Development of Multiscale Models for Complex Chemical Systems From $H+H_2$ to Biomolecules

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> "Do not go where the path may lead, go instead where there is no path and leave a trail."
>
> RALPH WALDO EMERSON

Paraphrasing Ralph Waldo Emerson, a 19th century New England philosopher and essayist, I shall try to show in this lecture how I have gone where there was no path and left a trail. It leads from trajectory studies of the reactions of small molecules to molecular dynamics simulations of macromolecules of biological interest.

In developing computational methods to study complex chemical systems, the essential element has been to introduce classical concepts wherever possible, to replace the much more time-consuming quantum mechanical calculations. In 1929 [1] Paul Dirac (Nobel Prize in Physics, 1933) wrote (Fig. 1) the now familiar statement:

> The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus

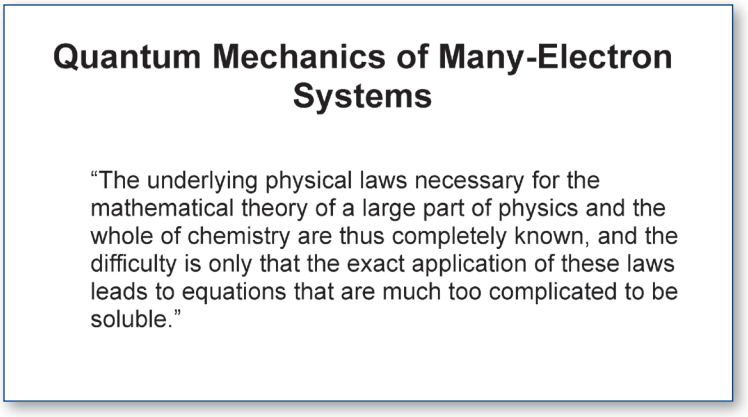


FIGURE 1. Quote from P.A.M. Dirac in 1929 (reference 1).

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.

However, the paragraph goes on to a less familiar part (Fig. 2):

It therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed, which can lead

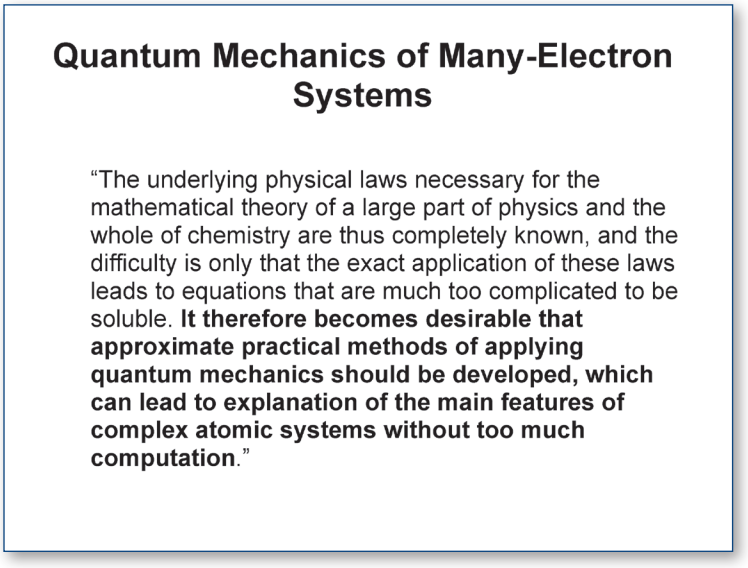


FIGURE 2. Continuation of quote from P.A.M. Dirac in 1929 (reference 1).

> to an explanation of the main features of complex atomic systems without too much computation.

This statement could be regarded as the *leitmotif* of this year's Nobel Prize in Chemistry, but actually Dirac's paper refers not to introducing classical mechanics, but rather to simplifying the quantum mechanical approaches.

To develop methods to study complex chemical systems, including biomolecules, we have to consider (Fig. 3) the two elements that govern their behavior: (1) The potential surface on which the atoms move; and (2) the laws of motion that determine the dynamics of the atoms on the potential surfaces.

The Nobel Prize focused on the development of models for the potential surface. When I visited the Lifson group in 1969, there was considerable excitement about developing empirical potential energy functions primarily for small molecules. The important "new" idea was to use a functional form that could serve not only for calculating vibrational frequencies, as did the expansion of the potential about a known or assumed energy minimum, but also for determining the molecular structure at the minimum. This approach gave rise to molecular mechanics or force fields, as they are now called, in which the energy is expanded in terms of empirical functions that are easy to calculate; the groups of Allinger [2], Scheraga [3], and Lifson [4] all made important contributions to the development. The possibility of using such energy functions for larger systems, such as proteins, struck me as very exciting, though I did not work on this for a while.

Since Michael Levitt and Arieh Warshel of the Lifson group are here, I will leave further discussion of potential surfaces to them (Fig. 4). In what follows

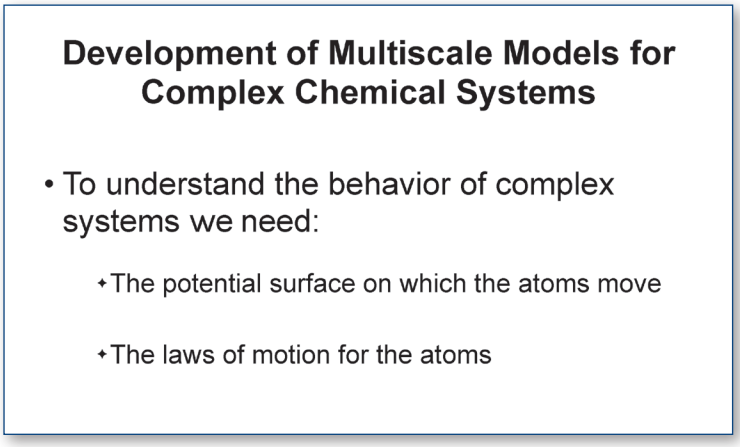


FIGURE 3. Essential elements for calculating the behavior of complex chemical systems.

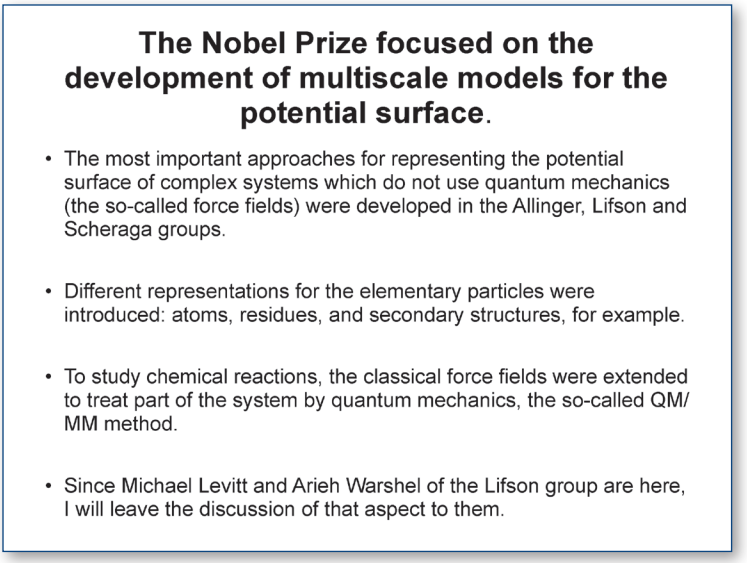


FIGURE 4. Aspects of potential surface for complex chemical systems.

I will focus on the classical treatment of the atomic motions, whether in small molecules or large (Fig. 5). Although the laws governing the motions of atoms are quantum mechanical, the key realization that made possible the simulation of the dynamics of complex systems, including biomolecules, was that a classical mechanical description of the atomic motions is adequate in most cases.

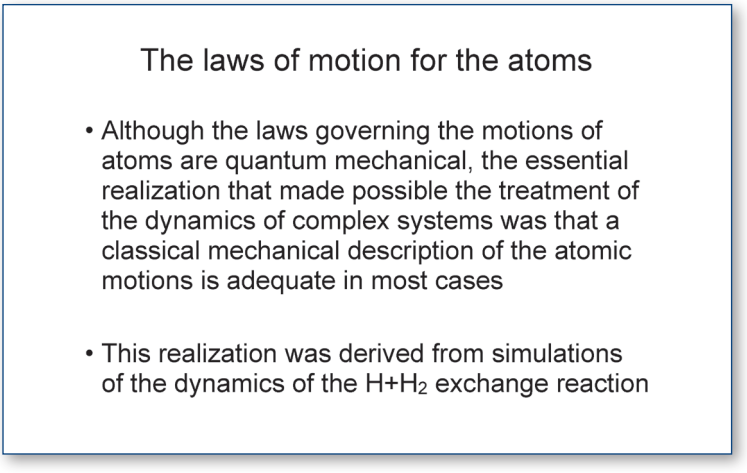


FIGURE 5. Laws of Motion: Quantum vs Classical

From my own perspective, this realization was derived from calculations that my group did in the 1960s, when we studied a very simple reaction, the symmetric exchange reaction, $H+H_2 \rightarrow H_2+H$. As shown in Fig. 6 (upper part), this involves the atom H_C colliding with the molecule H_A–H_B with the result that a new molecule H_B–H_C is formed and the atom A escapes. To determine the trajectories describing the reaction, it is necessary (Fig. 3) to know the potential surface governing the interactions between the three atoms. What Richard Porter and I used was a semi-empirical valence-bond surface [5]. This is not surprising since I had been a student of Linus Pauling (Nobel Prize in Chemistry, 1954; Nobel Prize for Peace, 1962), who believed that valence bond theory was the best approach for understanding chemical bonding. When compared with high-level quantum mechanical calculations [6], the Porter-Karplus (PK) surface, as it has come to be called, has turned out to be surprisingly accurate, in spite of the simplicity of the approach. The PK surface has been used by several groups in testing calculational methods for studying the $H+H_2$ reaction, as described below [7].

The energy as a function of the reaction coordinate for a collinear collision, which corresponds to the lowest energy reaction path, is shown in the lower part of Fig. 6. The essential feature of the surface is that there is a high activation barrier for the reaction. Although Fig. 6 shows the collinear surface, the actual trajectories describing the reaction were determined by solving Newton's equation of motion in the full three-dimensional space [8].

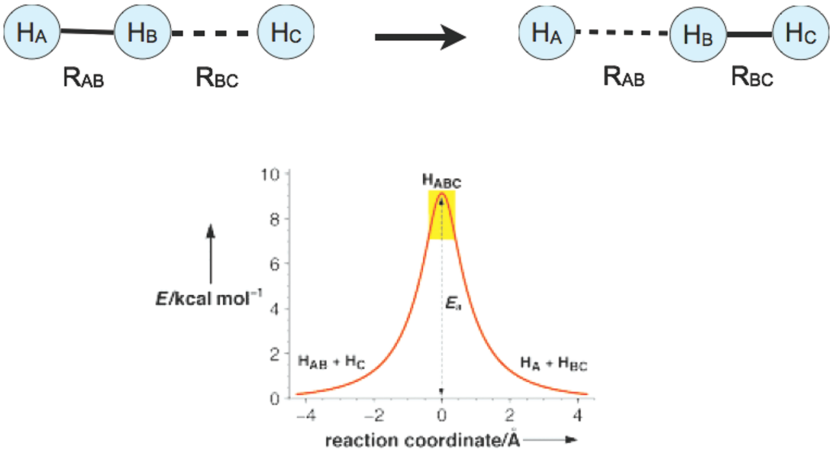


FIGURE 6. $H+H_2$ Reaction. Upper: collinear reactive collision; Lower: PK potential surface for a collinear reaction (see ref. 5).

