Development of Multiscale Models for Complex Chemical Systems

From $H+H_2$ to Biomolecules

Do not go where the pathway leads, go instead where there is no path and leave a trail.

Ralph Waldo Emerson

UNIVERSITÉ DE STRASBOURG

Quantum Mechanics of Many-Electron Systems (Dirac ’29)

“The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations that are much too complicated to be soluble.”

Quantum Mechanics of Many-Electron Systems (Dirac '29)

"The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations that are much too complicated to be soluble. **It therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed, which can lead to explanation of the main features of complex atomic systems without too much computation**."

Development of Multiscale Models for Complex Chemical Systems

- To understand the behavior of complex systems need:
  - The potential surface on which the atoms move
  - The laws of motion for the atoms

The Nobel Prize focused on the development of multiscale models for the potential surface.

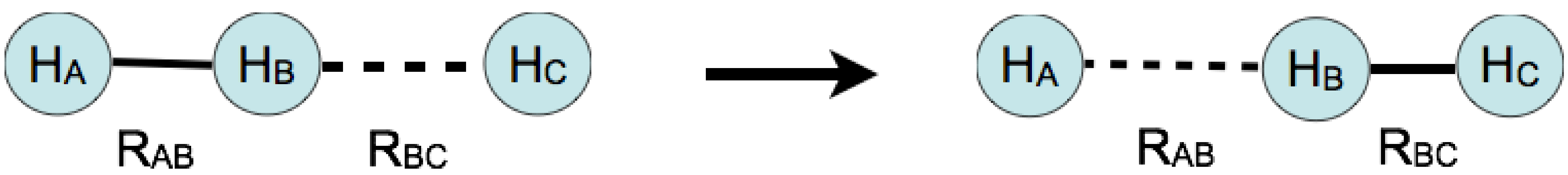
- The most important approaches for representing the potential surface of complex systems which do not use quantum mechanics (the so-called force fields) were developed in the Allinger, Lifson and Scheraga groups.
- To study chemical reactions, the classical force fields were extended to treat part of the system by quantum mechanics, the so-called QM/MM method.
- Since Michael Levitt and Arieh Warshel of the Lifson group are here, I will leave the discussion of that aspect to them.

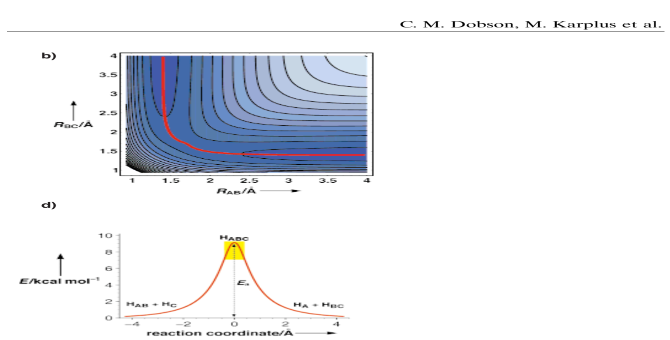
The laws of motion for the atoms

- Although the laws governing the motions of atoms are quantum mechanical, the essential realization that made possible the treatment of the dynamics of complex systems was that a classical mechanical description of the atomic motions is adequate in most cases

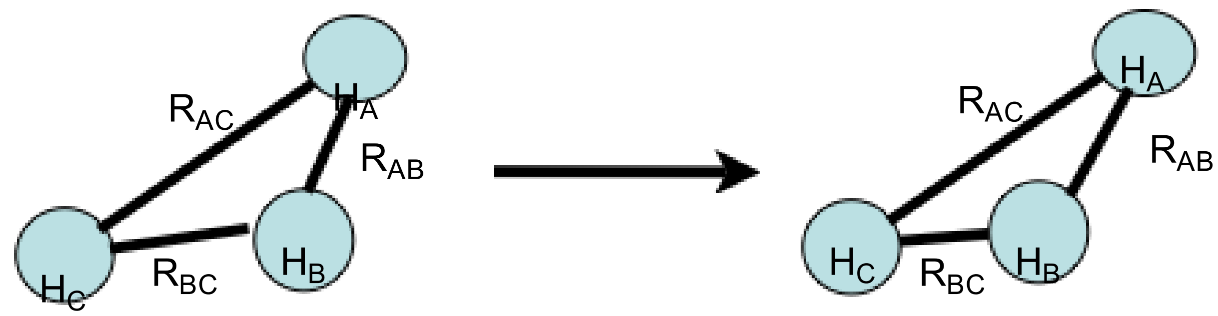
- This realization was derived from simulations of the $H+H_2$ exchange reaction

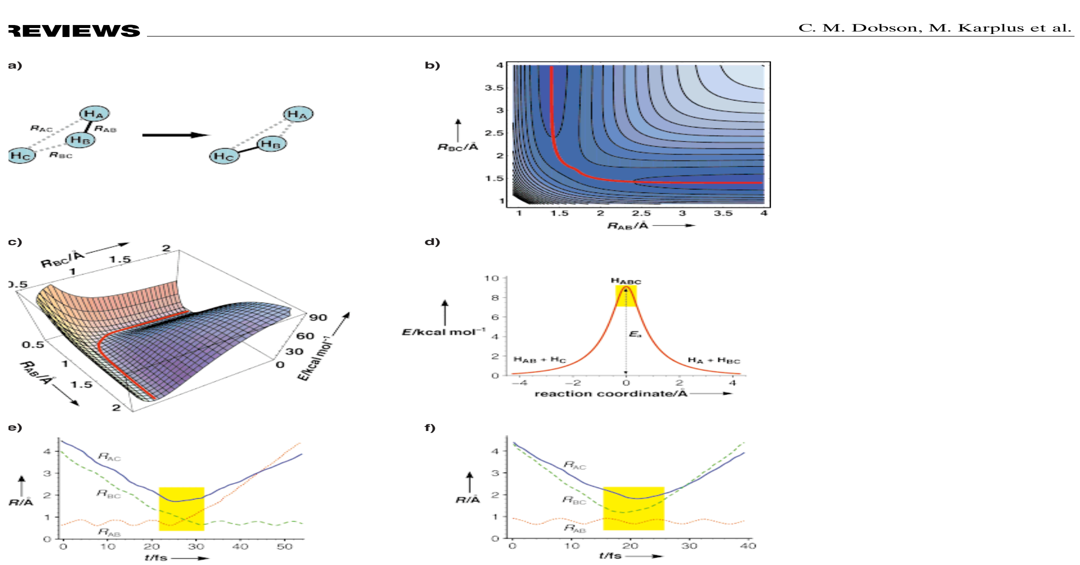
$H+H_2$ Potential Surface Based on a Semiempirical Valence Bond Approximation (Porter & K, ’64)

