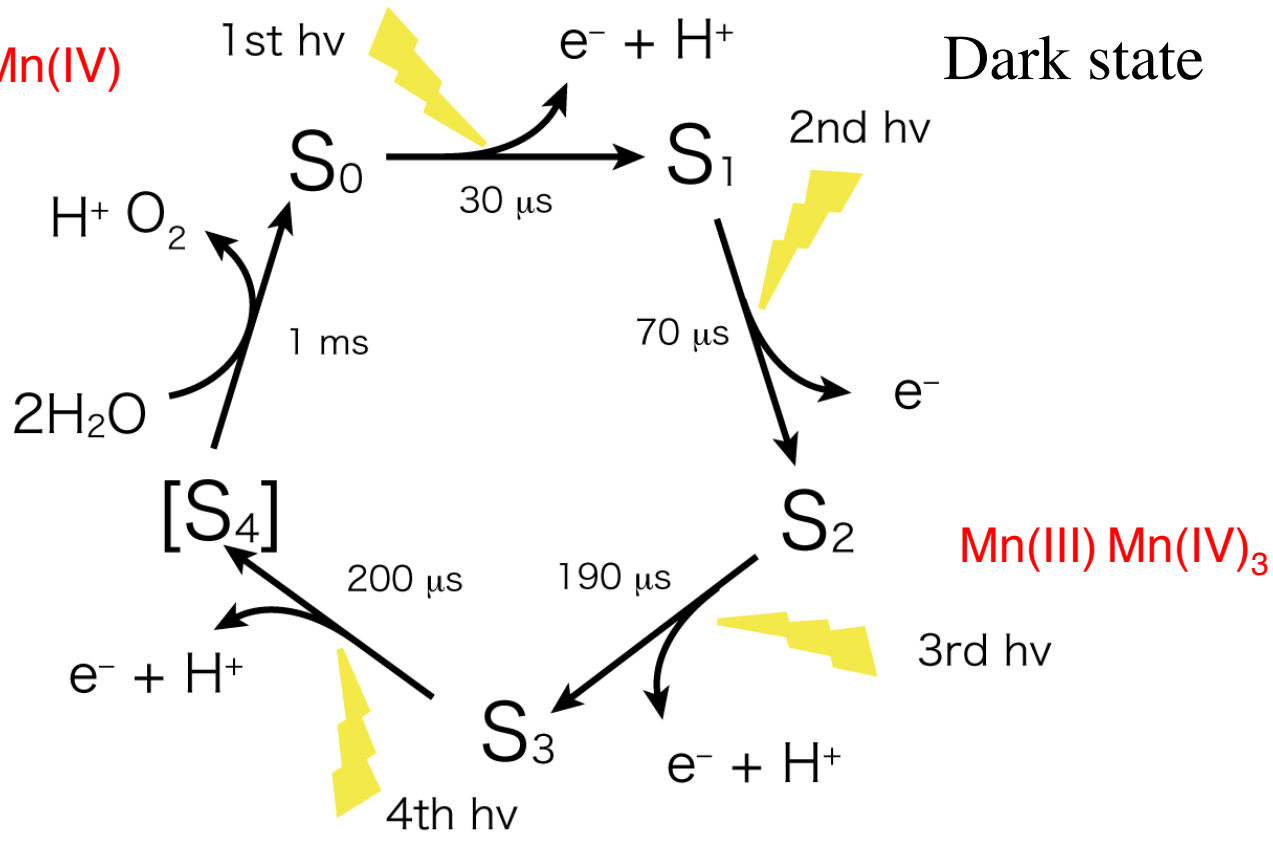


• OEC reaction: $2H_2O \rightarrow O_2 + 4H^+ + 4e^-$

• A 1.9 Å resolution X-ray structure of PSII was solved [1].
- Clear OEC structure and surrounding water molecules were identified.

[1] Y. Umena, K. Kawakami, J-R. Shen, N. Kamiya, nature 473, 53 (2011).

