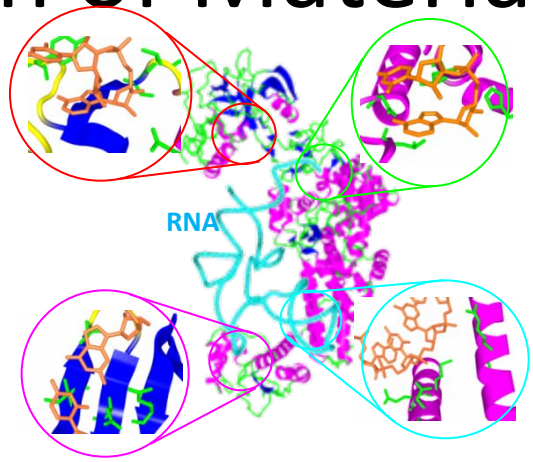
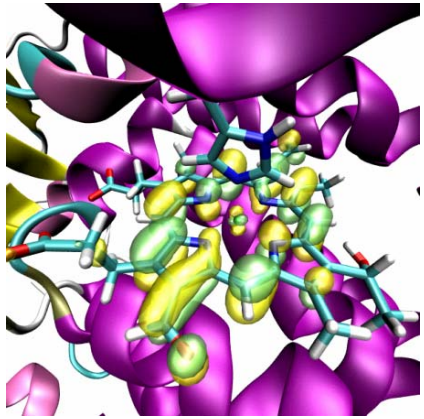
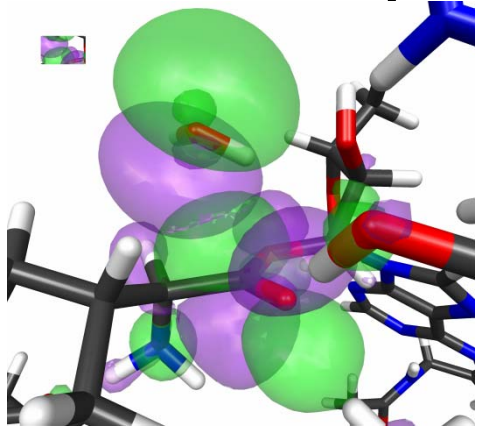
Computational Life Science Group (Division of Materials and Life Sciences)







<Group Member>
(alphabetical order)

1) Stuffs

Boero, Mauro (Assoc. Prof): First principles molecular dynamics (CPMD) simulation

Tateno, Masaru (Assoc. Prof): Quantum structural biology and structural bioinformatics

2) Students

Hagiwara, Yohsuke (D1): Computational biophysics on protein structure and reactions

Miura, Kazutaka (D1): Computational molecular design of biological materials

Nishimura, Tatsunori (D1): Bioinformatics on cellular reaction network systems

Kitta, Kazushi (M2): Structural bioinformatics on protein-protein recognition

Kang Ji Young (M1): Computational biophysics on protein structure and reactions

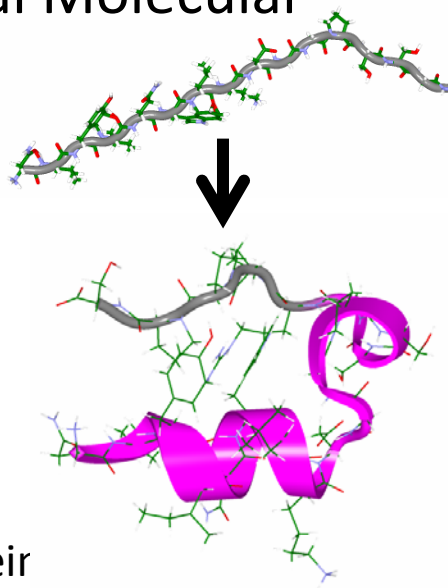
Kuroyanagi, Shigehide (M1): Computational biophysics on molecular transport and reactions

3) Post-doc

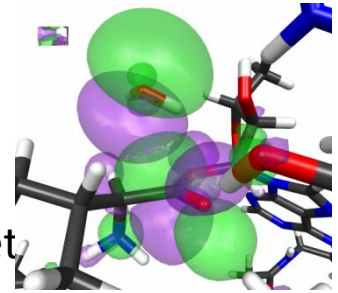
from January of the next year (**Kamiya, Katsumasa**: moved)

Research themes in our group

Mechanisms of Formation and Reactions of Biological Molecular systems → Fundamental Principles



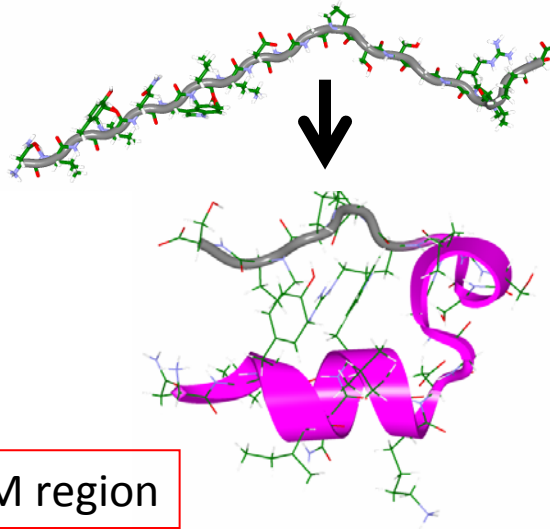
1) Dynamical mechanisms in the formation of **protein 3D structure**
   For the van der Waals energy, conventional MM and QM calculations cannot accurately evaluate in some cases !
   → Serious problems: misleading of formation processes of protein 3D structures
   → Both of accuracy and efficiency are required in MD calculations.
2) **Reaction** mechanisms of biological macromolecules such as proteir
   Enzymatic reaction:
   Riboyzme, ATP synthase (ATPase), Aminoacyl-tRNA synthetase (ARS), Cytochrome c oxydase (CcO), Transamidase, etc.
   Electron / proton transport:
   Cytochrome c oxydase (CcO), double-stranded DNA
   Binding reaction:
   Specific recognition of protein-protein, protein-DNA, et



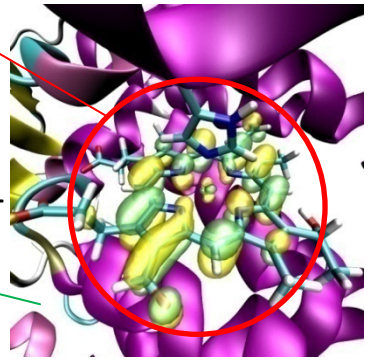
3) Dynamical behavior of **cellular reaction network systems** in a cell
   Signal transduction of external signals into a cell
   High S/N ratio, Amplification of weak signals in a cell
4) Engineering and design of functions of biologocal macromolecules
   Pharmaceutical drugs against serious deceases, such as cancer, diabetes, etc.

Development of algorithms and calculation systems

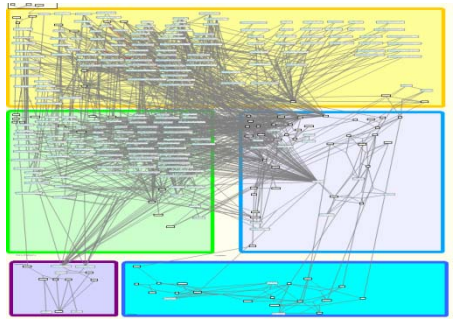
1) Dynamical mechanisms in the formation of **protein 3D structure**
   Development of calculation algorithm of **van der Waals** energy/force with the high level accuracy and efficiency
   → 100 ns scale molecular dynamics simulations (coupled with Replica Exchange method)



2) **Reaction** mechanisms of biological macromolecules
   Enzymatic reaction, Electron / proton transport
   → **QM/MM hybrid calculation program** using the all electron based DFT
   Binding reaction:
   → Docking algorithm and system of protein and DNA molecules
   → **Fully-solvated dynamical docking** (**FSDD**) algorithm for protein-ligand molecules

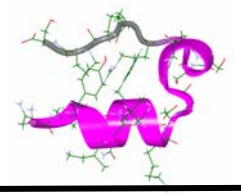
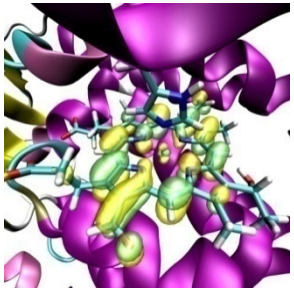
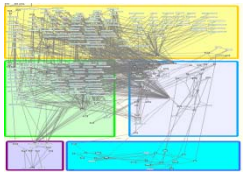


3) Dynamical behavior of **cellular reaction network systems** in a cell
   Systems have been developed in order to **solve** a large set of ordinary differential equations (ODE) and to **optimize** parameters in reaction network systems.