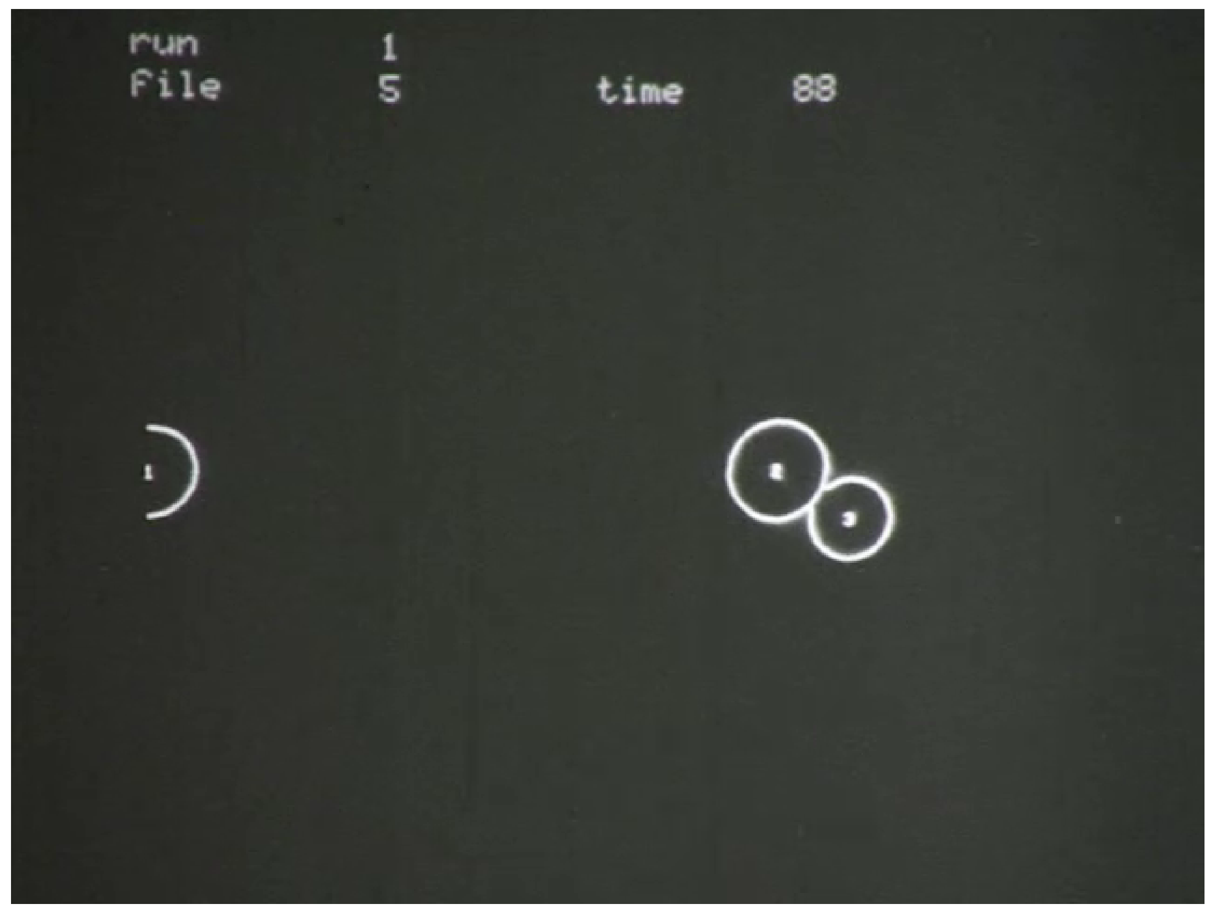




Dynamics Based on the Integrating Newton's Classical Equation of Motion(KPS,'65)







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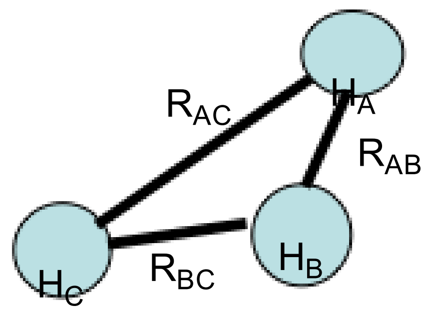
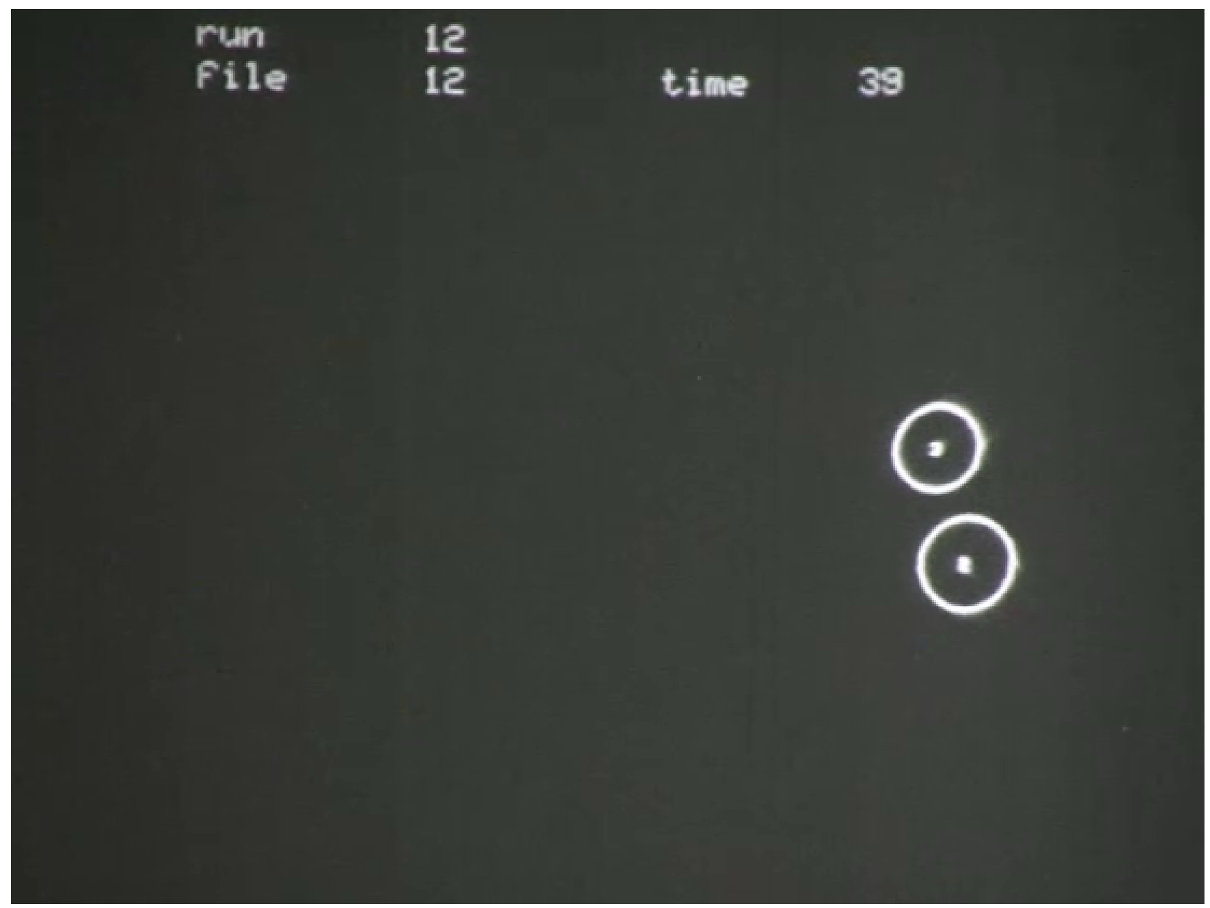
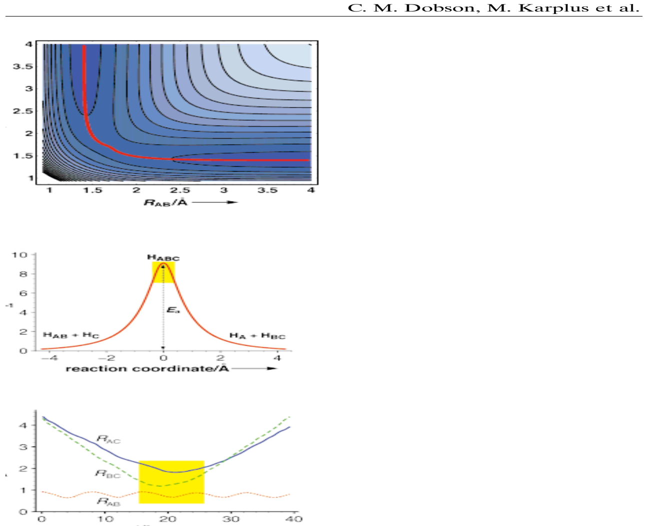