Kok cycle



Mn formal charges

Mn(IV)$_4$

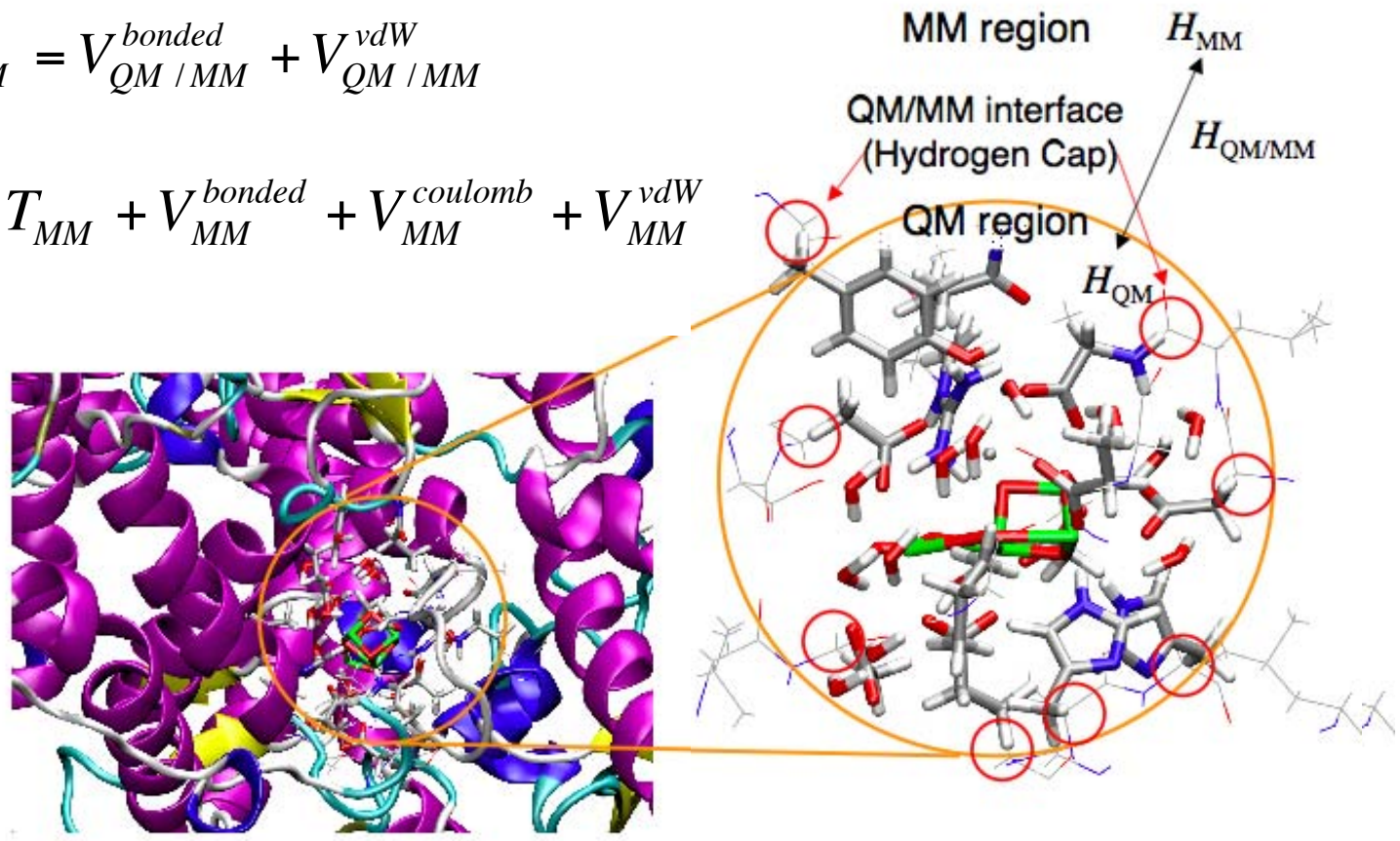
QM/MM

$$H_{\text{system}} = H_{\text{QM}} + H_{\text{QM/MM}} + H_{\text{MM}}$$

$$H_{QM} = \sum_{i}^{e} \frac{1}{2}\nabla_{ri}^{2} + \sum_{\langle i,j \rangle}^{N_e,N_e} \frac{1}{r_{i,j}} - \sum_{i,a}^{e,N_{QM}} \frac{Z_a}{r_{i,a}} - \sum_{i,q}^{e,N_{MM}} \frac{Z_q}{r_{i,q}} + \sum_{<a,b>}^{N_{QM}N_{QM+MM}} \frac{Z_a Z_b}{r_{a,b}}$$

$$H_{QM/MM} = V_{QM/MM}^{bonded} + V_{QM/MM}^{vdW}$$

$$H_{MM} = T_{MM} + V_{MM}^{bonded} + V_{MM}^{coulomb} + V_{MM}^{vdW}$$



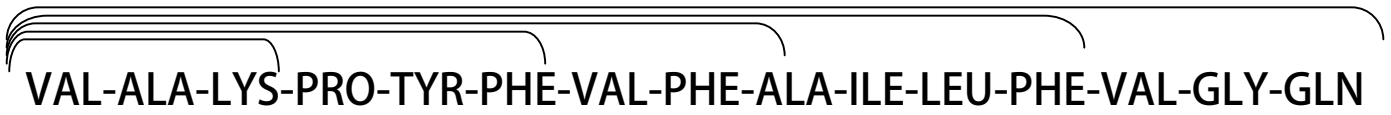
3. Performance Benchmarks for First Principle Calculations in Supercomputers

(T2K-Tsukuba, HECToR, SystemB, RX300)

First Principle Calculations (Quantum Mechanics)