4) **Engineering and design** of functions of biologocal macromolecules
   Molecular docking schemes for protei-lligand have been developed and sophisticated.

Research phase of several projects in our group

Themes	Phase I	Phase II	Phase III
Protein Folding 	Development & implementation of fast & accurate calculation method of the vdW interaction	Replica exchange molecular dynamics (REMD) simulations are being performed now.	Extension of the analyses to several large proteins
		Calculations using PACS-CS	
Reaction Mechanisms 	Development of a QM/MM hybrid calculation program based on the all-electron calculation	Applications of the QM/MM hybrid calculation program: aminoacyl-tRNA synthetase, cytochrome c oxydase, transamidase, Ah receptor, etc.	
		Calculations using PACS-CS	
	Applications of the QM/MM hybrid calculation program based on Car-Parrinello MD (CPMD): riboyzme, ATP synthase, cytochrome c oxydase, charge transfer of double-stranded DNA, etc.		
	Collaborations with the Computer Science Group	Collaborations with the Condensed Matter Physics Group	Calculations using PACS-CS
Cellular signaling network 	Mathematical modeling and development of calculation & optimization program, of cellular signaling reaction network	Applications of the calculation / optimization program: FGF signaling network cascade, multicellular network systems, etc.	
		Parallelization of the program	
			Collaborations with the Computer Science Group
			Calculations using PACS-CS
Year	2005	2007	2009

Start from Sep. 2005 → Dec. 2007

Car-Parrinello Molecular Dynamics

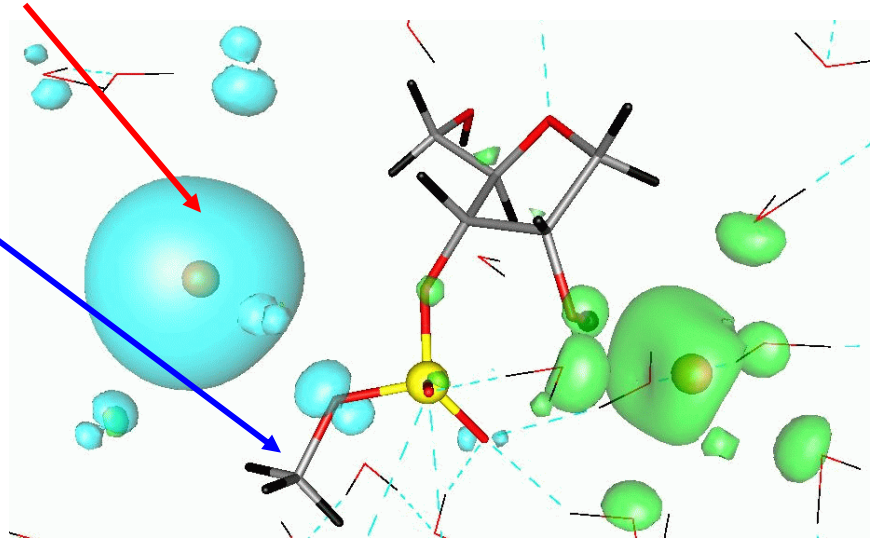
- Euler-Lagrange equations of motion for electrons, ions thermostats & Co.

$$\mu\ddot{\psi}_i = -\frac{\delta E^{DFT}}{\delta \psi_i^*} + \sum_j \Lambda_{ij}\psi_j$$

$$M_I\ddot{\mathbf{R}}_I = -\nabla_{\mathbf{R}_I} E^{DFT}$$

$$\mu_q\ddot{\alpha}_q = -\frac{\partial E^{DFT}}{\partial \alpha_q}$$

温度（temperature）



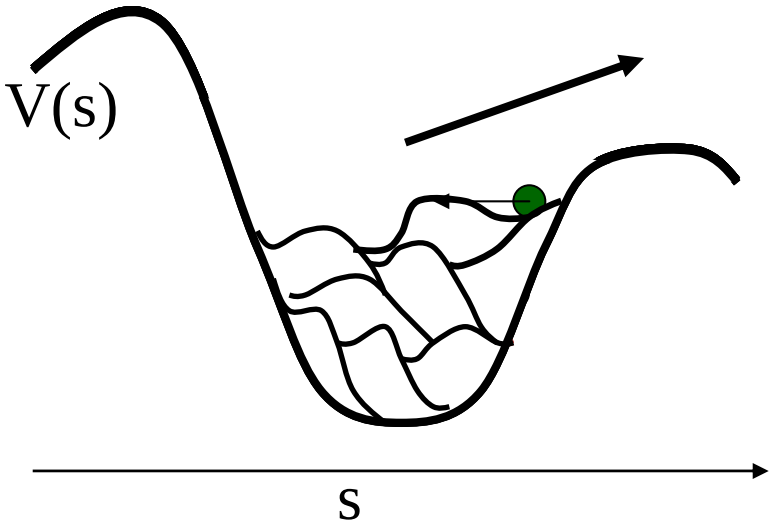
Metadynamics: filling the minima of the FES

- Free MD with an additional penalty potential
- Always move in the direction that minimizes the total energy, i.e. following the minimum energy path (Car-Parrinello)
- Continuous and smooth dynamics

cf.:

M. Iannuzzi, A. Laio and M. Parrinello, *Phys. Rev. Lett.* **2003**, *90*, 238302

A. Laio and M. Parrinello, *Proc. Nat. Ac. Sci.* **2002**, *99*, 12562



Reconstruction of the FES: what the $V(\mathbf{s},t)$ potential does

The (meta)dynamical gaussian potential $V(\mathbf{s},t)$ has the shape

$$V(\vec{s},t) = \sum_{t'<t} W \cdot \exp\left(-\frac{\left|\vec{s} - \vec{s}^{\,t'}\right|}{2\,\delta\sigma^2} \right)$$

and when it has completed its job (large t) and filled all the local minima, then its shape is similar to the FES:

