QM/MMハイブリッドシミュレーションによるタンパク質機能の解析

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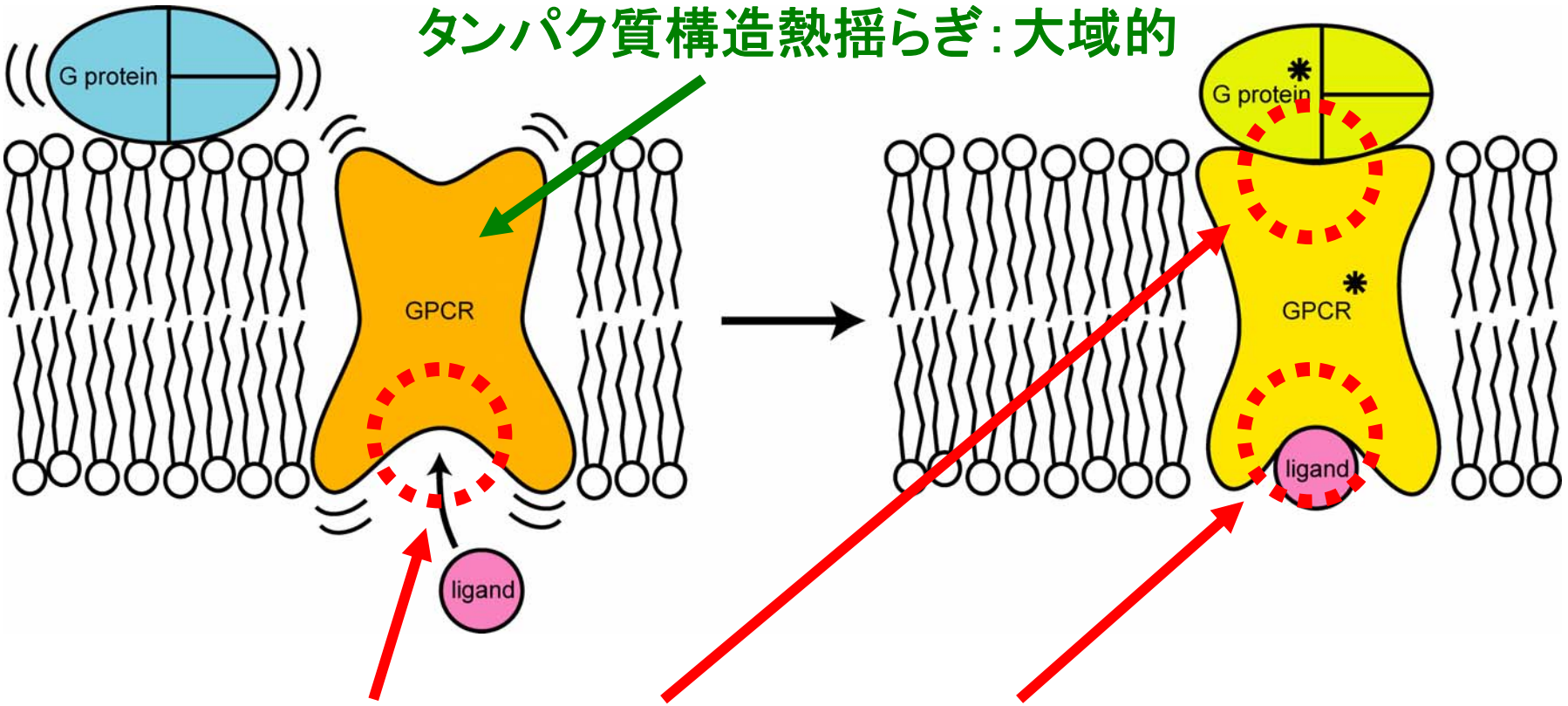
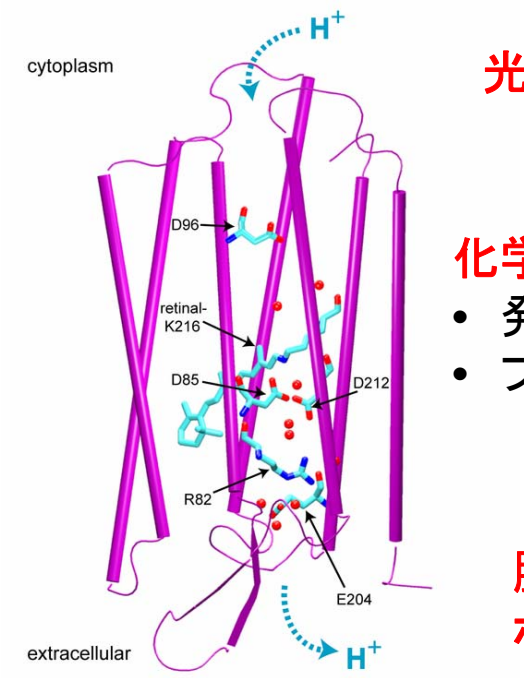
タンパク質の機能に織り込まれている分子過程