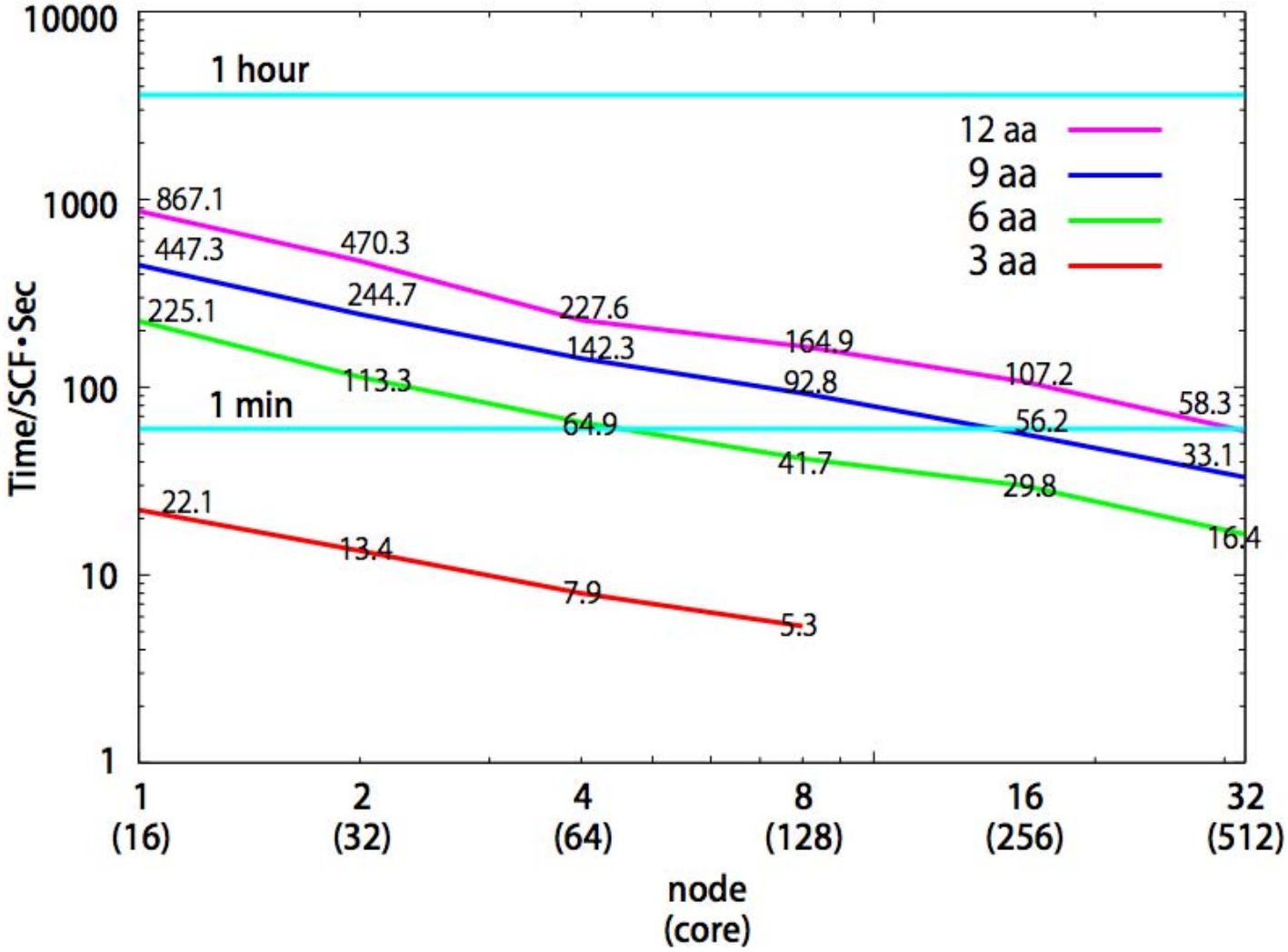
- Method: B3LYP/6-31G* using NWChem(Ver 6.0)
- System: Alpha Helix # amino acids (# basis sets)

  3(388) 6(1011) 9(1421) 12(1888) 15(2228)