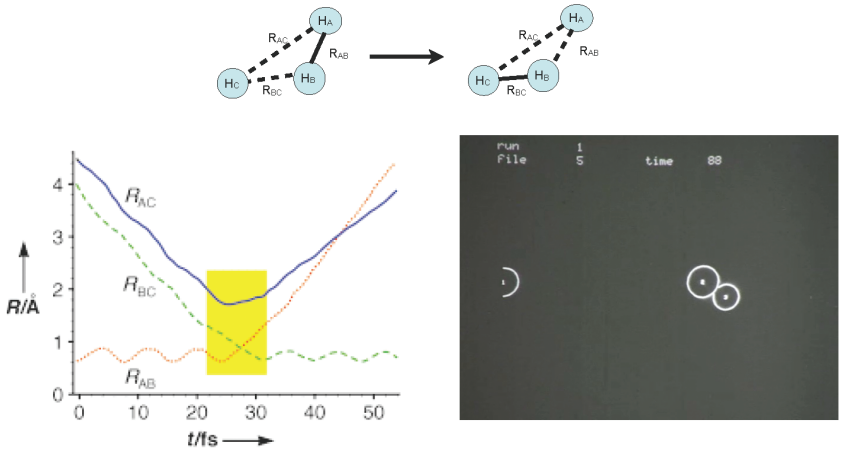


FIGURE 7. $H+H_2$ Reactive Collision. Upper: non-collinear reactive collision; Lower-left: atom distances during reactive collision with yellow box indicating the strong interaction region; Lower-right: snapshot of a reactive collision (from Film 1) (see refs. 8 and 36).

Since there are only three atoms, their relative positions can be described in terms of the three distances between the three pairs of atoms. On the lower left of Fig. 7 are shown the distances between the atoms as a function of time in femtoseconds, which is the appropriate timescale for the collision. In this figure, which represents a reactive collision, the distances R_{AC} and R_{BC} decrease as atom H_C collides with molecule H_A-H_B, which is vibrating before the reaction takes place; after the reaction, the newly formed molecule, H_B-H_C, vibrates and atom H_A escapes. The yellow box in the figure indicates the time during which strong interactions between the atoms are present; it corresponds to about 10 femtoseconds.

Figure 8 (lower left) shows a nonreactive collision in the same way as the reactive collision is shown in Fig. 7. Again, the interaction time (yellow box) is on the femtosecond timescale. In this case, the internuclear distance R_A–R_B continues as a molecule vibration and the colliding atom H_C escapes.

Soon after the calculations were done, Lee Pedersen and Keiji Morokuma, postdoctoral fellows in my group, discovered that there was a graphics laboratory at Harvard and obtained permission to make a film, which shows a series of reactive and non-reactive collisions. A snapshot from the film segments showing a reactive and a nonreactive trajectory are on the lower right of Figs. 7 and 8, respectively. A brief description of each of the films is given in the Appendix. The films are available via the links given in the Appendix.

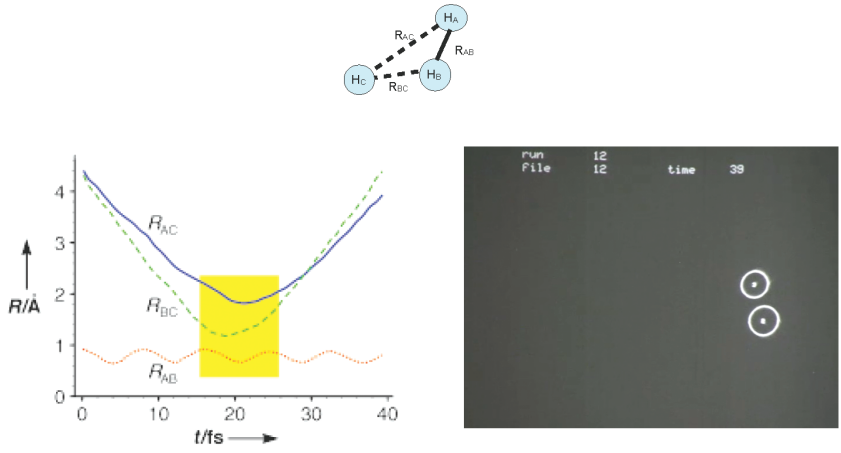


FIGURE 8. $H+H_2$ Nonreactive Collision. Upper: non-collinear non-reactive collision; Lower-left: atom distances during nonreactive collision with yellow box indicating the strong interaction region; Lower-right: snapshot of a nonreactive collision (from Film 1) (see refs. 8 and 36).

Even though an individual reaction takes place on the femtosecond timescale, the macroscopic rate is much slower. This difference in timescales arises from the fact that the reaction rate is determined by averaging over a large number of trajectories with an energy distribution corresponding to the Boltzmann Law. Even at 1000K, a temperature high enough for the reaction to be easily measured [9], most of the collisions do not have enough energy to get over the barrier. Consequently, although an individual event is very fast, the overall rate is many orders of magnitude slower.

The classical trajectory calculations of the $H+H_2$ reaction were in approximate agreement with the available experimental data [9,10]. However, it seemed to me important to ascertain that the details of the classical results were correct. For this purpose, it was necessary to have a full quantum mechanical calculation for the $H+H_2$ reaction, which was not available at the time. A significant theoretical development and much more computer time were required. It was only ten years later that a good friend of mine, Aron Kuppermann [11], and also Bob Wyatt [12] were able to do such a calculation (Fig. 9).

Since we had used the approximate PK potential for the classical mechanical calculation, both groups also used the PK potential; i.e., they were testing not whether the results agreed with Nature but whether the classical calculations were valid. As stated in the figure, they found that the classical results were as

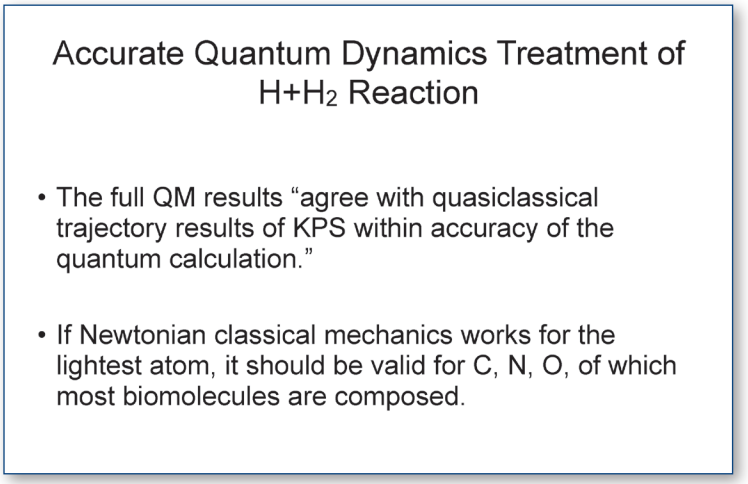


FIGURE 9. Importance of an accurate quantum treatment for validating the classical treatment (see refs. 8 and 11).

accurate as the quantum mechanical results that they obtained with much more work.

The comparison showed that the reaction of hydrogen atoms, for which you would expect the largest quantum effects, can be described classically in most cases. At low temperatures, significant tunneling can occur, so that quantum corrections are required [13]. Consequently, for heavier atoms, as well as for hydrogen atoms, classical mechanics should be valid for studying the dynamics at ambient temperatures. Since biomolecules are composed mainly of carbon, nitrogen and oxygen, with hydrogen atoms bonded to them, I concluded that classical mechanical molecular dynamics simulations would be meaningful.

Before focusing on the dynamics of larger molecules, I will discuss some work related to one of the papers mentioned in the "Scientific Background" to the Nobel Prize in Chemistry. I had become interested in the chemistry of vision as an undergraduate at Harvard and did research with Ruth Hubbard and George Wald (Nobel Prize in Physiology in 1967). After I returned to Harvard in 1966 as a Professor, I came across an article by Ruth Hubbard and George Wald in a volume dedicated to Linus Pauling for his 65th birthday [14]. It was entitled, "Pauling and Carotenoid Stereochemistry." In it, Hubbard and Wald reviewed Pauling's contribution to the understanding of polyenes with emphasis on the visual chromophore, retinal. The article contained a paragraph, which I reproduce here because it describes an element of Pauling's approach to science that greatly influenced my research:

> One of the admirable things about Linus Pauling's thinking is that he pursues it always to the level of numbers. As a result, there is usually no doubt of exactly what he means. Sometimes his initial thought is tentative because the data are not yet adequate, and then it may require some later elaboration or revision. But it is frequently he who refines the first formulation.

On looking through the article, it was clear to me that the theory of the electronic absorption spectrum of retinal and its geometric changes on excitation, which play an essential role in vision, had not advanced significantly since my discussions with Hubbard and Wald during my undergraduate days at Harvard. I realized, in part from my time in Oxford as a postdoctoral fellow with Charles Coulson, that polyenes, such as retinal, were ideal systems for study by the available semi-empirical approaches; that is, if any biologically interesting system in which quantum effects are important could be treated adequately, retinal was it. Barry Honig, who had received his PhD in theoretical chemistry working with Joshua Jortner, joined my research group at that time. He was the perfect candidate to work on the retinal problem.

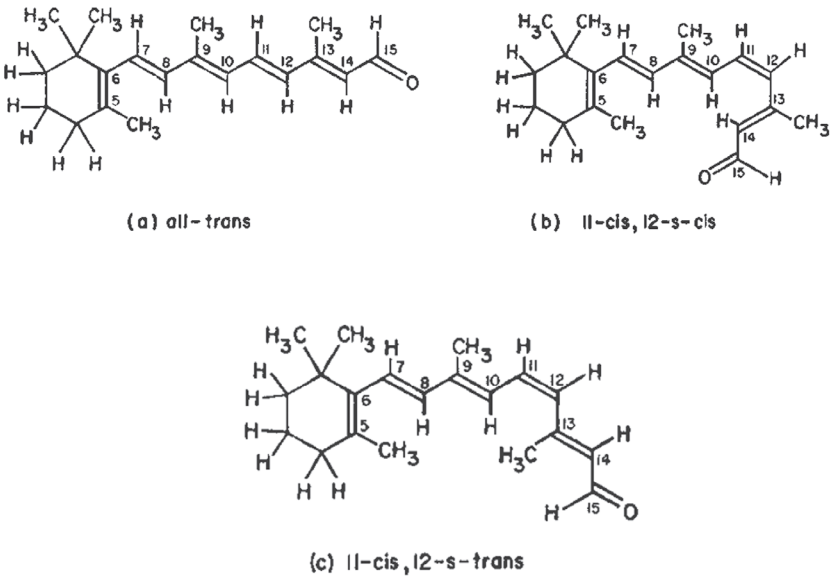


FIGURE 10. Retinal Conformers. (a) all-trans: the stable conformer after absorption of light and photoisomerization; (b) 11-cis,12-s-cis: one possible photoactive conformer; (c) 11-cis,12-s-trans: the other possible photoactive conformer (from ref. 15).

