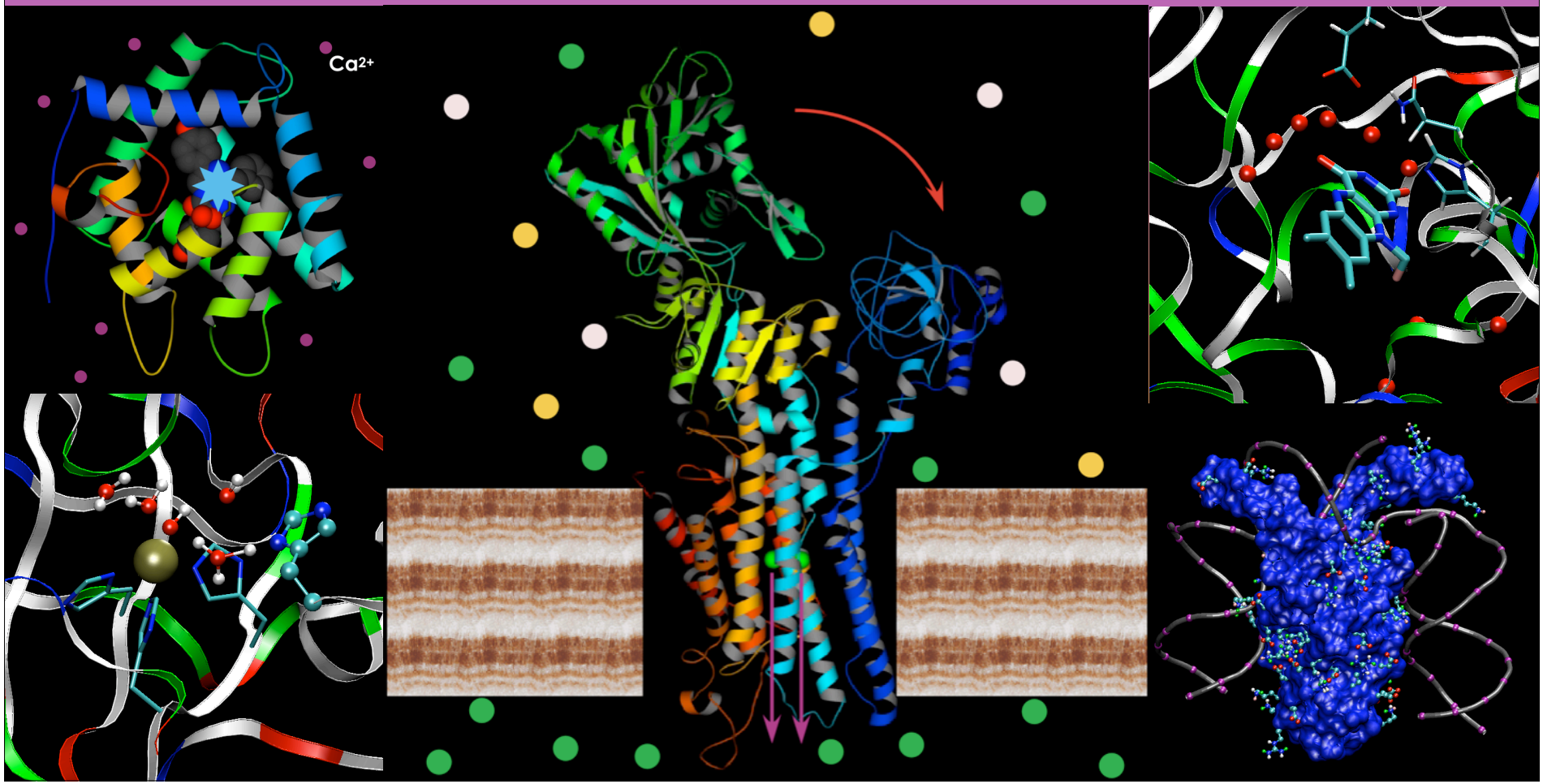
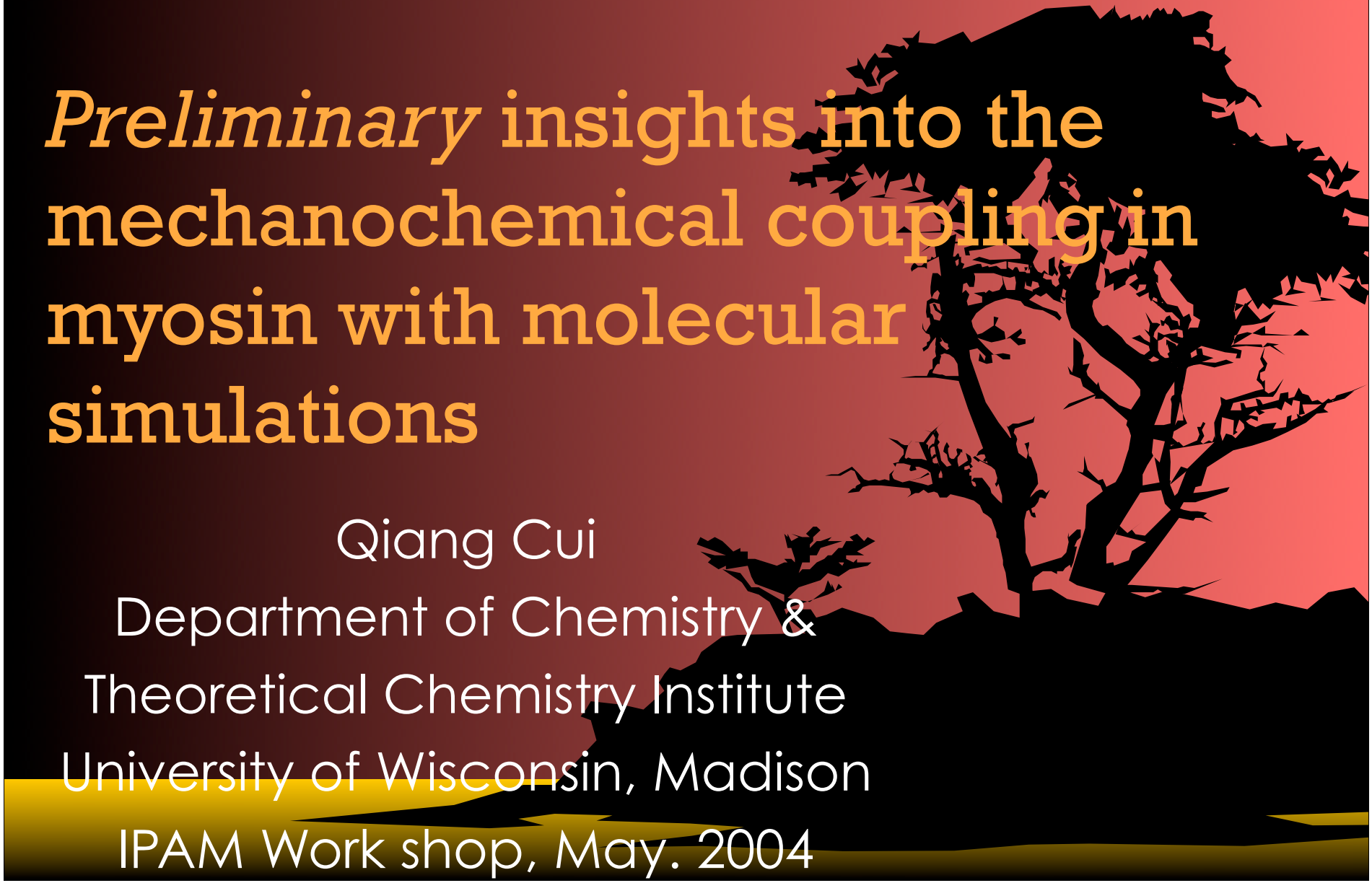
Theoretical/computational study of complex chemistry in biological systems



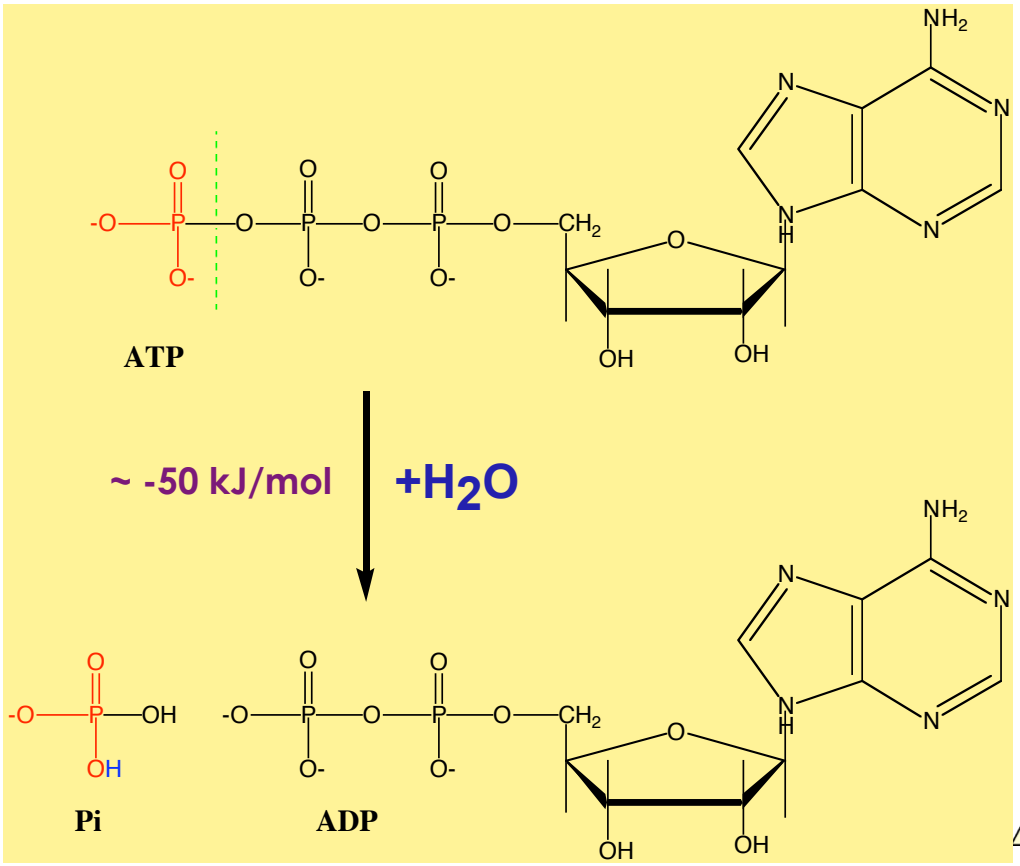
Preliminary insights into the mechanochemical coupling in myosin with molecular simulations

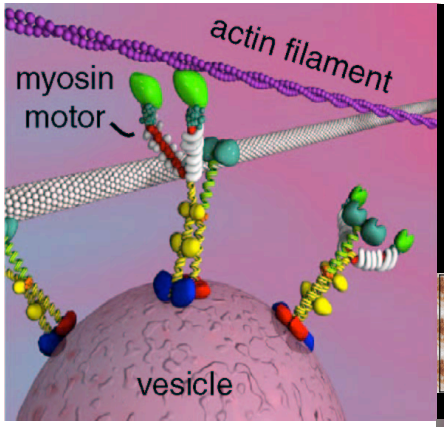


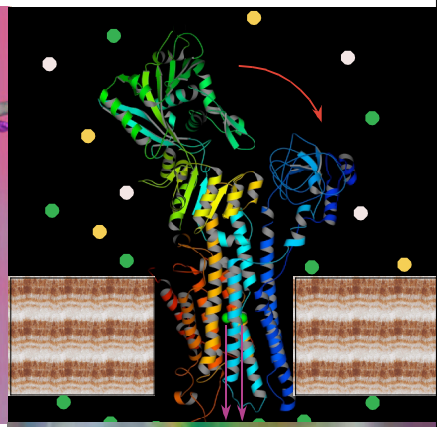
Qiang Cui
Department of Chemistry &
Theoretical Chemistry Institute
University of Wisconsin, Madison

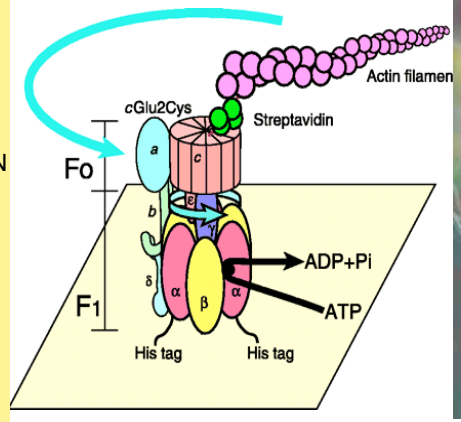
IPAM Work shop, May. 2004

Rise of the Machines™



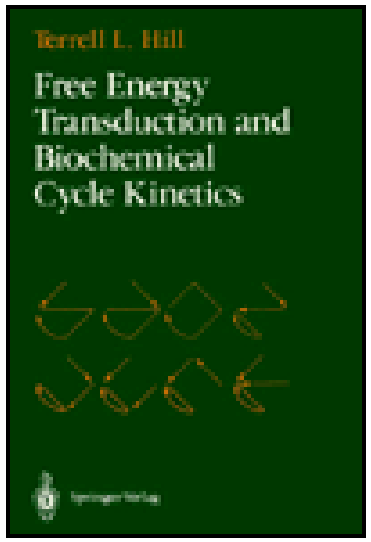


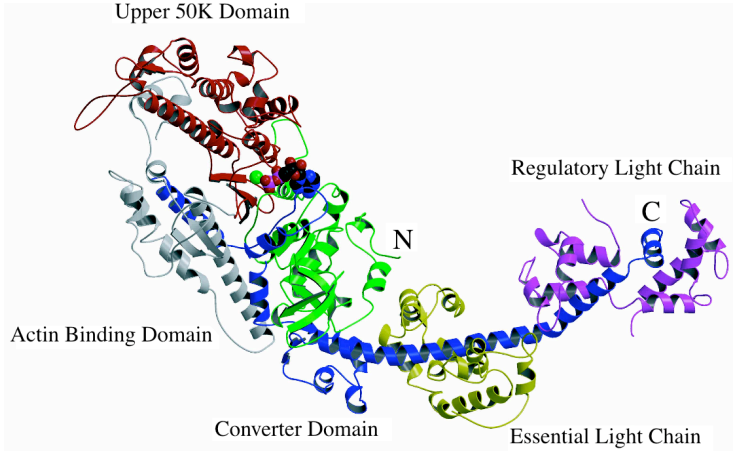


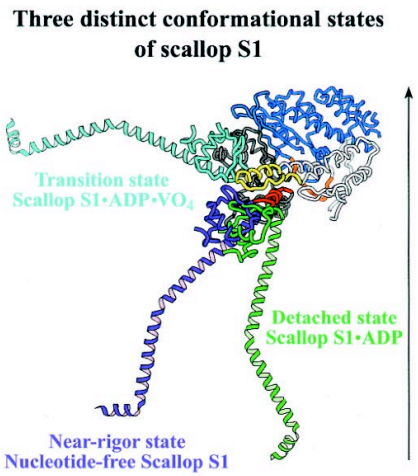


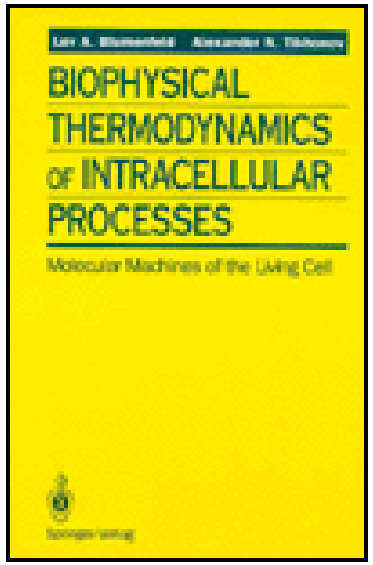
- Explore mechanisms of bioenergy transduction (bridge static structural data, low-resolution dynamical studies and phenomenological models)