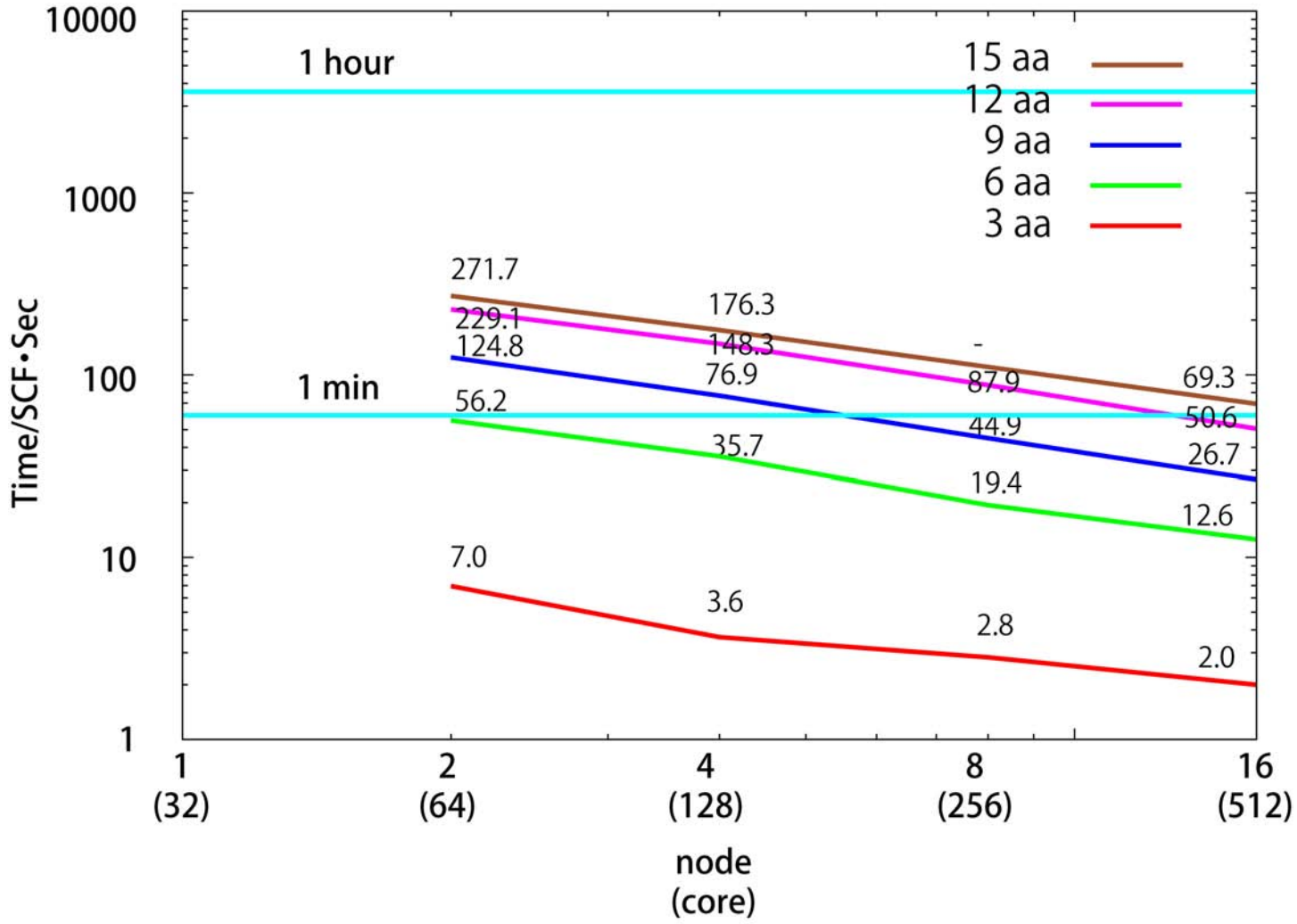
T2K-Tsukuba

- Opteron 8000 Quad-core x 4 sockets/node (16 core/node)
- 32GB memory/node , Infiniband
- ~95Tflops



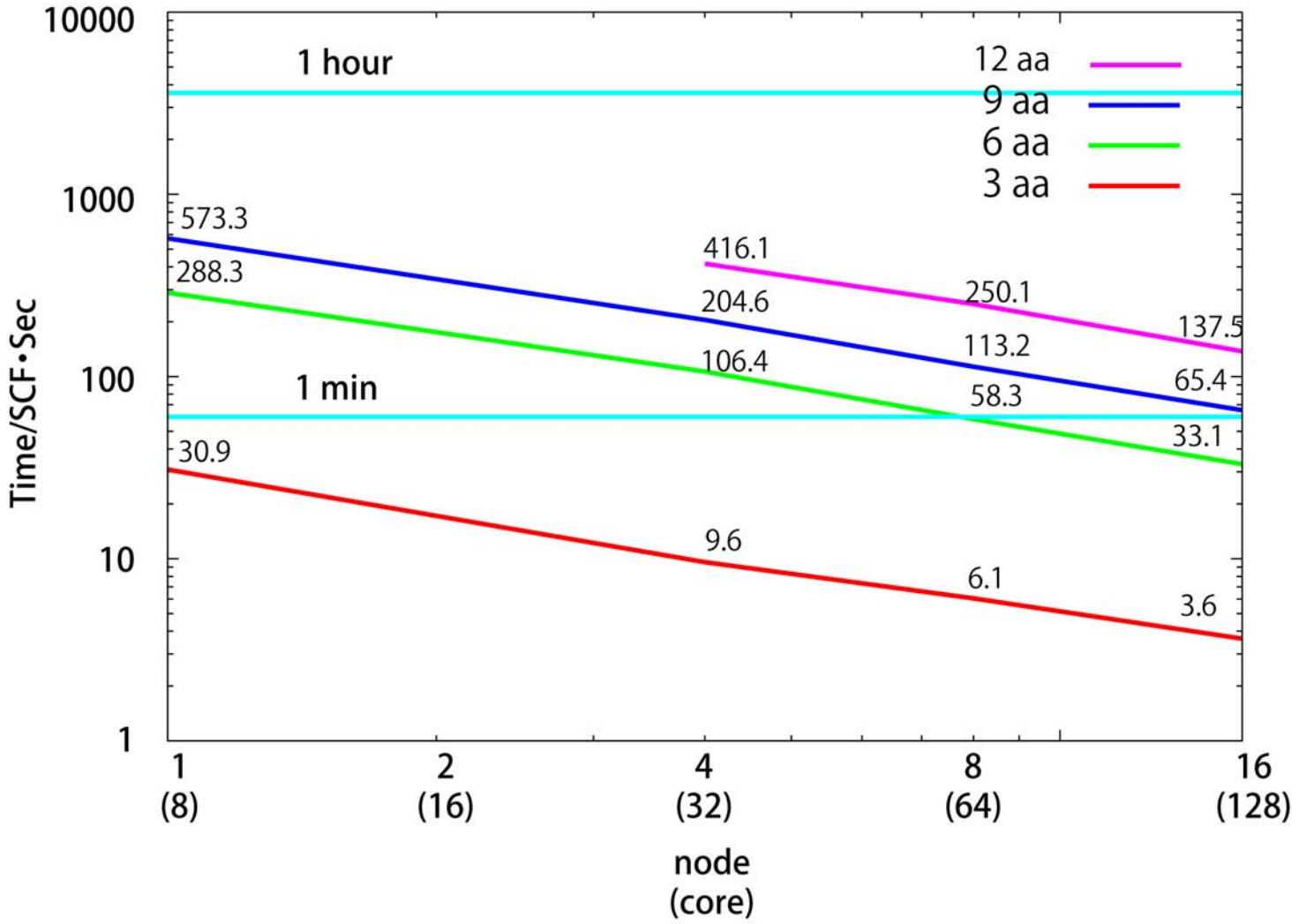
HECToR Phase3

- Opteron (Interlagos)x 2 sockets/node (32core/node) X 2816 node
- 32GB memory/node
- ~800Tflops