C. M. Dobson, M. Karplus et al.

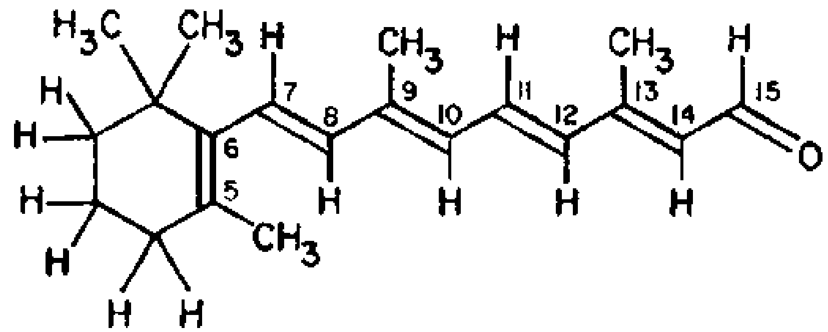


Accurate Quantum Dynamics Treatment of $H+H_2$ Reaction (Kuppermann et al.;Wyatt et al.;’75)

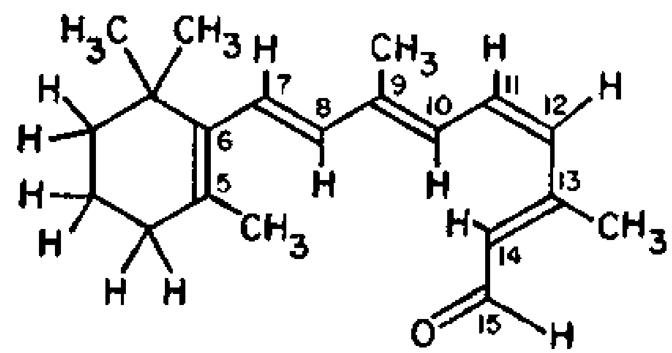
- The full QM results “agree with quasiclassical trajectory results of KPS within accuracy of the quantum calculation.”

- If Newtonian classical mechanics works for the lightest atom, it should be valid for C, N, O, of which most biomolecules are composed.

Retinal Isomerization Dynamics

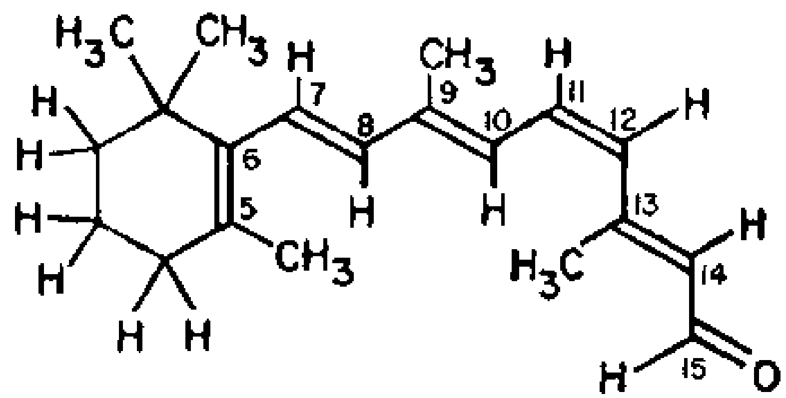


(a) all-trans



(b) 11-cis, 12-s-cis

Honig & K, '71



(c) 11-cis, 12-s-trans

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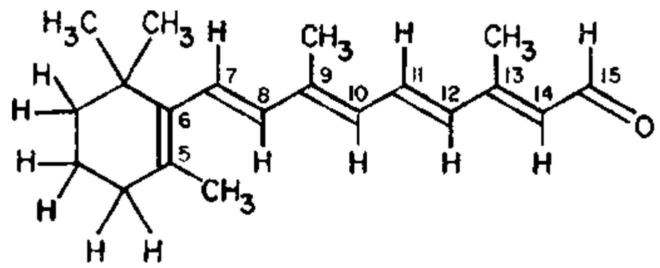

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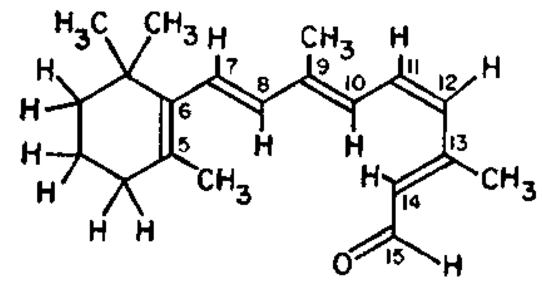

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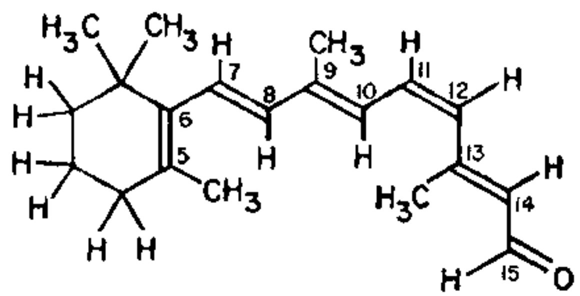
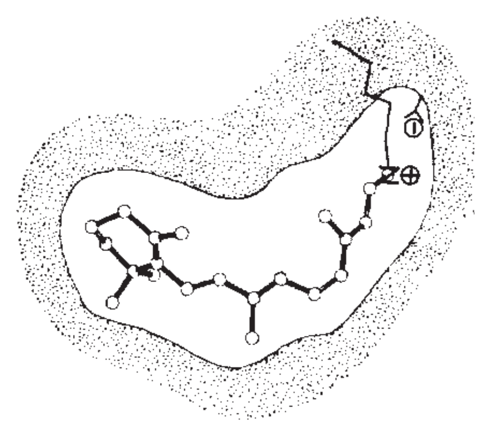


(c) 11-cis, 12-s-trans

Semiclassical trajectory approach to photoisomerization (Warshel &K ’75)