Figure 10 shows the important conformations of retinal. The active chromophore is 11-*cis*; i.e., the C_{11}–C_{12} double bond is in a *cis* configuration (see Fig. 10b and 10c). When retinal is photoisomerized, the initial step of vision, it is transformed to 11-*trans*; i.e., the C_{11}–C_{12} double bond is isomerized from *cis* (Fig. 10b and 10c) to *trans* (Fig. 10a). In the 11-*cis* state, it is possible to have the two isomers: 11-*cis*,12-s-*cis* (i.e., the C_{12}–C_{13} single bond is *cis*, Fig. 10b) and 11-*cis*, 12-s-trans (Fig. 10c). From looking at the two conformers, one would guess that the 12-s-*cis* conformer would be significantly lower in energy, because the H_{10} and H_{14} hydrogens, which appear close enough to repel each other are smaller (see Fig. 10b) than H_{10} and $(CH_3)_{13}$ (see Fig. 10c), which would be expected to have a greater repulsion.

However, when Barry Honig and I calculated the energies in the first paper [15] that used a quantum mechanical model for the π-electrons and a pairwise nonbonded van der Waals interaction energy for the σ-bond framework, we found that the two conformers are very close in energy because the larger expected repulsion in 12-s-*trans* can be reduced significantly by twisting around the single bonds; the difference is only about 1.5 kcal/mol, with 12-s-*cis* lower. Since these and other results in the paper had significant implications for the visual cycle, we submitted the paper describing them to *Nature*. It received excellent reviews, but came back with a rejection letter stating that because there was no experimental evidence to support our results, it was not certain that the conclusions were correct. This was my first experience with *Nature* and with the difficulty of publishing theoretical results related to biology, particularly in "high impact" journals. The problem is almost as prevalent today as it was then; i.e., if theory agrees with experiment it is not interesting because the result is already known, whereas if one is making a prediction, then it is not publishable because there is no evidence that the prediction is correct. I was sufficiently upset by the editorial decision that I phoned John Maddox, the Editor of *Nature*, and explained the situation to him. Apparently, I was successful, as the paper was finally accepted. Fortunately for Maddox and for us, about six months later, an X-ray structure by Jerome Karle (Nobel Prize in Chemistry, 1985) and coworkers [16] was published which confirmed our results. In a review of studies of the visual chromophore [17], we noted that "Theoretical chemists tend to use the word 'prediction' rather loosely to refer to any calculation that agrees with experiment, even when the latter was done before the former; the 12 s-*cis* geometry was a prediction in the true meaning of the word."

While Arieh Warshel was a postdoctoral fellow in my group, we extended the mixed quantum/classical mechanical method introduced in ref. [15] to calculations of the spectrum and vibrations of retinal [18] and similar molecules.

This was followed by the use of classical trajectories of the type employed for $H+H_2$ with a simple surface crossing model treatment of the photoisomerization process [19]. Figure 11 (bottom left) illustrates the case that was studied. It was the photoisomerization of 2-butene from the *cis* configuration with the two methyl groups on the same side of the double bond to the trans configuration with the two methyl groups on opposite sides of the double bond.

From looking at Fig. 11 (top), it is clear that the photosiomerization of retinal from 11-*cis* to all-*trans*, involves a large displacement of the two ends of the molecule relative to each other for both 12-s-*cis* and 12-s-*trans*. Shortly after Warshel left my group, he published a paper [20] based on the idea that when bound to the protein rhodopsin in the rods of the eye, the ends of the molecule would be restricted from moving significantly during the isomerization. As indicated in Fig. 11 (lower right), the model used fixed end groups. To allow the retinal to isomerize without movement of the end groups, he proposed the so-called "bicycle pedal" model. Of course, the rhodopsin was not included in the calculation (i.e., no protein was present) since its structure was not known at the time. Recent studies [21] have shown that the actual isomerization is more

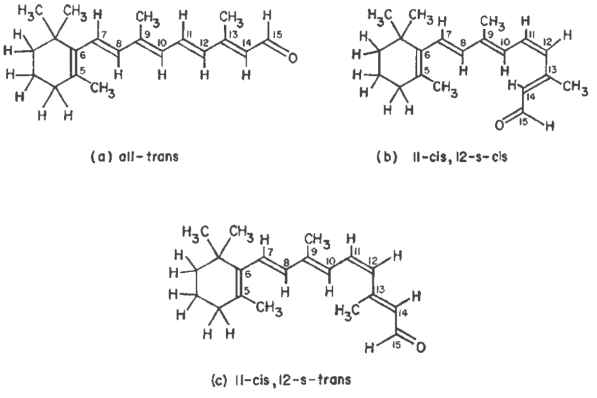


FIGURE 11. Photoisomerization Dynamics. Bottom-left: transformation from cis to trans 2-butene; Bottom-right: suggested constraints on retinal in protein rhodopsin (adapted from refs. 19 and 20).

complicated than proposed by Warshel and that relaxation of rhodopsin plays a significant role.

In the same year (1976), J. Andrew (Andy) McCammon, Bruce Gelin, and I did the first calculation applying the classical trajectory methodology to a protein, the bovine pancreatic trypsin inhibitor (BPTI). We chose this protein because it was small (only 58 residues and only 458 (pseudo) atoms in the extended atom model) and because it was one of the few proteins for which a high resolution crystal structure was available [22]. In the mid-1970s, it was difficult to obtain the computer time required to do such a simulation in the United States; the NSF centers did not yet exist. However, CECAM (Centre Européen de Calcul Atomic et Moléculaire) in Orsay, France, directed by Carl Moser, a person with an unusual vision for the future of computations in science, had access to a large computer for scientific research. In the summer of 1976, a two-month workshop was organized at CECAM by Herman Berendsen. Realizing that the workshop was a great opportunity, perhaps the only opportunity, to do the required calculations, Andy McCammon and Bruce Gelin worked very hard to prepare and test a program to do the molecular dynamics simulation of BPTI (Fig. 12). Because of their intense preparatory work, Andy was able to start running the molecular dynamics simulation as soon as he arrived. It was essentially completed at the workshop and published in 1977 [23]. It is worth mentioning that during this workshop, stimulated by the description of the BPTI simulation, a number of groups began to use molecular dynamics for studying biomolecules. They include W. F. van Gunsteren and H.J.C. Berendsen, J. Hermans and A. Rahman, and M. Levitt (see CECAM Workshop Report on "Models of Protein Dynamics," Orsay, May 24–July 17, 1976).

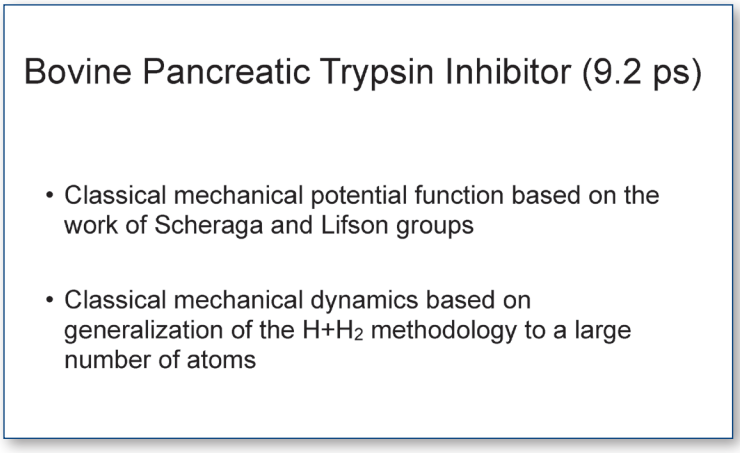


FIGURE 12. Methodology of BPTI simulation (see text and ref. 23).

We used a potential function developed by Bruce Gelin [24] that was a combination of the Scheraga and Lifson group potential functions. The molecular dynamics simulation of BPTI was an extension of what we had done for $H+H_2$ from a system of 3 atoms to one of 458 (pseudo) atoms. As mentioned earlier, it was a very natural generalization since the classical equations of motions should be applicable, regardless of the number of atoms. It is also important to remember that the BPTI simulation was not the first simulation for a many-particle system with a realistic potential function for the interactions. In particular, Aneesur Rahman, a pioneer in the simulation field who unfortunately died young, had studied liquid argon in 1964 [25] and liquid water, in a collaboration with Frank Stillinger in 1974 [26]. They seem not to have been concerned with the validity of classical mechanics for these systems; perhaps I was overly cautious.

The 9.2 ps simulation of BPTI [23] gave results concerning the fluid-like internal motions of proteins that contrast sharply with the rigid view inferred from the X-ray structures. The extent of the protein mobility was, in fact, a great surprise to many crystallographers [27] and is an early example of the conceptual insights concerning molecular properties that have been derived from molecular dynamics simulations.

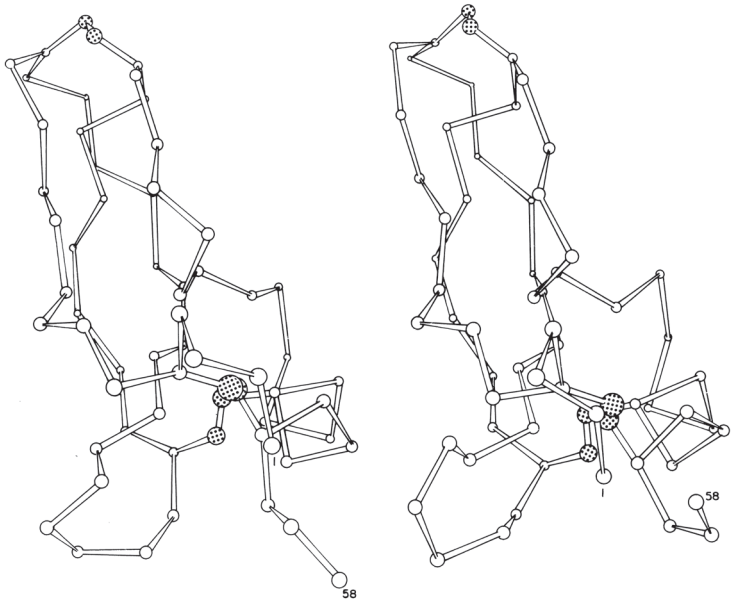


FIGURE 13. BPTI simulation. Left: Initial structure; Right: Structure after 3.2 ps. The Cα carbons are indicated by circles, the sulfurs in disulfide bonds by stippled circles, the Cα carbons are connected by rods (from ref. 23).

Obviously, the best way to illustrate the motions would have been a film of the trajectory. However, the computer graphics facilities available to us were not advanced enough to treat a 458 (pseudo)-atom system in a finite time. Instead, Bruce Gelin made two drawings of the structure of BPTI (Fig. 13), one at the beginning of the simulation (left) and the other (right) after 3.2 picoseconds. If you look carefully at the figure, you can see that although the two structures are very similar, every residue has moved by a small amount. Given that computer graphics can now make the desired film of the trajectory very easily, Victor Ovchinnikov, a postdoctoral fellow in my group, produced a film for the Nobel Lecture using the corresponding representation (see Fig. 14 and Film 2)

In an oral history that Andy McCammon recorded in 1995 [28], he made the prescient statement (Fig. 15): "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."