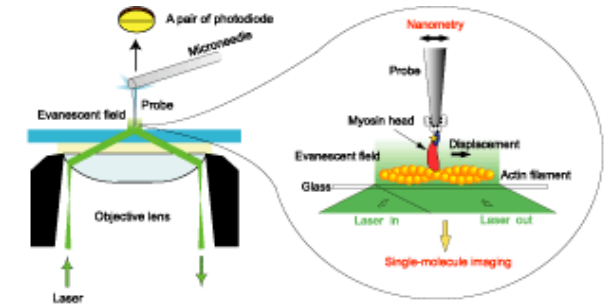
Studying energy conversion

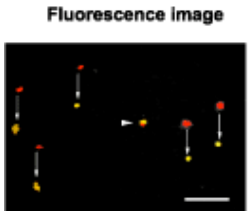


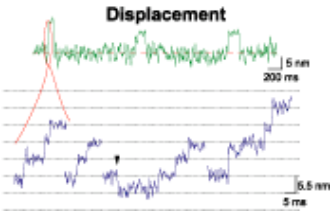


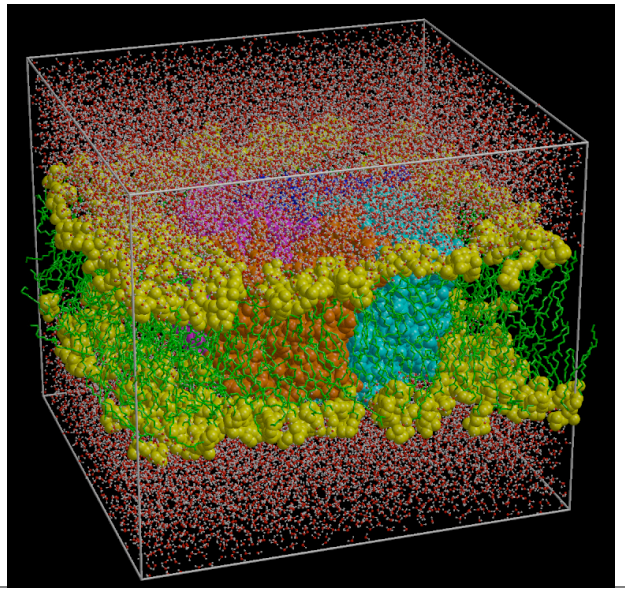






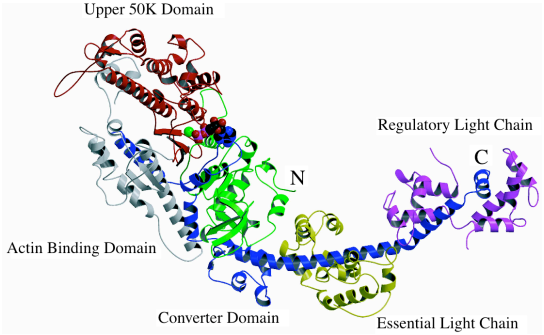


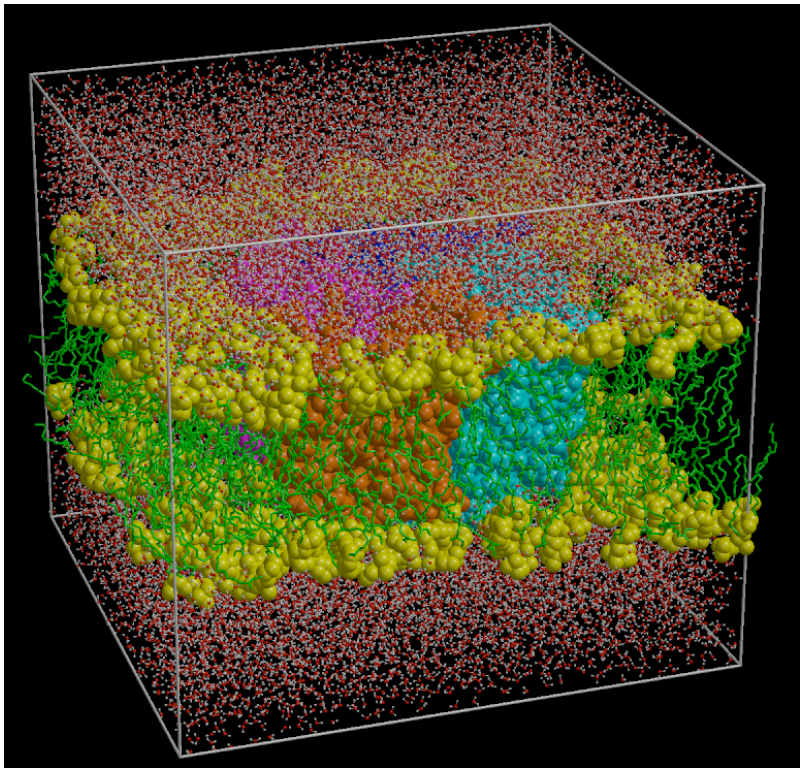


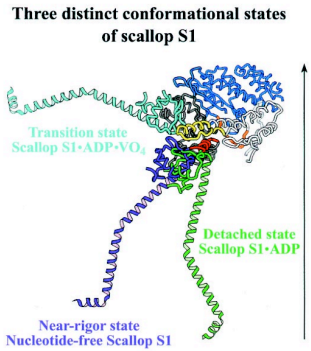


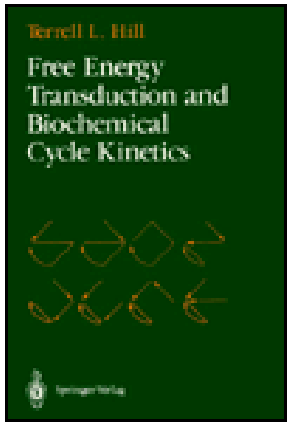
Why molecular simulations?

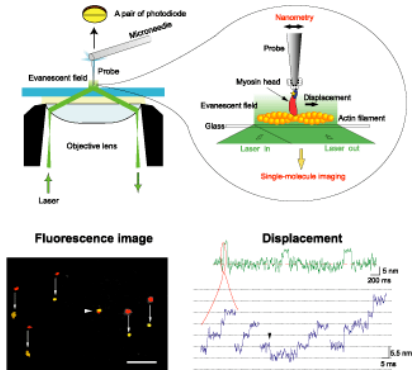
Bridging structural, dynamical and phenomenological studies











Structural studies: do not explicitly provide dynamical information; may not correspond to kinetic state

Dynamical/kinetic studies (e.g., single molecule FRET): do not have sufficient spatial resolution

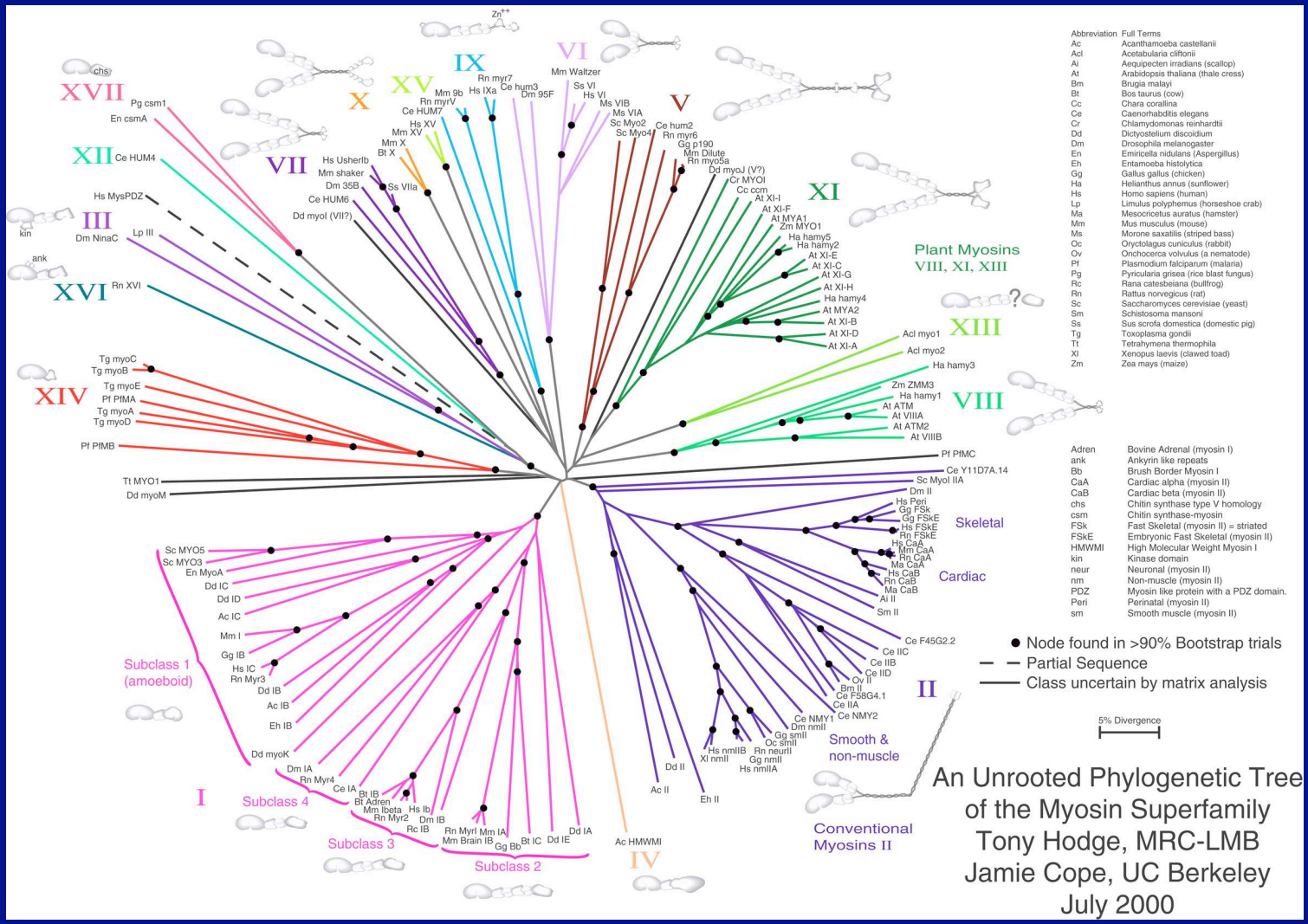
Phenomenological theories: some parameters/assumptions difficult to justify; several models seem to work

Our long-term goal: evaluate dynamical properties & parameters used in theoretical models in terms of microscopic details *; i.e., "jiggling and wiggling of atoms"*

Outline

- Myosin: a classical molecular motor
- QM/MM studies, molecular dynamics and free energy simulations on the coupling between conformation and ATP hydrolysis (mechanochemical coupling)
- Initial looks on conformational transitions

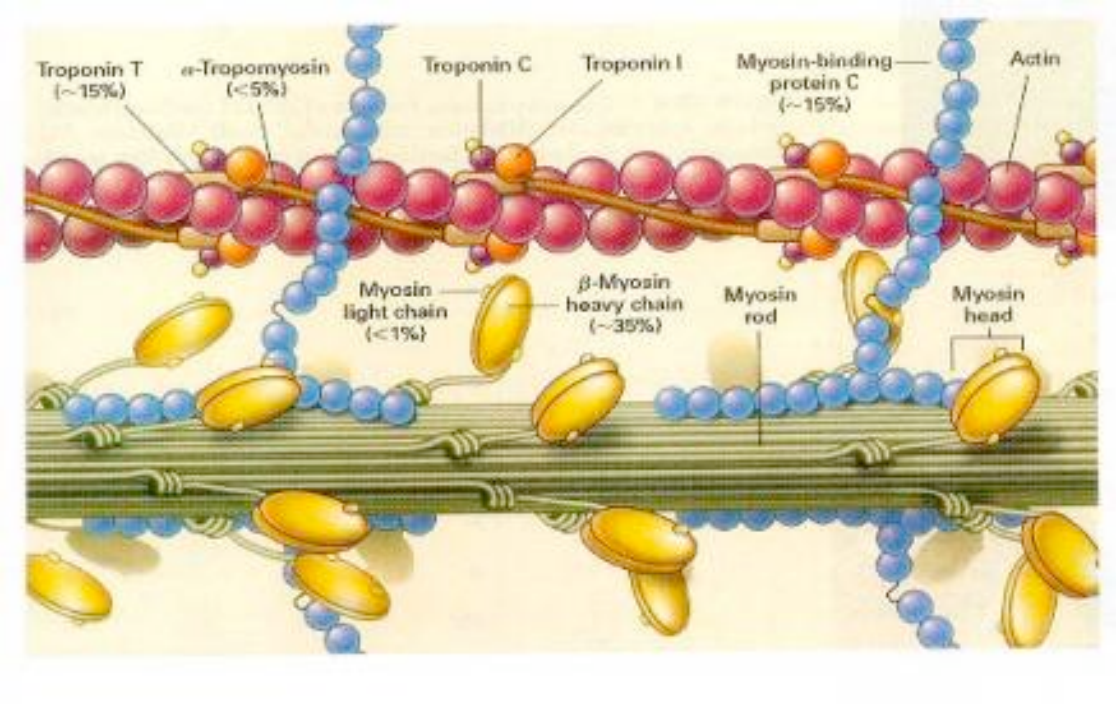
Myosin: a diverse superfamily

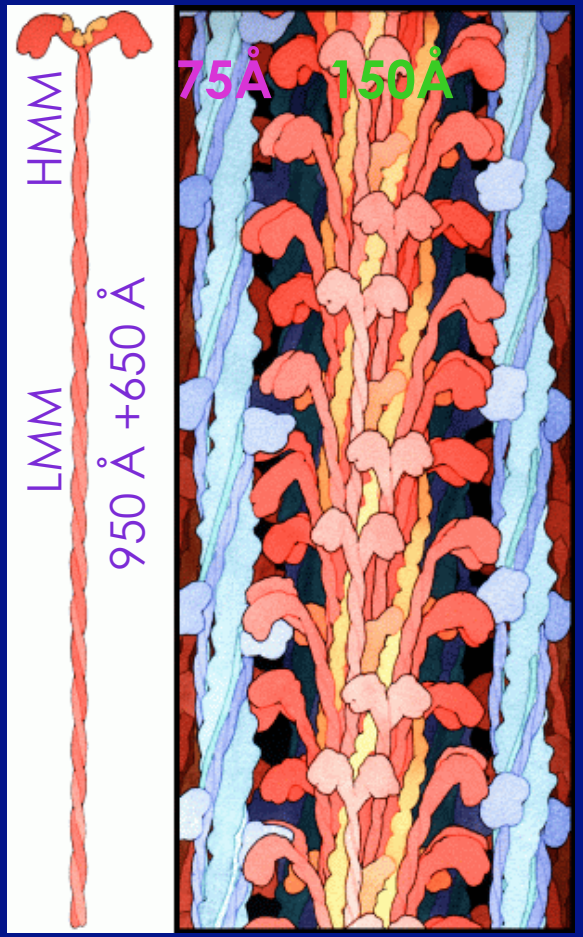


http://www.mrc-lmb.cam.ac.uk/myosin/

Myosin-II: a classical molecular motor

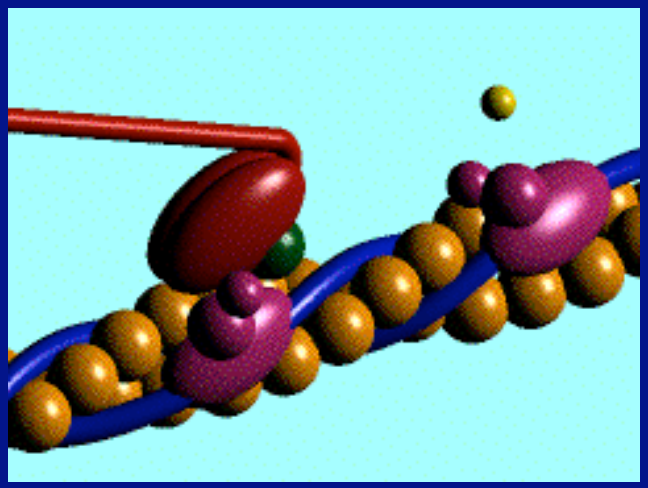
Muscle contraction: relative displacements of the thick filaments (myosin) and thin filaments (F-actin)

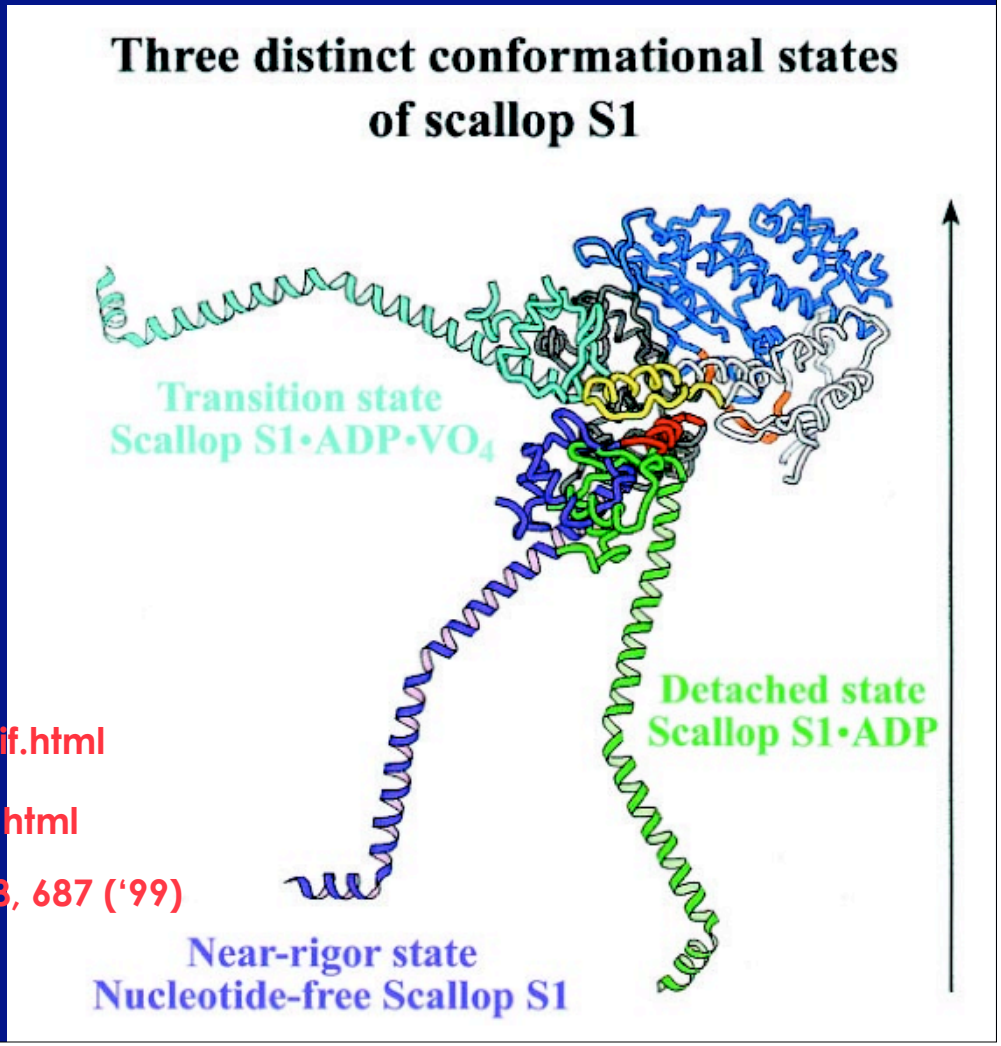




H. E. Huxley: cross-bridge model of contraction (1969)

Myosin-II: a classical molecular motor





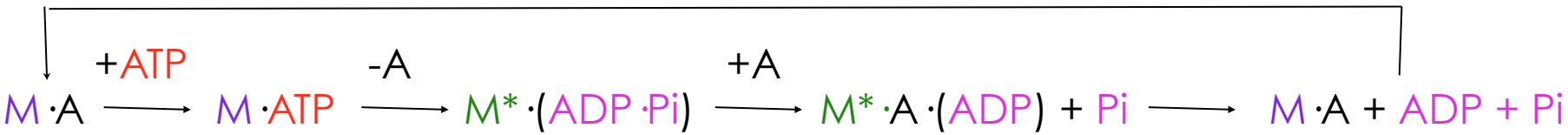
http://www.sci.sdsu.edu/movies/actin_myosin_gif.html