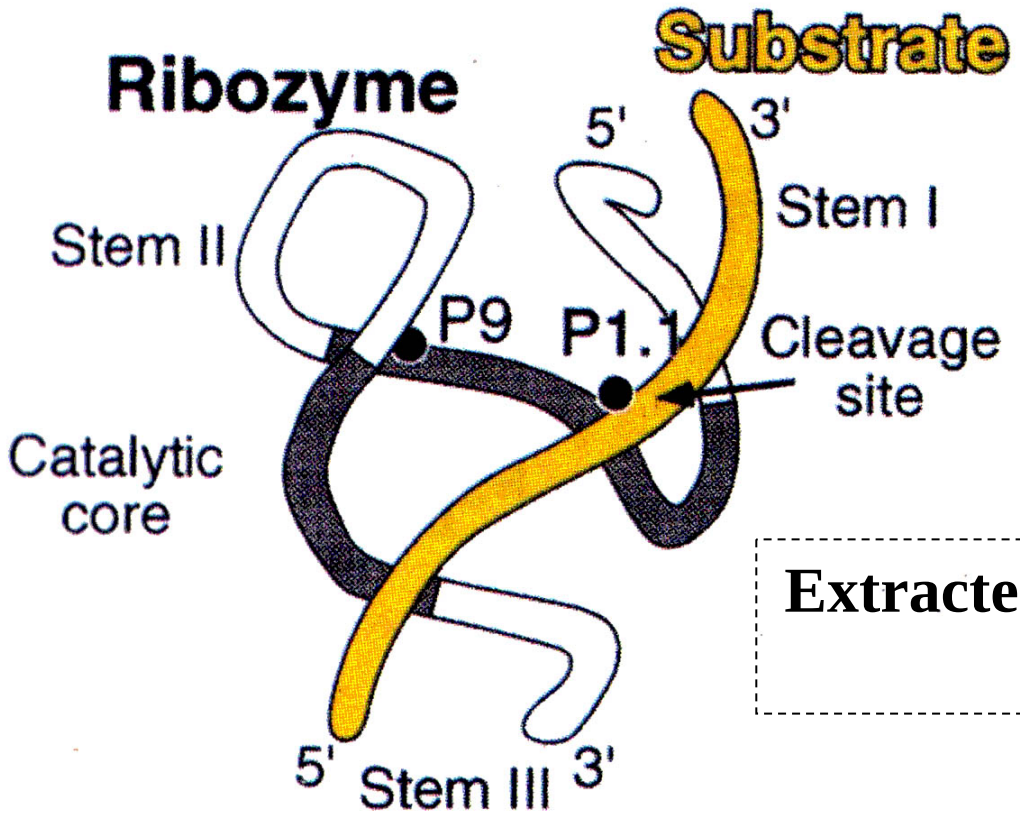
$$\lim_{t\to\infty} V(\vec{s},t) = -F(\vec{s}) + const.$$

In practice: the number of gaussians required to fill a minimum is proportional to $(1/\delta\sigma)^{\boldsymbol{n}}$ ($\boldsymbol{n}$ = dimensionality of the problem) and

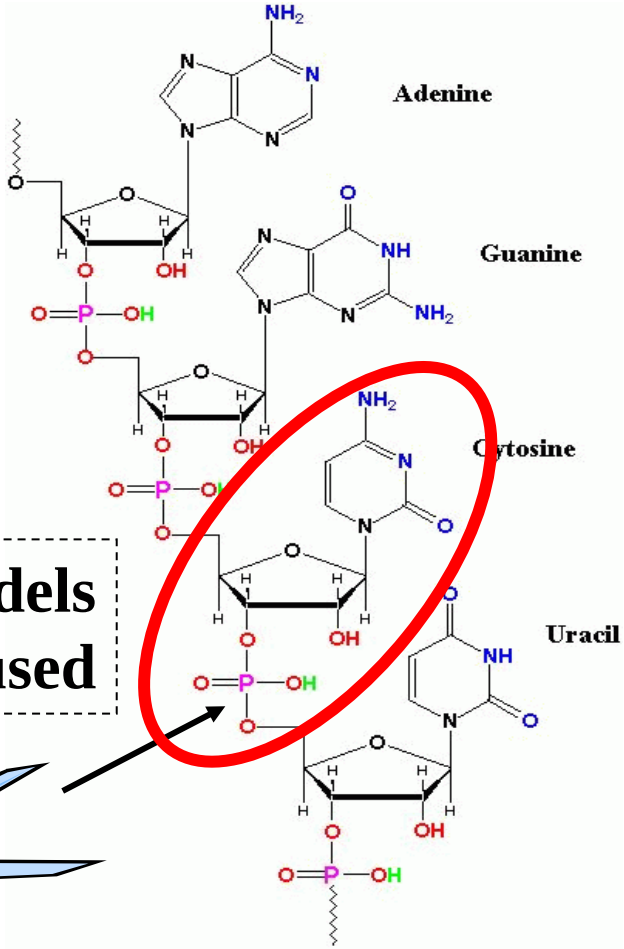
$$W / \delta\sigma\, e^{-1/2} = \gamma \left\langle f_\alpha^{\,2} \right\rangle^{1/2} \qquad \gamma \approx 0.5$$

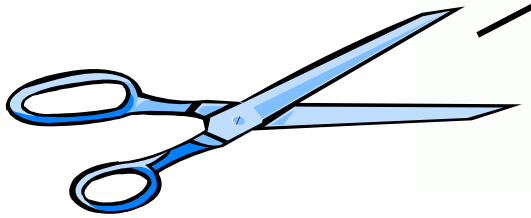
Computational analysis of reaction mechanisms of biomacromolecules: Ribozyme (RNA enzyme)

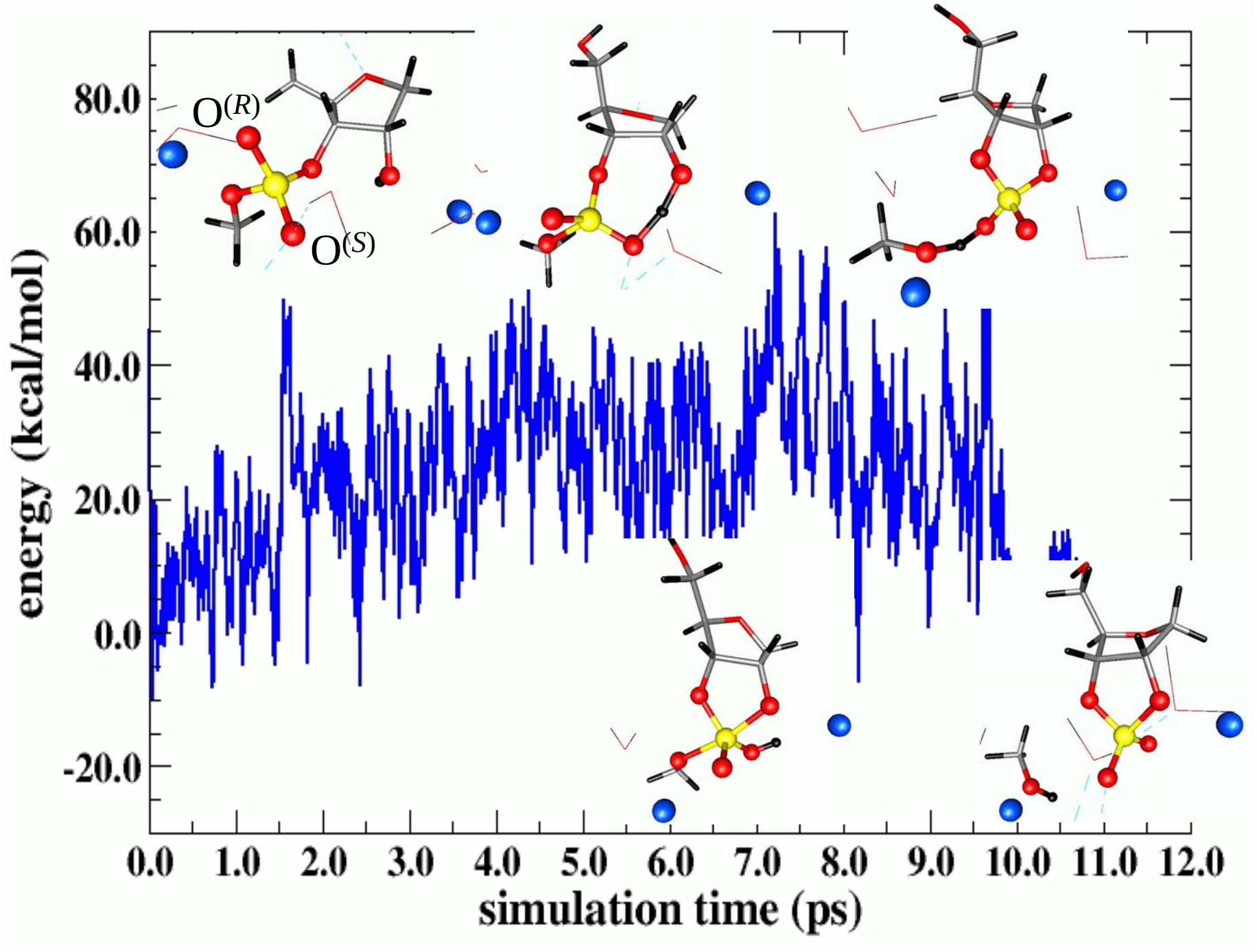
3D structure of riboyzme:
An example of hammerhead ribozyme