Today, when thousands of molecular dynamics simulations of biomolecules are being done by hundreds of scientists, it is clear that what we felt at that time was indeed the beginning of a new era in the understanding of biological

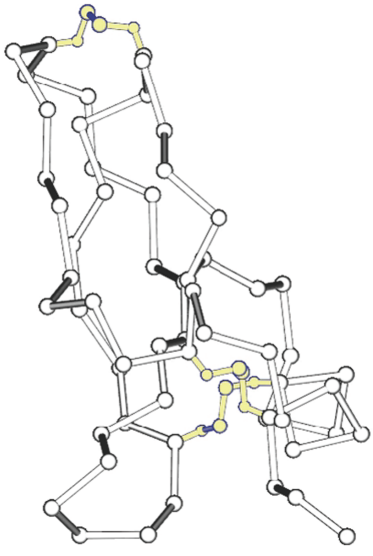


FIGURE 14. BPTI simulation. Image for Film 2. Same as Fig. 13, except that the disulfide bonds are indicated with yellow circles and connecting rods and light/dark Cα connectors represent the result of light shining on the image. (Drawing made by Victor Ovchinnikov with VMD.)

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)

FIGURE 15. Based on an interview with J. A. McCammon in 1995, after he received the 1995 Cray Research Leadership Award for Breakthrough Science from the Computer World Foundation (see ref. 28).

systems. As computers became faster, one could improve the results, not only by refining the potentials, but also by doing longer simulations of more realistic model systems. At the same CECAM workshop where the first BPTI simulation was done, Peter Rossky and I [29,30], in a collaboration with Aneesur Rahman, did a simulation of the alanine-dipeptide (Fig. 16) in a box of water molecules and showed that the water around the hydrophobic methyl groups behaved differently from the water interacting with the polar C=O and N–H groups.

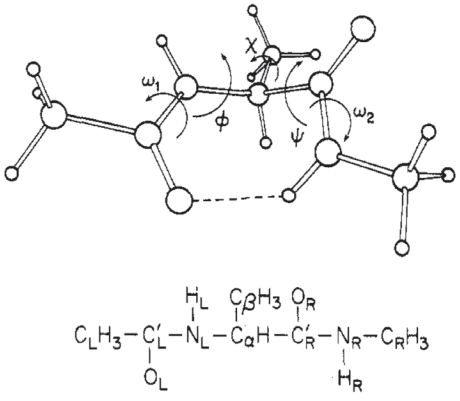


FIGURE 16. Drawing of Alanine Dipeptide for the Solution Simulation. Top: Conformation used in simulation; Bottom: Chemical formula (ref. 29).

In 1988 Michael Levitt and Ruth Sharon [31] published a simulation of BPTI (see Fig. 17) that was more than twenty times longer than the original simulation and very importantly, the simulation was done in a box of water molecules. The Levitt-Sharon simulation confirmed the water behavior observed in the Rossky et al. papers [29,30]. Further, the simulation was qualitatively in agreement with the original BPTI vacuum simulation results, although the motions of the residues were somewhat smaller and because of the water friction, they were also slightly slower. Recent work [32,33] has elaborated our understanding of the role of the water environment in protein dynamics.

In 2010 Shaw and his coworkers [34] (Fig. 17) performed a 1 millisecond simulation of BPTI described by a standard force field using a specially designed computer. The paper analyzed the long time dynamics in detail, but for me the most important aspect of the simulation is that they found that BPTI was stable on the millisecond timescale. I had always wondered, perhaps been "scared" is a better word, whether with the relatively crude potentials we were using the protein would fall apart (denature) if the molecular dynamics simulations were extended to such long times, the timescales that are of interest for many biological processes.

In relation to such considerations, I would like to remind the audience that a very difficult problem in the field of molecular dynamics simulations of

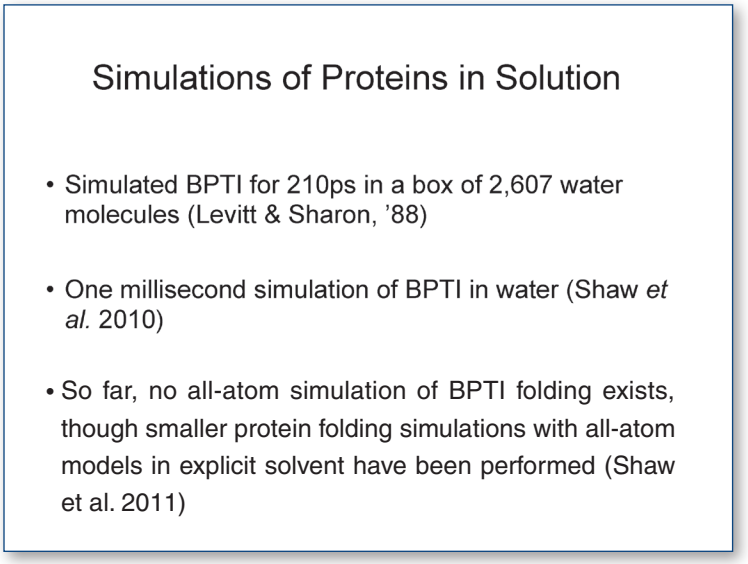


FIGURE 17. Summary of BPTI Solution Simulations (see text).

biomolecules is to have a way of checking that the results are correct. Experimental data (e.g. NMR measurements) that can be used for validation of the results are important but limited; i.e., they do not provide enough information for a quantitative test. Despite what the Nobel Prize press citation implies ("The computer is just as important as the test tube"), experiments are essential to verify that what we are doing is meaningful. It is often possible to verify that the statistical error is sufficiently small that the simulations can be used to understand the phenomenon being studied [35], but the systematic error due to the approximations in the potentials is difficult to quantify.

In addition to the dynamics of the native proteins like BPTI, how the polypeptide chain folds to the native state is of great interest [36]. No folding simulation of BPTI is available as yet (Fig. 17), though such simulations have been performed for smaller proteins [37]. The present status of our knowledge of BPTI folding, which was first studied by Levitt and Warshel with an ultra-simplified model [38], is summarized in ref. [39].

An early example of "multiscale" modeling, in the sense emphasized by the Nobel Prize citation, is the diffusion-collision model for protein folding, which was developed in 1976 by David Weaver and me [40]. It used a coarse-grained description of the protein with helices as the elementary particles, and it showed how the search problem for the native state could be solved by a divide-and-conquer approach. Formulated by Cy Levinthal, the so-called Levinthal Paradox points out that to find the native state by a random search of the astronomically large configuration space of a polypeptide chain would take longer than the age of the earth, while proteins fold experimentally on a timescale of microseconds to seconds. In addition to providing a conceptional answer to the question posed by Levinthal, the diffusion-collision model made possible the estimation of folding rates. The model was ahead of its time because data to test it were not available. Only relatively recently have experimental studies demonstrated that the diffusion-collision model describes the folding mechanism of many helical proteins [41], as well as some others [42].

In the lecture so far, I have focused on the history of molecular dynamics simulations of proteins and the qualitative insights about protein motions that were obtained from them. An essential conclusion from the early work, as already mentioned, is that fluid-like internal motions occur in proteins at room temperature. Like so many things that occur naturally, Nature is likely to have made use of them by evolutionary developments. The importance of the internal motions is encapsulated in the now very well-known statement (Fig. 18): ". . . everything that living things do can be understood in terms of the jigglings and wigglings of atoms" [43]. However, I was amazed when I first found that 2000

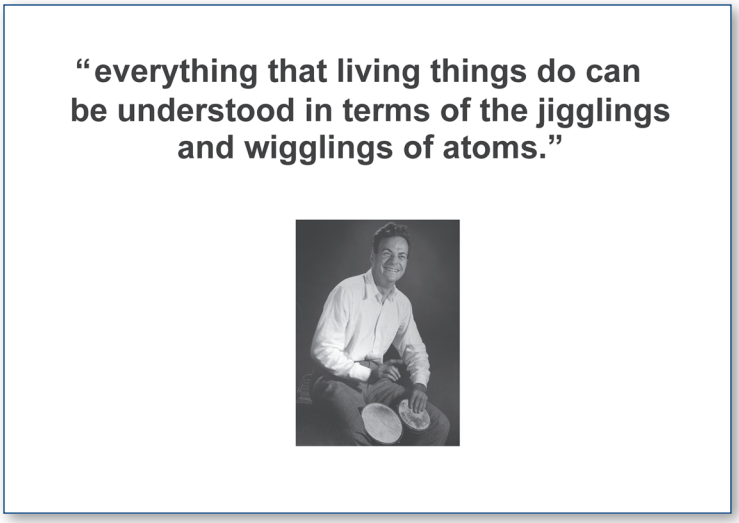


FIGURE 18. Top: Quote from "Feynman Lectures" (see ref. 43); Bottom: Richard Feynman (Nobel Prize in Physics, 1965) playing bongo drums (from http://www.richard-feynman.net/index.htm).

years earlier, a Roman poet, Titus Lucretius, who is known for only one poem, *De Rerum Natura*, made the following statement (Fig. 19):

> 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

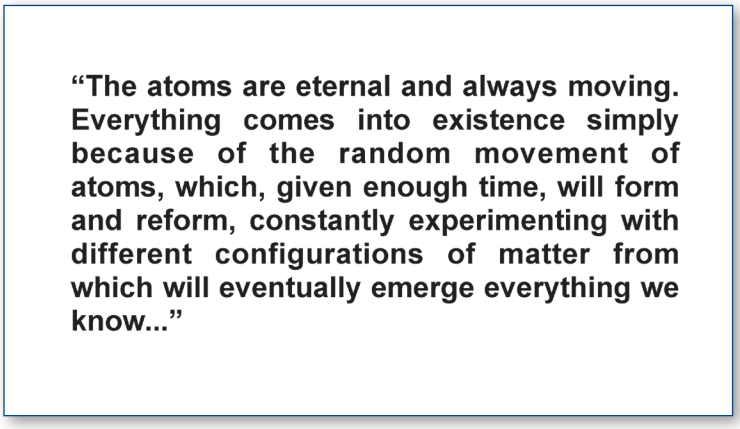


FIGURE 19. A rendition by Stephen Greenblatt of Titus Lucretius "The Way Things Are: De Rerum Natura" (Vol. 1:1023ff), based on the translation of the poem by Martin Ferguson Smith (Hacket Publishing Co., Cambridge, 2001).

with different configurations of matter from which will eventually emerge everything we know . . .

Titus Lucretius based his poem on the detailed atomic theory of matter developed by the Greek philosopher Democritus (about 400 BC). It distinguishes, for example, the bonding between atoms in liquids and solids. The atomic theory of matter apparently was lost for hundreds of years and revived in Europe only in the 1800s by John Dalton.

These quotations raise the question as to how Nature through evolution has developed the structures of proteins so that their "jigglings and wigglings" have a functional role. As Fig. 20 indicates, there are two aspects to this. First, evolution determines the protein structure, which in many cases, though not all, is made up of relatively rigid units that are connected by hinges. They allow the units to move with respect to one another. Second, there is a signal, usually the binding of a ligand, that changes the equilibrium between two structures with the rigid units in different positions.