See also: http://www.scripps.edu/milligan/index.html

M. A. Geeves, K. C. Holms, *Ann. Rev. Biochem.* 68, 687 ('99)

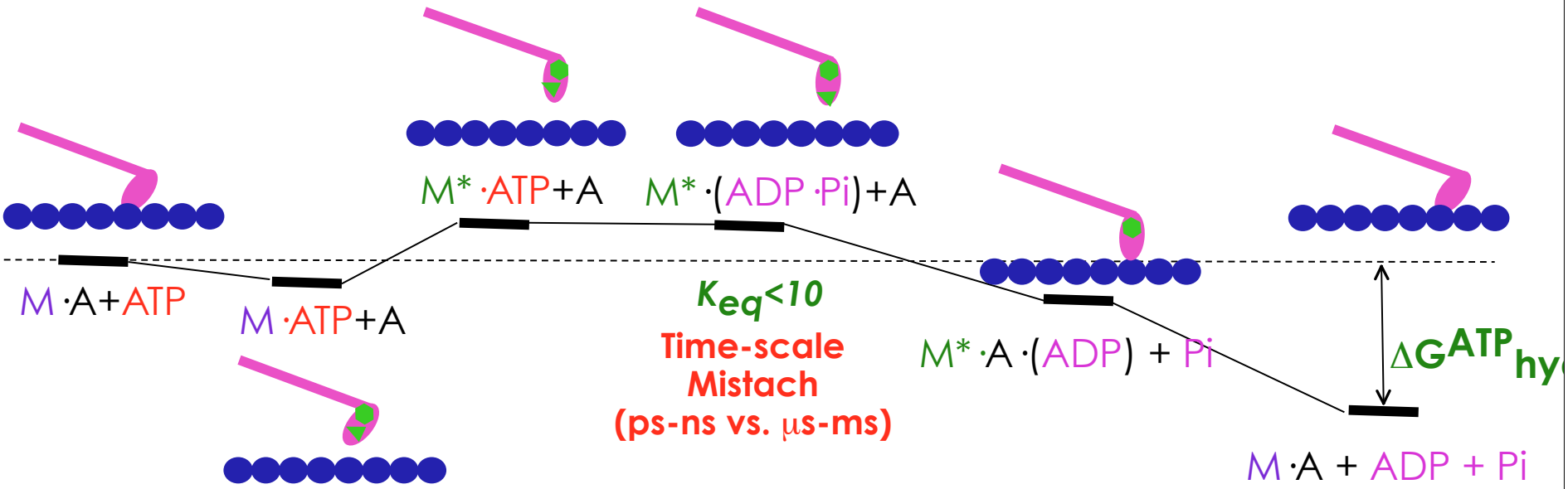
R. W. Lymn, E. W. Taylor, *Biochem.* 10, 4617 ('71)

Mechanochemical cycles in myosin



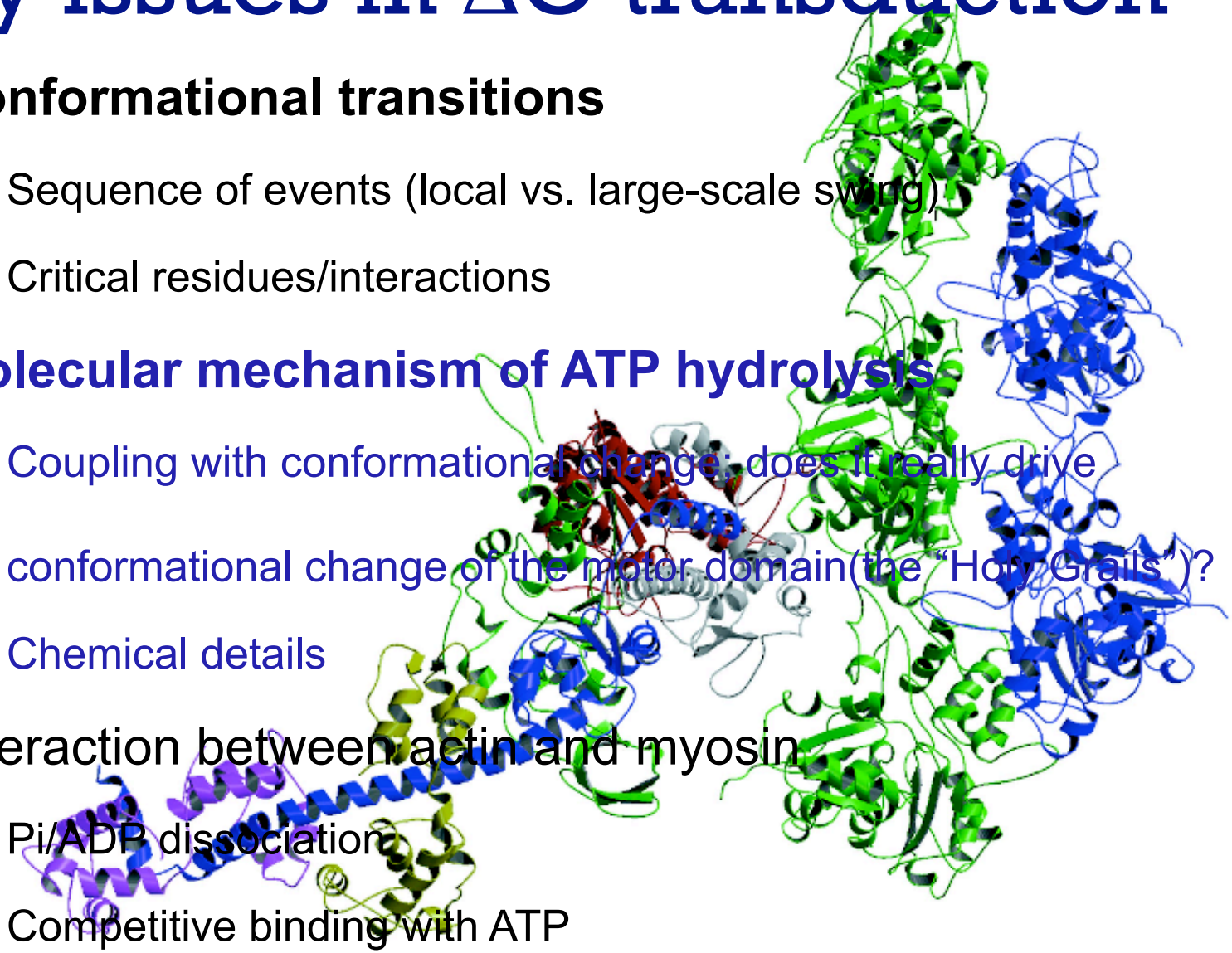
Utilization of ATP hydrolysis ΔG?

Tight coordination among level-arm swing, chemistry and actin binding

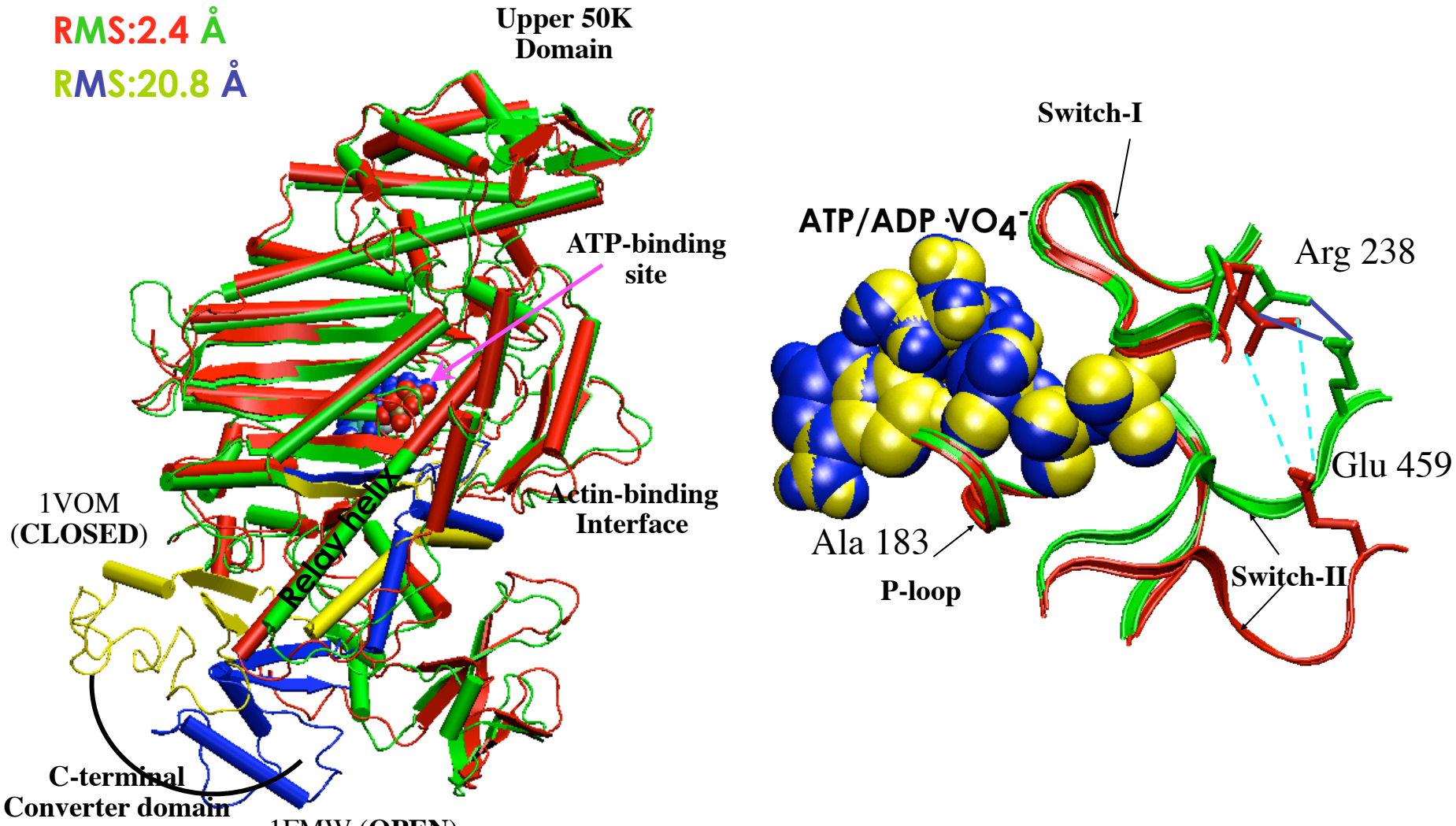


Key issues in ΔG transduction

- **Conformational transitions**
  - Sequence of events (local vs. large-scale swing)
  - Critical residues/interactions
- **Molecular mechanism of ATP hydrolysis**
  - Coupling with conformational change: does it really drive conformational change of the motor domain(the "Holy Grails")?
  - Chemical details
- Interaction between actin and myosin
  - Pi/ADP dissociation
  - Competitive binding with ATP

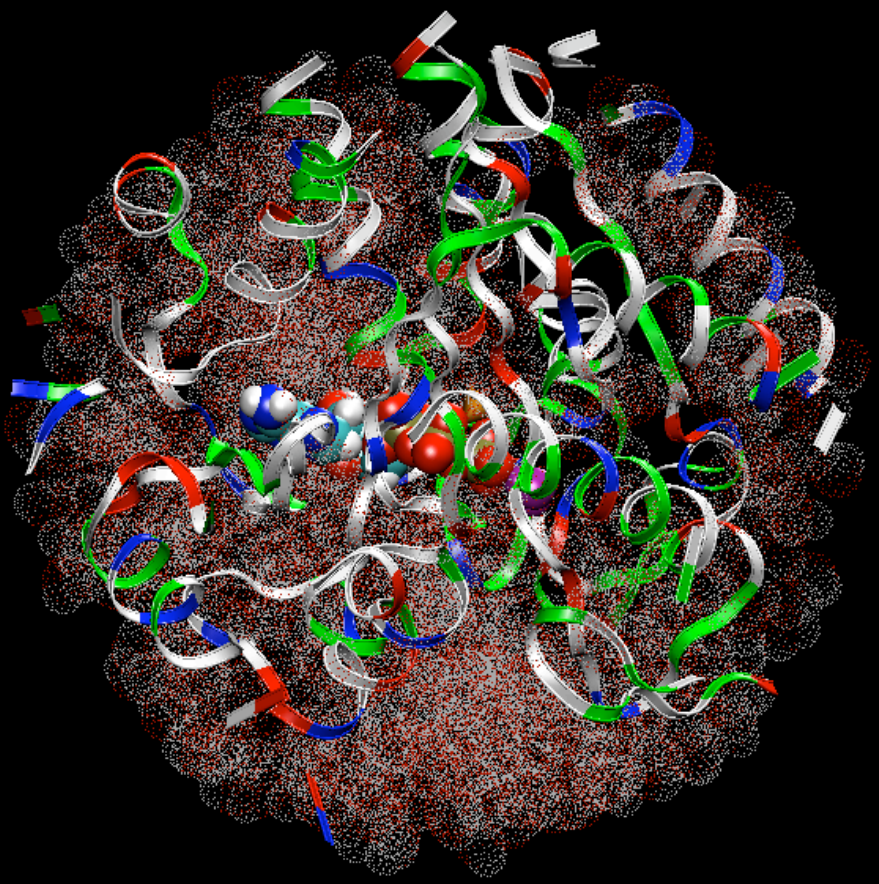


Conformational transition in myosin



Rayment et al. *J. Biol. Chem.*, **2000**, 275, 38494; *Biochem*. **1996** 35, 5405 (*Dictyostelium discoideum*: amoeba)

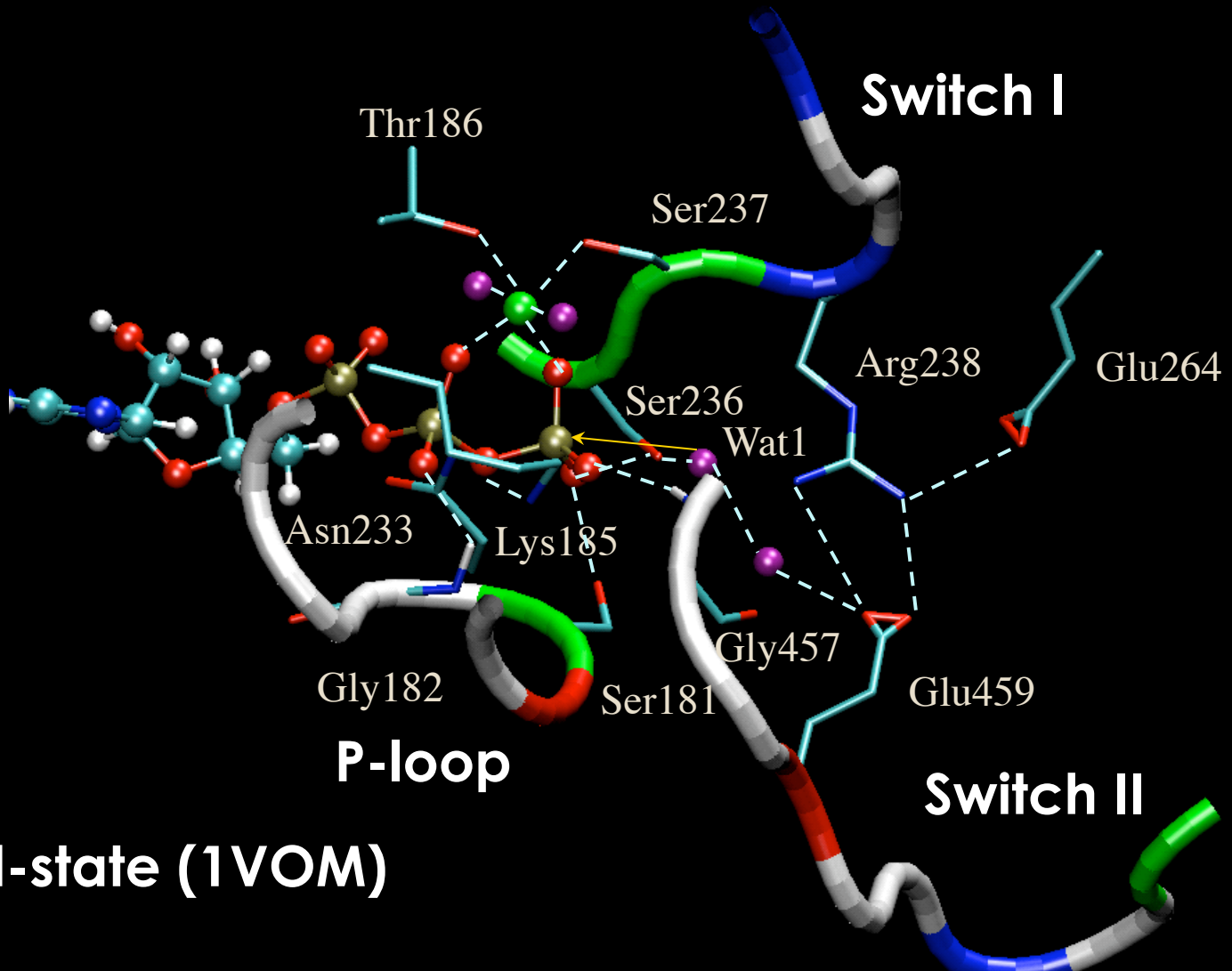
Simulations of ATP hydrolysis



Stochastic boundary simulation

- Classical MD simulation
  - Position of key residues/water
- QM/MM rx path
  - hydrolysis mechanism
  - coupling with conformation
- Alchemical free energy
  - Include structural fluctuations
  - Component analysis