例： **G-Protein Coupled Receptor**



生体機能における化学反応の役割

エネルギー変換、機能制御の主役



光エネルギー

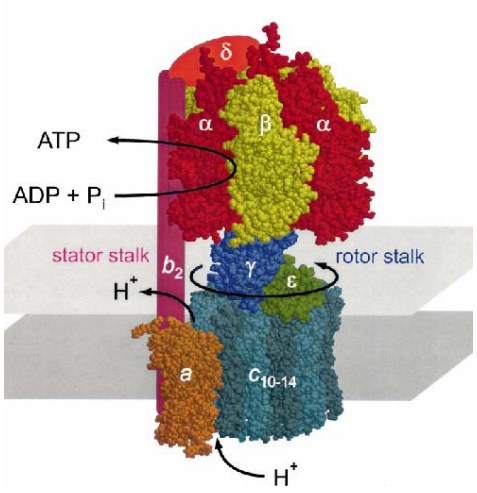
↓

化学的エネルギー

- 発色団の光異性化
- プロトン移動

↓

膜間プロトン
ポテンシャル



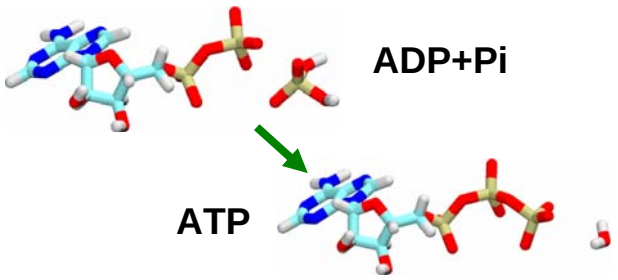
膜間プロトン
ポテンシャル

↓

力学エネルギー
（Fo及びγの回転）

↓

化学的エネルギー
（ATPの合成）



化学反応 ⟷ **機能発現過程**

電子状態変化 — タンパク質の構造変化

局所的 — 大域的

反応基質とタンパク質
環境の相互作用

生体内化学反応の分子物理的記述
QM/MM 法

1. Molecular dynamics (MD) simulations

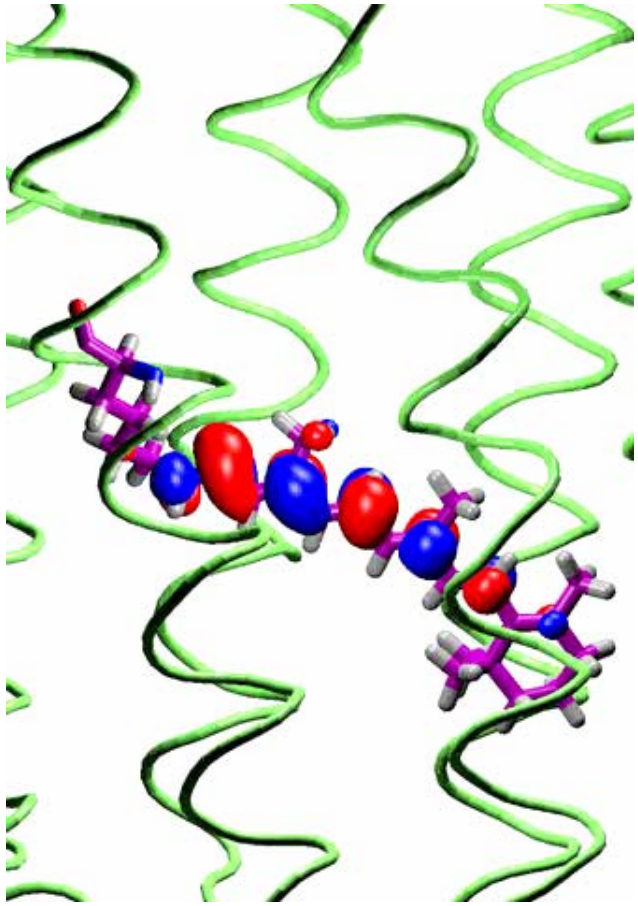
- Large protein systems
- Empirical force fields (MM)
- No explicit description of electronic states

2. Molecular orbital or density functional theories (QM)

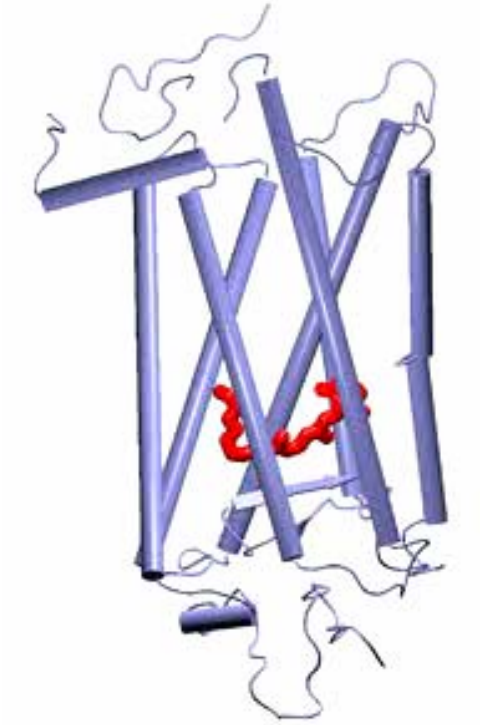
- Explicit description of electronic states
- Huge computational cost

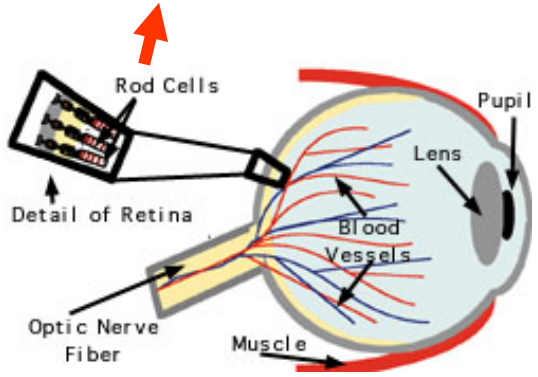
3. QM/MM simulations (2000~)

- Reactive moieties are described by *ab initio* QM methods.
- Protein environment is treated by MM.