As an example, I will briefly discuss adenylate kinase, an enzyme which has two major conformations (Fig. 21). Its function is to transfer one phosphate group from adenosine diphosphate (A-P-P) to another A-P-P to produce adenosine triphosphate (A-P-P-P) and adenosine monophosphate (A-P). On the left of the figure is shown the open structure, which permits the substrates to

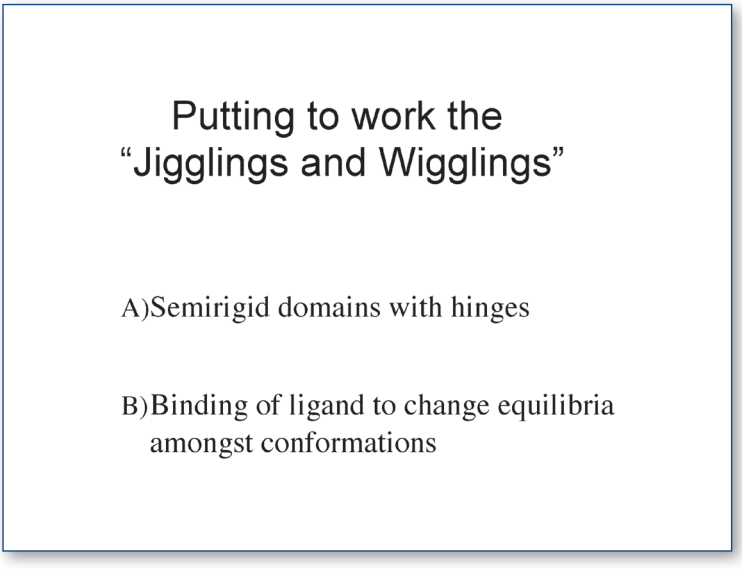
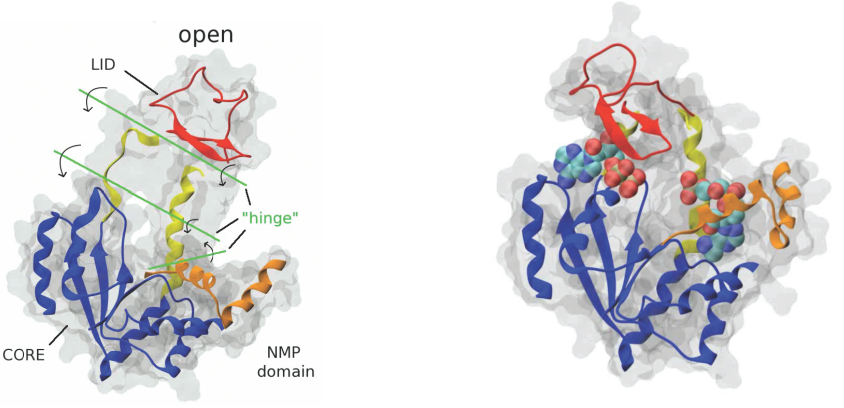


FIGURE 20. How the "Jigglings and Wigglings" in the Feynman quote are used by Nature (as interpreted in this lecture).



$$2A\text{-}P\text{-}P \rightleftharpoons A\text{-}P\text{-}P\text{-}P + A\text{-}P$$

FIGURE 21. Cartoon of Adenylate Kinase. Left: Open structure with no bound substrate showing the hinges; Right: Closed structure with two bound adenosine diphosphates (A-P-P) (prepared by Victor Ovchinnikov with VMD).

come in and the product to go out, and on the right is shown the closed structure. The closed structure creates a reaction "chamber," which is isolated from the solvent and has the catalytic residues in position for the reaction to take place. Figure 22 (top) shows a series of snapshots from a cartoon movie (see Film 3) with the substrate coming in and the enzyme closing; Fig. 22 (bottom) shows the reaction taking place and the enzyme opening up to allow the products to escape.

This type of conformational change occurs in many enzymes as an essential part of their mechanism. Moreover, in adenylate kinase and many other enzymes, the chemistry has been optimized such that it is not the rate-limiting step for the overall reaction [44,45]. Jeremy Knowles [46] has called such enzymes "perfect" since there is no rationale for evolution to further optimize the chemistry when the opening of the enzyme to let the products escape is rate-limiting.

Molecular motors are the prime example of how the "jigglings and wigglings" are put to work to do something that is essential for life (see Fig. 23). My group has studied several different motors, including myosin V [47,48], F_1 ATPase [49,50,51], and kinesin [52,53]. I will talk just about one of them, kinesin, because of its relation to this year's Physiology or Medicine Prize, which was awarded for the "discoveries of machinery regulating vesicle traffic, a major transport system in the cell." The work was concerned with genetic analyses of

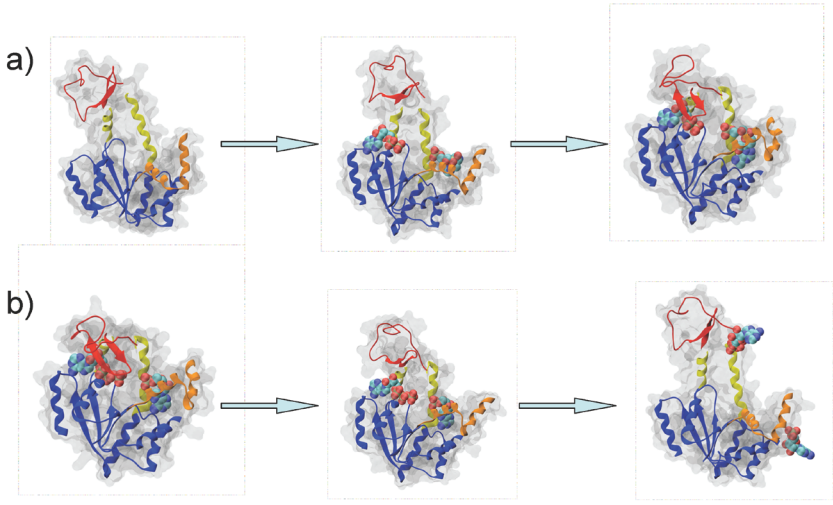


FIGURE 22. Snapshots from Adenylate Kinase film (Film 3). (a) Closing of enzyme as substrates bind; (b) Reaction of substrates and opening for product release (prepared by Victor Ovchinnikov with VMD and FFMPEG).

how vesicles open to discharge their cargo at the right time in the right place. Although not all vesicles need to be moved from one place to another, the kinesins, which were discovered in 1982 in the giant squid axon [54], are very important in the function of many vesicles. The kinesins transport the vesicles large distances along the microtubule cytoskeleton of the cell.

Figure 24 shows a set of snapshots from a film (see Film 4) that illustrates how kinesin functions. The two globular "feet" are visible. Actually there are two molecules, each with a globular foot, and they are joined together by a protein strands one from each molecule (see also Fig. 25), to form a coil-coil at the top of which the vesicle is carried. We know very little about the structure of the vesicles or how they are attached at the top of the coiled-coil. Our research is concerned with understanding the mechanism by which the kinesin dimer walks along the microtubule cytoskeleton. If you look carefully at Film 4, you can see that kinesin walks in the same way as we do: it puts the left foot forward, then the right foot forward, and so on. However, as the film shows the molecules do not walk "normally." The way they walk is like a person who has artificial legs. When you consider the complex muscular and nervous system involved in our walking, how kinesin walks still appears amazing, at least to me.

To understand the walking mechanism, Wonmuk Hwang, Matt Lang and coworkers, and I [52] have been doing molecular dynamics simulations. The

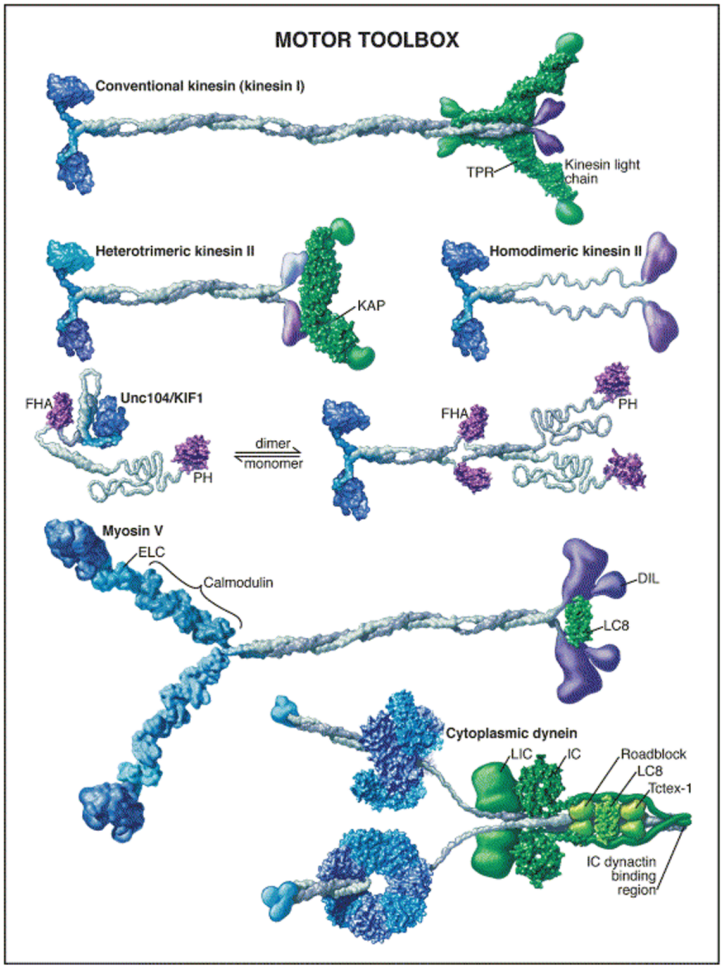


FIGURE 23. Cartoon of different types of molecular motors (see R. D. Vale, *Cell* **112**, 467–480 (2003) for details concerning the image).

snapshots from the film (Fig. 24) show that the molecule ATP and its hydrolysis products, ADP and Pi are involved in the stepping mechanism. It is the binding of ATP that trigger the motion by which the back "foot" is "thrown" forward to take a step on the microtubule. To examine the mechanism in more detail, the X-ray structure of a kinesin dimer shown in Fig. 25 was used as the basis for the simulations [56]. Calculations showed that the β-strand, labeled β_{10} in the figure, which serves as the connector, is not sufficiently rigid to be able to perform the so-called "power stroke," in which the back foot is thrown forward.

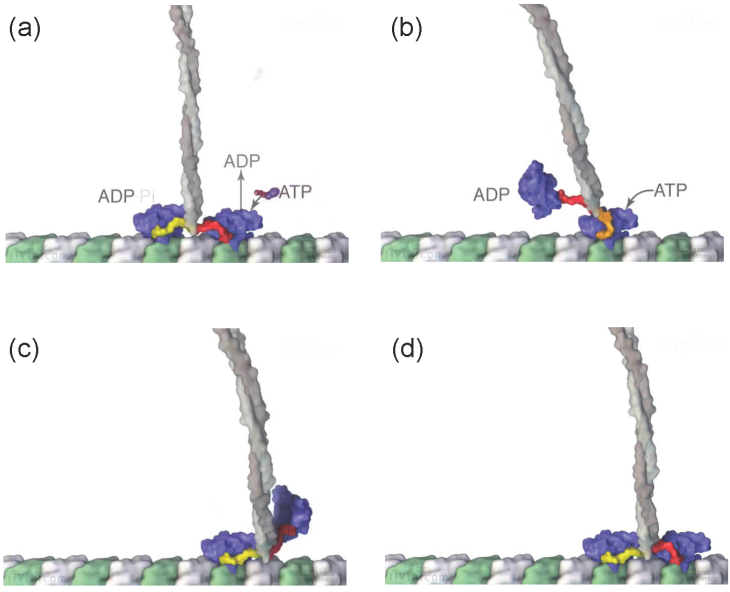


FIGURE 24. Kinesin walking. Snapshots from Film 4 (created by Graham Johnson for R. D. Vale and R. A. Milligan, 2000; see ref. 55). (a) View of two globular domains (the "feet") bound to a microtubule; ADP has been released and ATP is binding to the front foot, triggering the power stroke (see Fig. 26 and text); (b) release of rear foot; (c) partly complete power stroke; (d) completed step.