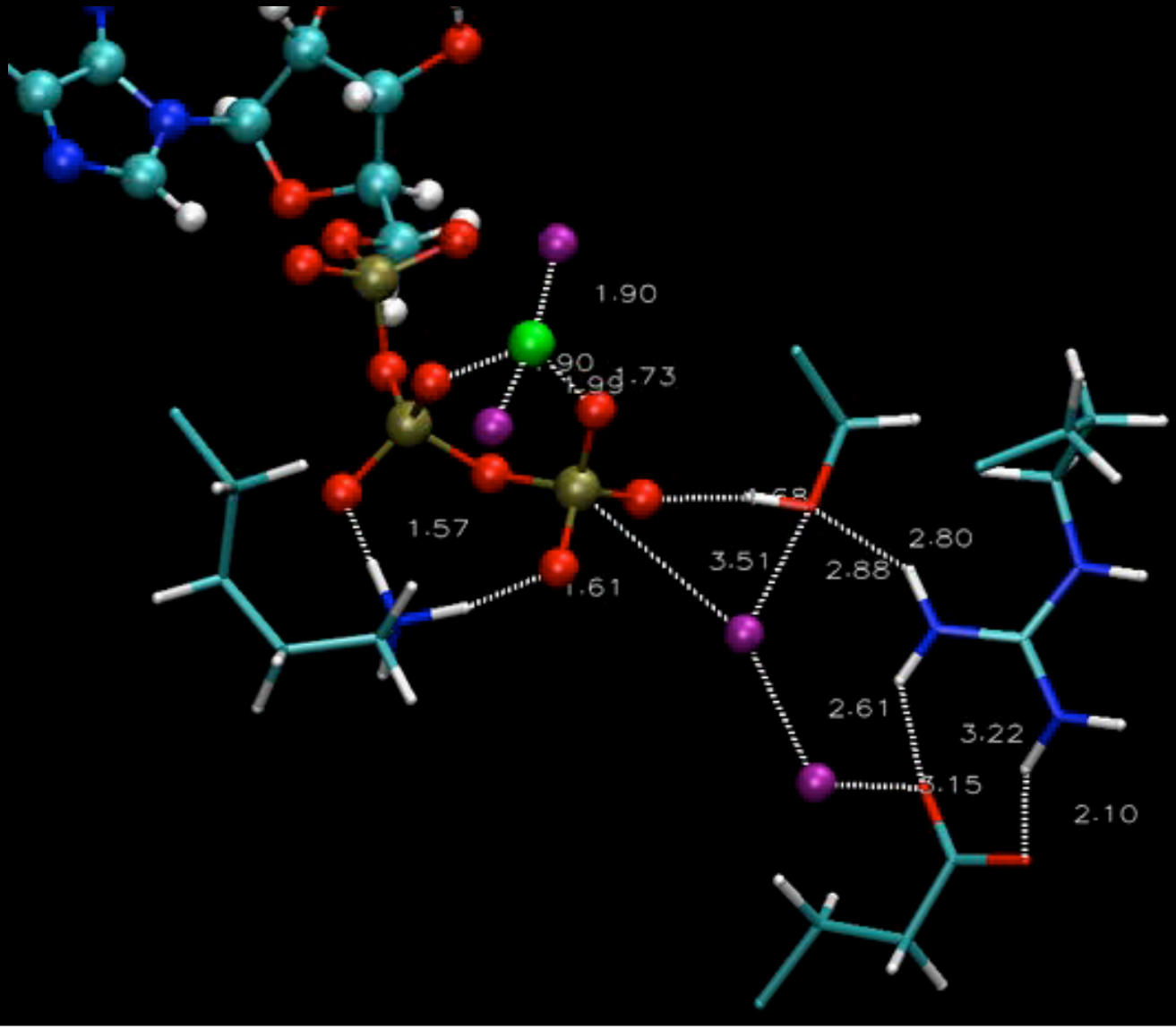
Myosin II active site



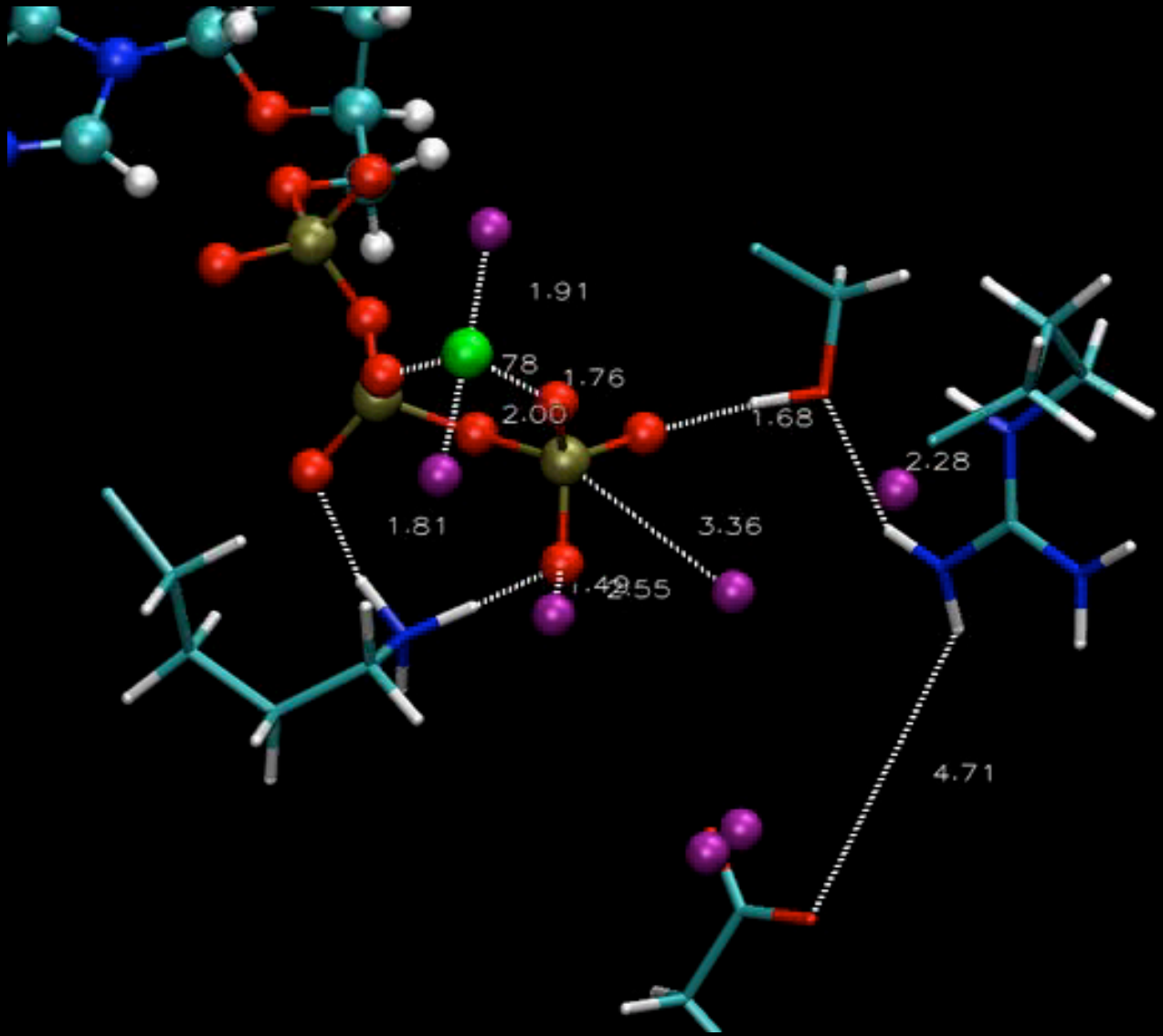
Closed-state (1VOM)

Rayment et al. *J. Biol. Chem.*, **2000**, 275, 38494; *Biochem.* **1996** 35, 5405 (*Dictyostelium discoideum*: amoeba)

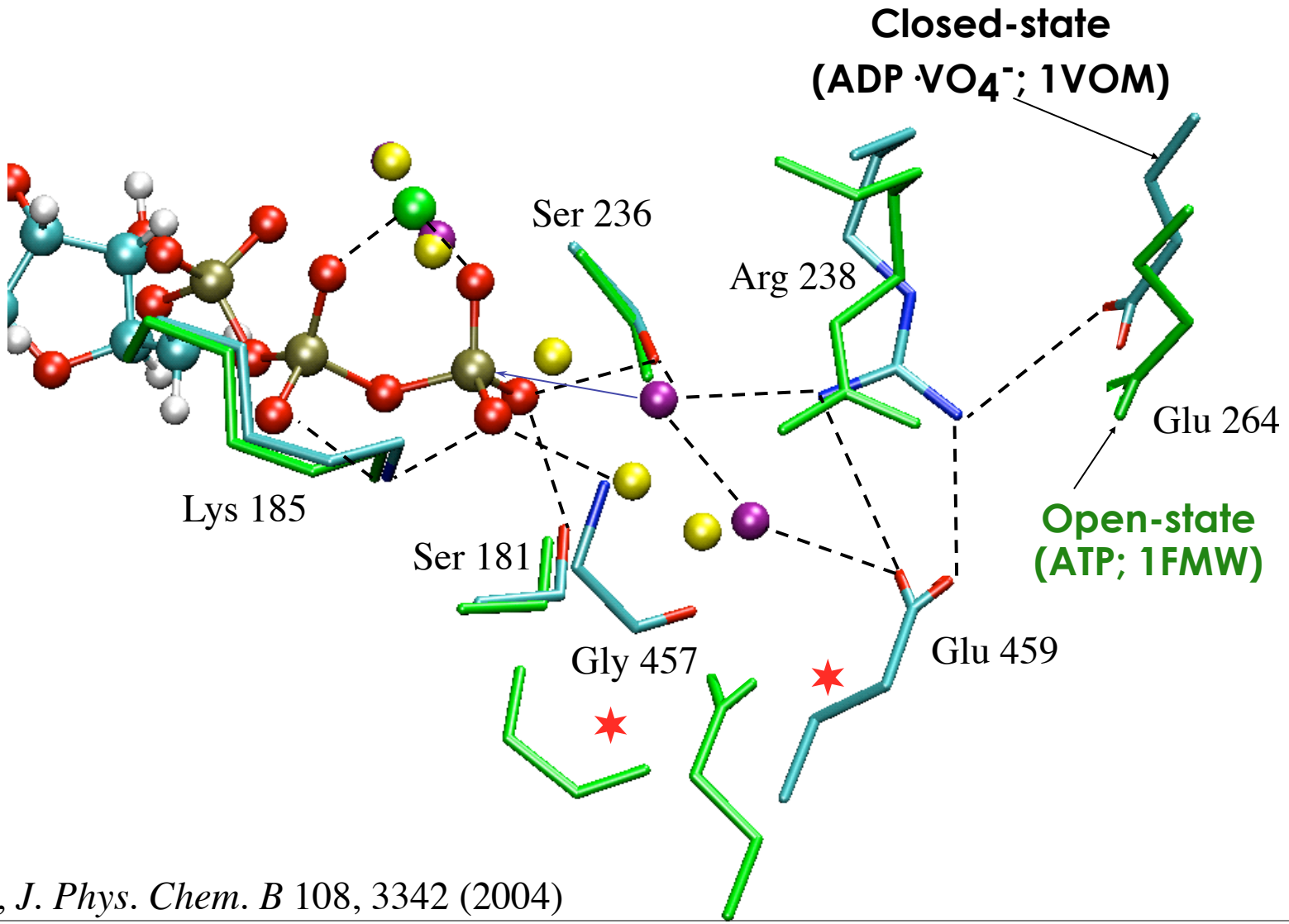
Classical MD simulations: the closed state