Extracted models used






O(R)
O(S)
80.0
60.0
40.0
20.0
0.0
-20.0
energy (kcal/mol)
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
simulation time (ps)

Activation barriers in solution for the different cases considered

	No metal ions	One Mg^{2+} (close to $O^{2'}$)	One Mg^{2+} (close to $O^{5'}$)	Two Mg^{2+}	One Mg^{2+} +OH^-	Two Mg^{2+} +OH^-
ΔE (kcal/mol)	60.1	57.3	55.2	46.5	51.6	43.8
ΔF (kcal/mol)	58.5	55.5	54.0	44.7	49.2	41.9

Error bar ~ 2.0 kcal/mol

Single-metal-ion reaction:
only one Mg close to $O^{2'}$

1. RNA structure is distorted. → High energy barrier !

2. Reaction path is inconsistent to the known experimental result → Incorrect reaction path !

   cf. Sawata, S., et al, *J. Am. Chem. Soc.*, **117** (1995), 2357-2358.

   Therefore, absence of kinetic isotope effects on the cleavage of the phosphodiester bonds by ribozymes can be interpreted only by a mechanism in which ***transfer of a proton does not take place in the transition state***.

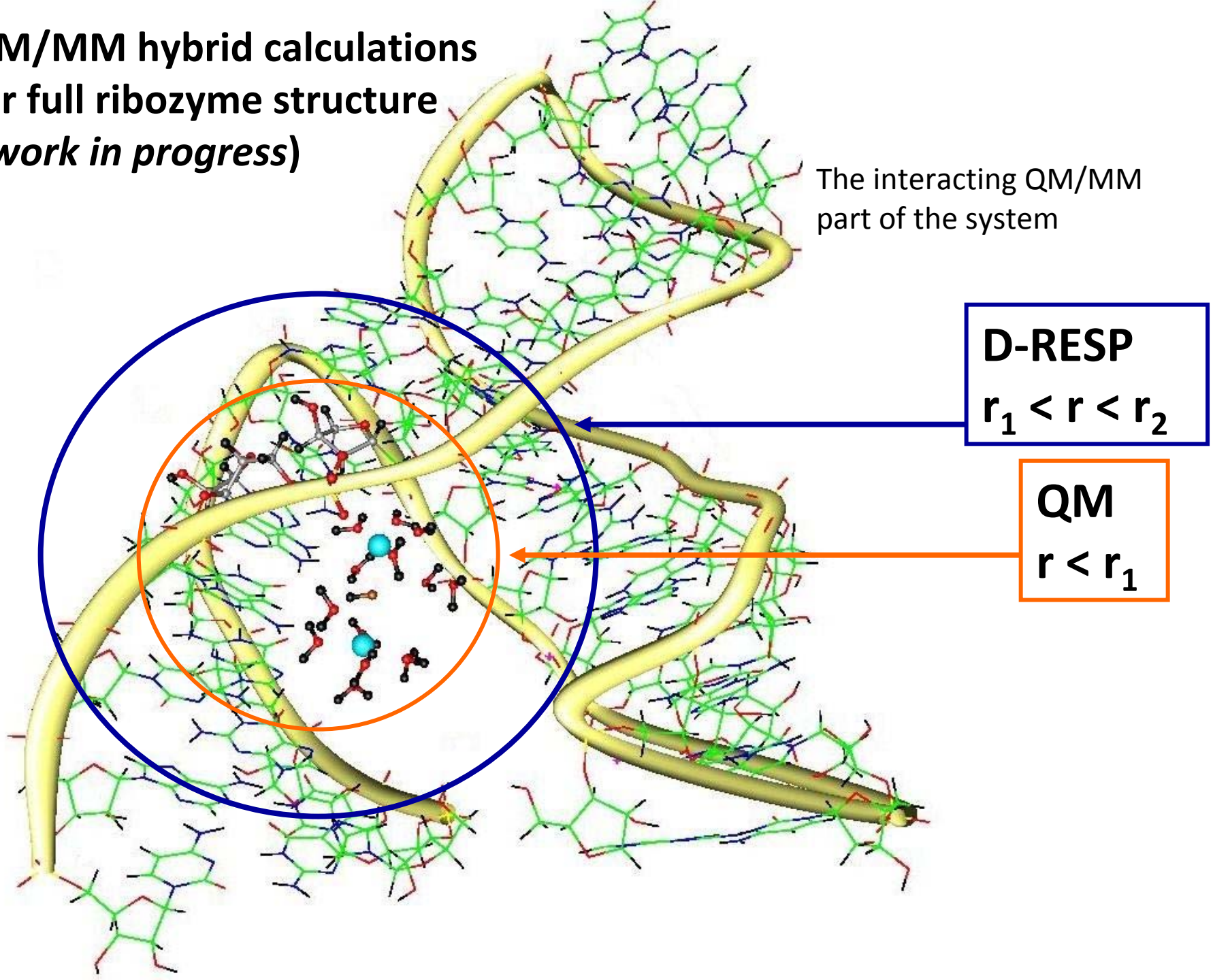
Conclusions

1. The **double-metal-ion mechanism** in the presence of **OH-** is definitely identified to be favored in the ribozyme catalytic reaction.

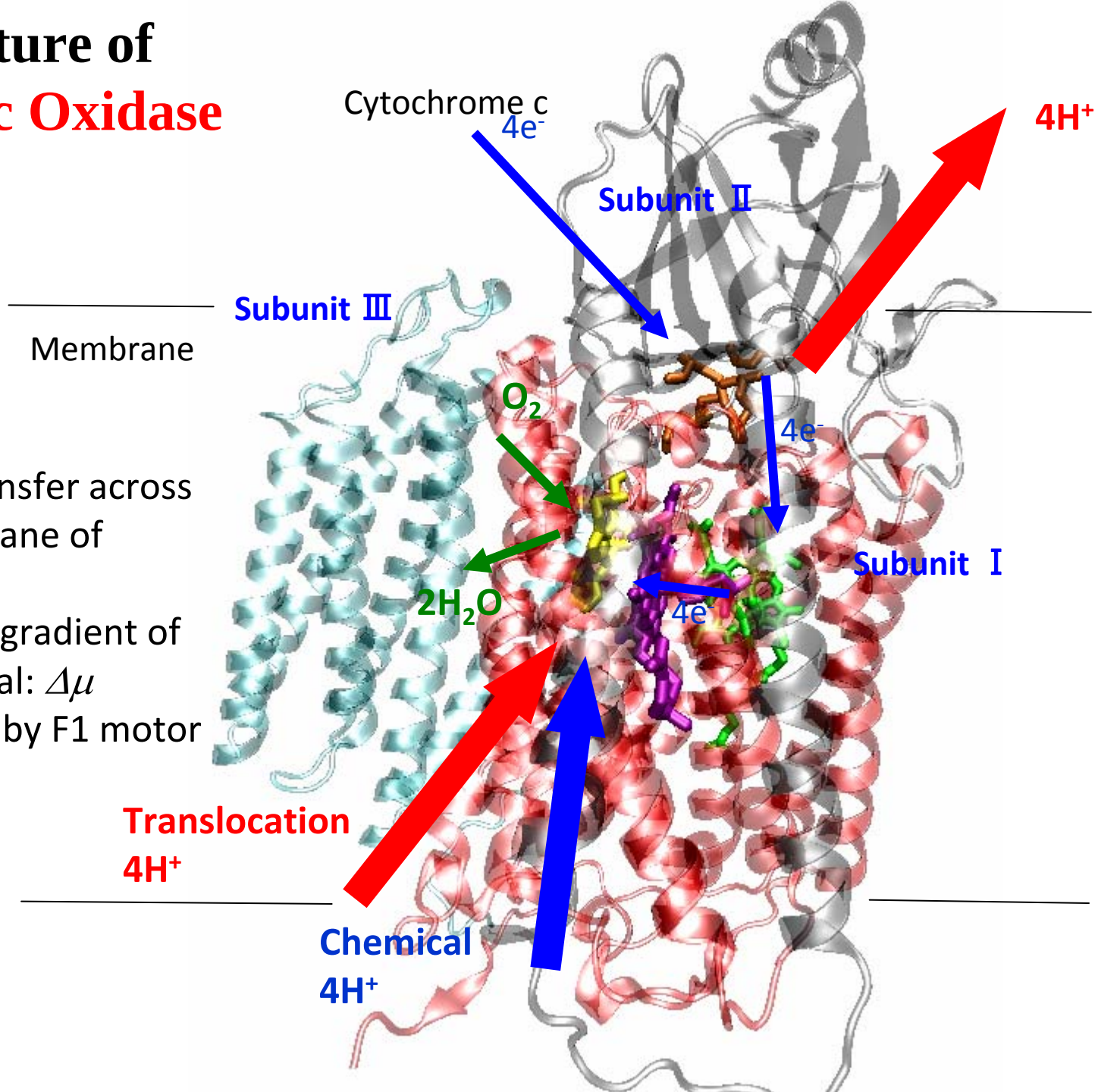
2. In the **single-metal-ion mechanism**, the intermediate structure was distorted, and thus, the activation barrier was increased.
3. Furthermore, the reaction path simulated was inconsistent to the previous experimental results, thus being incorrect.