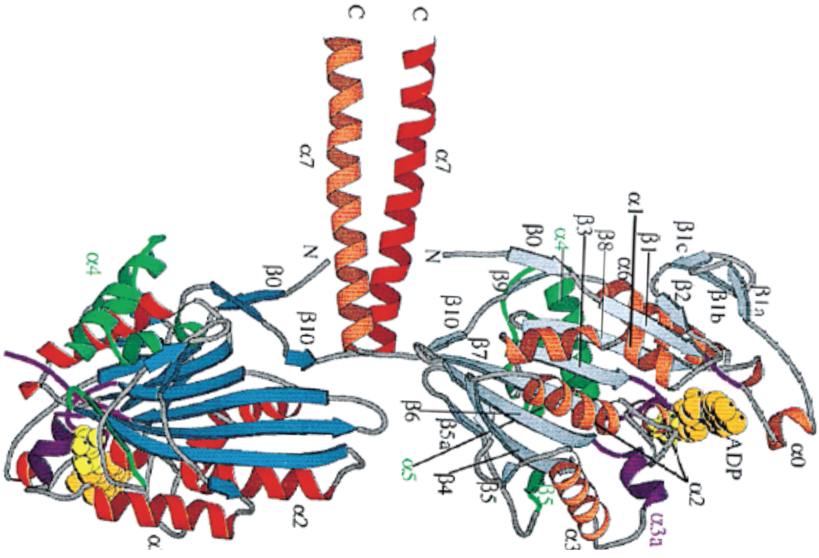


FIGURE 25. X-ray structure of rat brain kinesin dimer. The β10 strand of each monomer connecting to the coiled-coil and the β0 strand which is the CS are evident (from ref. 56).

We noticed that there was another β-strand, labeled β_0, at the N-terminus of the molecule. It is disordered in certain structures, but in others it forms a two-stranded β-sheet with β_{10}. We called β_0 the "cover strand" (CS) and the two-stranded β-sheet, the "cover-neck bundle" (CNB).

Figure 26 shows a pictorial representation of the simulation results. In each of the three diagrams on the left we can see the two feet with a model of the microtubule below. In the top diagram (A) the forward foot has a disordered cover strand in blue. When ATP binds, the simulations show (middle panel (B)) that the two-stranded cover-neck bundle is formed. It looks very much like a spring and appears to be a high-energy construct. Simulations suggest that, in fact, it acts like a spring with a forward bias that generates the power stroke by propelling the back foot forward (bottom panel (C)) in readiness for the next step.

To test the model based on the simulations, optical trapping experiments in the presence of an external force were performed for a wild-type kinesin and

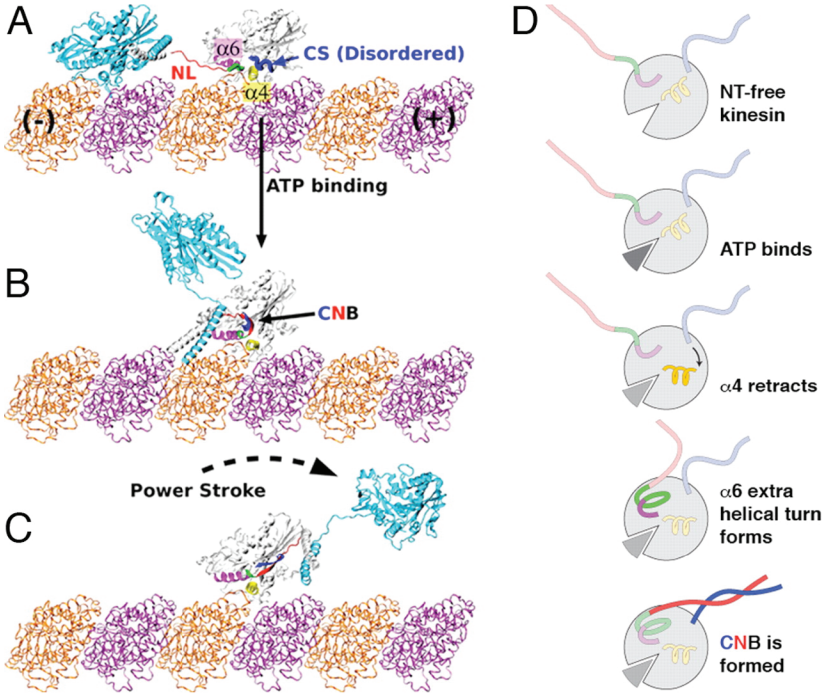


FIGURE 26. Schematic representation of the generation of the power stroke based on the simulations. (A) Before ATP binding; (B) After ATP binding; (C) Power stroke; (D) Diagram highlighting the major molecular events leading to CNB formation and the power stroke (see ref. 53 and text).

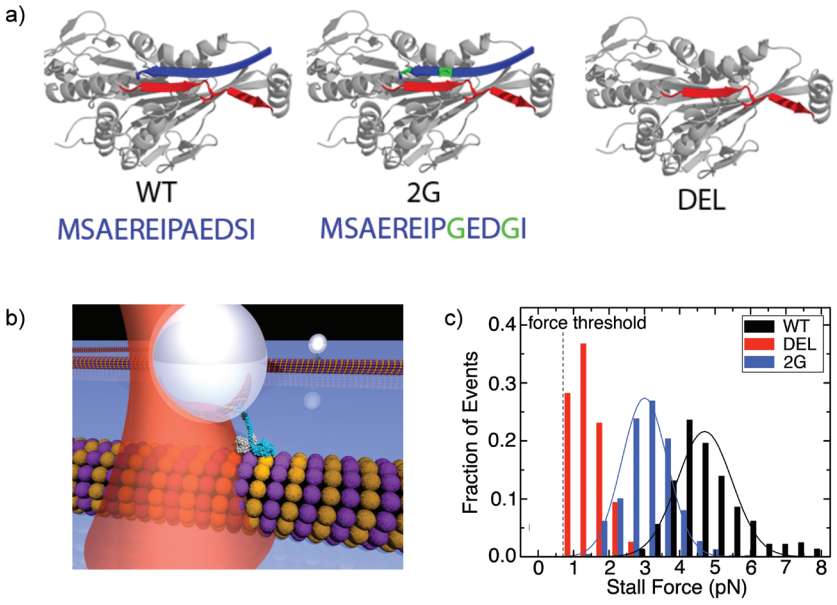


FIGURE 27. Mutant Data for Testing the Power Stroke Mechanism (from ref. 53).

for two mutants [53]. One set of mutations introduced two glycines (G2), which are expected to make the CNB more flexible and the other completely deleted the cover strand (DEL) (Fig. 27a). Figure 27b shows a cartoon of the experiment. Figure 27c presents one set of results, namely the decrease of the stall force required for the G2 mutant and the almost zero stall force required for DEL, which appears at best to "limp" along the microtubule; more details of the experimental studies that support the CNB model are described separately [53]. Additional simulations are in progress to increase our understanding of how kinesins function. An essential element that is being investigated concerns the role of the interactions between kinesin and the microtubule in the walking mechanism.

Kinesin motors, like other molecular motors, are very important in making life possible [57]. As indicated in Fig. 28, mitosis and cell division are inhibited when kinesins do not function due to deleterious mutations. Their importance in cell division makes them a target for cancer chemotherapy. Kinesins are also essential for axonal transport where material has to be delivered over long distances. Some viruses have learned that if they attach themselves to kinesins where the normal cargo would be located, they are transported along the

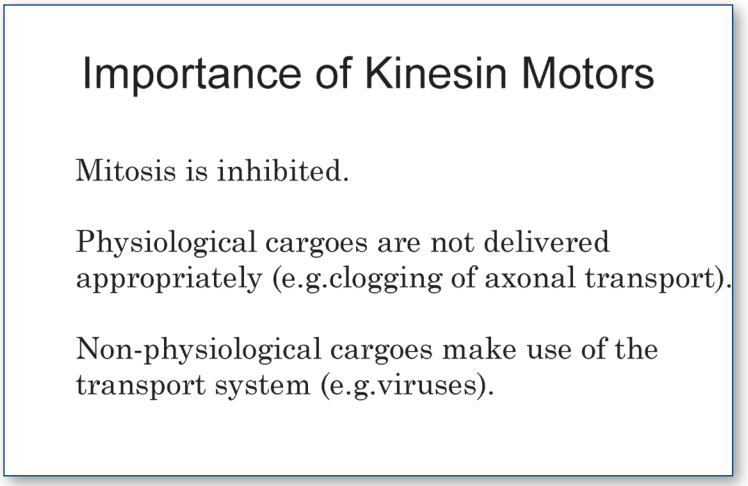


FIGURE 28. Importance of Kinesin Motors.

microtubules from one part of the cell to another in a few minutes instead of the ten or so hours that would be required by diffusion in the complex cellular medium.

What does the future hold (Fig. 29)? All of us know that real predictions are hard, so I have included relatively conservative ones in the figure. The first, which was mentioned in the introduction, has been a dream of mine since I began to do biomolecular simulations. It is not that simulations can replace all experiments, as the Nobel press announcement seems to imply, but rather that experimentalists would use simulations as a tool like any other (such as X-rays or NMR) in their work to get a better understanding than they could derive from either experiments or simulations alone. That experimentalists are beginning to employ simulations in this way is evidenced by the literature [58]. The respectability for molecular dynamics simulations provided by the Nobel Prize is likely to increase their utilization by the scientific community.

In terms of actual simulations, people are studying more complicated systems. They are beginning to use molecular dynamics simulations for viruses, ribosomes, and even cells so as to gain insights into how they function. If I were thirty years younger I would be simulating the brain. About twenty years ago, I spent a couple of years learning what was known about the brain and concluded that not enough data were available to permit me to contribute significantly by making studies on the molecular level. I do not regret the time spent in this way since I learned much of interest and my research group continued to focus on problems that we could solve. Our knowledge of the brain has increased

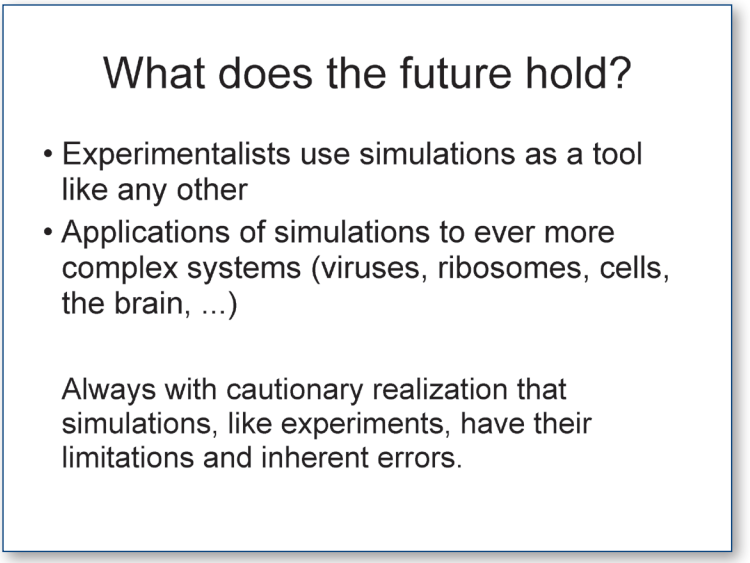


FIGURE 29. Future of Molecular Dynamics Simulations.

sufficiently that I would now urge young scientists to work at this exciting frontier, which is beginning to be probed by initiatives in both Europe and America.