SystemB (kashiwa)

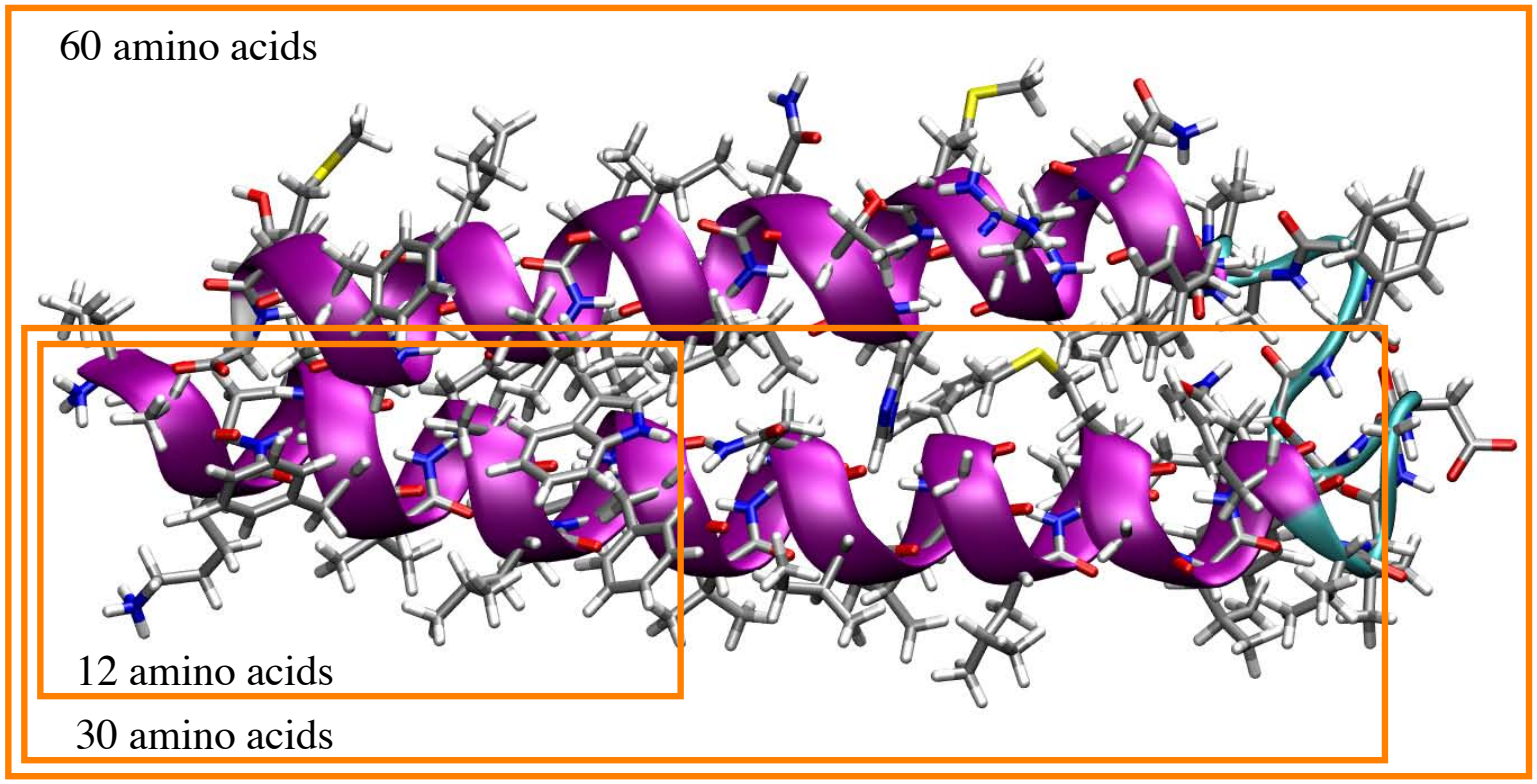
- Xeon X5570 4-core ×2 (8 core/node)
- 24GB memory/node, Infiniband
- Top 48(2011/6)