4. Thus, the two Mg2+ cations avoid the structural distortion **in a concerted way** !
5. In this way, the **double metal ions** exclusively select the reaction path.

QM/MM hybrid calculations for full ribozyme structure (*work in progress*)

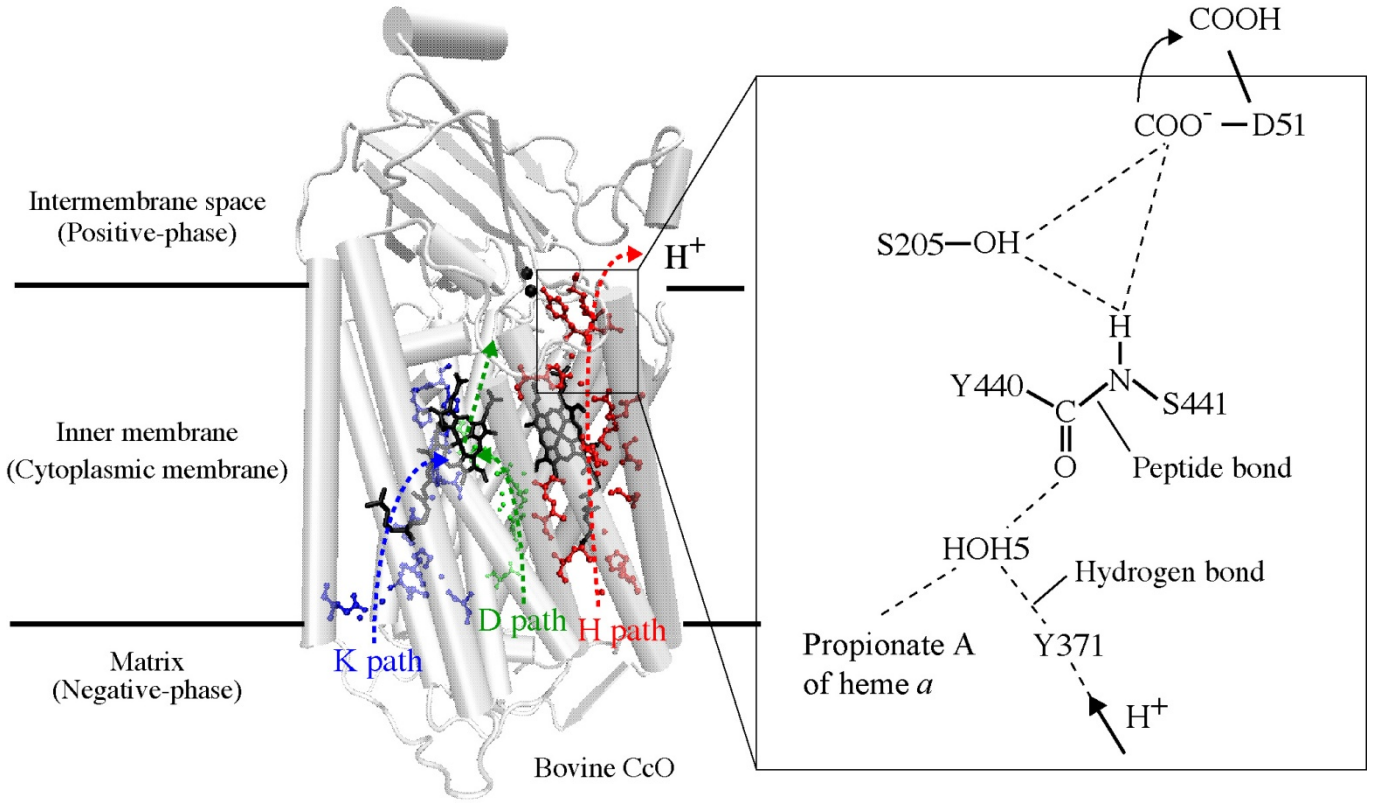


Crystal structure of Cytochrome c Oxidase (CcO)



Function of CcO:
active proton transfer across the inner membrane of mitochondria
→ generation of gradient of chemical potential: $\Delta\mu$
→ ATP synthesis by F1 motor (ATP syntase)

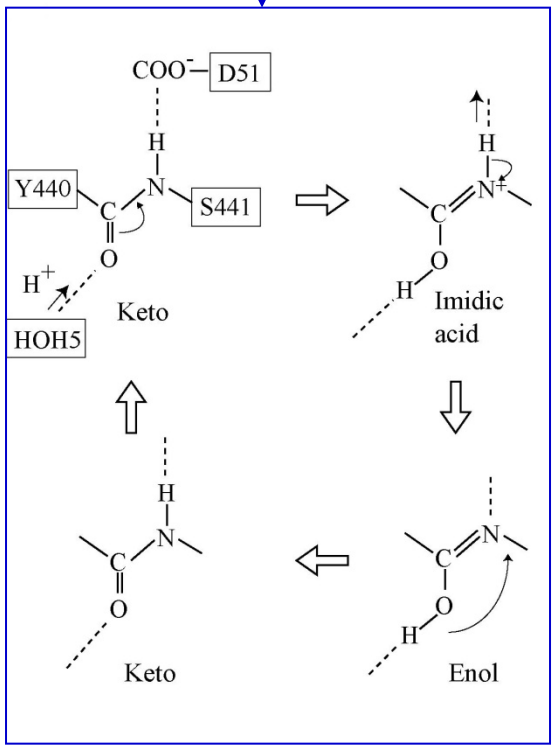
Proton transfer across a peptide bond in the H-pathway of **Cytochrome c Oxidase (CcO)**



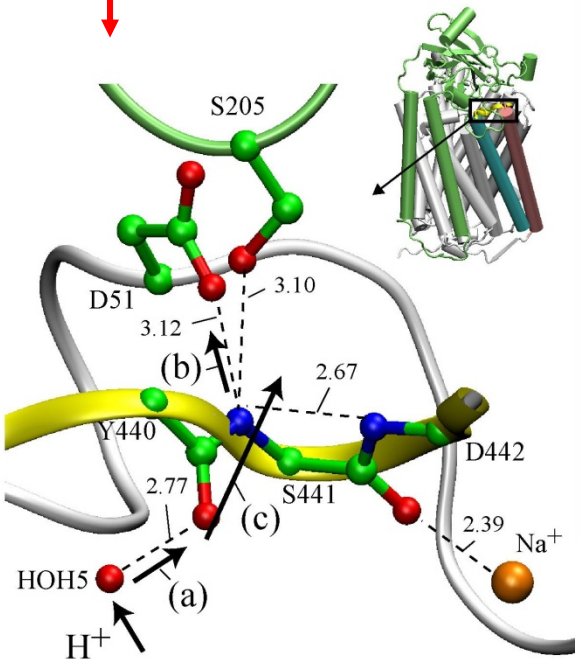
- Contrary to the K- and D- paths, involving only a proton wire mechanism along a regular hydrogen bond network, this peculiar path implies the transit of protons across a peptide group..