However bright the future, I want to caution the audience (as I always do with my students) that simulations have limitations, just as do experiments. In particular, when you appear to have discovered something new and exciting, you should be doubly careful to make certain that there is no mistake in what you have done. Moreover, the example of my exploration of brain research permits me to make an important point. In working at the interface of chemistry and biology with simulation techniques, it is essential to realize that of the many exciting systems that are being studied experimentally, only relatively few pose questions for which molecular dynamics simulations can provide useful insights at their present stage of development.

Figure 30 lists the people to whom this lecture is dedicated. They are the Karplusians: 244 people who have worked in my "laboratory" in Illinois, Columbia, Harvard, Paris and Strasbourg. Without them, I would not be here today. Over the last forty years, many of them have contributed to the methodology and applications of molecular dynamics simulations. In writing this, I find it curious that molecular dynamics simulations were not mentioned in the description of the "Scientific Background" of the Nobel Prize. The large community involved in molecular dynamics simulations, which includes all of this year's Nobel Laureates in Chemistry, has transformed the field from an esoteric subject of interest

Karplusian: 1955–2013

Ivana Adamovic
Yuri Alexeev
David H. Anderson
Ioan Andricioaei
Yasuhide Arata
Georgios Archontis
Gabriel G. Balint-Kurti
Christian Bartels
Paul Bash
Donald Bashford
Mark Bathe
Oren M. Becker
Robert Best
Anton Beyer
Robert Birge
Ryan Bitetti-Putzer
Arnaud Blondel
Stefan Boresch
John Brady
Bernard Brooks
Charles L. Brooks III
Thomas H. Brown
Robert E. Bruccoleri
Paul W. Brumer
Axel T. Brünger
Rafael P. Brüschweiler
Matthias Buck
Amedeo Caflisch
William J. Campion
William Carlson
David A. Case
Leo Caves
Thomas C. Caves
Marco Cecchini
John-Marc Chandonia
Ta-Yuan Chang
Xavier Chapuisat
Sergei Chekmarev
Rob D. Coalson
François Colonna-Cesari
Michael R. Cook

Qiang Cui
Tara Prasad Das
Annick Dejaegere
Philippe Derreumaux
Aaron Dinner
Uri Dinur
Roland L. Dunbrack, Jr.
Chizuko Dutta
Nader Dutta
Claus Ehrhardt
Ron Elber
Marcus Elstner
Byung Chan Eu
Jeffrey Evanseck
Erik Evensen
Jeffrey Evenson
Thomas C. Farrar
Martin J. Field
Stefan Fischer
David L. Freeman
Thomas Frimurer
Kevin Gaffney
Jiali Gao
Yi Qin Gao
Bruce Gelin
R. Benny Gerber
Paula M. Getzin
Debra A. Giammona
Martin Godfrey
Andrei Golosov
David M. Grant
Daniel Grell
Peter Grootenhuis
Hong Guo
Ogan Gurel
Robert Harris
Karen Haydock
Russell J. Hemley
Jeffrey C. Hoch
Milan Hodoscek
Gary G. Hoffman

L. Howard Holley
Barry Honig
Victor Hruby
Rod E. Hubbard
Robert P. Hurst
Vincent B.-H. Huynh
Toshiko Ichiye
K. K. Irikura
Alfonso Jaramillo
Tom Jordan
Diane Joseph-McCarthy
Sun-Hee Jung
C. William Kern
William Kirchhoff
Burton S. Kleinman
Gearld W. Koeppl
H. Jerrold Kolker
Yifei Kong
Lewis M. Koppel
J. Kottalam
Felix Koziol
Christoph Kratky
Sergei Krivov
Olga Kuchment
Krzysztof Kuczera
John Kuriyan
Joseph N. Kushick
Peter W. Langhoff
Antonio C. Lasaga
Frankie T. K. Lau
Themis Lazaridis
Fabrice LeClerc
Angel Wai-mun Lee
Irwin Lee
Sangyoub Lee
Ming Lei
Ronald M. Levy
Xiaoling Liang
Carmay Lim
Xabier Lopez
Guobin Luo

Paul D. Lyne
Jianpeng Ma
Alexander D. MacKerell, Jr.
Christoph Maerker
Paul Maragkakis
Marc Martí-Renom
Jean-Louis Martin
Carla Mattos
J. Andrew McCammon
H. Keith McDowell
Jorge A. Medrano
Morten Meeg
Marcus Meuwly
Olivier Michielin
Stephen Michnick
Fredrick L. Minn
Andrew Miranker
Keiji Morokuma
A. Mukherji
Adrian Mulholland
David Munch
Petra Munih
Robert Nagle
Setsuko Nakagawa
Kwango Nam
Eyal Neria
John-Thomas C. Ngo
Lennart Nilsson
Dzung Nguyen
Iwao Ohmine
Barry Olafson
Kenneth W. Olsen
Neil Ostlund
Victor Ovchinnikov
Emanuele Paci
Yuh-Kang Pan
C.S. Pangali
Richard W. Pastor
Lee Pedersen
David Perahia
Robert Petrella

B. Montgomery Pettitt
Ulrich Pezzeca
Richard N. Porter
Jay M. Portnow
Carol B. Post
Lawrence R. Pratt
Martine Prévost
Blaise Prod'hom
Jingzhi Pu
Dagnija Lazdins Purins
Lionel M. Raff
Mario Raimondi
Francesco Rao
Gene P. Reck
Swarna Yeturu Reddy
Walter E. Reiher III
Nathalie Reuter
Bruno Robert
Peter J. Rossky
Benoît Roux
Andrej Sali
Daniel Saltzberg
Michael Schaefer
Michael Schlenkrich
David M. Schrader
John C. Schug
Klaus Schulten
Eugene Shakhnovich
Moshe Shapiro
Ramesh D. Sharma
Isaiah Shavitt
Henry H.-L. Shih
Bernard Shizgal
David M. Silver
Manuel Simoes
Balvinder Singh
Jeremy Smith
Sung-Sau So
Michael Sommer
Ojars J. Sovers
Martin Spichty

David J. States
Richard M. Stevens
Roland Stote
John Straub
Collin Stultz
Neena Summers
Henry Suzukawa
S. Swaminathan
Attila L. Szabo
Antoine Taly
Kwong-Tin Tang
Bruce Tidor
Hideaki Umeyama
Arjan van der Vaart
Wilfred van Gunsteren
Herman van Vlijmen
Michele Vendruscuolo
Dennis Vitkup
Mark Wagman
Shunzhou Wan
Iris Shih-Yung Wang
Ariel Warshel
Masakatsu Watanabe
Kimberly Watson
David Weaver
Paul Weiner
Michael A. Weiss
Joanna Wiórkiewicz-K.
George Wolken
Youngdo Won
Yudong Wu
Robert E. Wyatt
Wei Yang
Robert Yelle
Darrin York
Hsiang-ai Yu
Guishan Zheng
Yaoqi Zhou
Vincent Zoete

FIGURE 30. List of Karplusians (2013). These are collaborators who have worked with me in Illinois, Columbia, Harvard, Paris, and Strasbourg.

to only a small group of specialists into a central element of modern chemistry and structural biology. Without molecular dynamics simulations and their explosive development, no Nobel Prize would have been awarded in this area.

There is perhaps a parallel here between the fact that molecular dynamics was not mentioned in the Nobel Prize citation and the citation for Einstein's Nobel Prize in Physics (1921). He was awarded the Nobel Prize for the theory of the photoelectric effect and not for his most important work, the general theory of relativity, which had already been verified by experiment and was the origin of his worldwide fame as a scientist. Interestingly, when he gave his Nobel Lecture, it was on relativity, even though he knew that he was supposed to talk about the photoelectric effect. Correspondingly, I traced the history of molecular dynamics simulations and their development in my lecture and did not emphasize the development of potential functions for simulations, the focus of the Chemistry Nobel Prize citation. The complex deliberations of the Physics Committee

in reaching its decision concerning Einstein's Nobel Prize are now known because his prize was awarded more than fifty years ago [59]. The public will again have to wait fifty years to find out what motivated the Chemistry Committee in awarding this year's Nobel Prize.

I very much want to mention one other person, my wife Marci, who was willing to live with me, someone "who spent all his time working," in her words. Even more than just living with me, she was brave enough to be my laboratory administrator. Among many aspects of our life, it made possible our working in both the U.S. and France over many years. Moreover, in preparing to come to Stockholm, the complexity of arranging to be in the right place at the right time would have been overwhelming if she had not been there to take care of what was needed.

REFERENCES

1. P. A. M. Dirac, *Proc. Royal Soc. of London*, Series A **123**, 714–733 (1929).
2. N. L. Allinger, M. A. Miller, L. W. Chow, R. A. Ford and J. C. Graham, *J. Amer. Chem. Soc.* **87**, 3430 (1965).
3. G. Némethy and H. Scheraga, *Biopolymers* 4, **155** (1965)
4. S. Lifson and A. Warshel, *J. Chem. Phys.* **49**, 5116 (1968)
5. R. N. Porter and M. Karplus, *J. Chem. Phys.* **40**, 1105–1115 (1964).
6. P. Siegbahn and B. Liu, *J. Chem. Phys.* **68**, 2457 (1978).
7. G. C. Schatz, *Theor. Chem. Acc.* **103**, 270–272 (2000).
8. M. Karplus, R. N. Porter, and R. D. Sharma, *J. Chem. Phys.* **45**, 3871–3873 (1966).
9. A. Farkas and L. Farkas, *Proc. Roy. Soc. (London)* **A152**, 124 (1935).
10. S. Datz and E. H. Taylor, *J. Chem. Phys.* **39**, 1896 (1963).
11. A. Kuppermann and G. C. Schatz, *J. Chem. Phys.* **62**, 2502 (1975).
12. A. B. Elkowitz and R. E. Wyatt, *J. Chem. Phys.* **62**, 2504 (1975).
13. M. Garcia-Viloca, J. Gao, M. Karplus, and D. G. Truhlar, *Science* **303**, 186–195 (2004).
14. R. Hubbard and G. Wald in "Structural implications of reaction kinetics," in *Structural Chemistry and Molecular Biology: a Volume dedicated to Linus Pauling by his Students, Colleagues, and Friends*, ed. A. Rich, N. Davidson, pp. 837–47. San Francisco: Freeman
15. B. Honig and M. Karplus, *Nature* **229**, 558–560 (1971).
16. R. Gilardi, I.L. Karle, J. Karle, W. Sperling, *Nature* **232**, 187–189 (1971).
17. B. Honig, A. Warshel, and M. Karplus, *Acc. Chem. Res.* **8**, 92–100 (1975).
18. A. Warshel and M. Karplus, *J. Am. Chem. Soc.* **94**, 5612–5625 (1972).
19. A. Warshel and M. Karplus, *Chem. Phys. Letters* **32**, 11–17 (1975).
20. A. Warshel, *Nature* **260**, 679–683 (1976).
21. V. R. I. Kaila, R. Send, and D. Sundholm, *J. Phys. Chem. B* **116**, 2249–2258 (2012).
22. J. Deisenhofer and W. Steigemann, *Acta Crystallogr. B* **31**:238–250 (1975).
23. J. A. McCammon, B. R. Gelin, and M. Karplus, *Nature* **267**, 585–590 (1977).