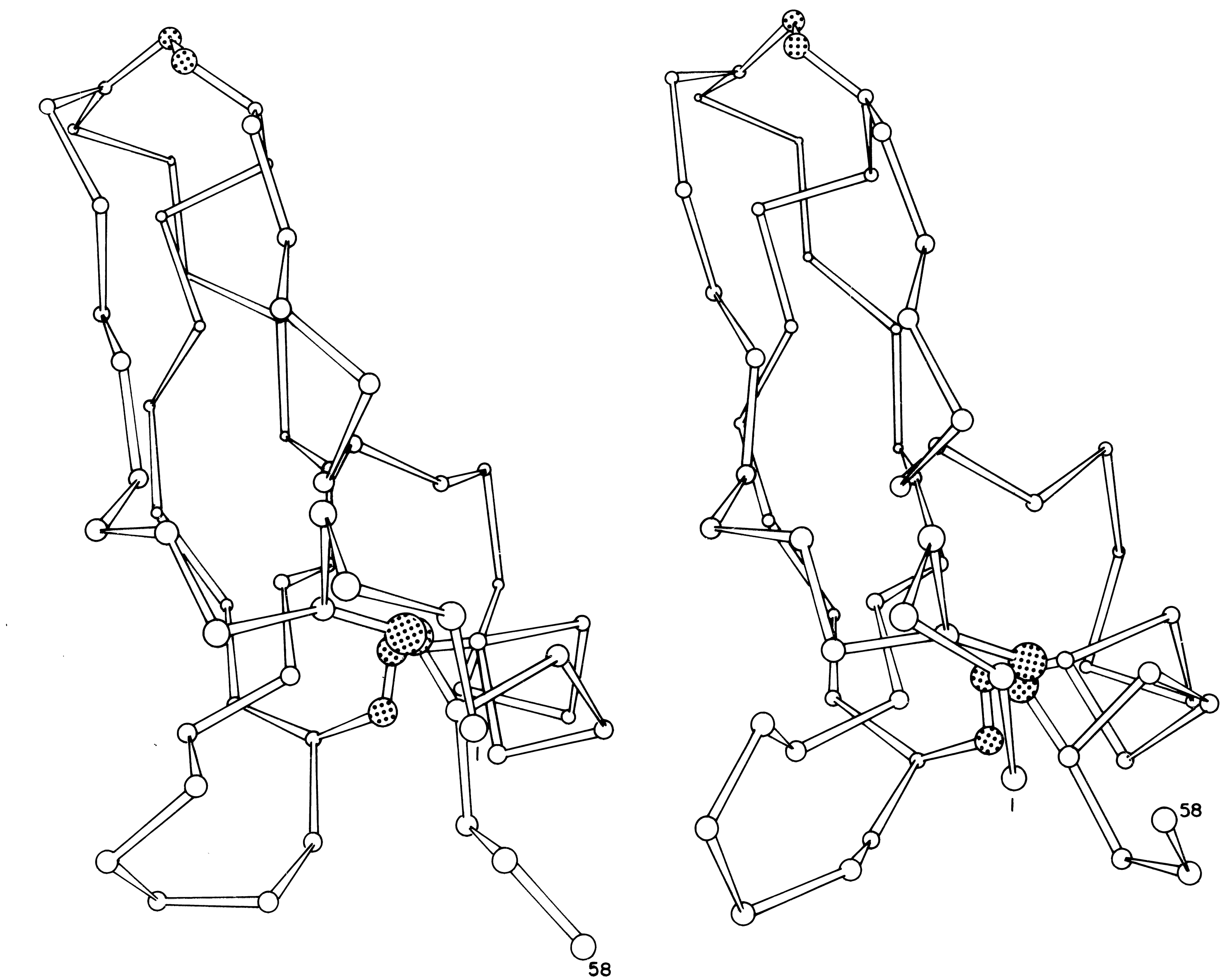


Warshel ’76

Bovine Pancreatic Trypsin Inhibitor (9.2 ps) McCammon, Gelin &K ’77

- Classical mechanical potential function based on the work of Scheraga and Lifson groups (Gelin & K ’75)
- Classical mechanical dynamics based on generalization of the $H+H_2$ methodology to a large number of atoms

BPTI Simulation (9.2ps)



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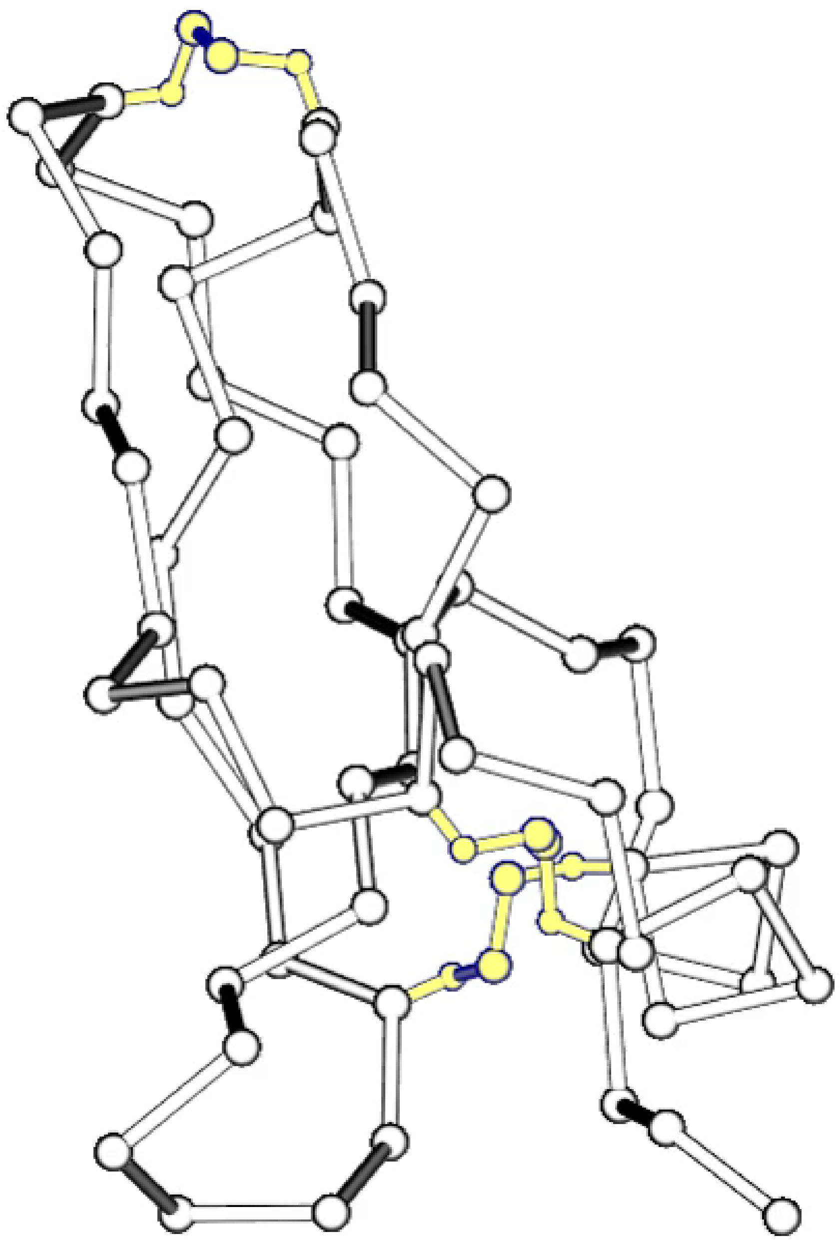


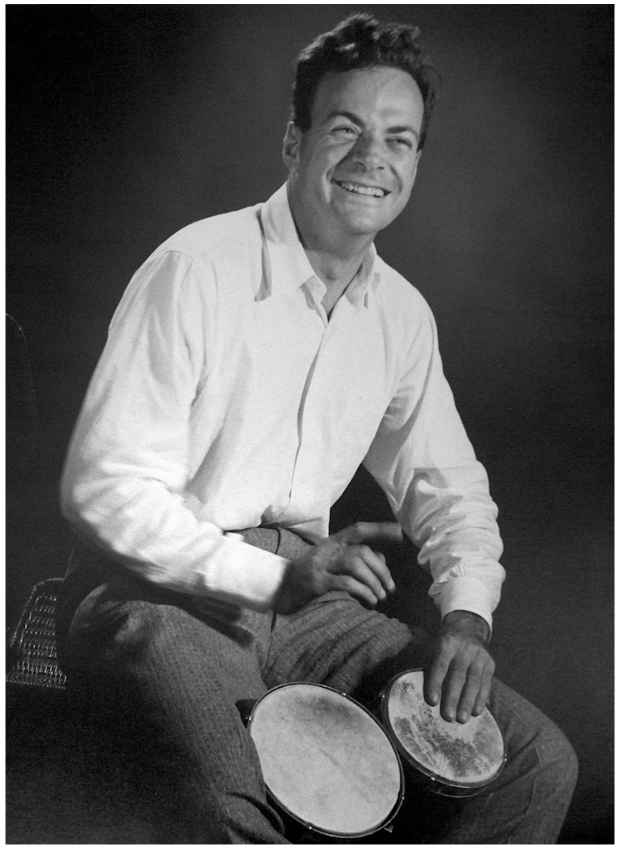
There was a sense, even at the time, of something truly historic going on, of getting these first glimpses of how an enzyme molecule for example, might undergo internal motions that allow it to function as a biological catalyst.