Classical MD simulations: the open state

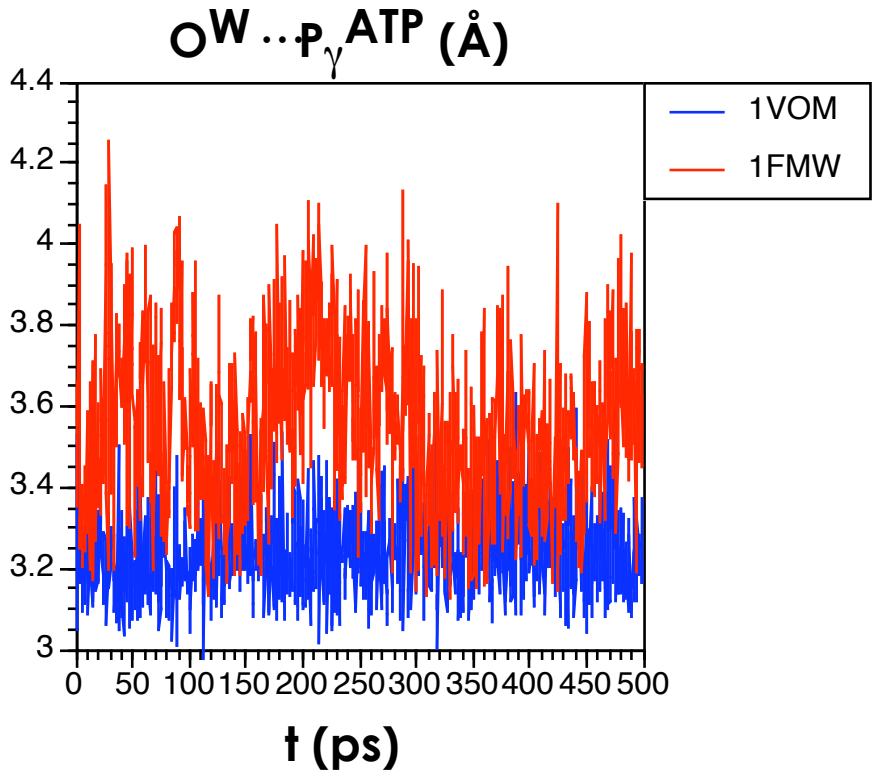


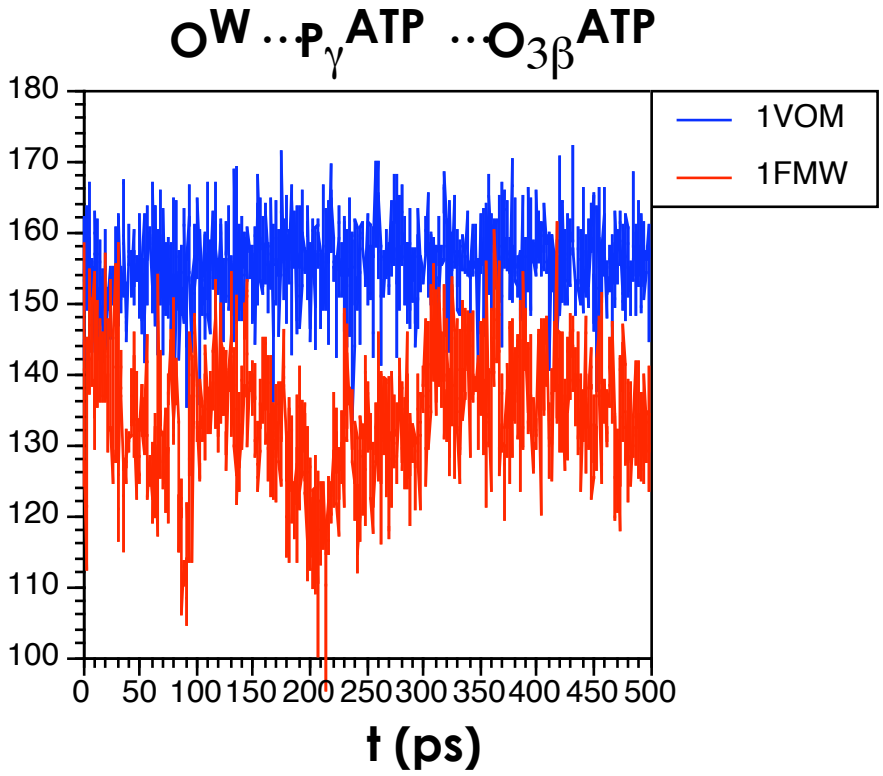
Salt-bridge and water positions



G. Li, QC, *J. Phys. Chem. B* 108, 3342 (2004)

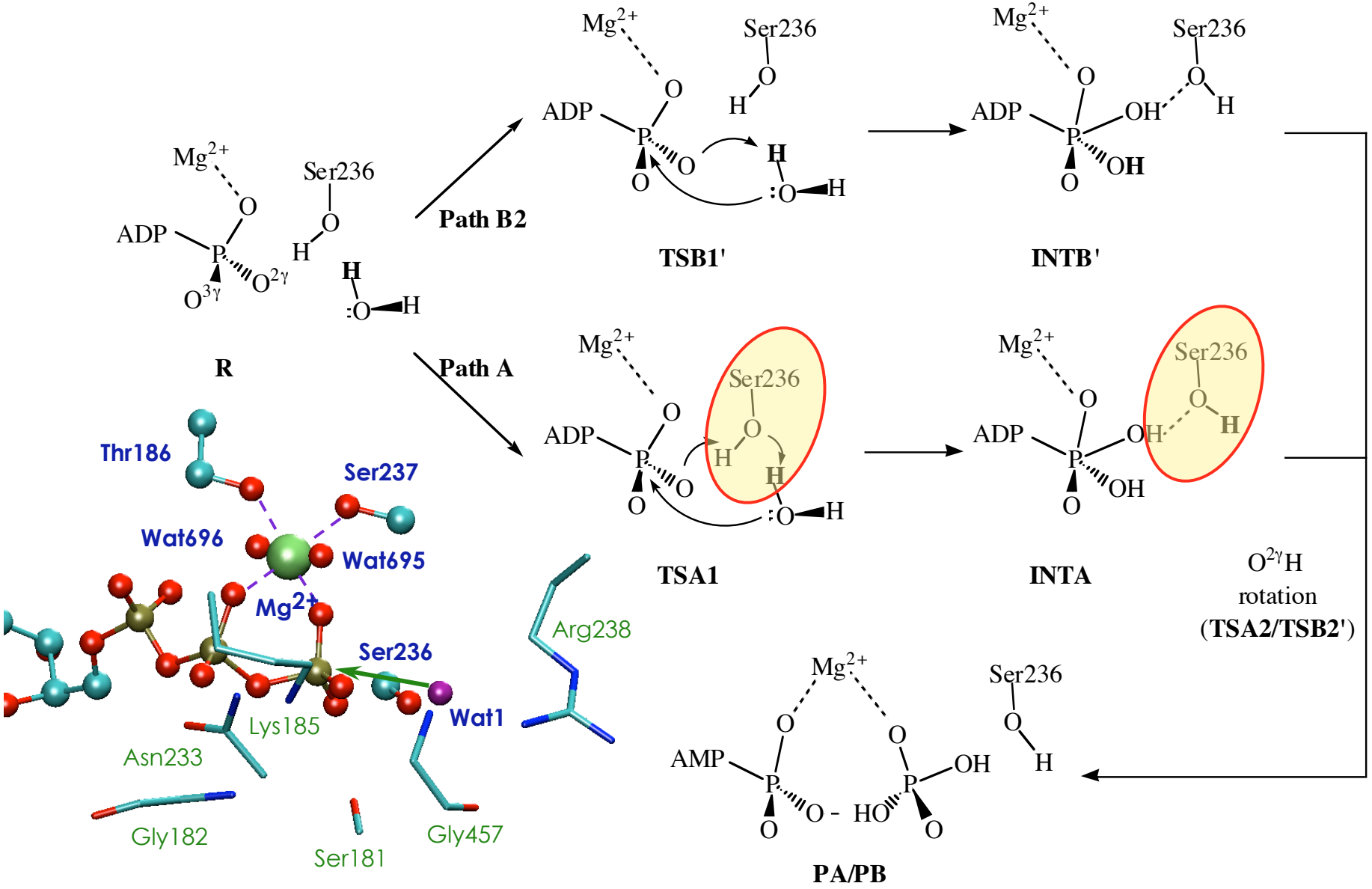
Open-state not set up for in-line attack



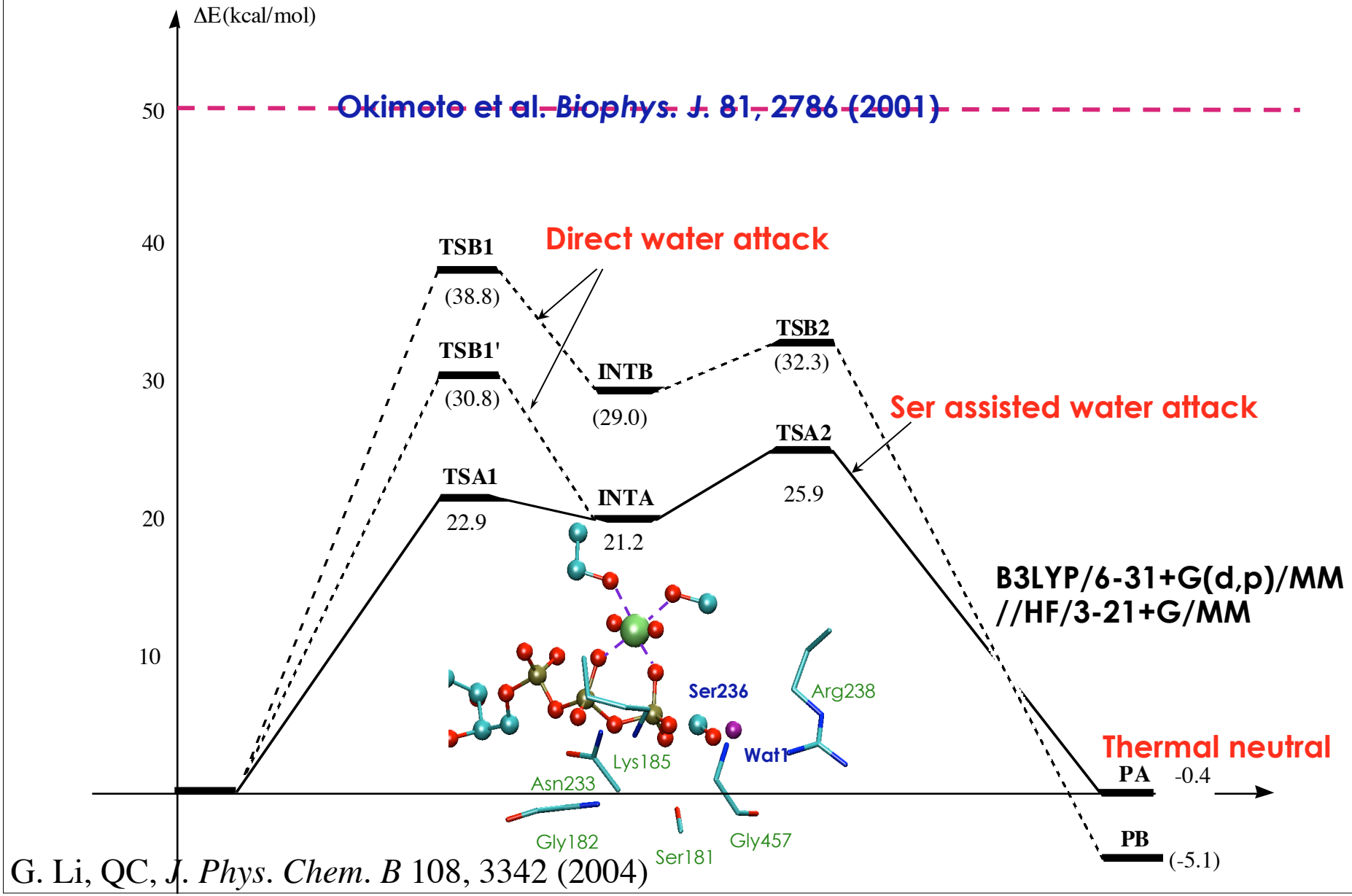


Appropriate positioning of the attacking water

QM/MM analysis of reaction paths

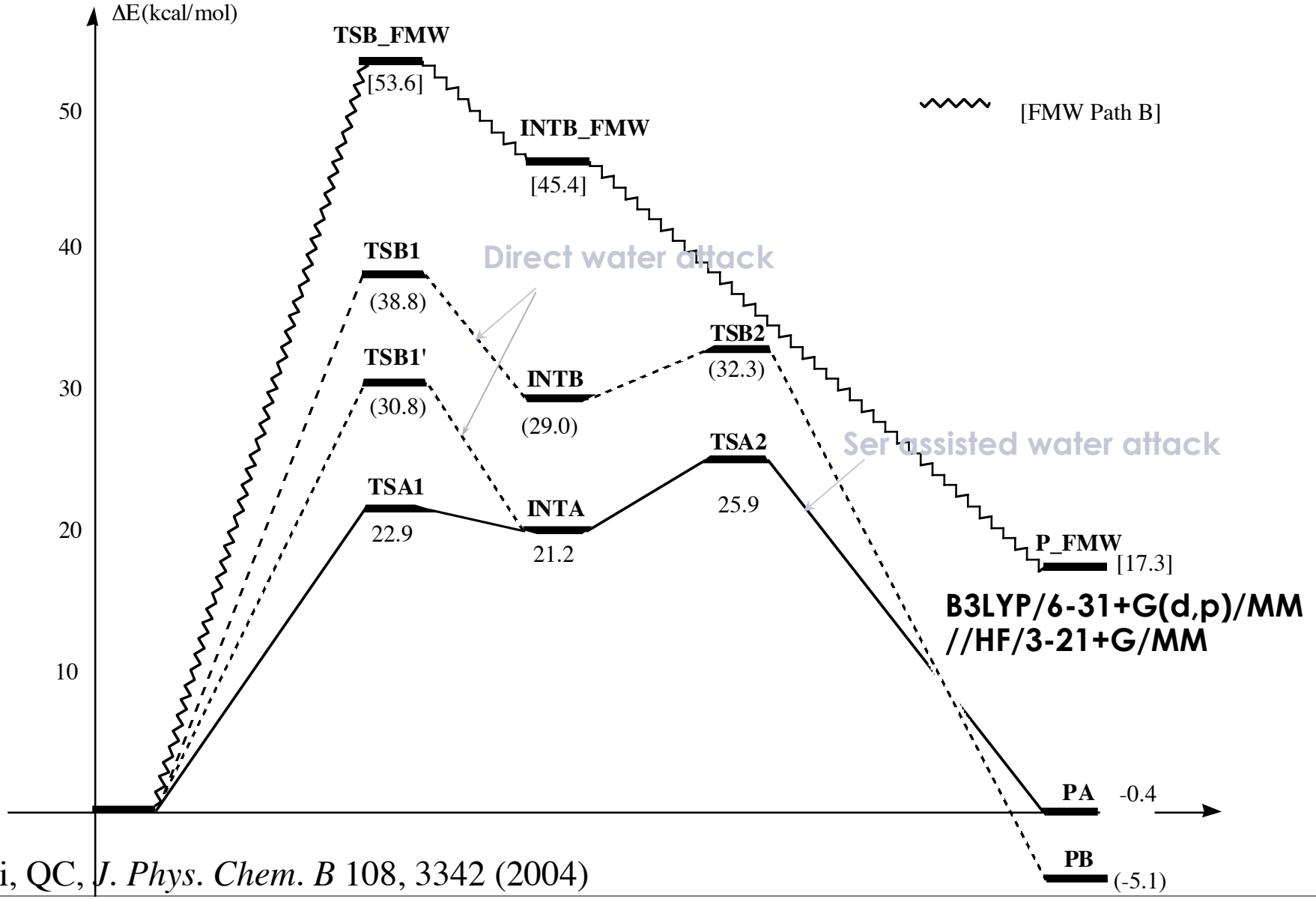


Ser236 plays a major role



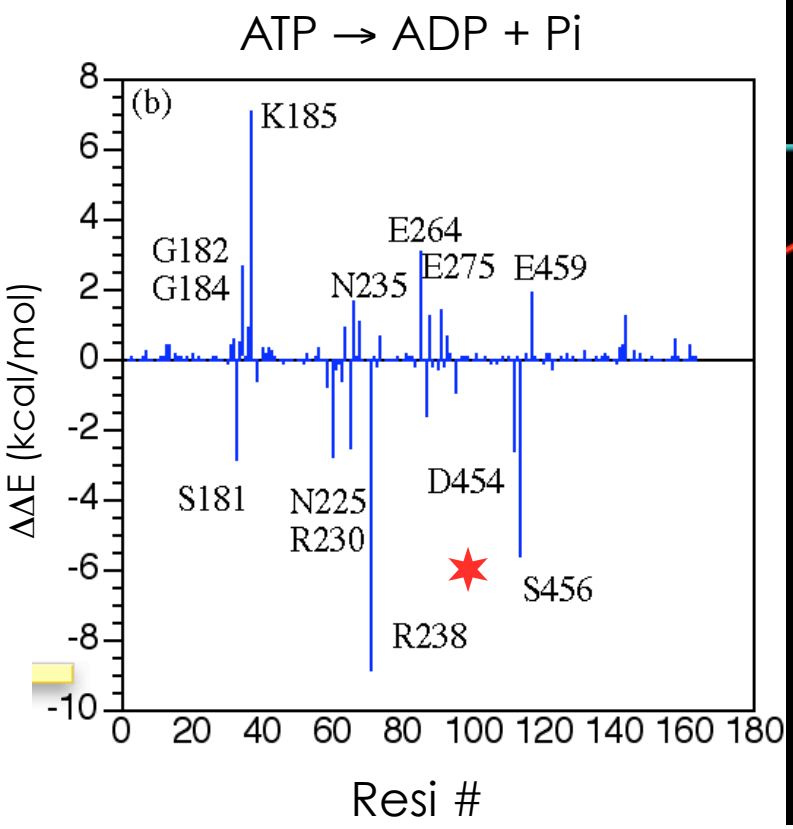
G. Li, QC, *J. Phys. Chem. B* 108, 3342 (2004)