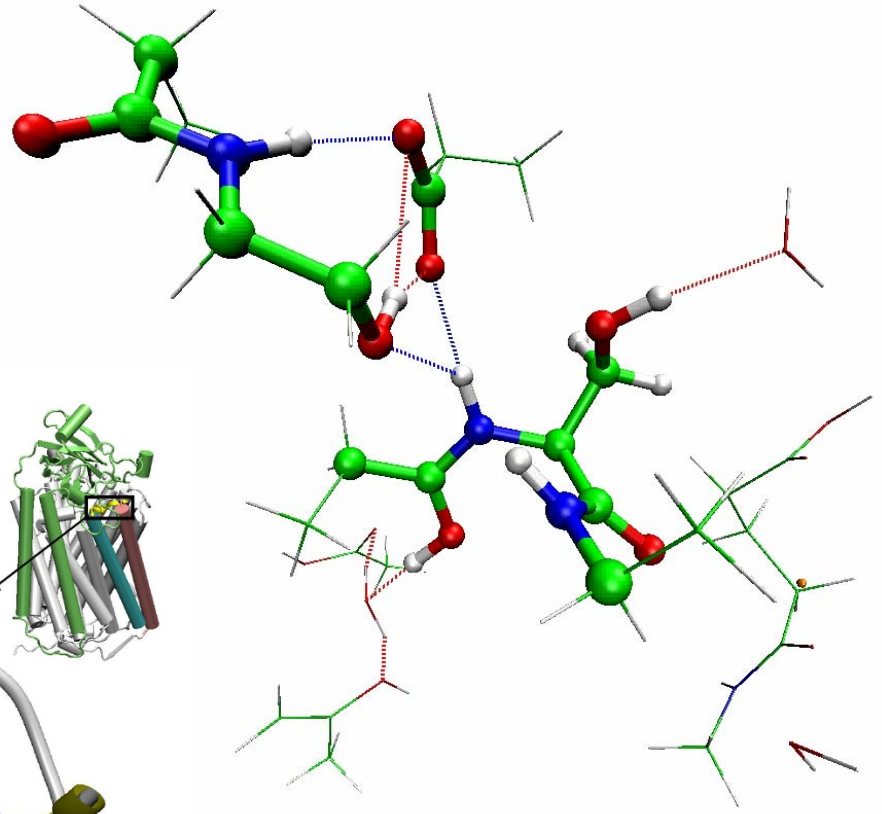
Reaction pathway as sampled by metadynamics