J. A. McCammon, Oral History (1995)

Simulations of Proteins in Solution

- Simulated BPTI for 210ps in a box of 2,607 water molecules (Levitt & Sharon, '88)
- One millisecond simulation of BPTI in water (Shaw *et al.* 2010)
- So far, no simulations of BPTI folding, though smaller protein folding with all-atom models in explicit solvent have been performed (Shaw *et al.* 2011)

“…everything that living things do can be understood in terms of the jigglings and wigglings of atoms.”



The Feynman Lectures in 1963

“The atoms are eternal and always moving. Everything comes into existence simply because of the random movement of atoms, which, given enough time, will form and reform, constantly experimenting with different configurations of matter from which will eventually emerge everything we know...”

Titus Lucretius

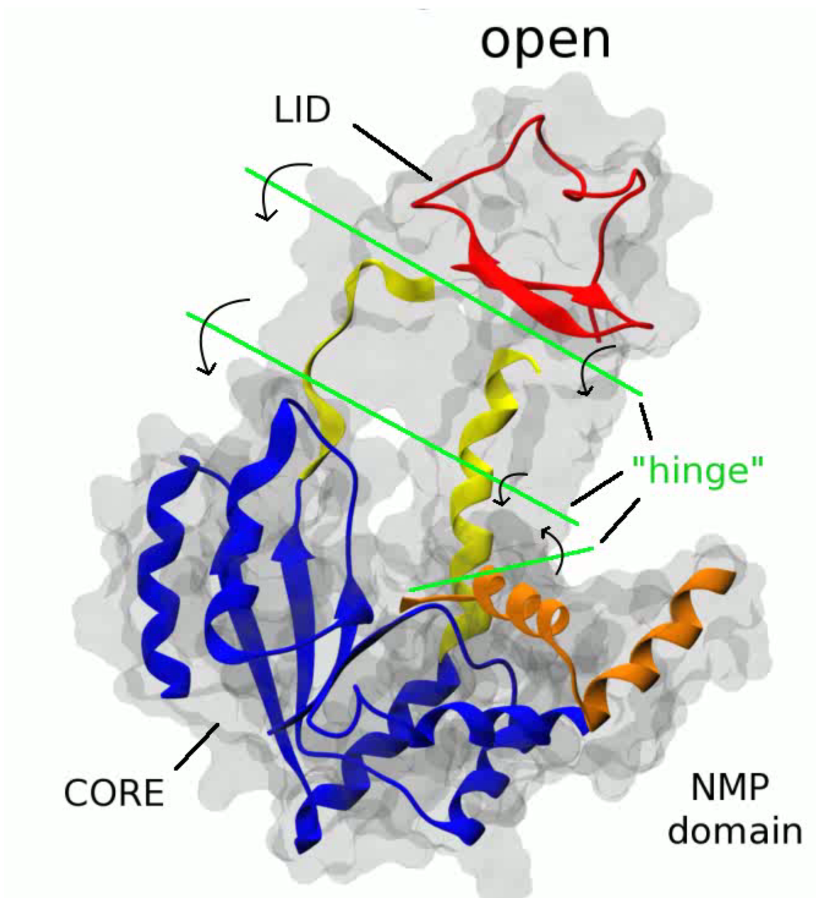
(99 BC - 55 BC)

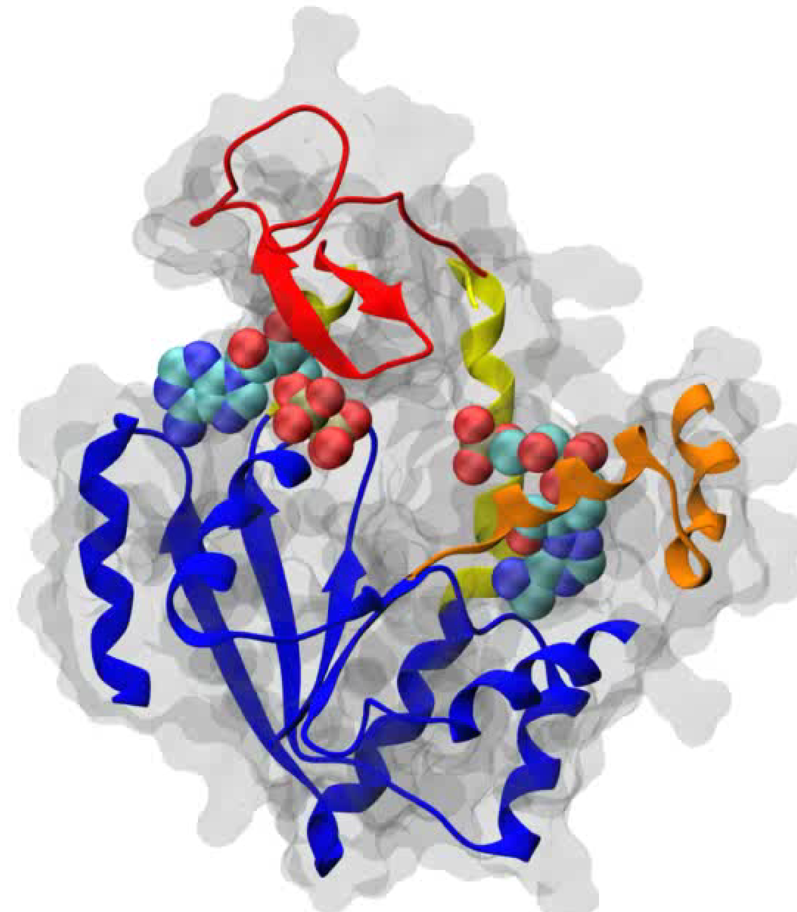
Putting to work the “Jigglings and Wigglings”