Large QM calculation

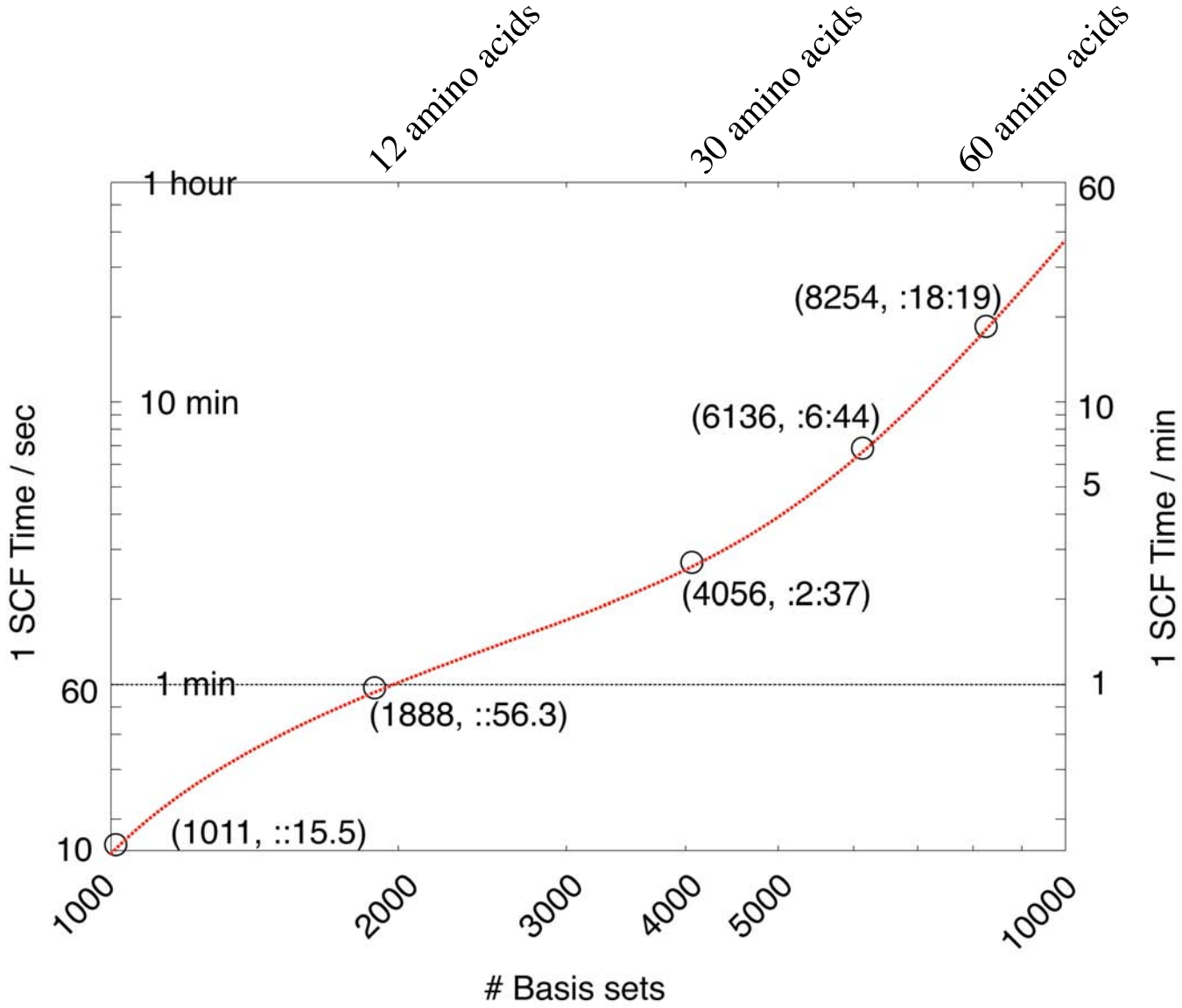
- Method: B3LYP/6-31G* using NWChem(Ver 6.0)
- System: Alpha Helix #Amino Acids (#Atoms: #Basis sets)

6(122: 1011), 12(229: 1888), 30(492: 2228), 45(737: 6136), 60(988: 8254)



1 SCF Calculation time @ T2K-Tsukuba

- Using 512 core (32 node)



Nitric oxide reductase (NOR)

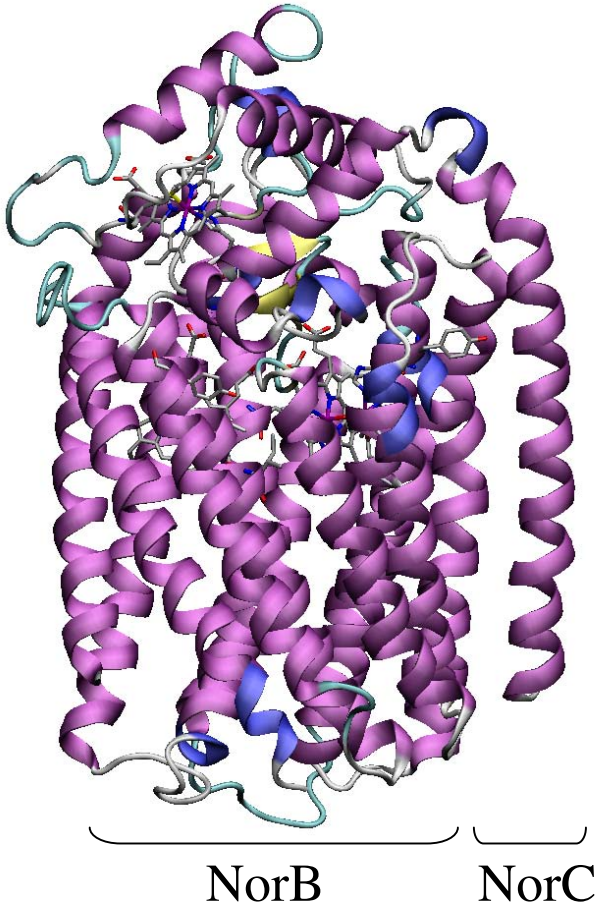
- Reduction of nitric oxide (NO) to nitrous oxide (N_2O)
  $2NO + 2\ e^- + 2H^+ \rightarrow N_2O + H_2O$
- Include a N-O bond cleavage and a N-N bond formation
- N_2O is a greenhouse gas