24. B. R. Gelin and M. Karplus, *Proc. Natl. Acad. Sci. USA* **72**, 2002–2006 (1975).
25. A. Rahman, *Phys. Rev.* **136**:A405–11 (1964).
26. F. H. Stillinger and A. Rahman, *J. Chem. Phys.* **60**:1545–1557 (1974).
27. D. C. Phillips, in *Biomolecular Stereodynamics*, II, R. H. Sarma, ed. (Adenine Press, Guilderland, New York 1981), p. 497.
28. The Computer World Information Technology Foundation, Oral History Collection Archives, 1995.
29. P. J. Rossky, M. Karplus, and A. Rahman, *Biopolymers* **18**, 825–854 (1979).
30. P. J. Rossky and M. Karplus, *J. Am. Chem. Soc.* **101**, 1913–1937 (1979).
31. M. Levitt and R. Sharon, *Proc. Natl. Acad. Sci. USA* **85**, 7557–7561 (1988).
32. D. Vitkup, D. Ringe, G. A. Petsko, and M. Karplus, *Nature Struc. Biol.* **7**, 34–38 (2000).
33. A. L. Tournier, J. C. Xu, and J. C. Smith, *Biophys. J.* **85**, 1871–1875 (2003).
34. D. E. Shaw, P. Maragakis, K. Lindorff-Larsen, et al., *Science* **330**, 341–346 (2010).
35. W. Yang, R. Bitetti-Putzer, and M. Karplus, *J. Chem. Phys.* **120**, 2618–2628 (2004).
36. C. M. Dobson, A. Sali, and M. Karplus, *Angew. Chem. Int. Ed.* **37**, 868–893 (1998).
37. K. Lindorff-Larsen, S. Piana, R. O. Dror, and D. E. Shaw, *Science* **334**, 517–520 (2011).
38. M. Levitt and A. Warshel, *Nature* **253**, 694 (1975).
39. J. C. Smith and B. Roux, *Structure* **21**, 2102–2105 (2013).
40. M. Karplus and D. L. Weaver, *Nature* **260**, 404–406 (1976).
41. M. Karplus and D. L. Weaver, *Biopolymers* **18**, 1421–1437 (1979).
42. M. Karplus and D. L. Weaver, *Protein Science* **3**, 650–668 (1994).
43. R. P. Feynman, R. B. Leighton, and M. Sands (1963), *The Feynman Lectures in Physics* (Addison-Wesley, Reading), Vol. I, Chapter 3.
44. K. A. Henzler-Wildman, V.Thai, M. Lei, M. Ott, M. Wolf-Watz, T. Fenn, E. Pozharski, M. A. Wilson, G. A. Petsko, M. Karplus, C. G. Hübner, and D. Kern, *Nature* **450**, 838–844 (2007).
45. K. A. Henzler-Wildman, M. Lei, V. Thai, S. J. Kerns, M. Karplus, and D. Kern, *Nature* **450**, 913–916 (2007).
46. A. L. Wendell, R. J. Raines, and J. R. Knowles, *Biochemistry* **27**, 1158–1167 (1988).
47. M. Cecchini, A. Houdusse, and M. Karplus, *PLoS Computational Biology* **4**, e1000129:1–19 (2008).
48. V. Ovchinnikov, B. L. Trout, and M. Karplus, *J. Mol. Biol.* **395**, 815–833 2010).
49. W. Yang, Y. Q. Gao, Q. Cui, J. Ma, and M. Karplus, *Proc. Natl. Acad. Sci. USA* **100**, 874–879 (2003).
50. Y. Q. Gao, W. Yang, and M. Karplus, *Cell* **123**, 195–205 (2005).
51. J. Pu and M. Karplus, *Proc. Natl. Acad. Sci. USA* **105**, 1192–1197 (2008).
52. W. Hwang, S. Zhang, R. D. Kamm, and M. Karplus, *Proc. Natl. Acad. Sci. USA* **101**, 12916–12921 (2004).
53. A. S. Khalil, D. C. Appleyard, A. K. Labno, A. Georges, M. Karplus, A. M. Belcher, W. Hwang, and M. J. Lang, *Proc. Natl. Acad. Sci. USA* **105**, 19246–19251 (2008).
54. S. T. Brady, R. J. Lasek, and R. D. Allen, *Science* **218**, 1129–1131 (1982).
55. R. D. Vale and R. A. Milligan, *Science* **288**, 88–95 (2000).
56. F. Kozielsky, S. Sack, A. Marx, et *Cell* **91**, 985–994 (1997).

57. E. Mandelkow and E. M. Mandelkow, *Trends in Cell Biology* **12**, 585–591 (2002).
58. M. A. Young, S. Gonfloni, G. Superti-Furga, B. Roux, and J. Kuriyan *Cell* **105**, 115–126 (2001).
59. M. Friedman, *The Politics of Excellence*, Chapter 7 (Henry Holt and Company, New York, 2001).

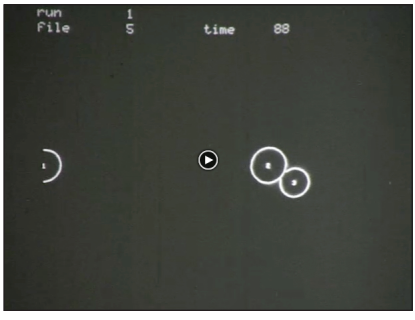
Portrait photo of Martin Karplus by photographer Alexander Mahmoud.

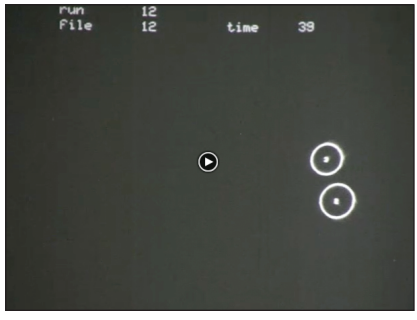
APPENDIX: BACKGROUND OF FILMS

The film shows two trajectories, the first reactive (Film 1a) and the second non-reactive (Film 1b). In the non-reactive trajectory, it is evident that one of the atoms in the molecule comes out in front of the plane of the reaction and the other goes into the back of the plane. This is done by introducing perspective; i.e., by having an atom grow larger as it comes forward toward you and become smaller as it goes away from you.

In making the film, a question arose as to how to represent the perspective. If the radius of the atomic circles was varied linearly with the distance in front or in back, the perspective was difficult to perceive. So we had to find a better way of showing the perspective.

What I did was to look at the paintings of Canaletto in visits to Venice, and compare the actual distances with how he presented them in his paintings. I found that he seemed to use an approximate exponential law, E αR, where R is the distance out of the plane and α is a coefficient, whose value I do not remember. If I had published this result (There are many things that I did, which were not published.) perhaps there would be a Karplus Law in art theory, as well as the Karplus Equation in nuclear magnetic resonance.



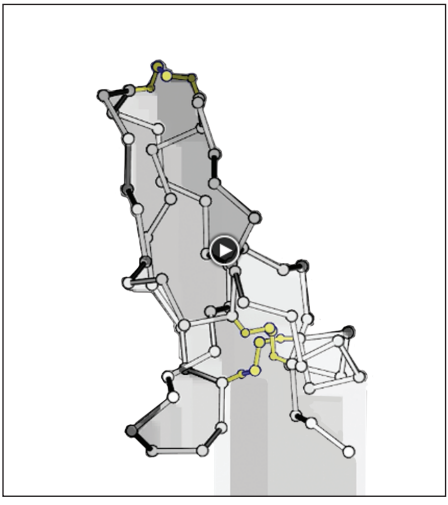


See Nobelprize.org for the films.

FILM 1a AND 1b. $H+H_2$ Collisions

It is also worth remembering the film is of historical interest for several reasons. Made in 1967, it is the first film to show pictorially the results of an accurate calculation of the motions of the atoms involved in a chemical reaction. The film was made in the laboratory of Professor Sutherland, who was developing the first computer ray-graphics machine. It was a prototype of the devices now manufactured by Evans and Sutherland, which are used, for example, for air traffic control.

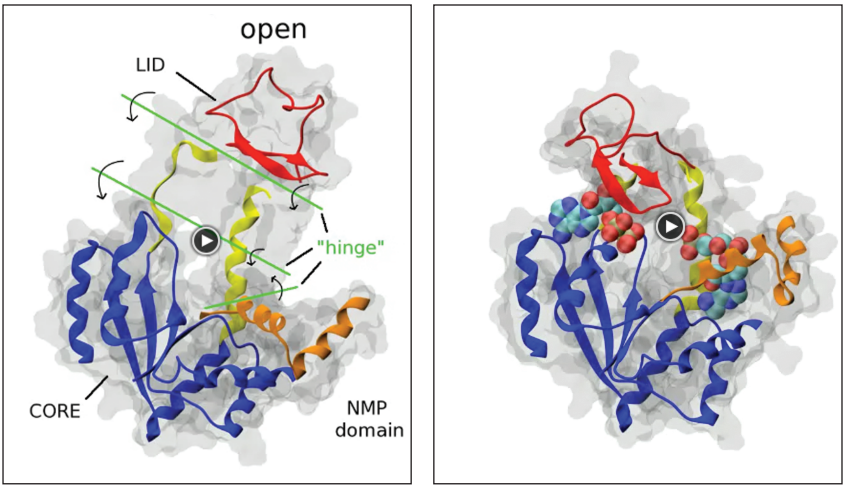
The film shows the dynamics of BPTI over about 10 ps, in correspondence with Fig. 14. The film was made by Victor Ovchinnikov with FFMPEG based on the images drawn with VMD.



See Nobelprize.org for the film.

FILM 2. BPTI Dynamics

Film 3a shows the closing of adenylate kinase by the hinge-bending motions as the two A-P-P substrates bind, and Film 3b shows the reaction to form A-P-P-P and A-P in the closed molecule followed by opening through hinge-bending motions as the products escape. The film was made by Victor Ovchinnikov with FFMPEG using images prepared with VMD.



See Nobelprize.org for the films.

FILM 3a AND 3b. Cartoon: Adenylate Kinase Dynamics

The film shows kinesin taking several steps on the microtubule (see Fig. 24 and text). It was made by the group of R. D. Vale and R. A. Milligan [55].

See Nobelprize.org for the film.

FILM 4. Cartoon: Kinesin Walking on Microtubules