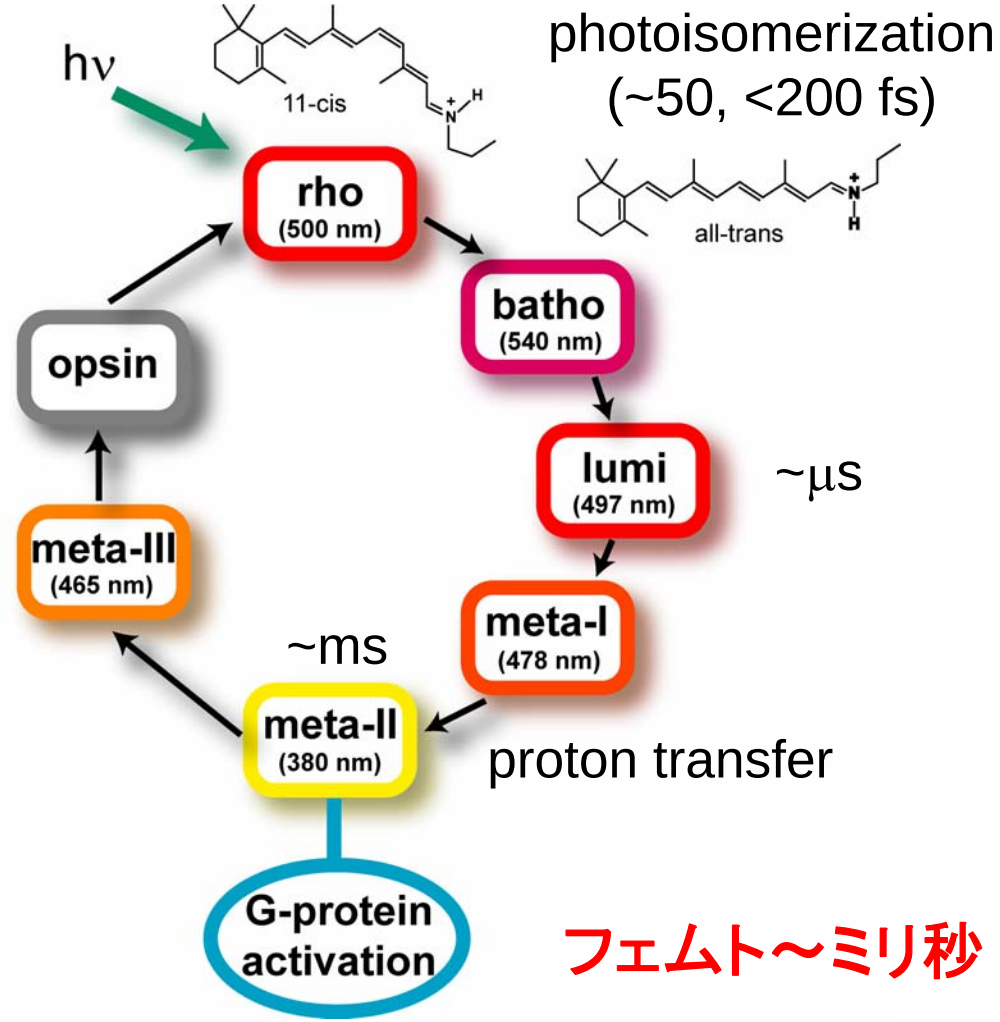
Visual Receptor Rhodopsin (Rh)





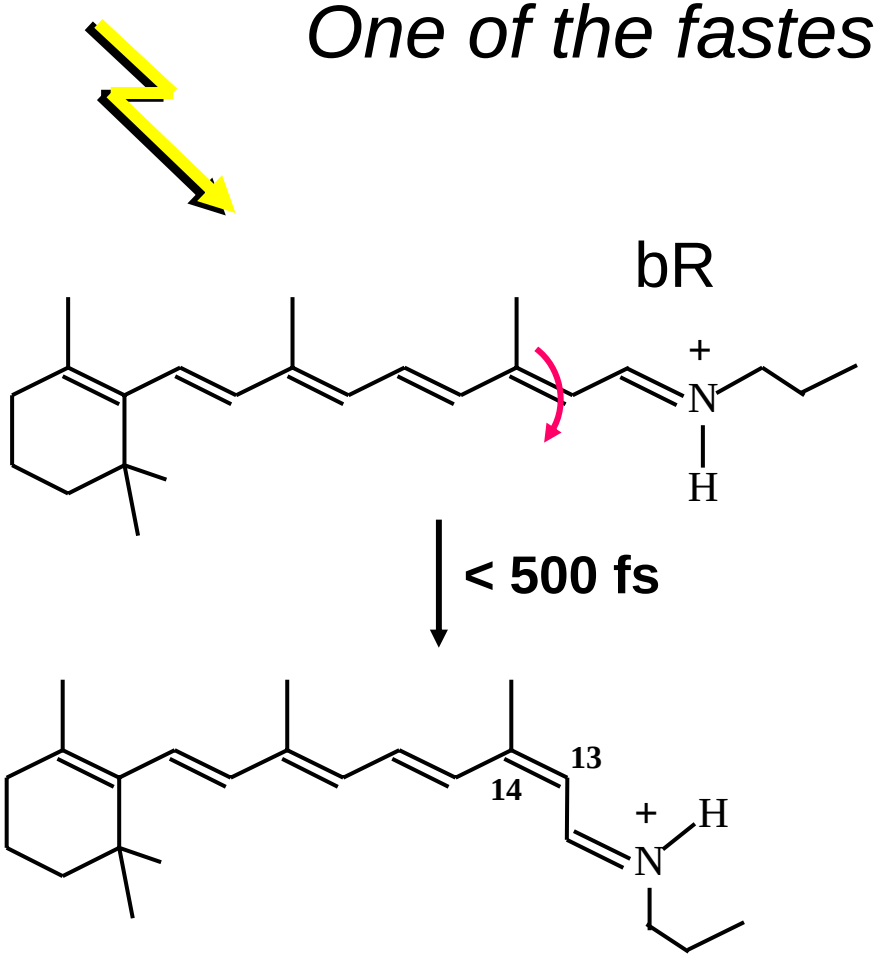
http://wunmr.wustl.edu/EduDev/LabTutorials/Vision/Vision.html

photocycle of Rh activation process



Photoisomerization of Retinal

One of the fastest reactions in nature



- Ultrafast rate (240-500 fs)
- High bond selectivity
- High quantum yield (0.6)

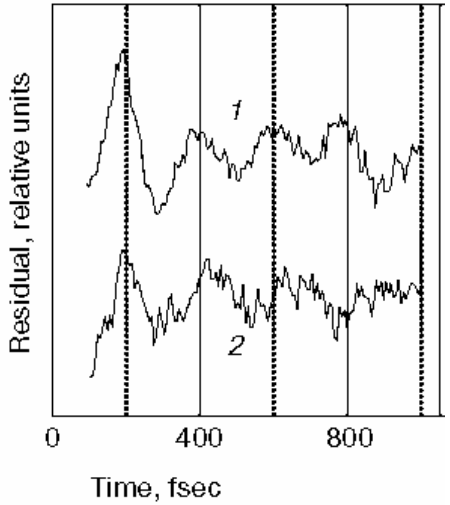
Recent progress in ultrafast spectroscopy has attained 10 femtosecond time resolution.