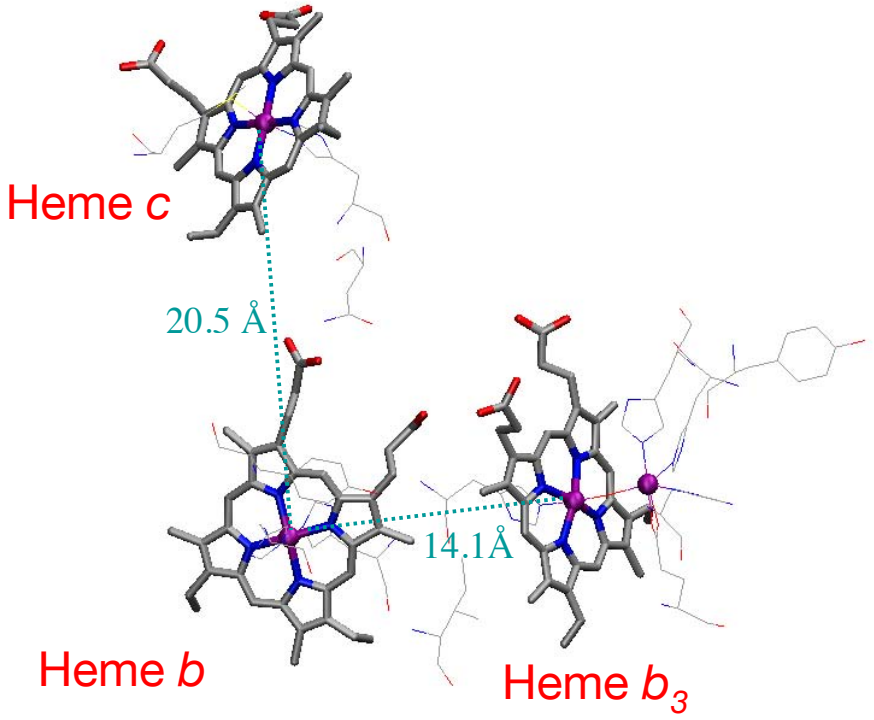
- First x-ray structure was resolved in 2010 [1].
- Many similarities to cytochrome c oxidase (COX)
- D, K-proton pathway is missing in NOR

[1] T. Hino et al, Science 330, 1666(2010)

- 3 reaction mechanisms are proposed.
  (*trans*, *cis*-Fe_B, *cis*-heme $_{b3}$)

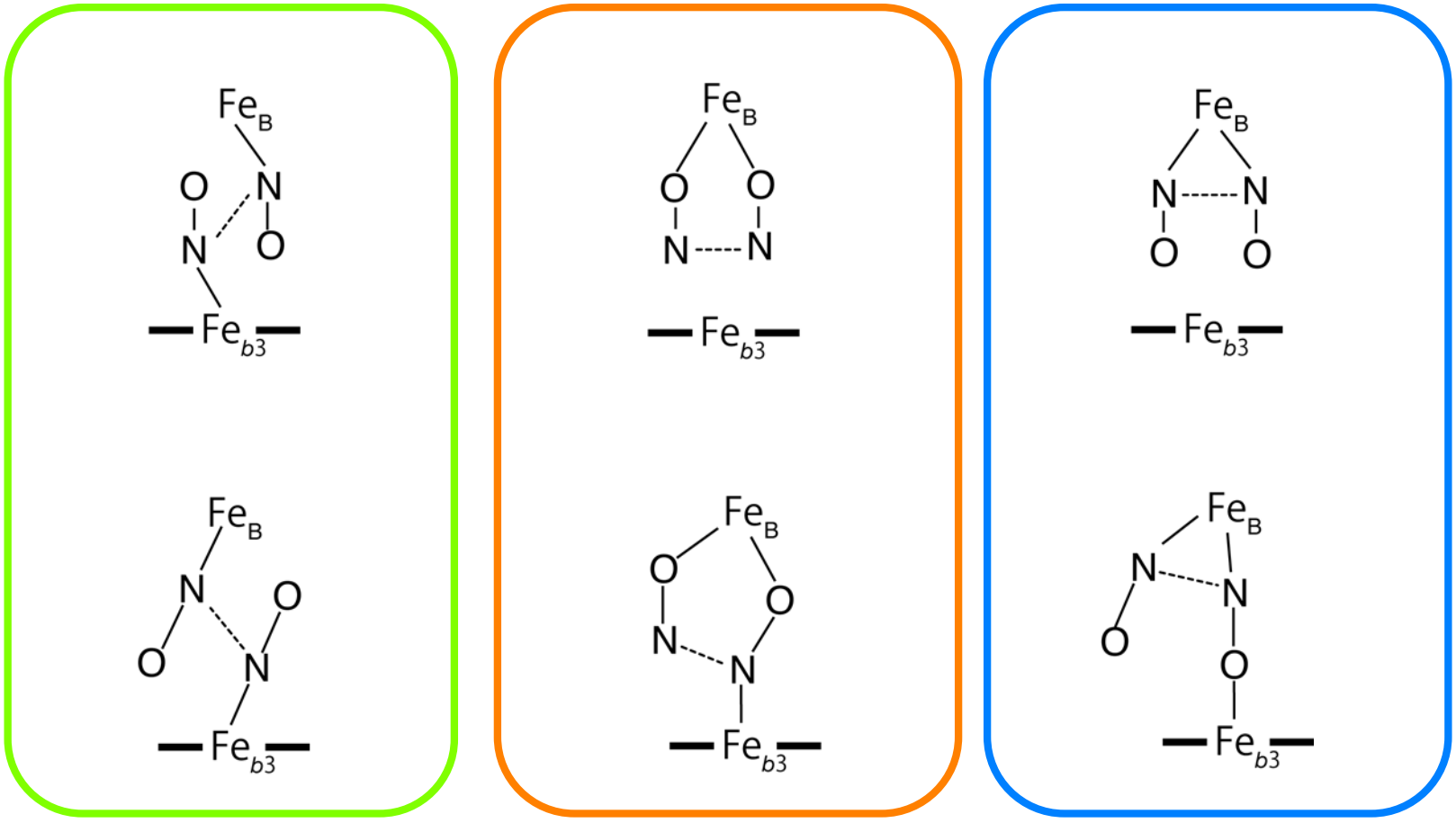
Structure of NOR [1]