A. Semirigid domains with hinges

B. Binding of ligand to change equilibria amongst conformations

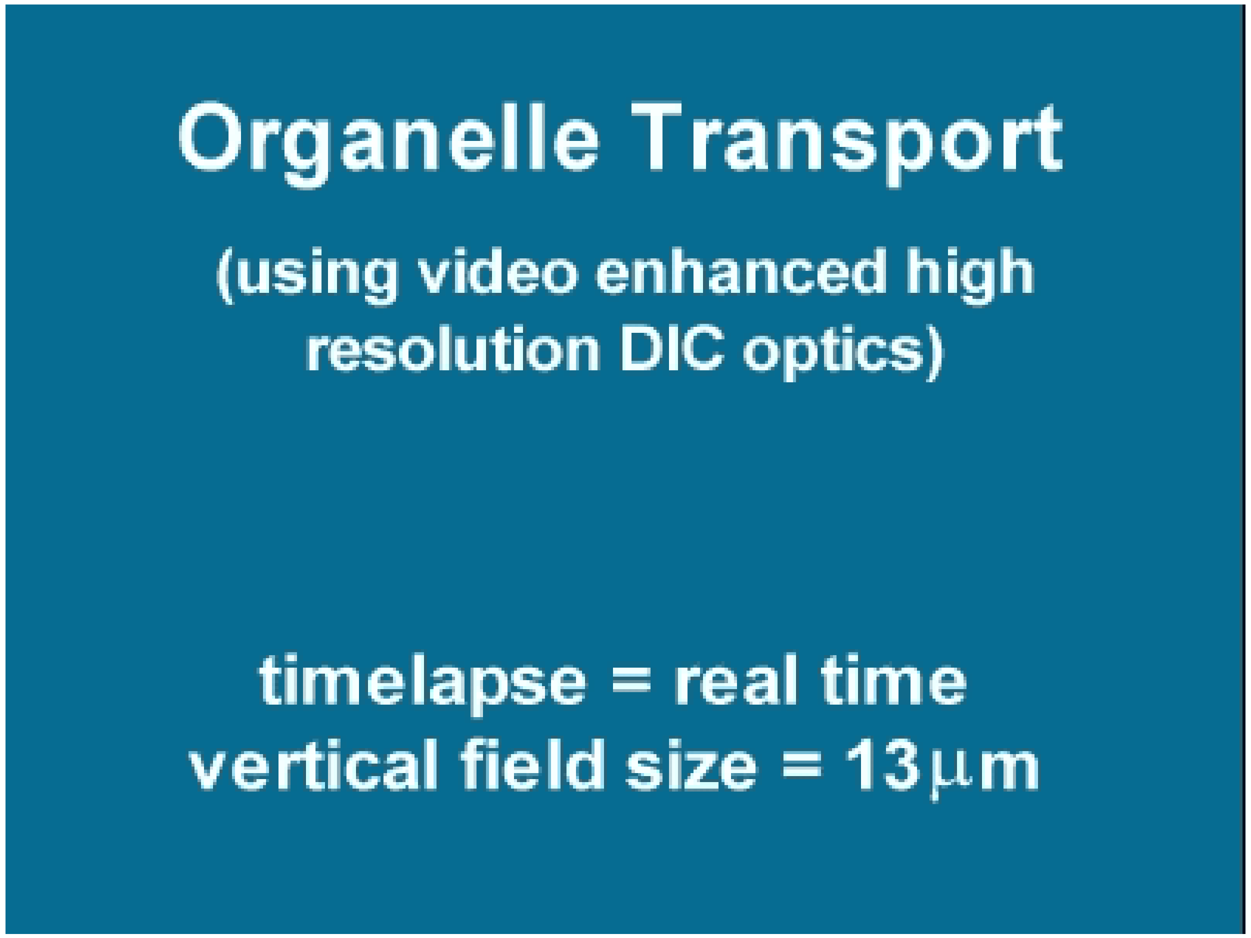
Adenylate Kinase Dynamics

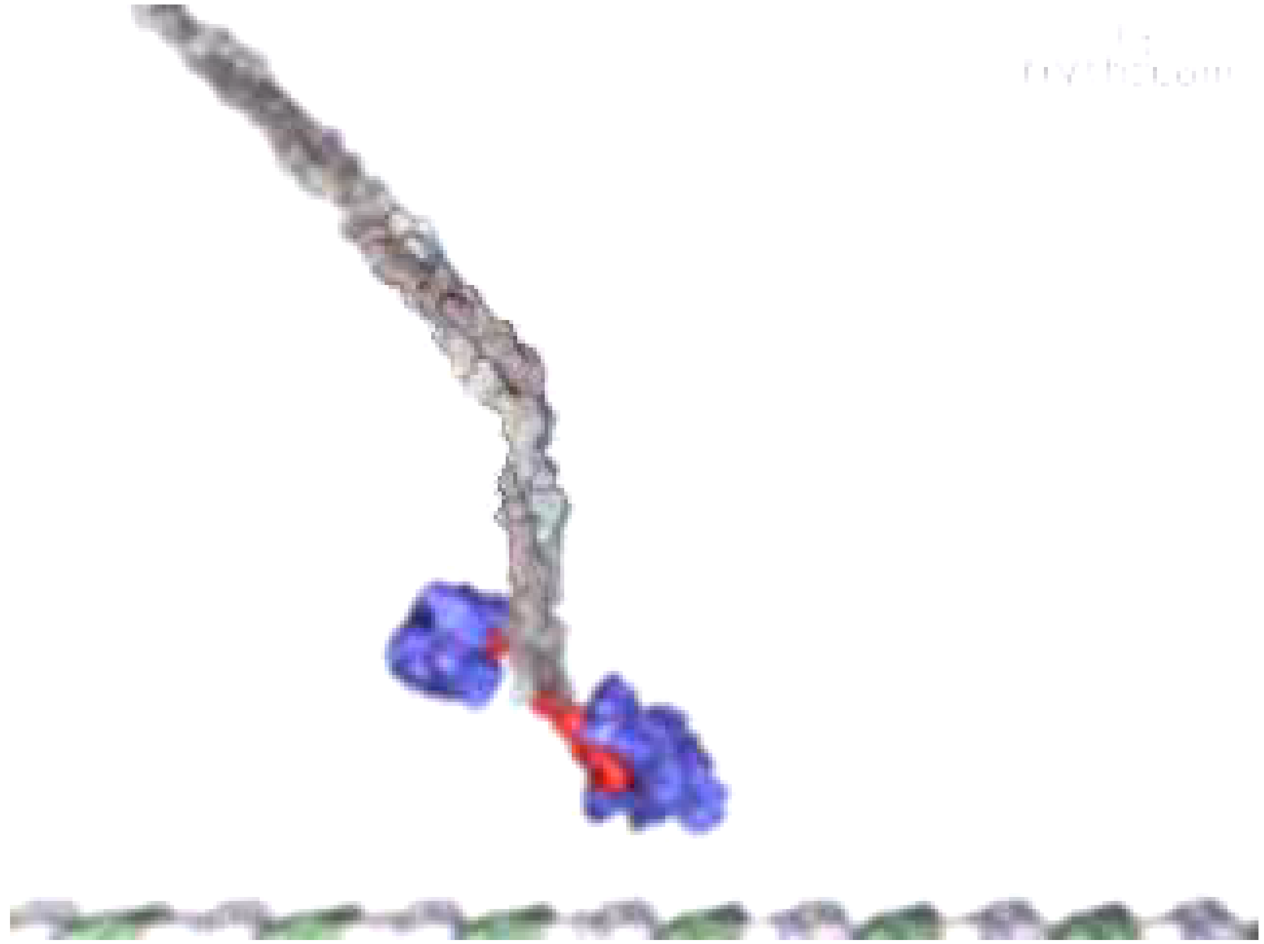