Kobayashi et al., Nature 414, 531 (2001)

pulse width: 5 fs

Ye et al., CPL 66, 1499 (2001)

Oscillations on pump-probe signals

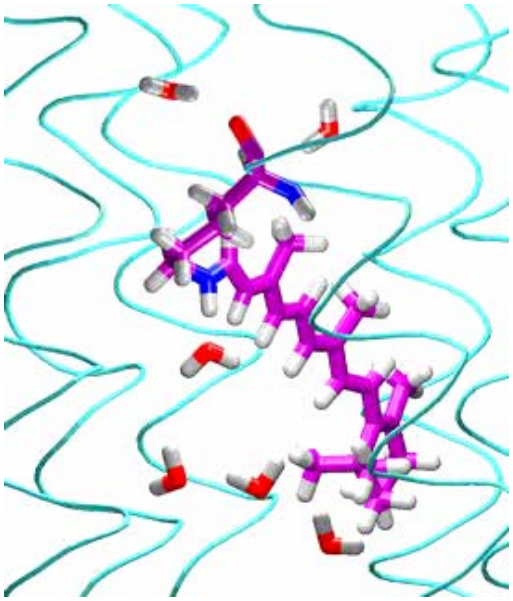


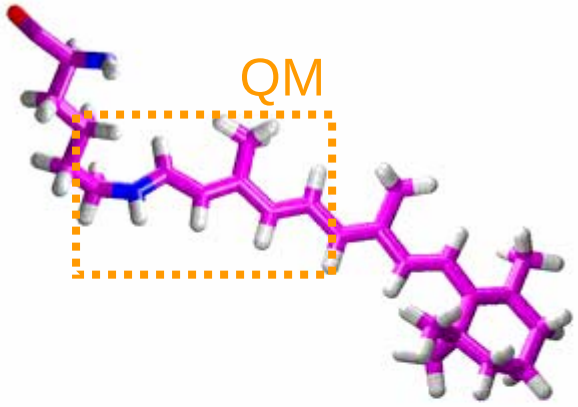
Direct real time observations of molecular motions in the transient photochemical events

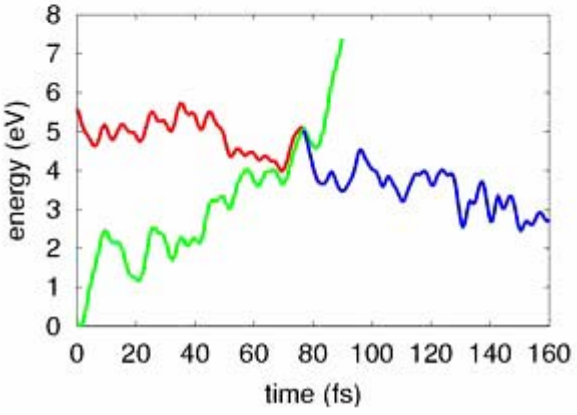
On-the-fly Ab Initio QM/MM Excited State MD Simulation

Photoisomerization in bR

Hayashi et al. (2003)





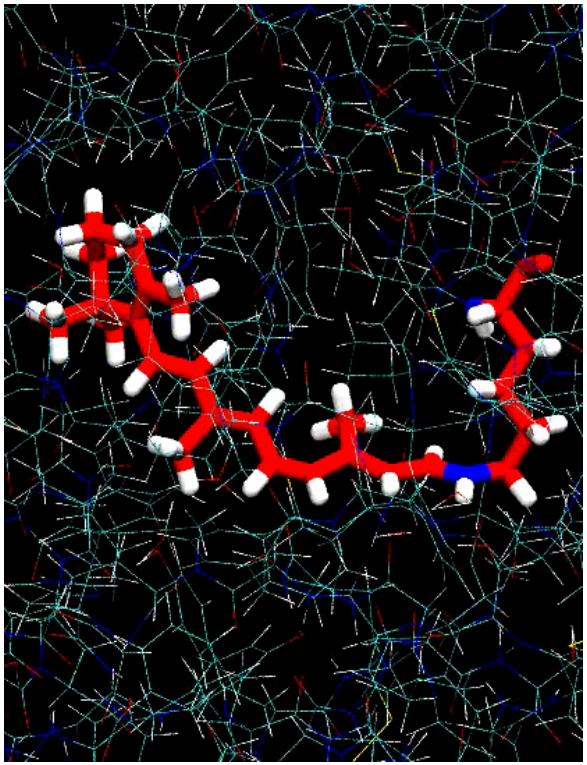


retinal : QM (sa-CASSCF/DZV)
protein: MM (Amber)

Complex molecular motions

Dynamic couplings between torsions and waggings

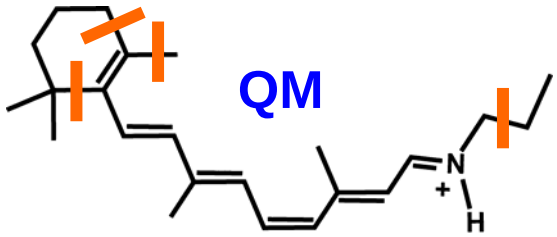
Photoisomerization of Rh at 300 K

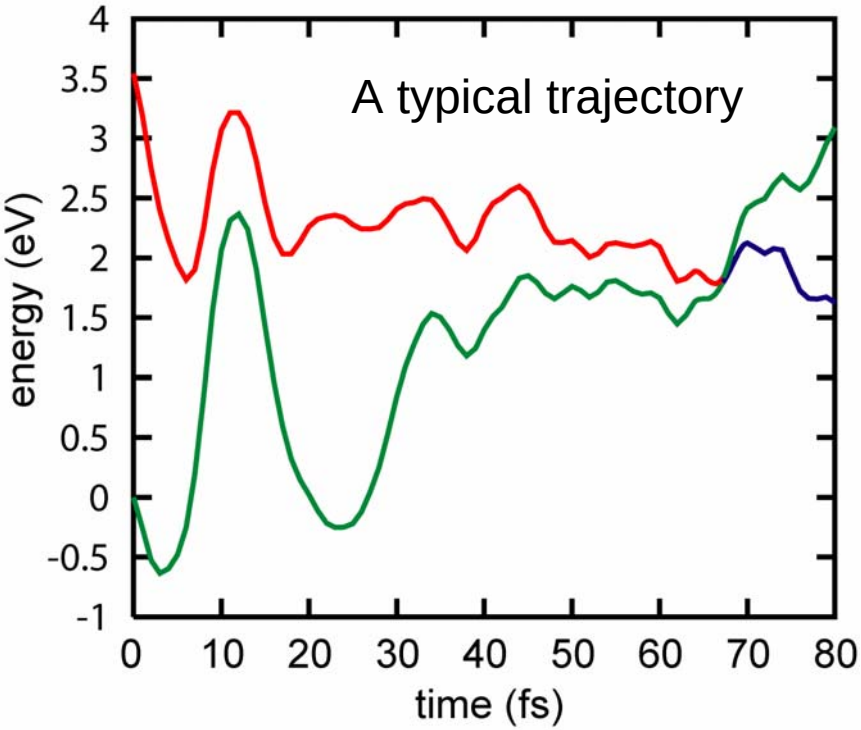


~ 4 hours/step on Athlon64(FX55)