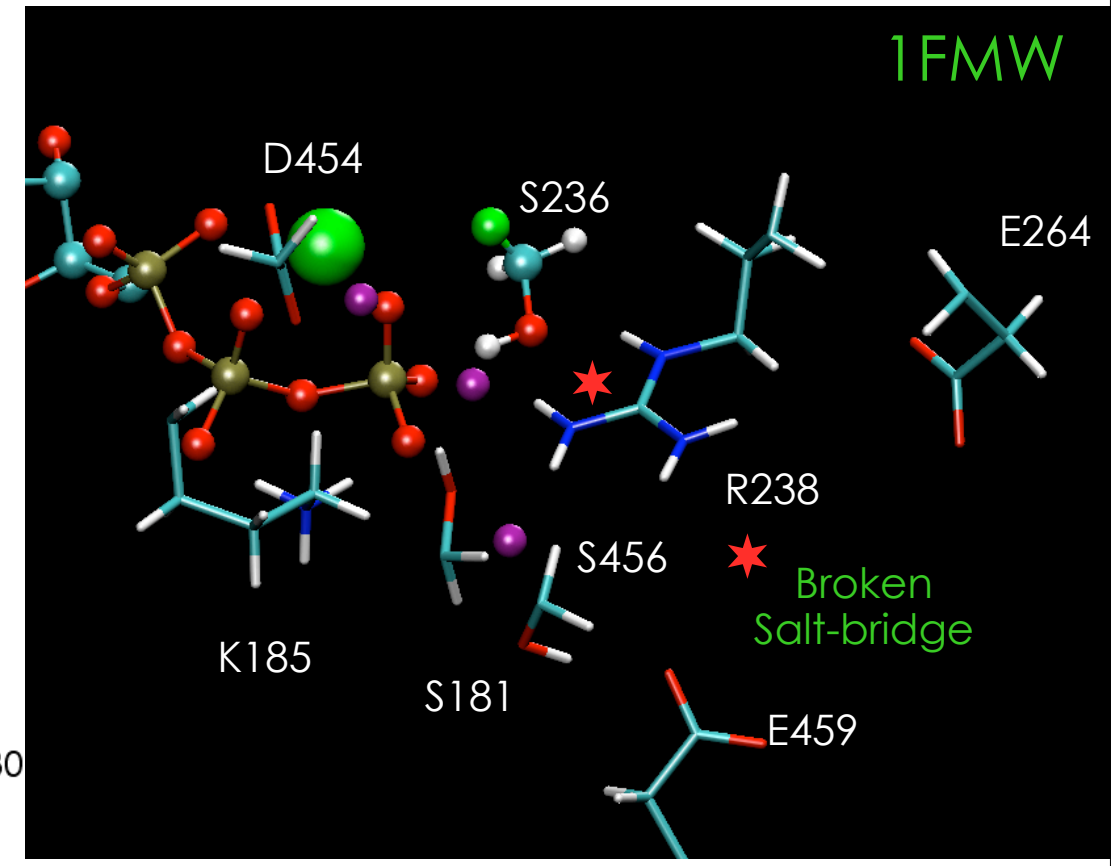
Conformational control of hydrolysis



G. Li, QC, *J. Phys. Chem. B* 108, 3342 (2004)

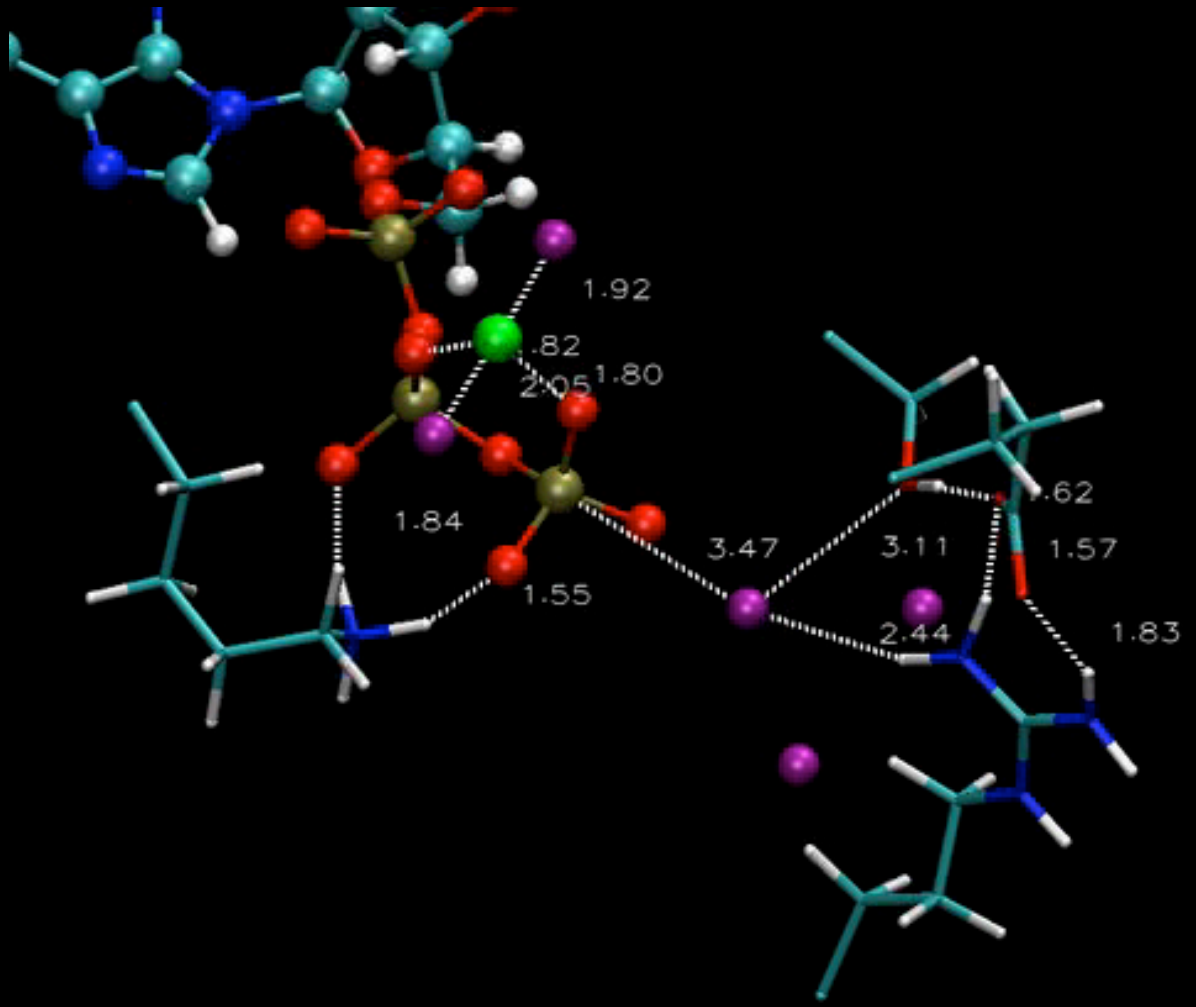
Dual roles of the salt-bridge





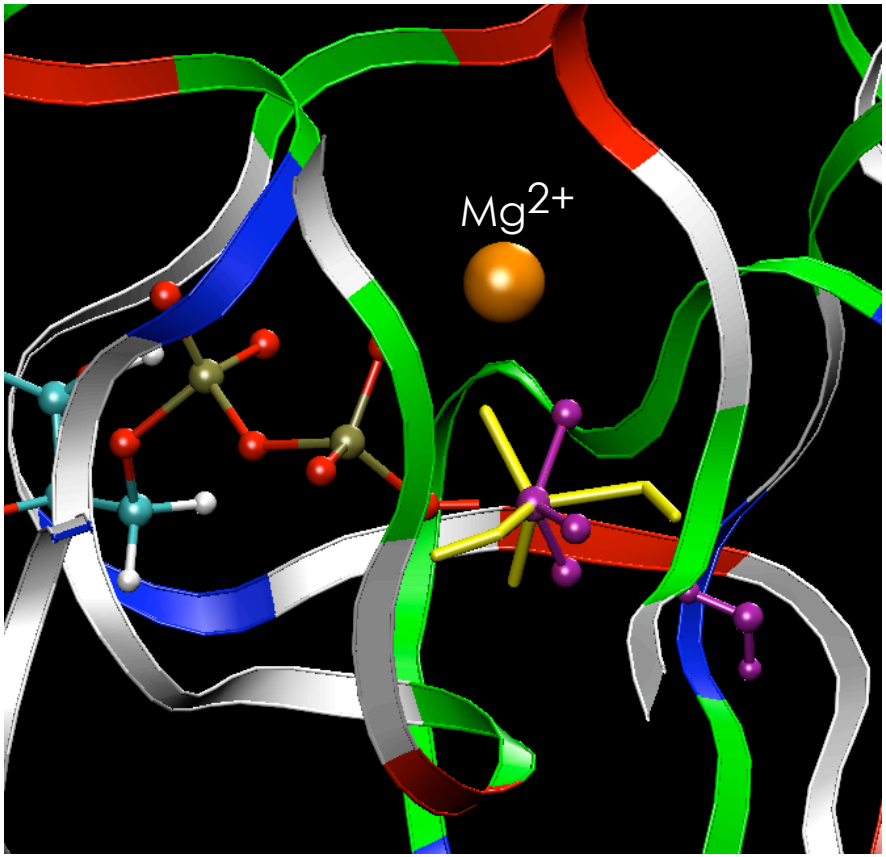
Consistent with mutation experiments of Onishi et al. *PNAS*,99, 15339 (**2002**)
Might apply to other molecular motor systems such as F1-ATPase, Ca^{2+}-ATPase

Active site of the R238E/E459R mutant?



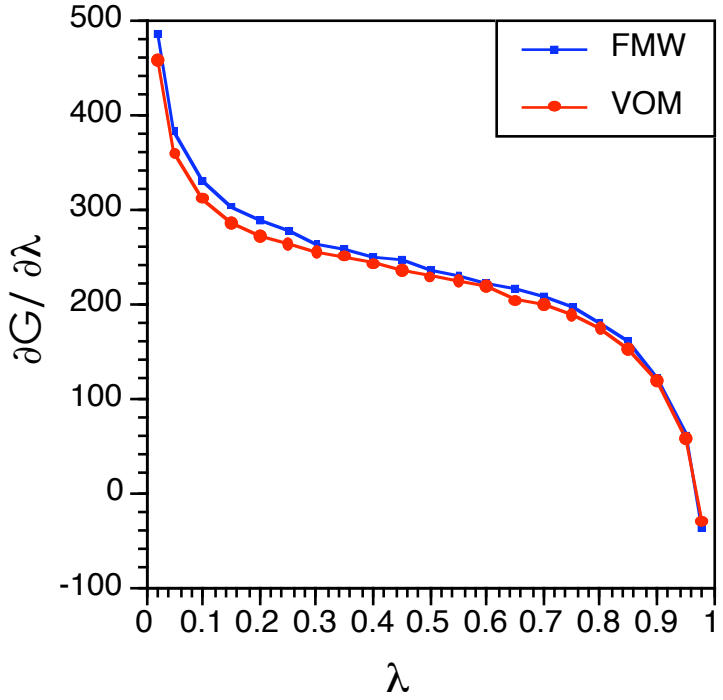
Alchemical free energy simulations

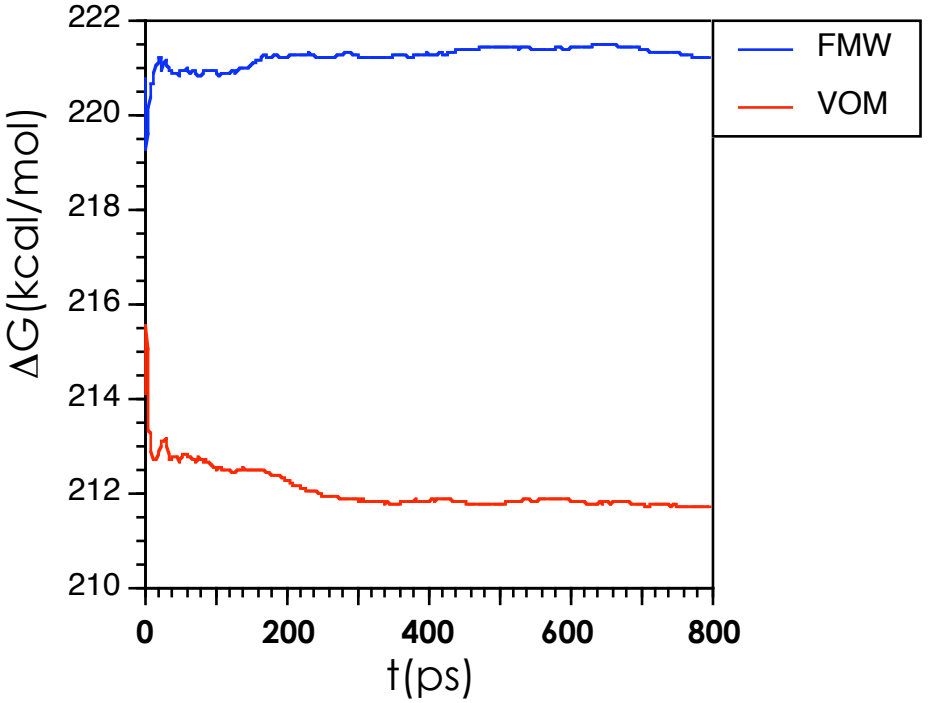
ADP-[PO_3^-] + H_2O → ADP + Pi



- Stochastic boundary condition (8061 atoms; 1020 water)
- 21 λ-windows (0.02, 0.05, 0.1···0.95, 0.98)
- SHAKE hbond, δt=1 fs
- Each window > 800 ps
- Charge-scaling protocols for bulk solvation effects
- Partial charges for PO_3^-/Pi fitted from B3LYP-ESP calculations
- Focus on the difference between Closed (1VOM) and Open (1FMW) structures

Alchemical free energy simulations

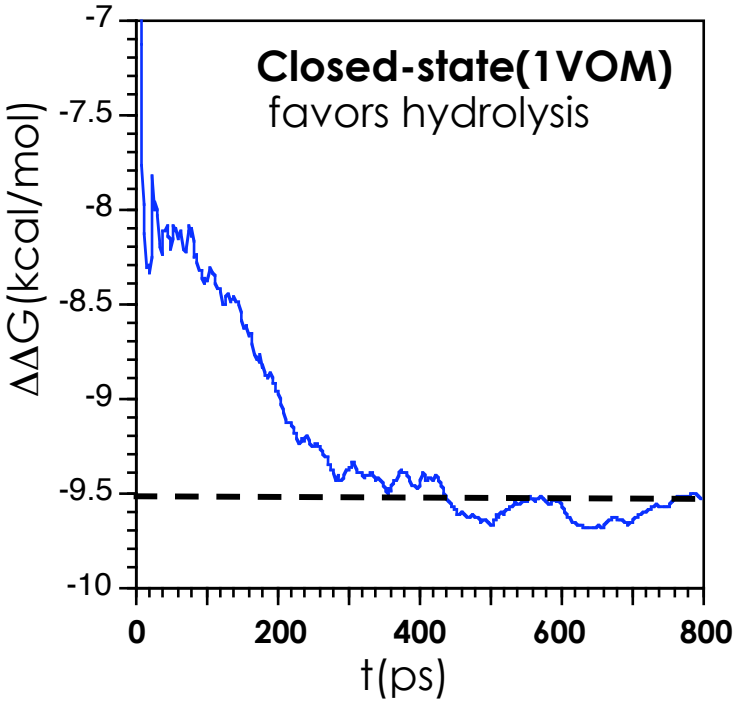


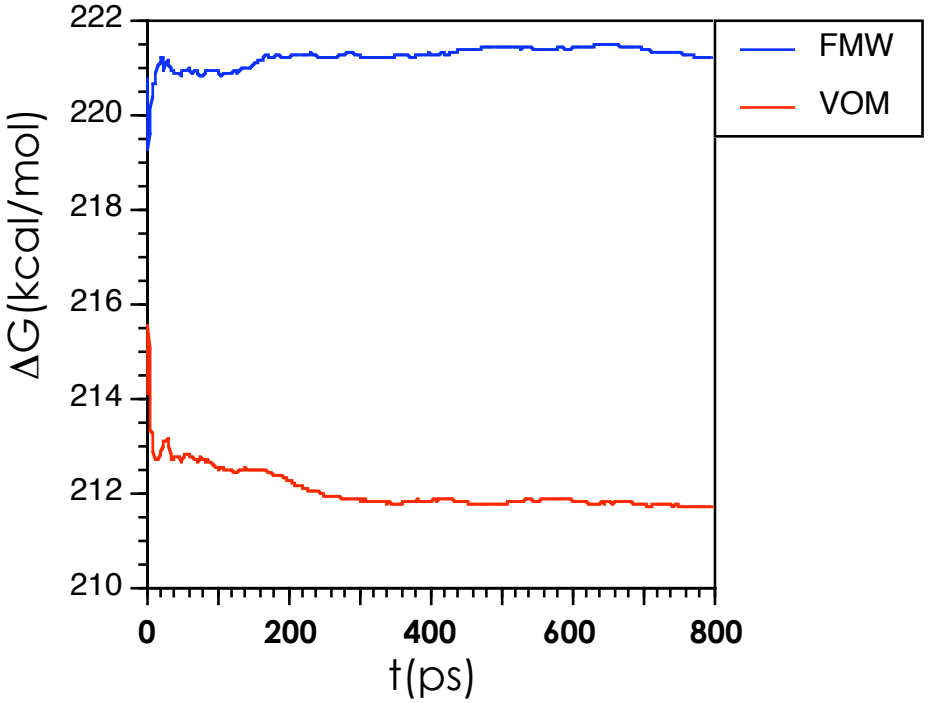


$$U^{Alchemy}(\mathbf{X}_A,\mathbf{X}_B,\mathbf{X}_C;\lambda) = (1-\lambda)\left[U_{AA}(\mathbf{X}_A)+U_{AC}(\mathbf{X}_A,\mathbf{X}_C)\right] + \lambda\left[U_{BB}(\mathbf{X}_B)+U_{BC}(\mathbf{X}_B,\mathbf{X}_C)\right] + U_{CC}(\mathbf{X}_C)$$

$$\Delta G_C^{AB} = \int_0^1 d\lambda \frac{\partial G}{\partial \lambda} = \int_0^1 d\lambda \left\langle \frac{\partial U^{Alchemy}(\vec{\mathbf{R}};\lambda)}{\partial \lambda} \right\rangle_\lambda$$

Alchemical free energy simulations





$$\Delta\Delta G^{AB}_{C,D} = \int_0^1 d\lambda \frac{\partial G^{A,B}_C}{\partial \lambda} - \int_0^1 d\lambda \frac{\partial G^{A,B}_D}{\partial \lambda}$$

$$\Delta G^{AB}_C = \int_0^1 d\lambda \frac{\partial G}{\partial \lambda} = \int_0^1 d\lambda \left\langle \frac{\partial U^{Alchemy}(\vec{\mathbf{R}};\lambda)}{\partial \lambda} \right\rangle_\lambda$$

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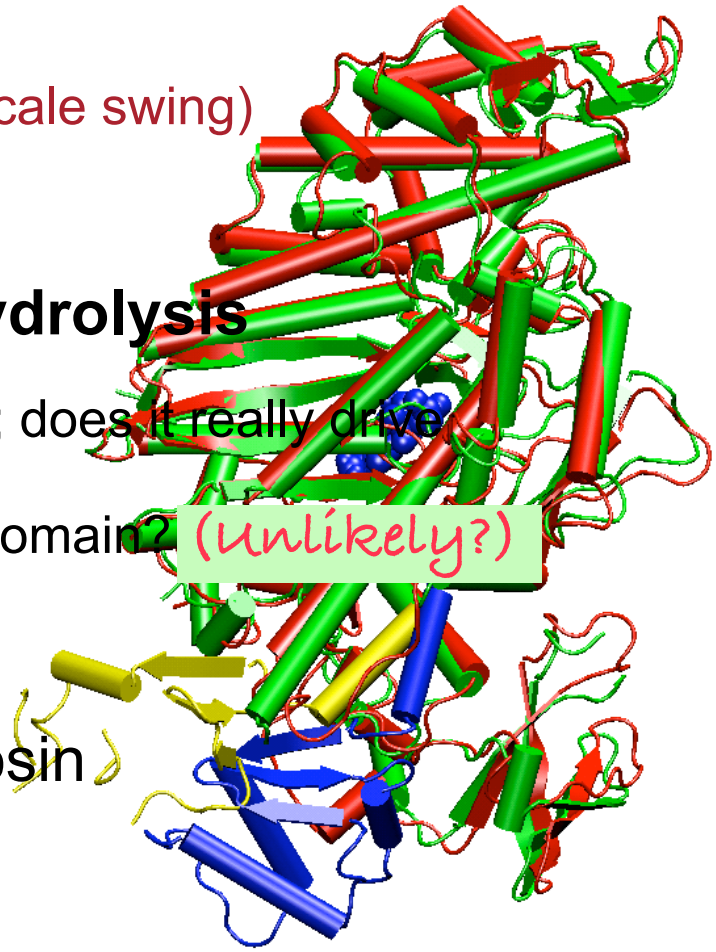
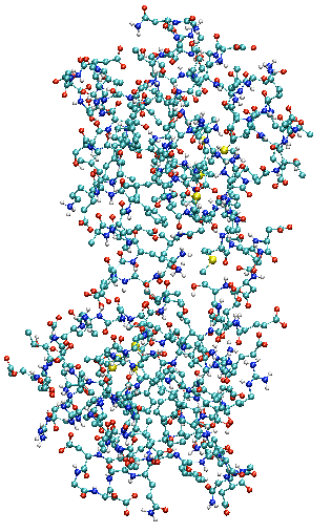
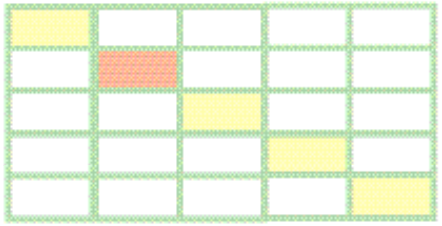
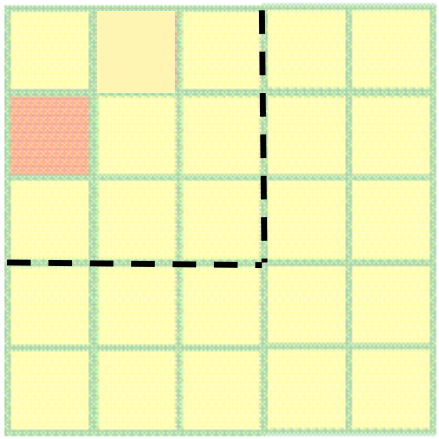
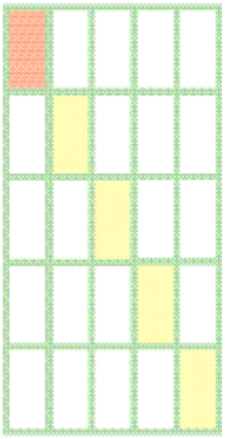