Tautomerization reaction scheme

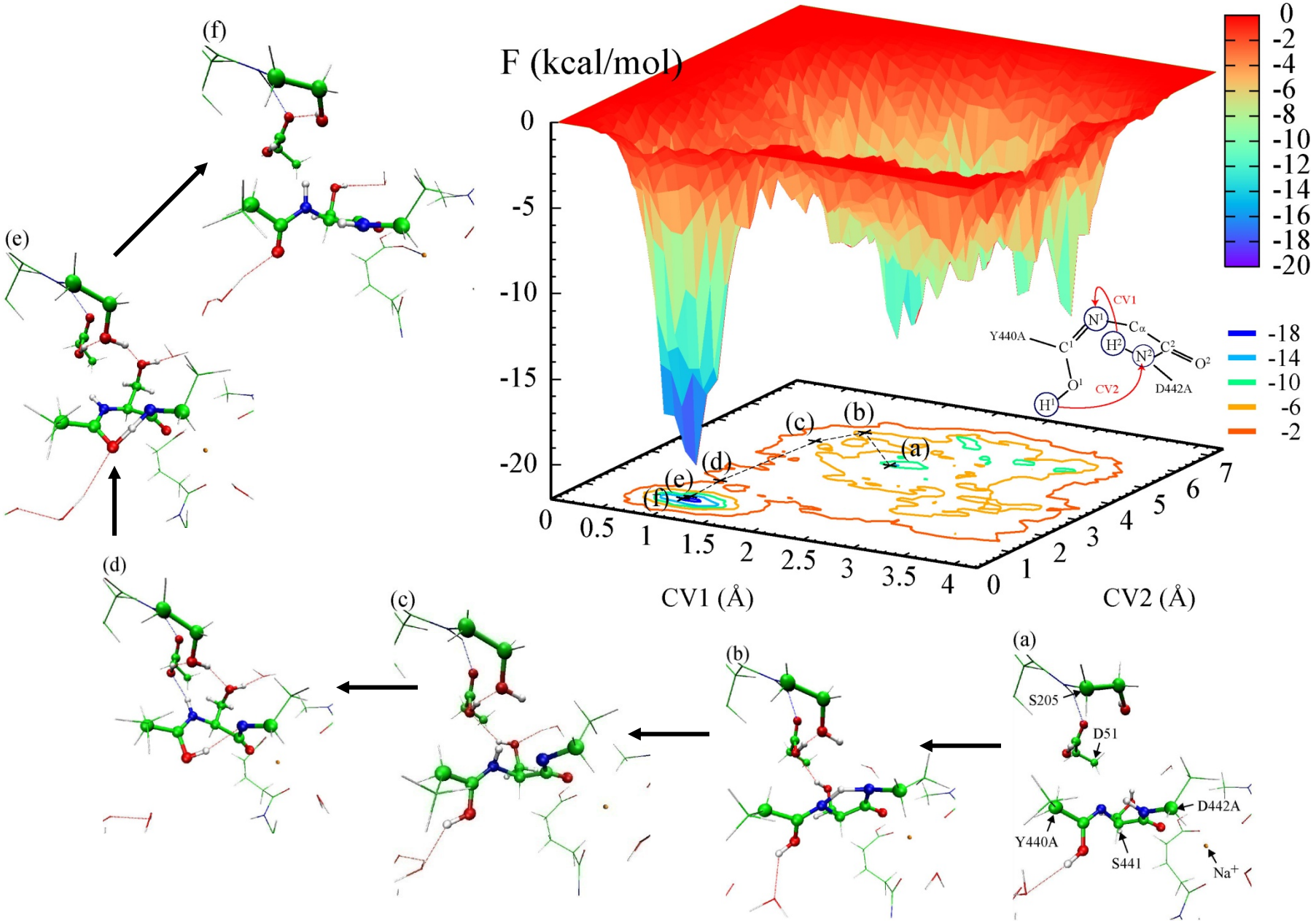


Simulated Reaction steps

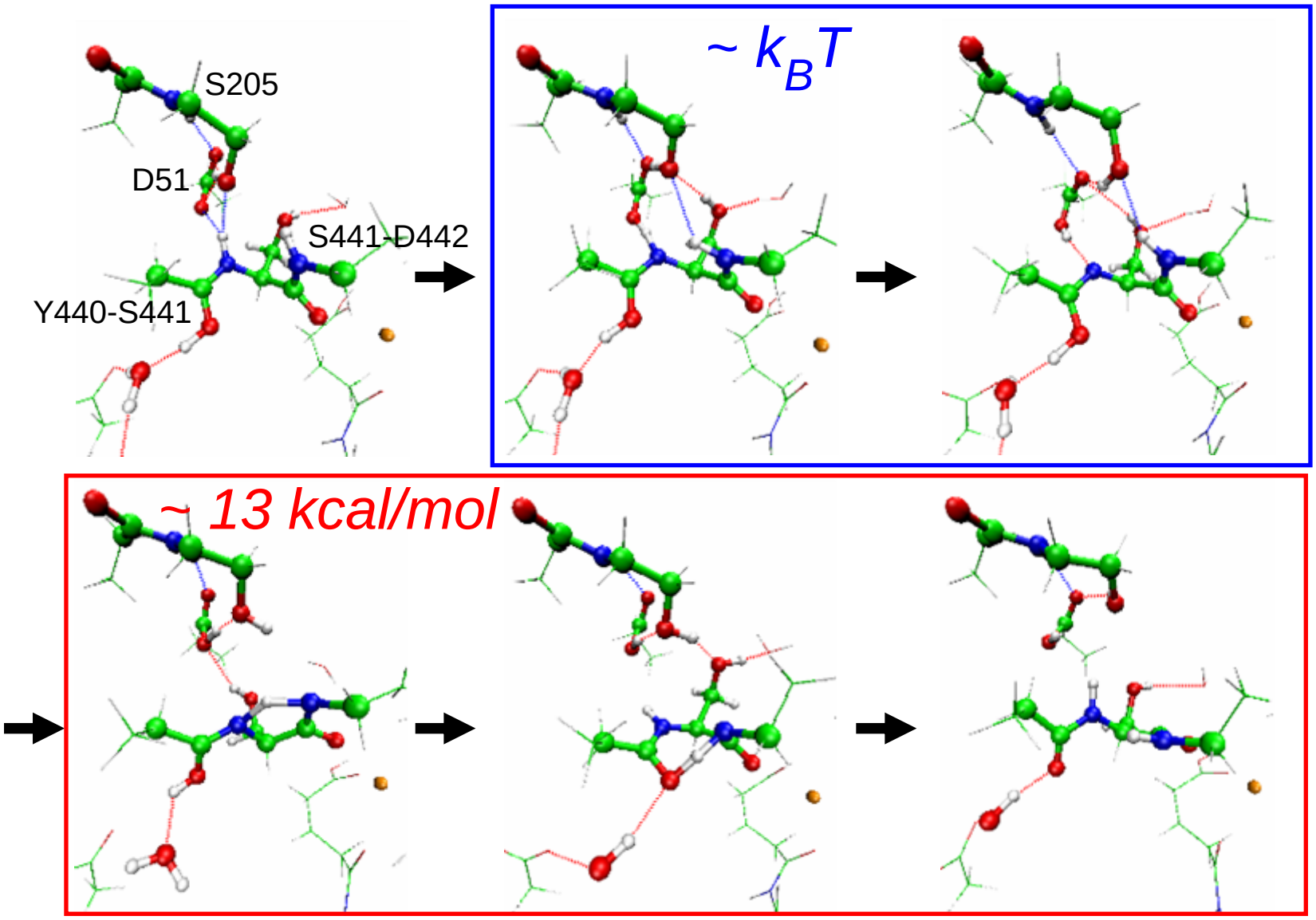




Free energy landscape and main configurations

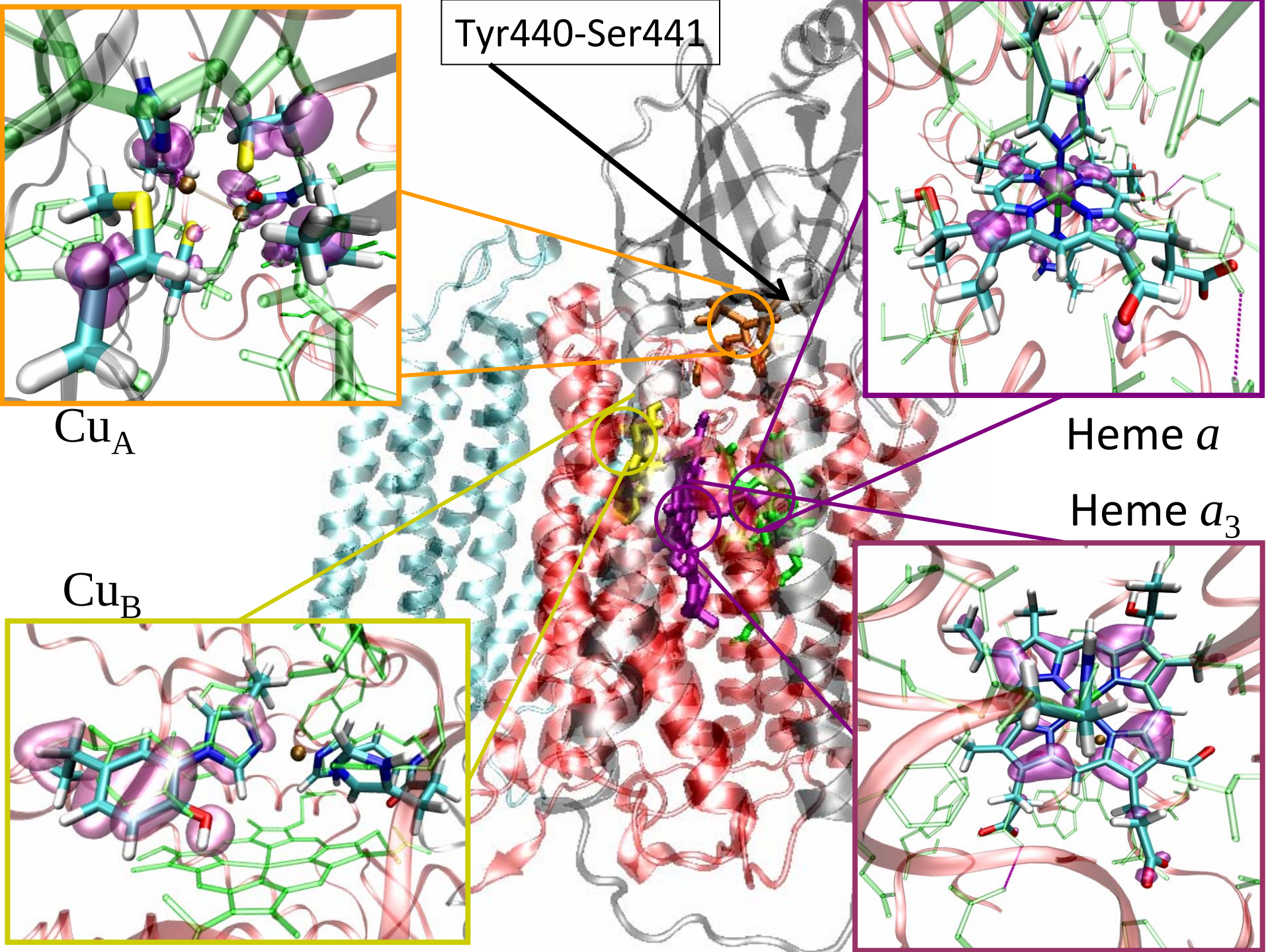


Main Steps of the Process



Conclusions on CcO

- Protons can be transferred across a peptide bond between Tyr-440 and Ser-441of CcO via a tautomerization
- A proton is initially provided to the Y440-S441 peptide group by a H-bound water molecule (becoming OH_3^+).
- Then the amide proton of the imidic acid is transferred in a barrierless way to the deprotonated carboxyl D51 group resulting in the formation of enol Y440-S441 ***without inducing substantial conformational changes***
- An enol-to-keto tautomerization completes the reaction via a two step H^+ transfer in the two adjacent Y440-S441 and S441-D442 peptide groups with a barrier ΔF = 13 kcal/mol.
- A direct proton transfer would require at least 60 kcal/mol and would induce a lot of bond stress, thus becoming unfeasible.