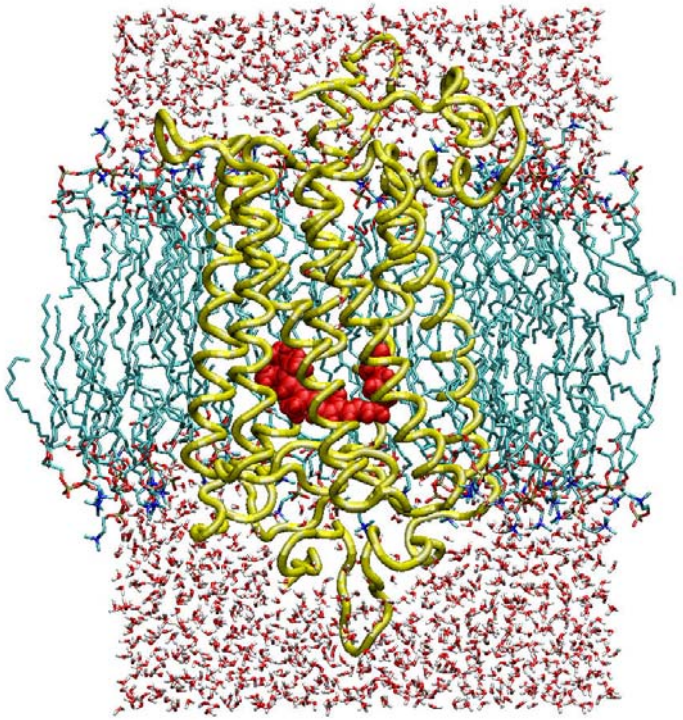
Initial coordinates and velocities were sampled from an equilibrium MD simulation (14 points from a 1.6 ns trajectory)

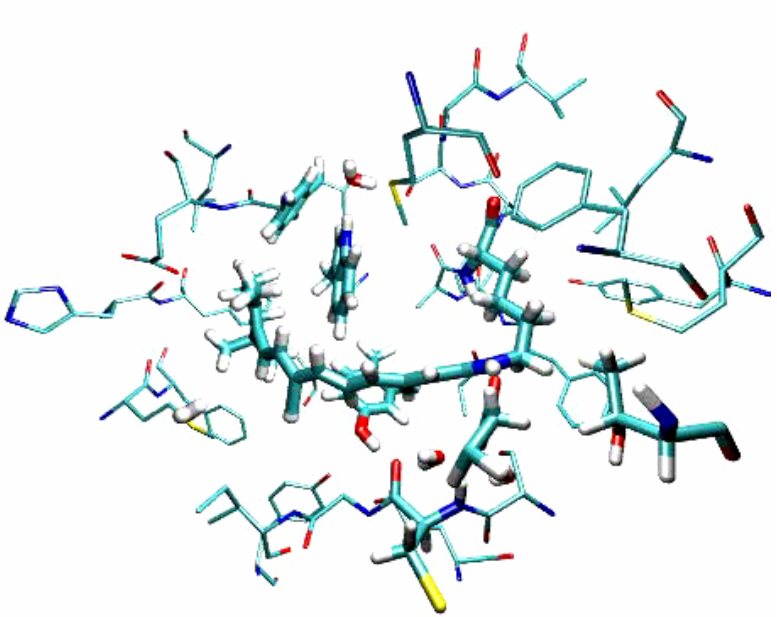
IMOMM-MD simulation
sa-CASSCF(12,12)/DZV/AMBER





Conformational Changes of Rhodopsin in Its Signaling Process



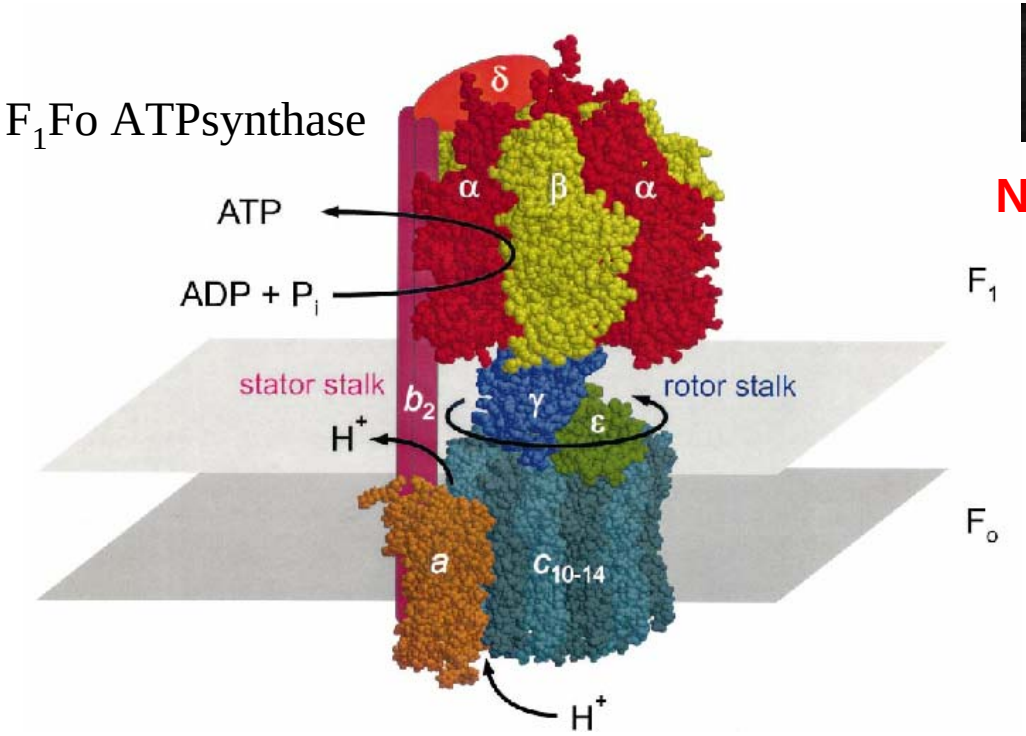


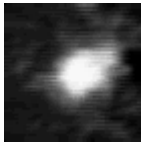
Classical MD simulations of bovine rhodopsinin membrane and water (40,000 atoms, 10 ns. NAMD).