2A-P-P A-P-P-P + A-P

Kinesin Walks on Microtubules

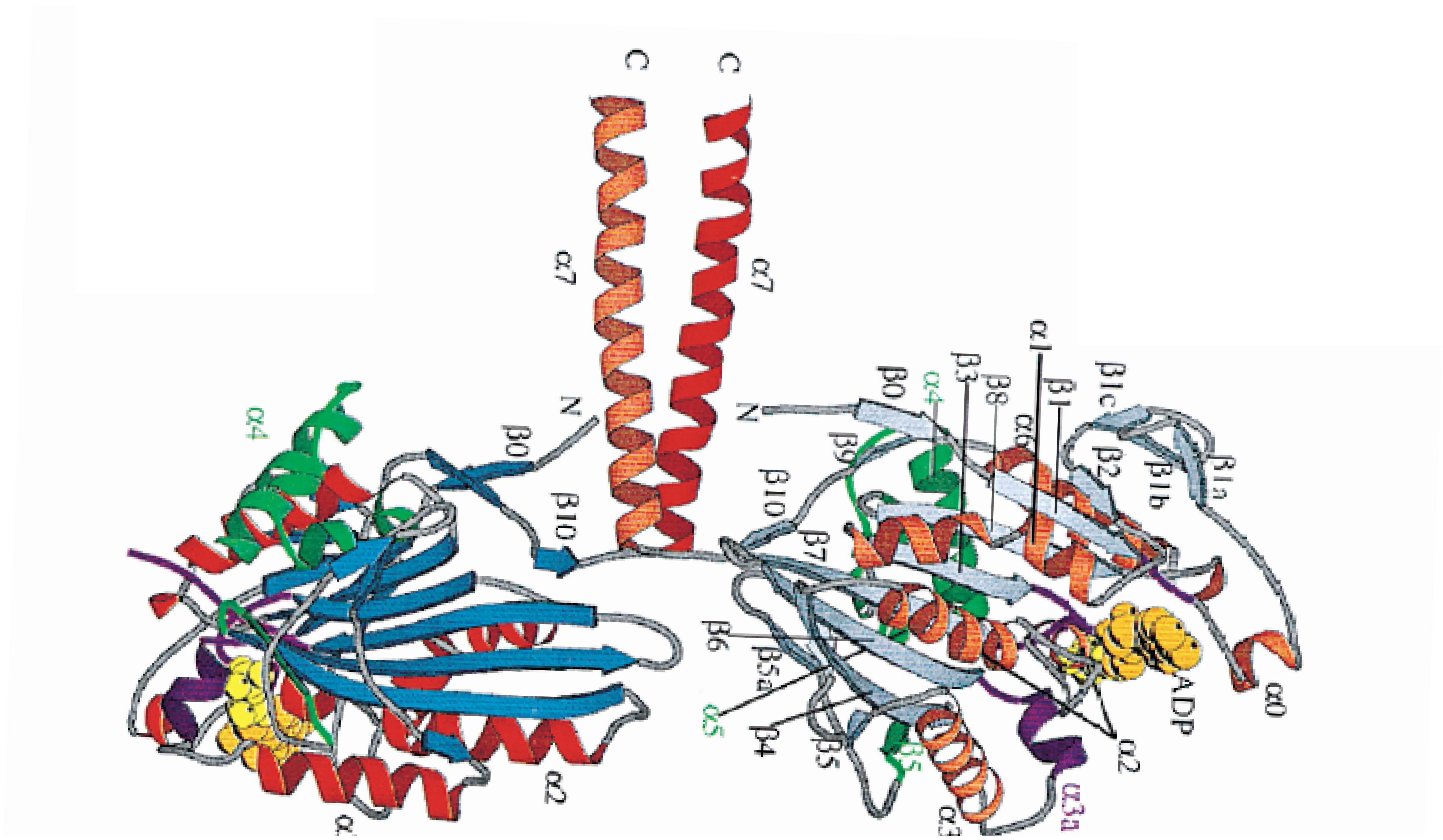




Vale, 2003

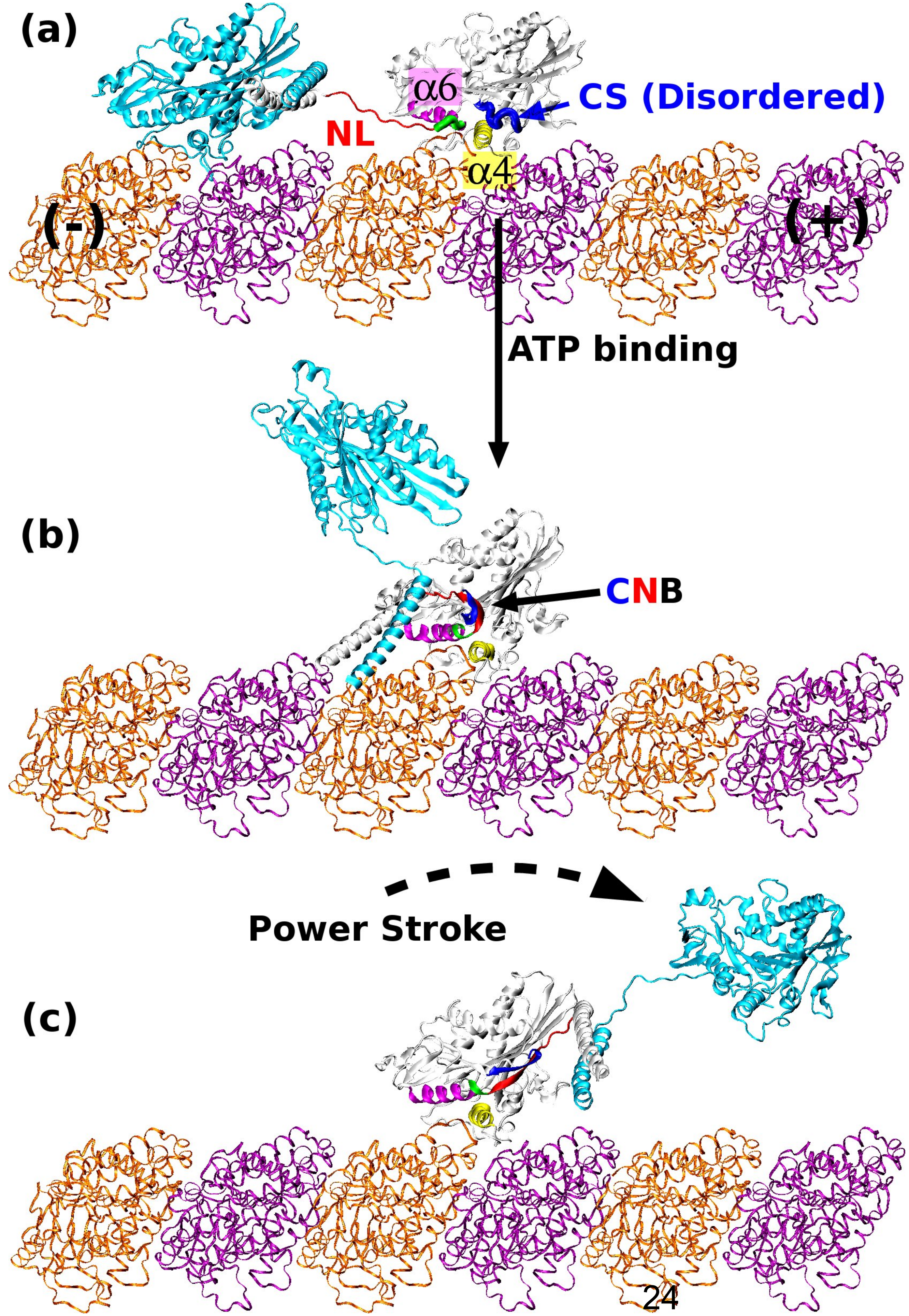
Rat Brain Dimeric Kinesin

(Mandelkow
1997)