Coarse-grained normal modes

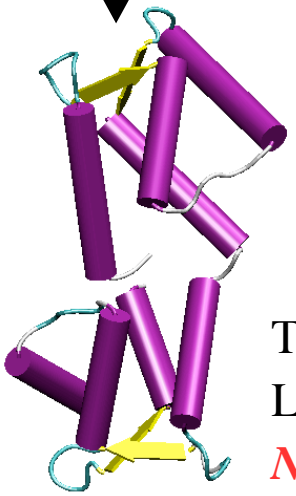








Coarse graining

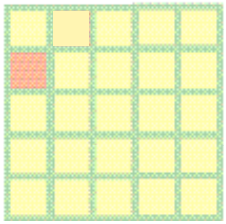


Direct construction of projected hessian

Sparse Matrix diagonalization (Lanczos)

Parallel computations

Physical intermolecular interactions



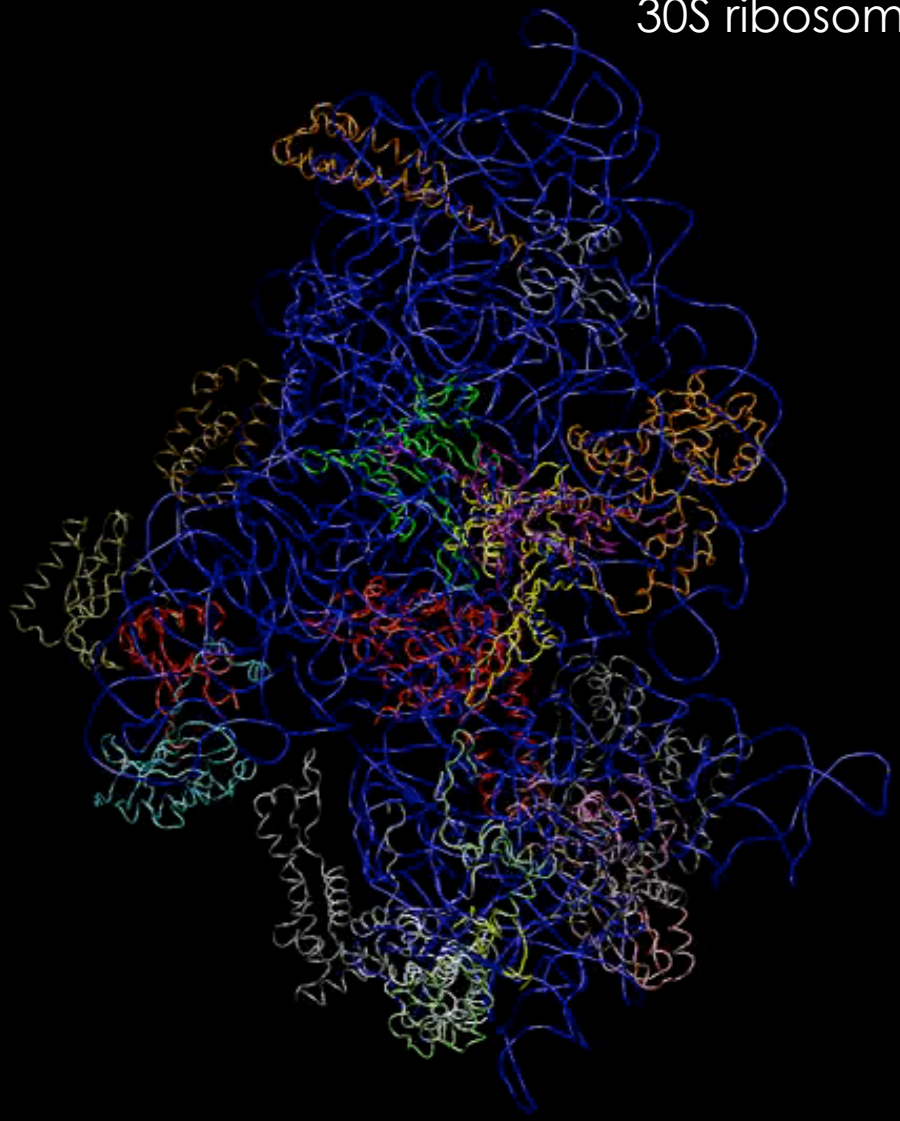
Tama, F.; Sanejouand, Y. *Proteins*, **41**, 1 (2000) RTB

Li, G.; Cui, Q. *Biophys. J.* **83**, 2457 (2002); *Biophys. J.* **86**, 743 (2004)

***NMA in Chemistry and Biology*, Ed. Q. Cui, I. Bahar (CRC Press, 2005)**

Coarse-grained normal modes

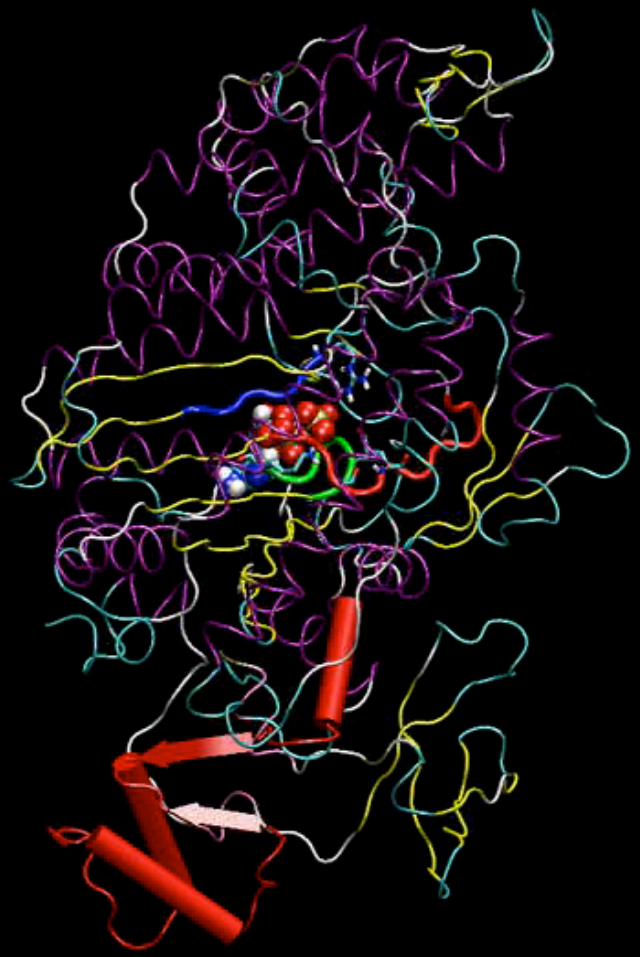
30S ribosome



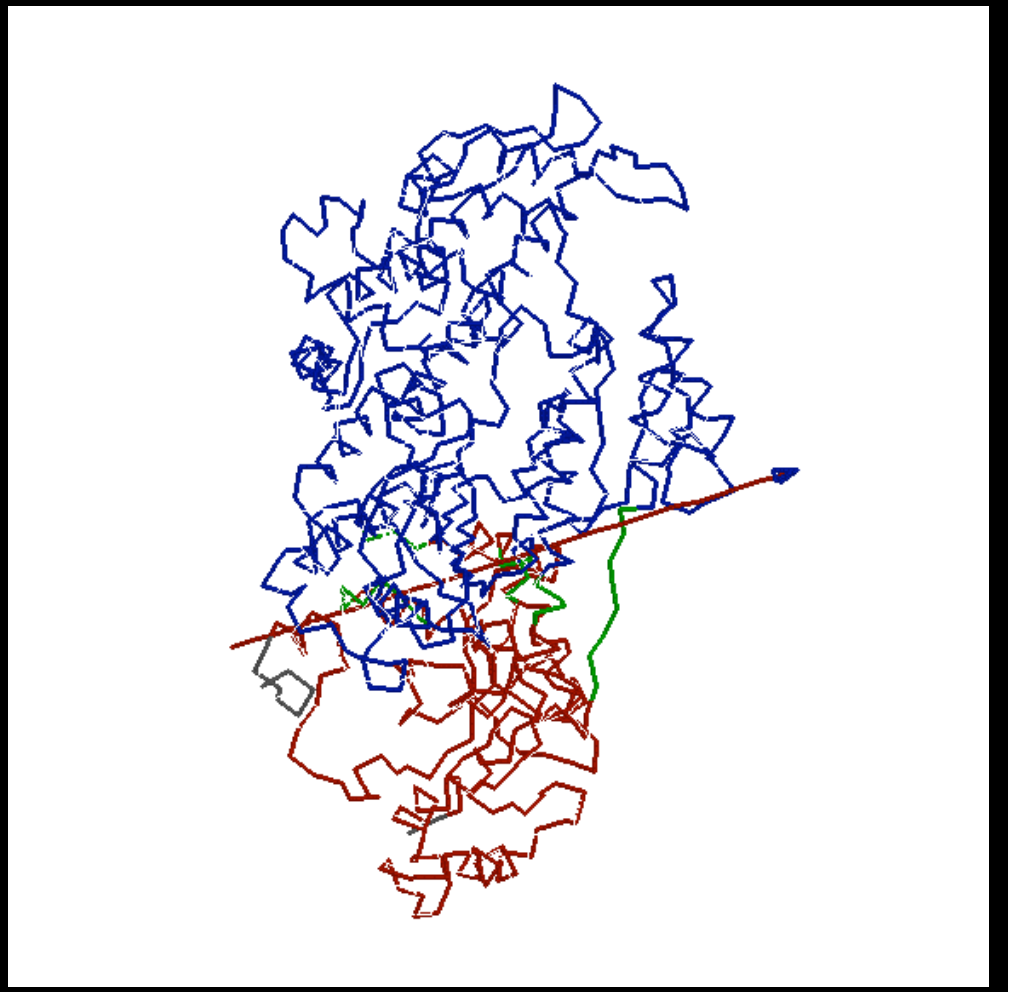
3910 residues ~200Å
1 residue per block
9.3 hrs @1.2 GHz
Sparsity: 140

G. Li; Q. Cui, *Biophys. J.* **83**: 2457, 2002; **86**: 743, 2004
A. Van Wynsberghe, G. Li, Q. Cui, *Biochem.* Submitted (RNAP)