Retinal isomerization induces substantial conformational changes of the binding pocket.

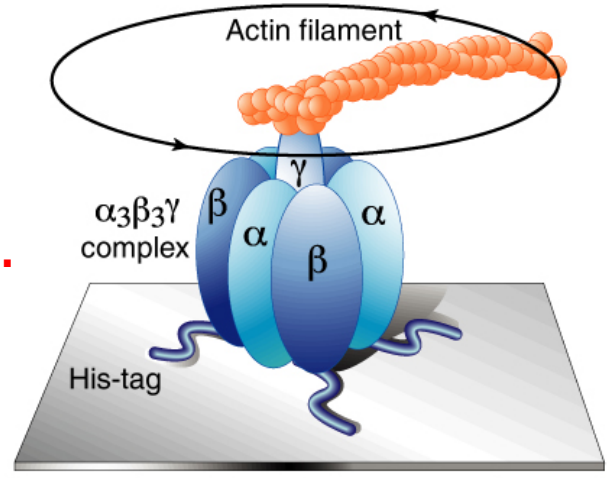
Saam, et al. Biophys J. 83, 3097-3112 (2002)

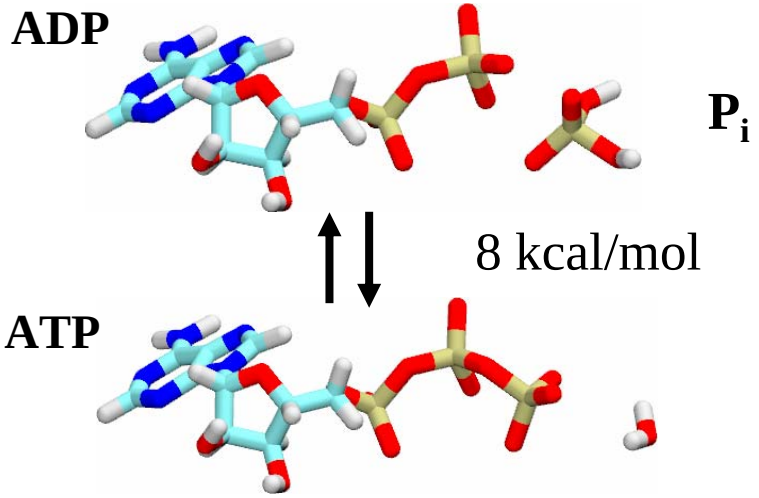
F_1-ATPase: A Chemical-Mechanical Energy Converter





Noji et al.





How are local chemical reactions coupled to large protein conformational changes?

Characterization of ATP Hydrolysis Reaction in F_1-ATPase

Dittrich et al. BJ, 85, 2253, (2003)
Dittrich et al. BJ, 87, 2954, (2004)

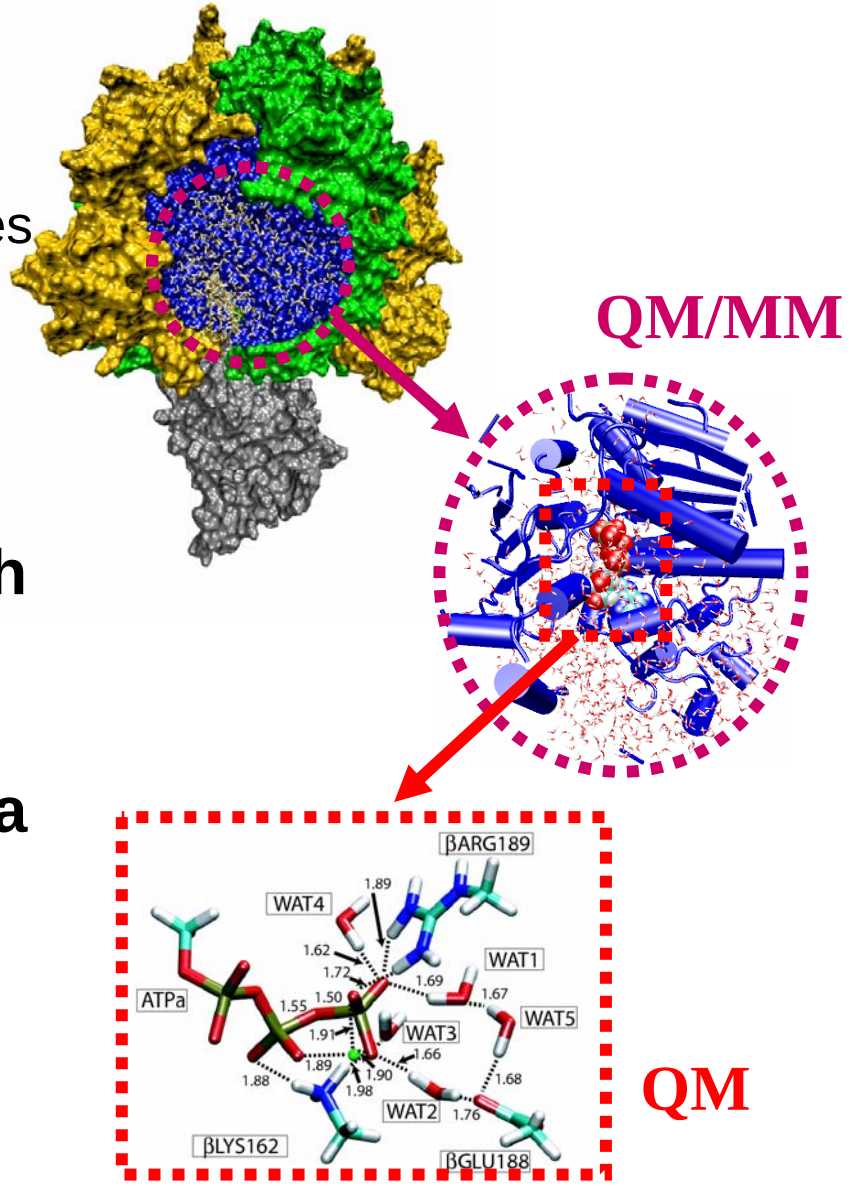
1. MD simulation in water box

- X-ray structure by Gibbons et al. (1E79)
- DOWSER placed several water molecules in cavities of the binding pocket.
- 327,506 atoms
- NPT, PME, NAMD (Isralewitz et al.)