[1] T. Hino et al, Science 330, 1666(2010)

Proposed reaction mechanisms



Trans

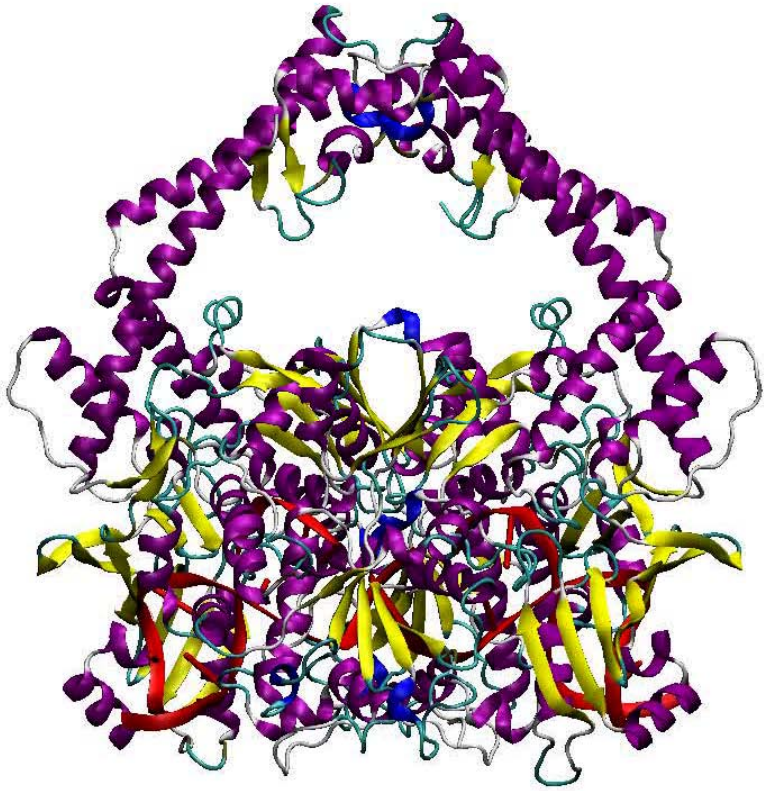
cis-heme $_{b3}$

cis-FeB

3. Recent results for Molecular Dynamics (DNA-Topoisomerase, Prion Protein)

DNA-Topoisomerase

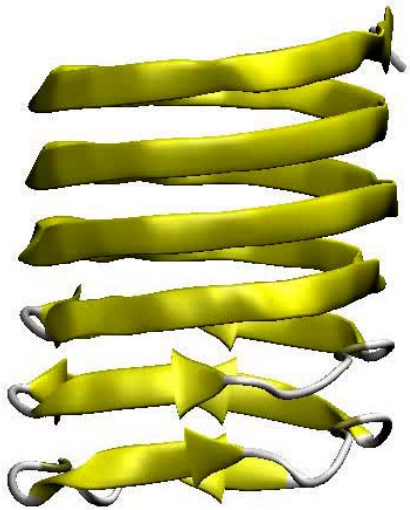
- DNA Topoisomerase: catalyzes interconversions of the different topological forms of DNA
- important drag target for cancer and antibiotical agent



Prion Protein

Prions are infectious proteins, where self-propagating amyloid conformations of proteins are transmitted.

Prions cause neurodegenerative disease such as bovine spongiform encephalopathy (BSE) and variant Creutzfeldt-Jakob disease (CJD)



Summary and future plan

- Elucidation of reaction mechanism in enzymes

- Development of QM and MM methods
  parallel efficiency, accuracy, conformational sampling, reaction pathways, free energy

- GPU acceleration for exa-scale supercomputers

- Collaboration with Related fields
  - Astrophysics, Molecular evolution, industrial company

Thank you for your attention

Group trip @ Mt. Tsukuba 14/3/2012