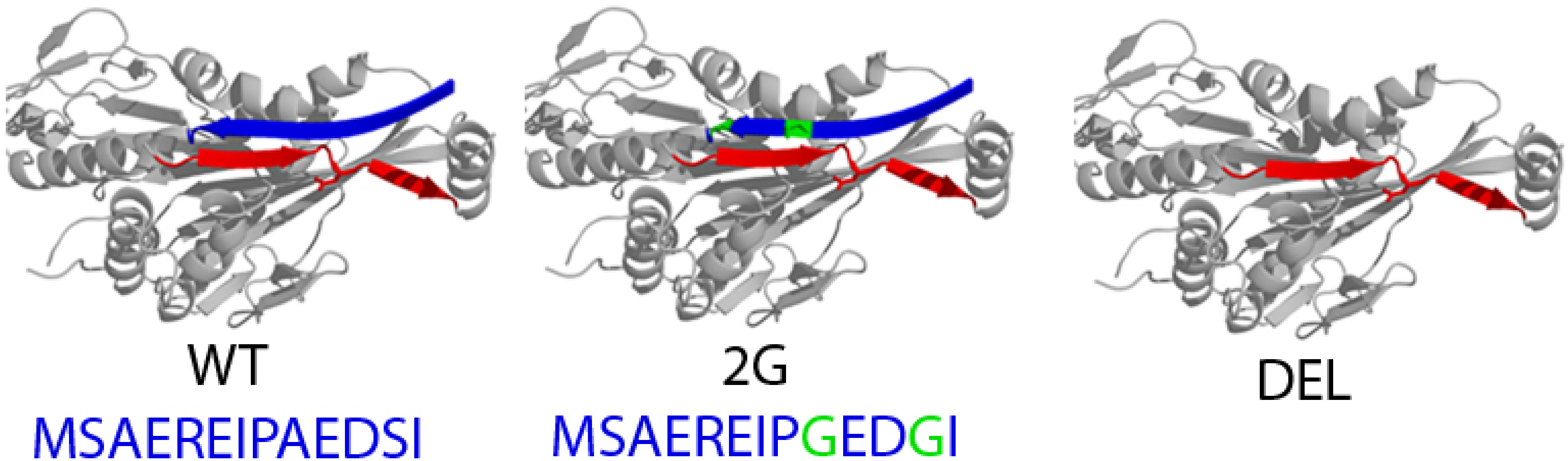


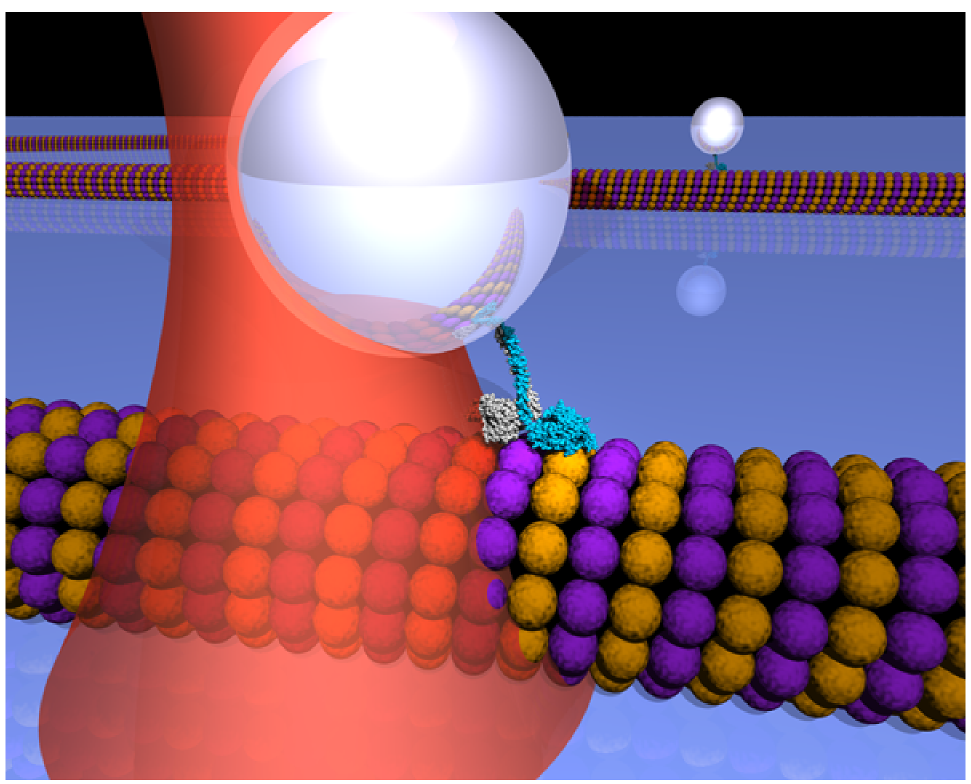
Force generation

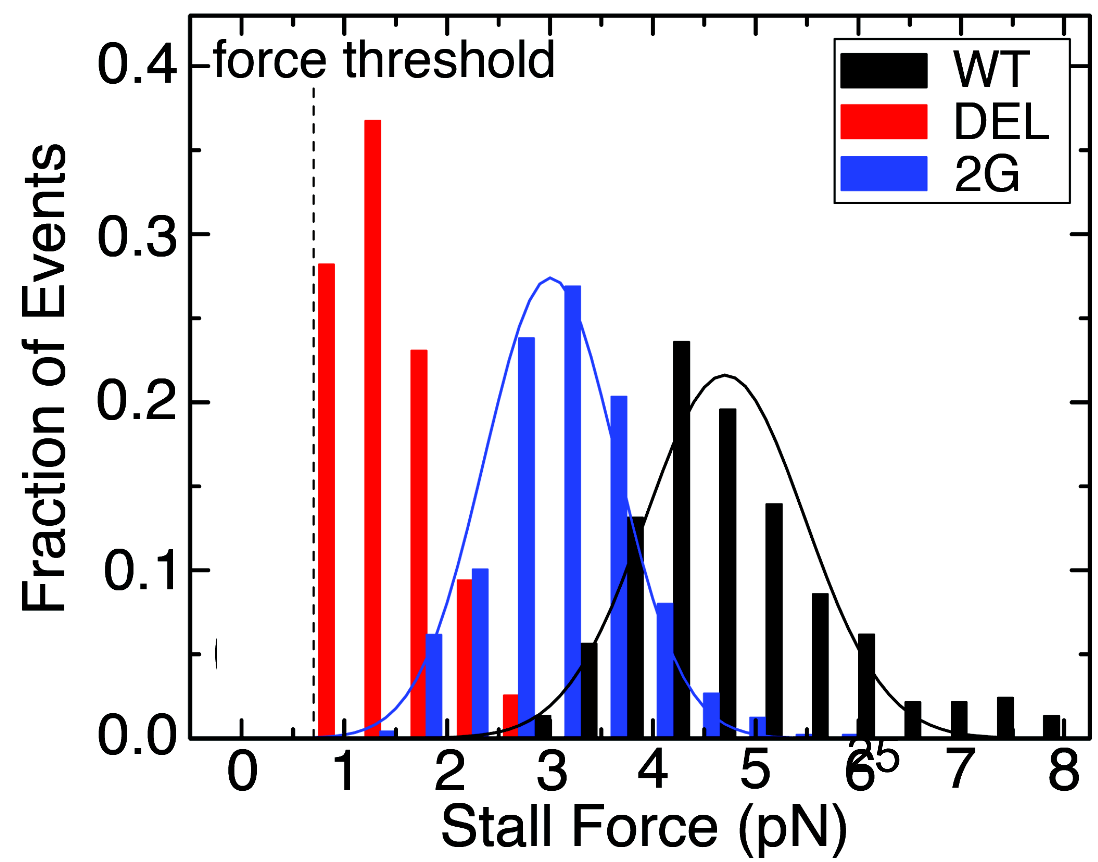
(Hwang, K *et al.*, 2008)



Mutant Measurements (Lane, Hwang, K *et al.*, 2008)







Importance of Kinesin Motors

Mitosis is inhibited.

Physiological cargoes are not delivered appropriately (e.g.clogging of axonal transport).

Non-physiological cargoes make use of the transport system (e.g.viruses).

What does the future hold?

- Experimentalists use simulations as a tool like any other
- Applications of simulations to ever more complex systems (viruses, ribosomes, cells, the brain, ...)

Always with cautionary realization that simulations, like experiments, have their limitations and inherent errors.

Karplusian: 1955-2013

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