2. Annealing and minimization with CHARMM27 force field

3. Ab initio QM/MM simulation for a partial system.

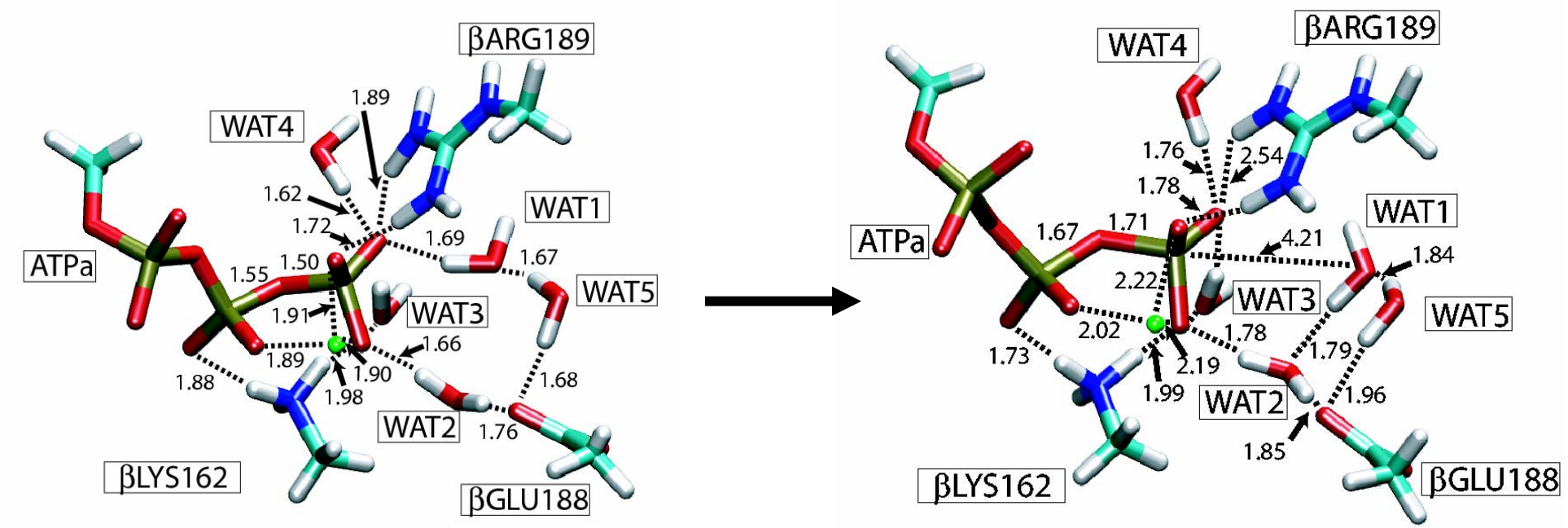
- 8,378 atoms (the QM/MM system)
- Geometry optimization and reaction path calculations (MP2/HF/(or DFT)6-31G,)



Ab Initio QM/MM Geometry Optimization

MM optimized structure

QM/MM optimized structure

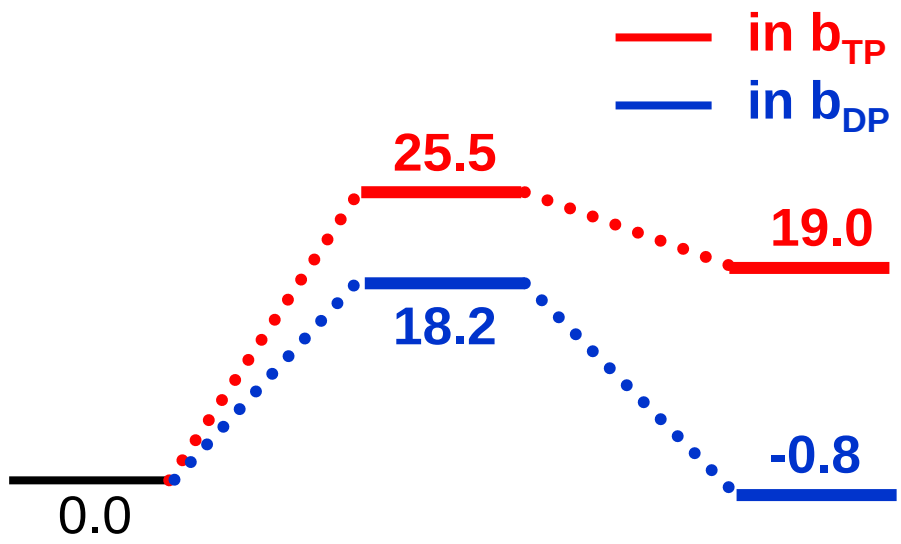


Electronic Effects on the Hydrogen-bond network structure

Wat1 rather than Wat2 is the attacking water molecule.

ATP Hydrolysis Before/After Rotation

B3LYP/6-31G (kcal/mol)

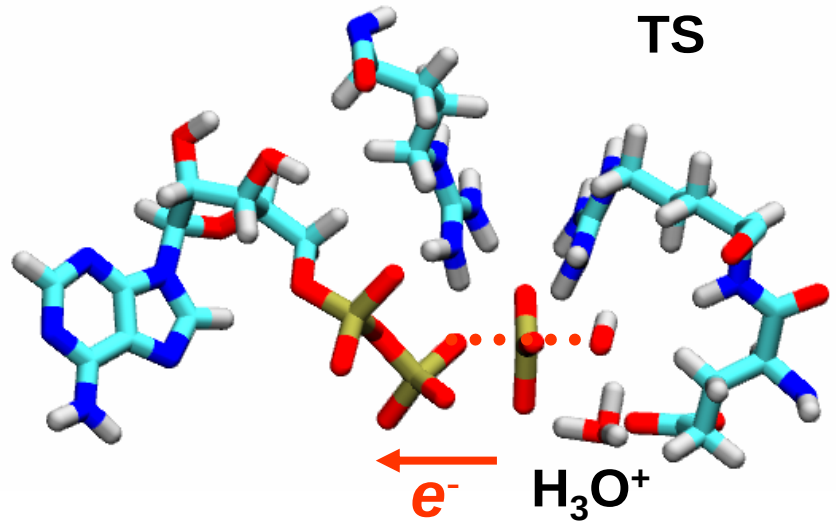


ATP+H_2O **TS** **ADP+Pi**

hydrolysis

phosphorylation

Arg finger

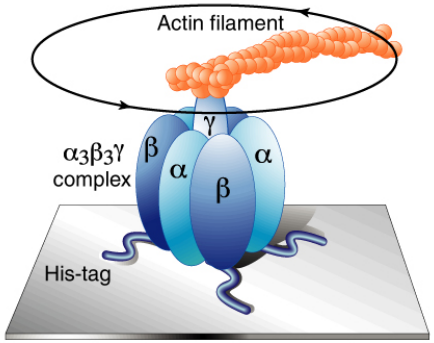


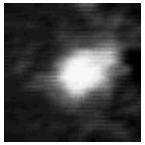
- ATP hydrolysis is equ-energetic.
- An arginine finger stabilizes TS and product.