Low-ω modes in myosin

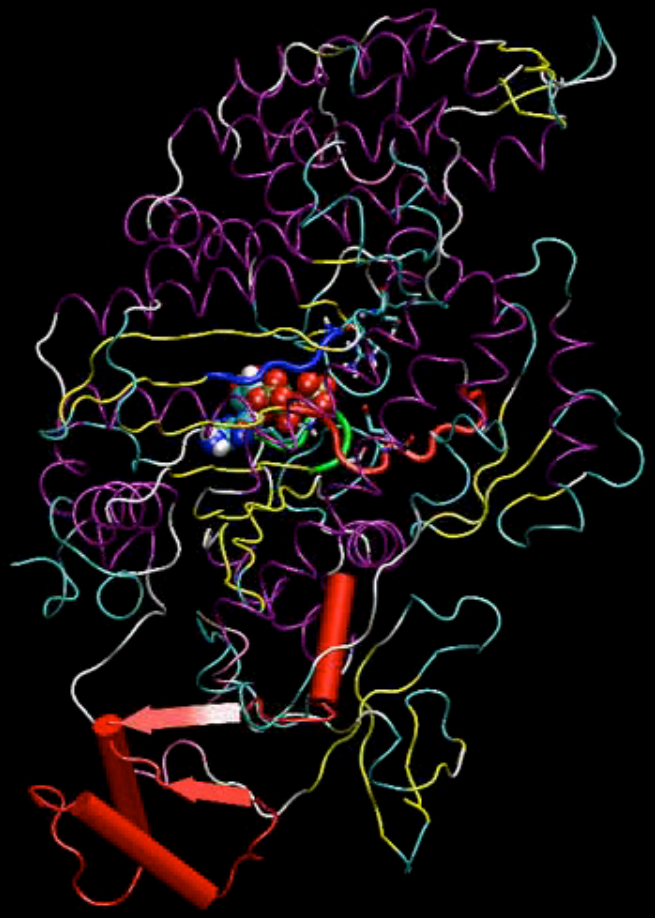


Q_1

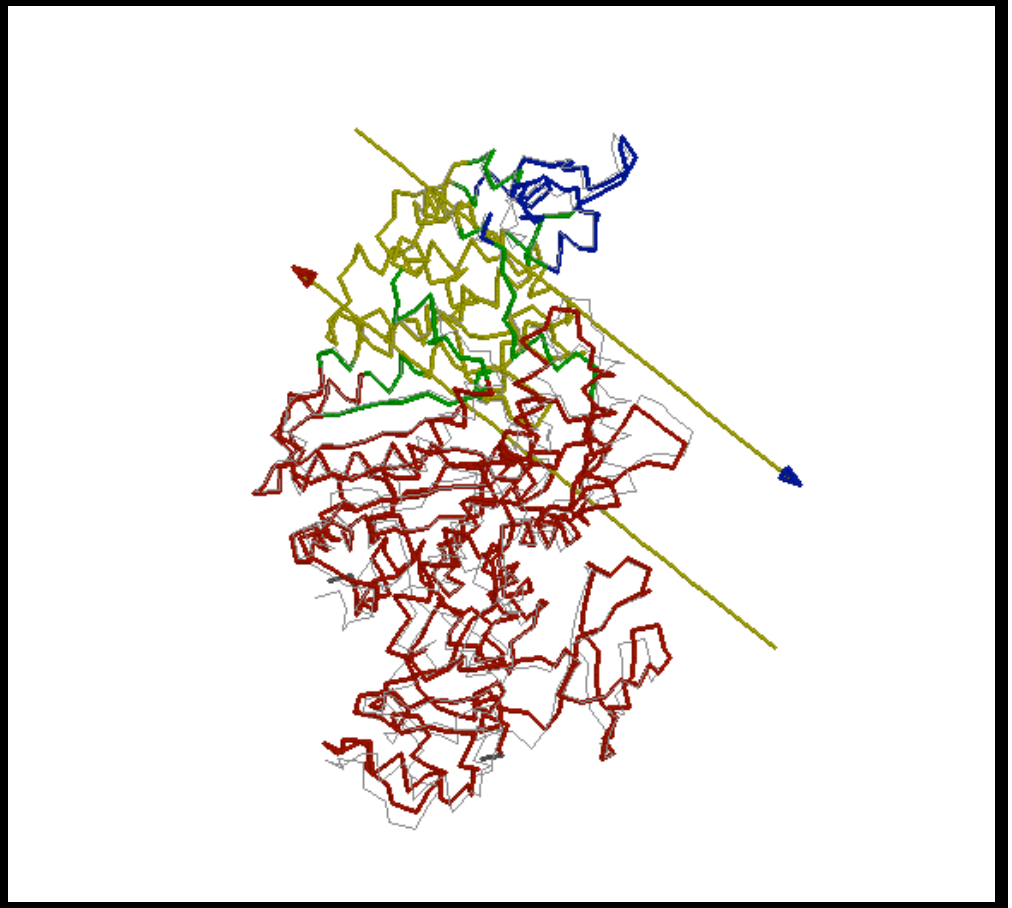


Q_1

Low-ω modes in myosin



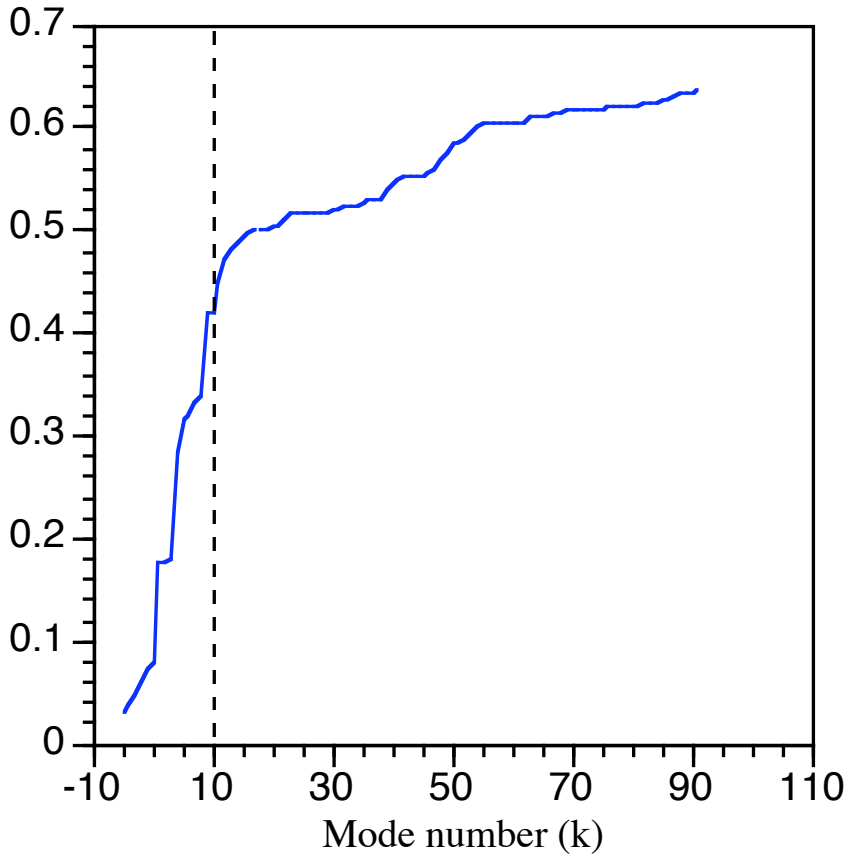
Q_2



Q_2

Converter swing and low-frequency modes

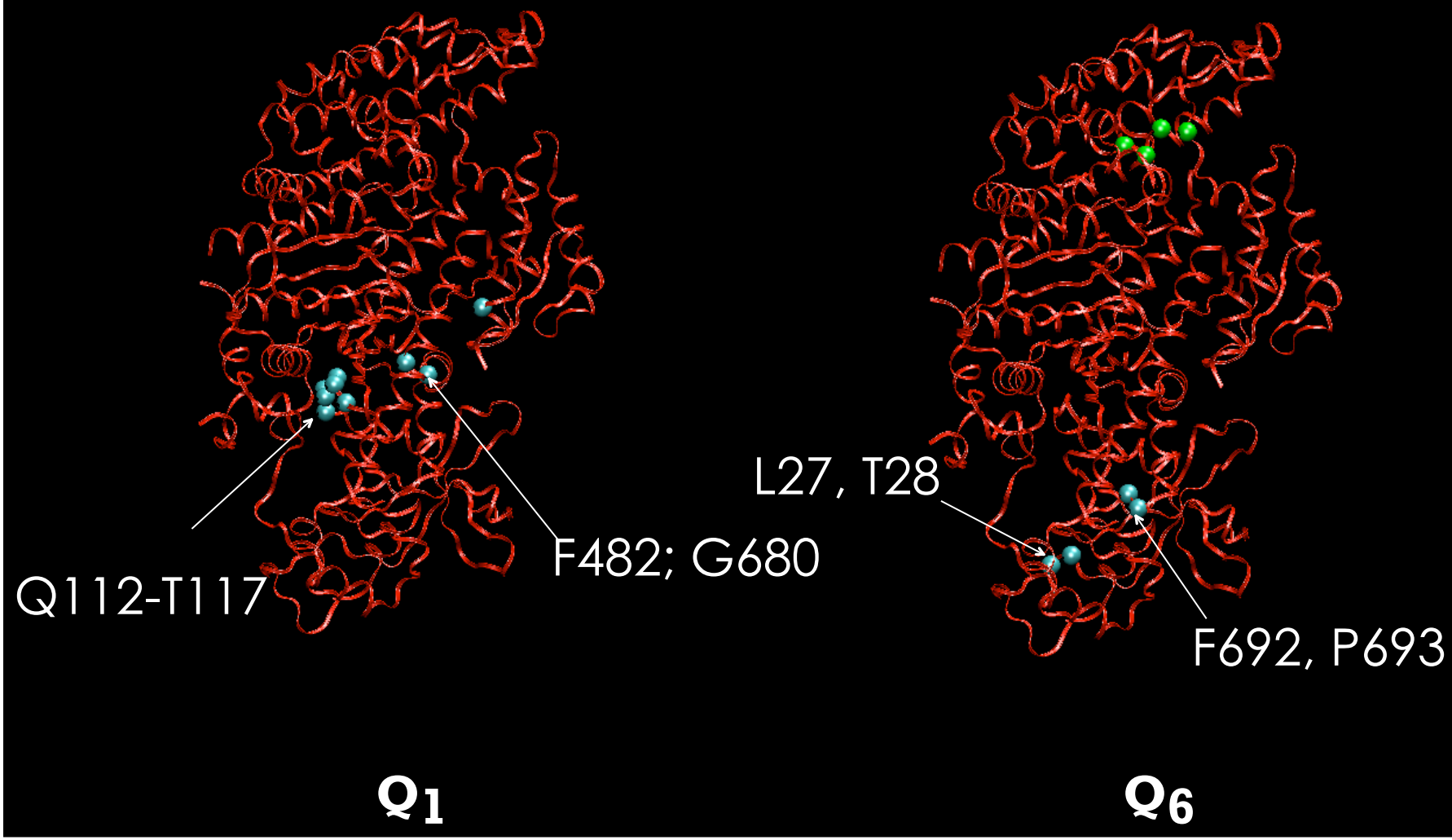
$$\sum_{j=1}^{k} I_j^2$$



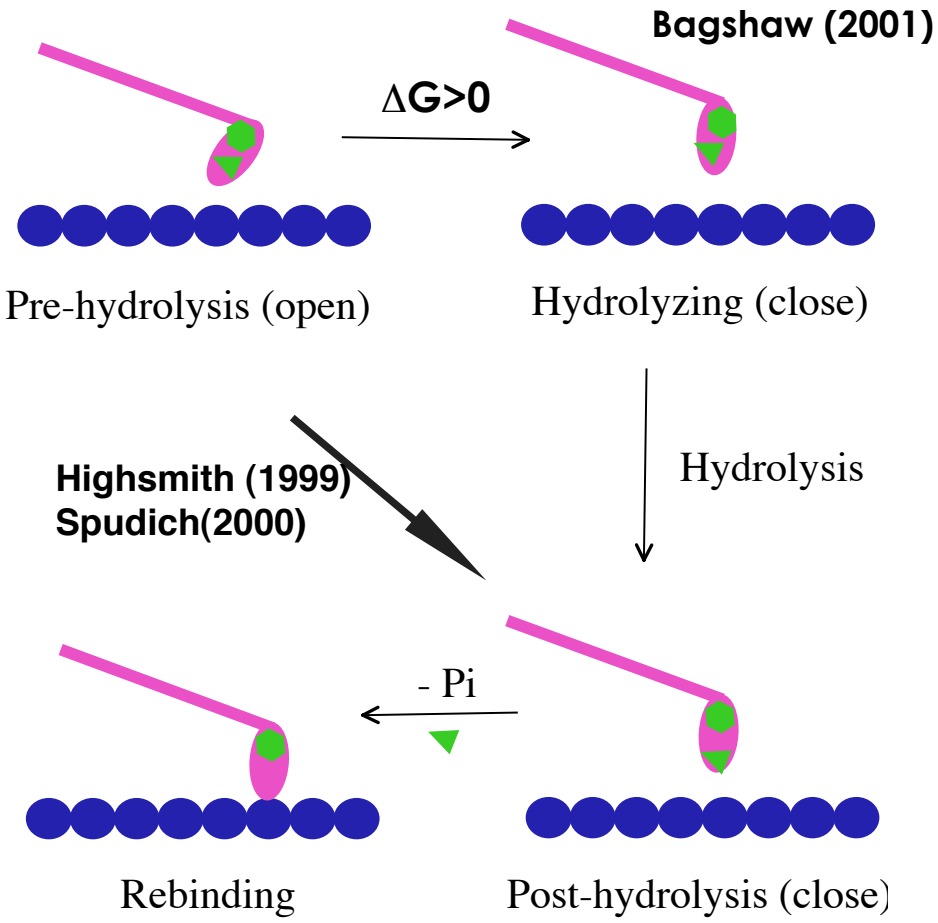
$$I_k = \frac{\mathbf{X_{open}} - \mathbf{X_{closed}}}{|\mathbf{X_{open}} - \mathbf{X_{closed}}|} \cdot \mathbf{L_k}$$

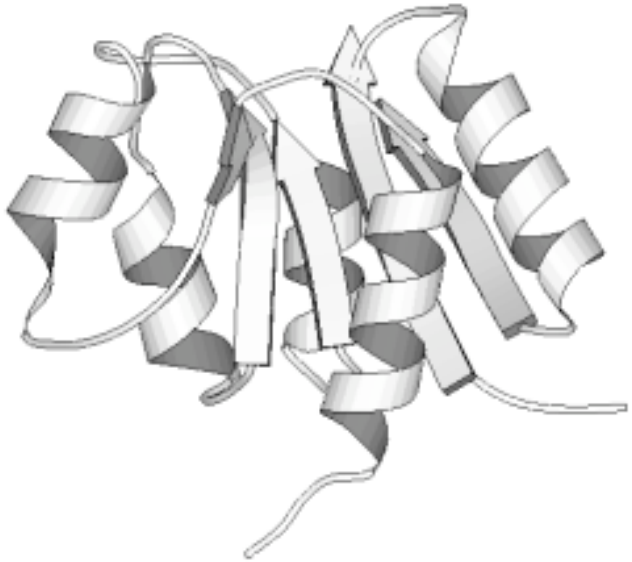
G. Li, QC, *Biophys. J.* 86, 743 (2004)

Hinges in low-frequency modes



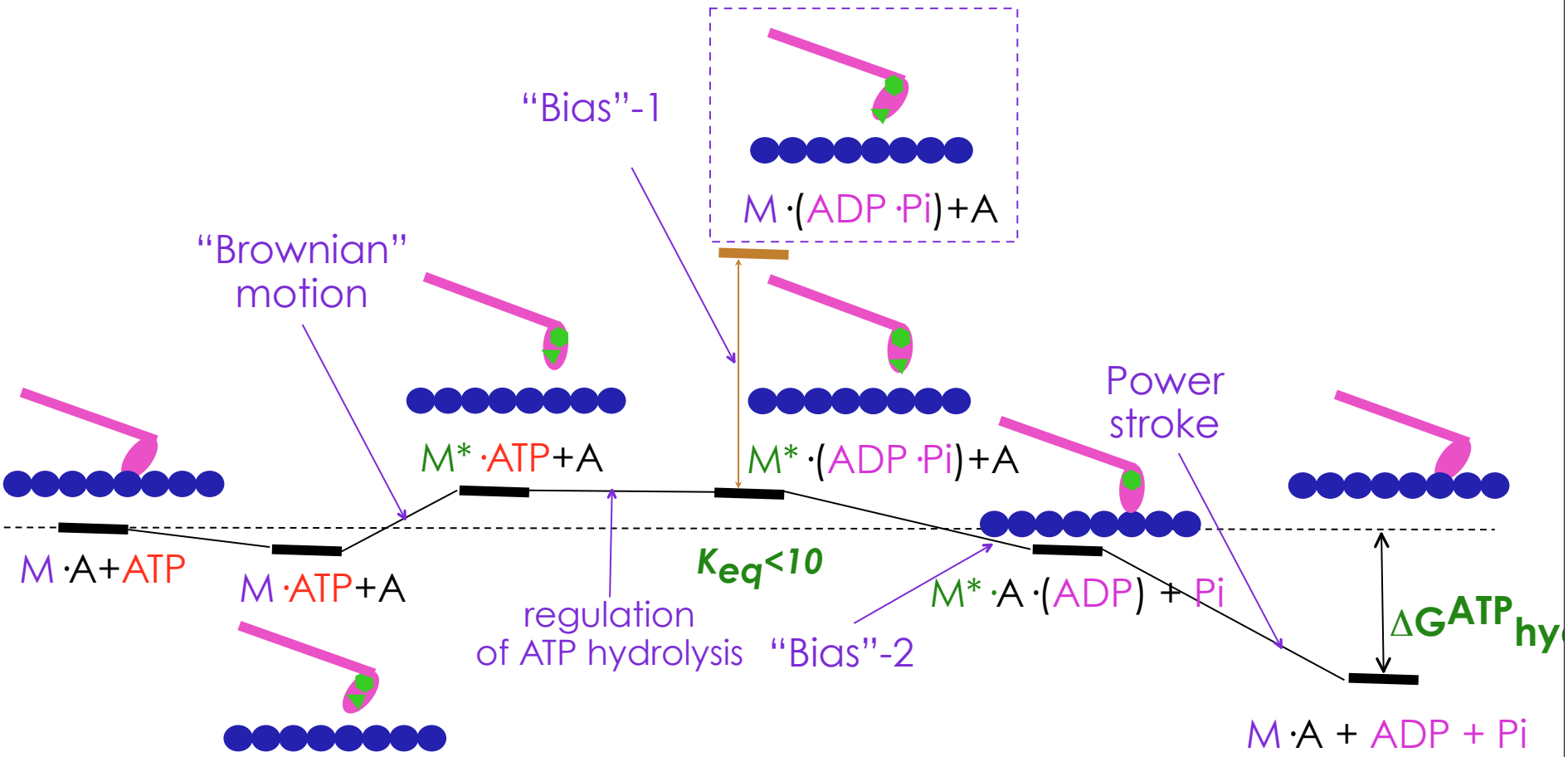
Key question: causality?





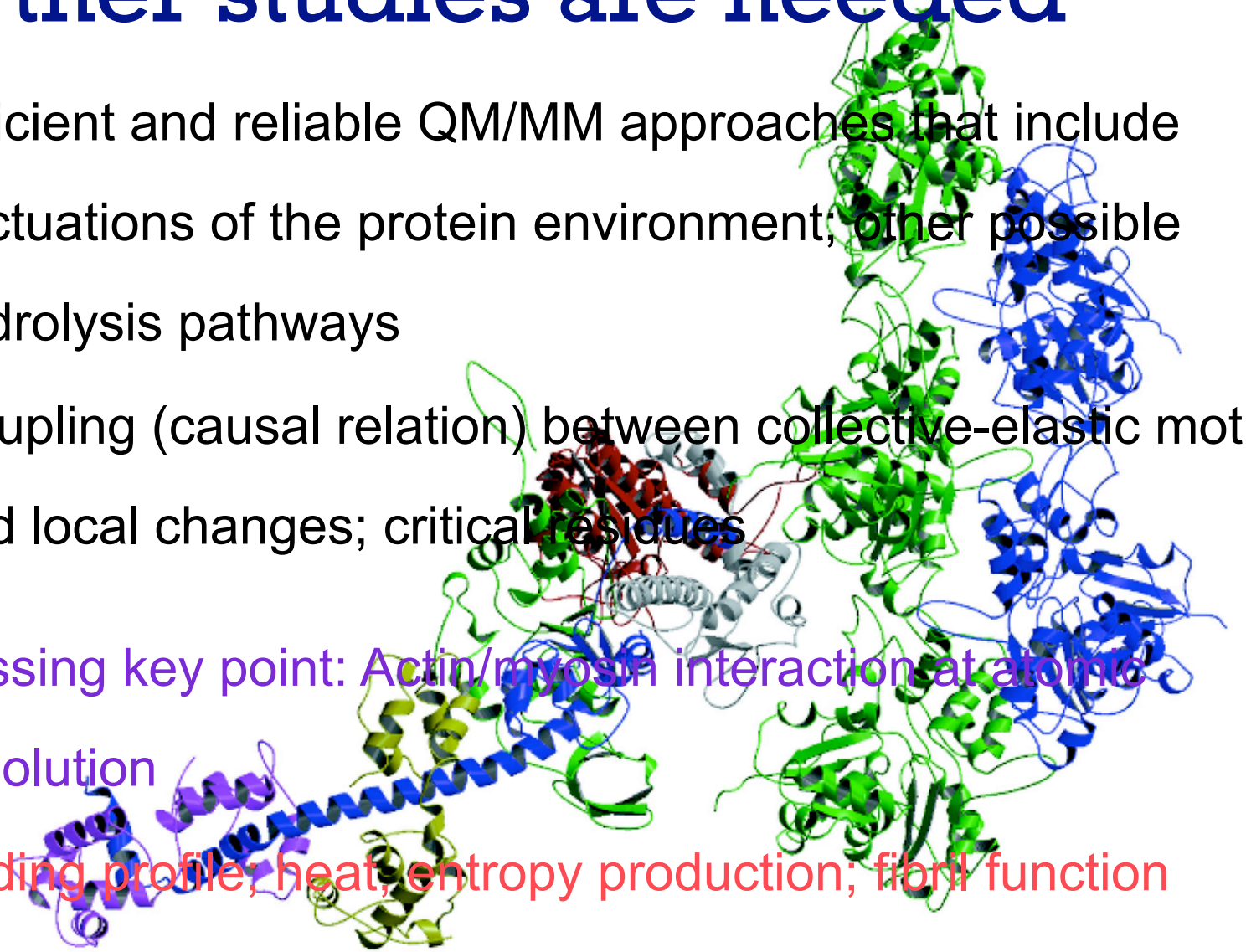
Volkman, BF; Lipson, D; Wemmer, D. E. Kern, D. *Science*, 291, 2429-33 (2001)

"Brownian" motion + Power stroke?



Further studies are needed

- Efficient and reliable QM/MM approaches that include fluctuations of the protein environment; other possible hydrolysis pathways
- Coupling (causal relation) between collective-elastic motions and local changes; critical residues
- Missing key point: Actin/myosin interaction at atomic resolution
- Sliding profile; heat, entropy production; fibril function



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- Discussions: Profs. D. Hackney (CMU), S. Gilbert (Pitt.), Dr. W. Yang, Prof. M. Karplus (ATP para.; Alchemy), Prof. I. Onishi
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