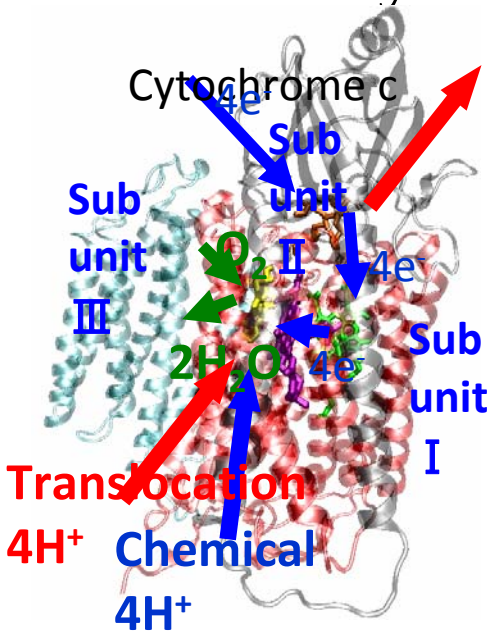

Tyr440-Ser441
Cu_A
Heme *a*
Heme a_3
Cu_B

Proton (H+) Transfer by Cytochrome *c* Oxydase (C*c*O)

$O_2 + 4H^+ + 4e^- \rightarrow 2H_2O$

Free Energy

Active Proton Transfer



Science 112 (1998), 923-930.

Electron (*e*-) Transfer by Cytochrome *c* (C*c*)

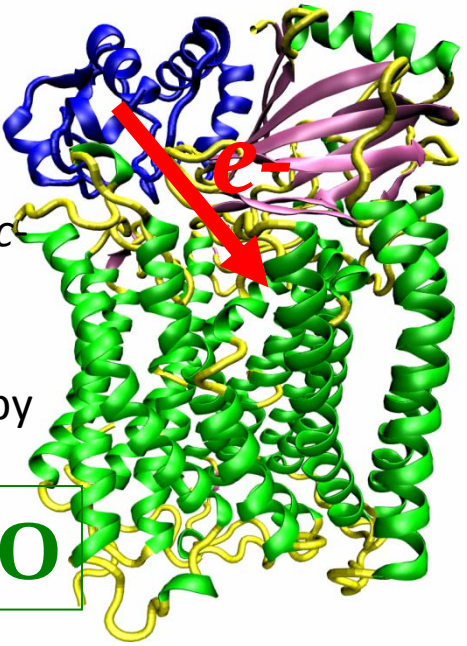
Cc → CcO
(*e*-)

Bioinformatics → classical MD
→ QM/MM hybrid calculations

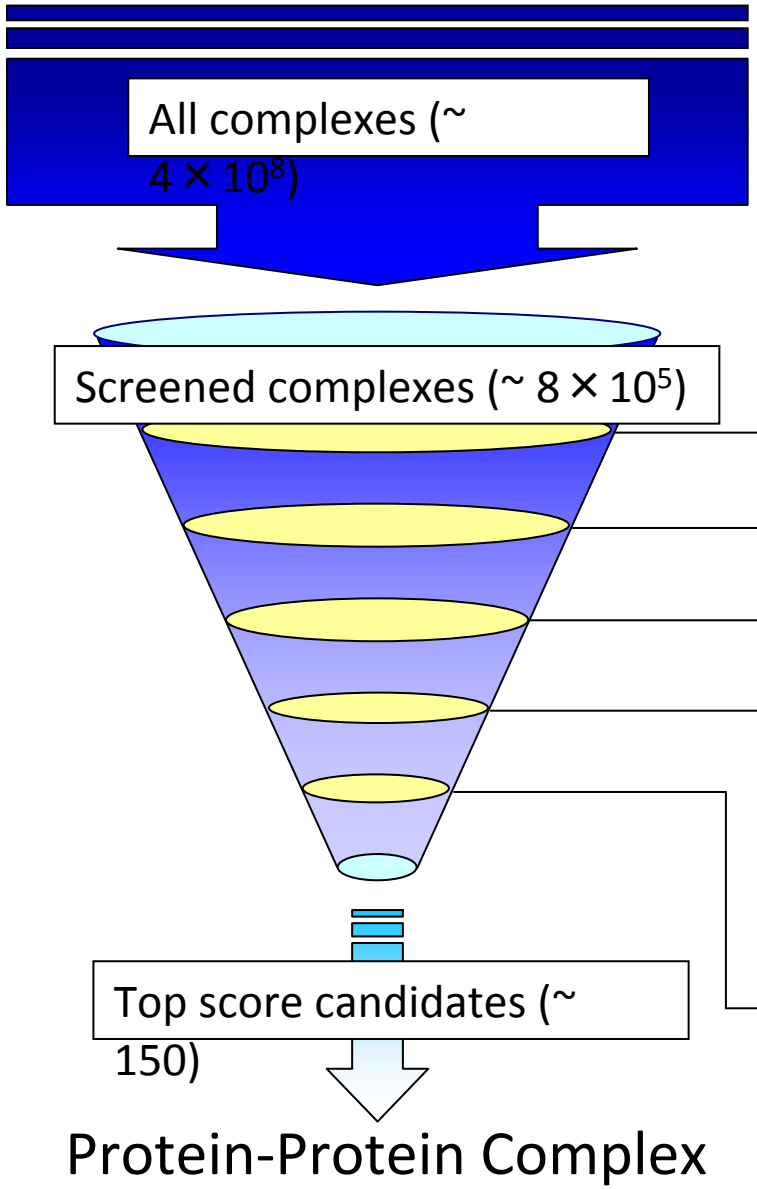
→ The **crystal** of the complex has not been obtained, in spite of much efforts by experimentalists!

→ Theoretical **molecular docking** method has been developed by our group, based on informatical graph theory coupled to molecular calculations.

Structural prediction of the C*c*-C*c*O complex by using bioinformatical molecular docking schemes developed by Kitta and Tateno.



Schematic representation of a novel docking calculation algorithm for protein-protein



Protein 1

Protein 2

Determination of the atoms located around the molecular surface

Selection of the atoms involving hydrogen bonds

Construction of the graph

Clique detection

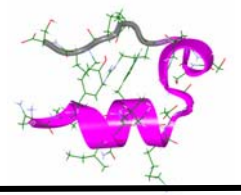
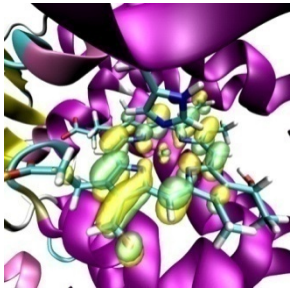
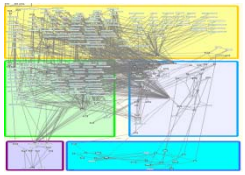
Docking

Steric-clash screening

Evaluation of the candidates

(implemented by using C/C++ and Perl)

Research phase of several projects in our group

Themes	Phase I	Phase II	Phase III
Protein Folding 	Development & implementation of fast & accurate calculation method of the vdW interaction	Replica exchange molecular dynamics (REMD) simulations are being performed now.	Extension of the analyses to several large proteins
		Calculations using PACS-CS	
Reaction Mechanisms 	Development of a QM/MM hybrid calculation program based on the all-electron calculation	Applications of the QM/MM hybrid calculation program: aminoacyl-tRNA synthetase, cytochrome c oxydase, transamidase, Ah receptor, etc.	
		Calculations using PACS-CS	
	Applications of the QM/MM hybrid calculation program based on Car-Parrinello MD (CPMD): riboyzme, ATP synthase, cytochrome c oxydase, charge transfer of double-stranded DNA, etc.		
	Collaborations with the Computer Science Group	Collaborations with the Condensed Matter Physics Group	Calculations using PACS-CS
Cellular signaling network 	Mathematical modeling and development of calculation & optimization program, of cellular signaling reaction network	Applications of the calculation / optimization program: FGF signaling network cascade, multicellular network systems, etc.	
		Parallelization of the program	
			Collaborations with the Computer Science Group
			Calculations using PACS-CS
Year	2005	2007	2009

Start from Sep. 2005 → Dec. 2007