Perspective

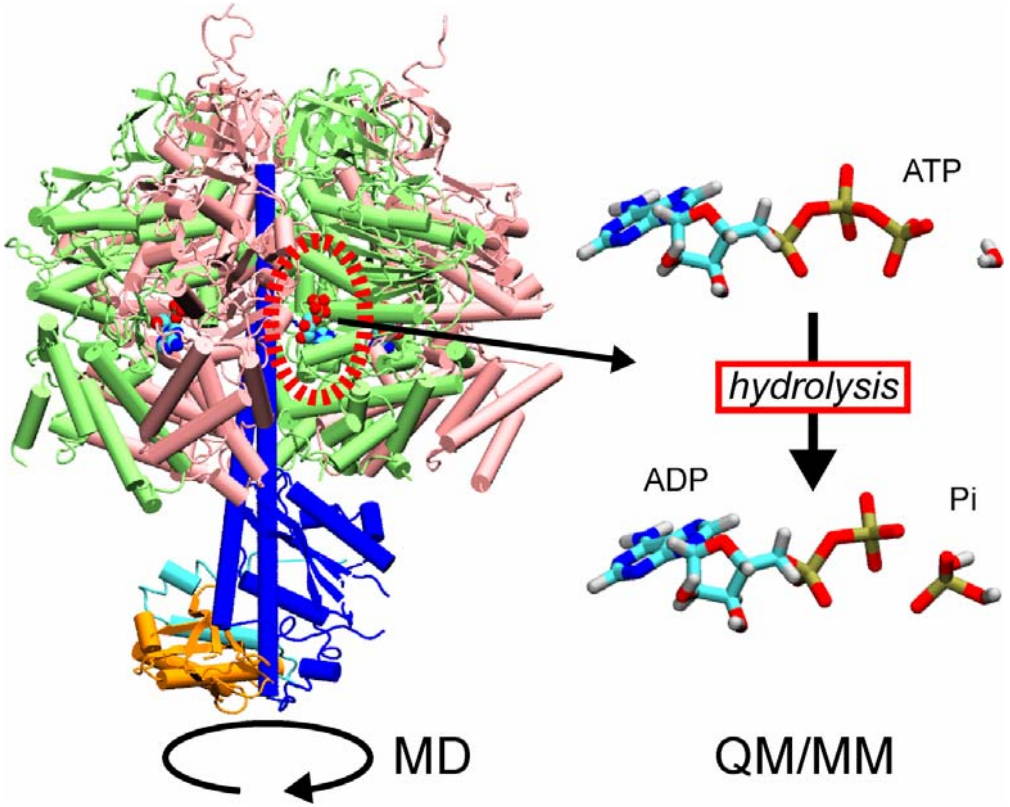
Understanding of Protein Function

F_1-ATPase molecular motor





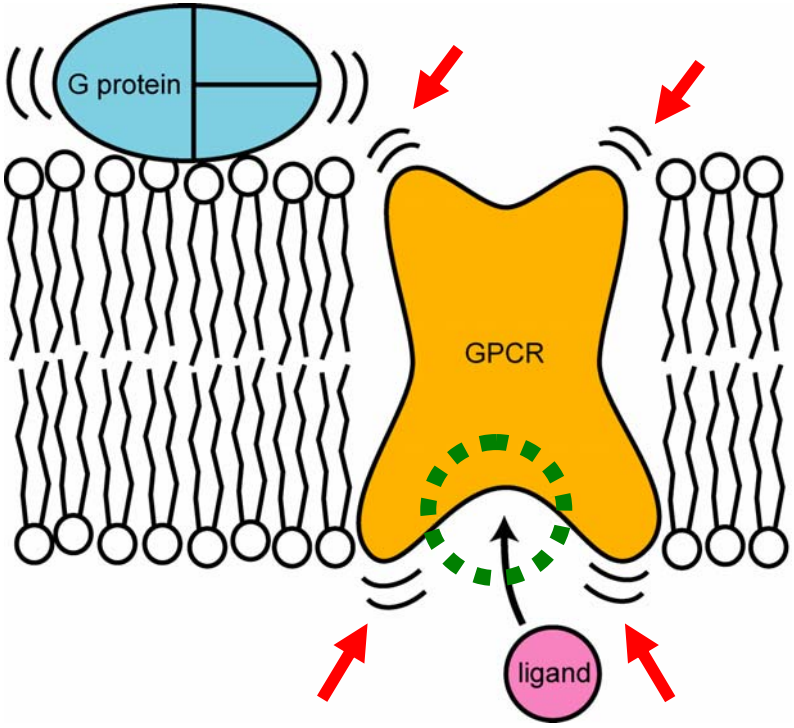
Noji (Osaka) single molecule exp.



Protein Dynamics **Chemical Reaction**

Chemical-mechanical energy conversion in the molecular motor

Heterogeneous Computational Techniques Are Required



分子認識・酵素反応

分子軌道法：高精度だが静的

タンパク質構造熱揺らぎ

分子動力学法：動的だが中精度

大規模計算による革新的サイエンス

超並列化：とにかく大きな系

例えば：　巨大生体分子の電子状態は、どうなっているのか（FMO,PDF)。タンパク質超複合体の力学特性（北尾）

ただし、、、

生体機能解析のボトルネックは、
系のサイズよりも時間!!

マイクロ~ミリ秒をどうするか

MD法：~ 10 ns：線形揺らぎ

中並列化・数・高速ネットワーク

方法論の開発（含、低精度手法の適用）