

# BIRTH & FUTURE OF MULTI-SCALE MODELING OF MACROMOLECULES

Nobel Lectures, Stockholm

8 December 2013

Michael Levitt

Structural Biology & Computer Science  
Stanford

<http://csb.stanford.edu/levitt>

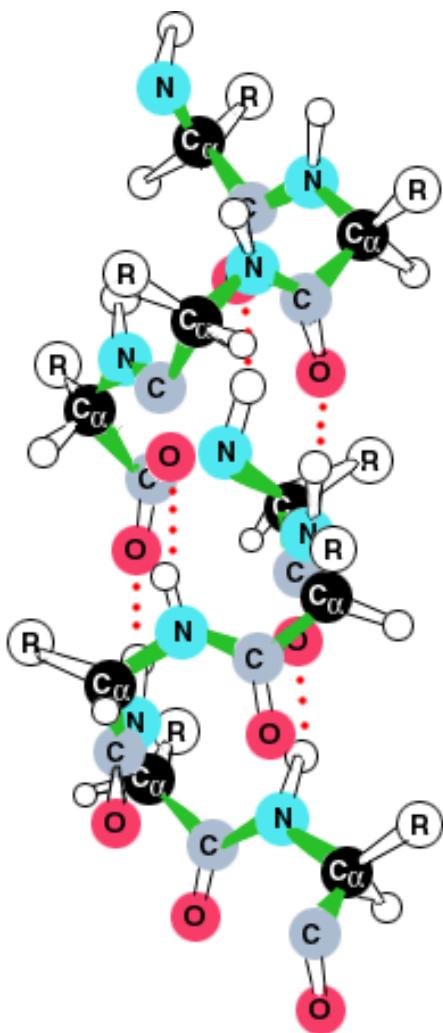
# SUMMARY

- 1. How It All Began.
- 2. Birth of Computational Structural Biology.
- 3. Future: Multi-Scale Dynamics of Huge Systems.
- 4. Some General Thoughts.

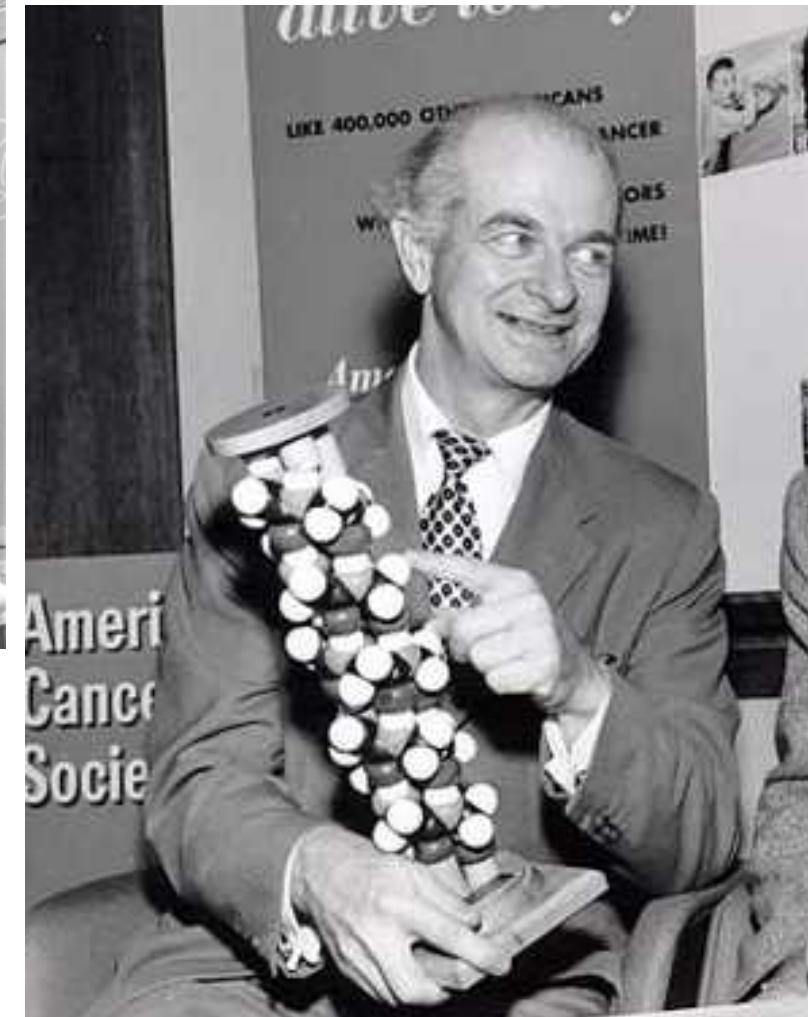
1. HOW IT  
ALL BEGAN

STAND ON THE  
SHOULDERS OF  
GIANTS

# 1951: PAULING THE GREAT CHEMIST



1951  
The alpha-helix



1901–1994

# 1953: FRANCIS CRICK

No. 4356 April 25, 1953

NATURE

737

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

- <sup>1</sup> Young, F. B., Gerard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).
- <sup>2</sup> Longuet-Higgins, M. S., *Mon. Not. Roy. Astr. Soc., Geophys. Suppl.*, **5**, 285 (1949).
- <sup>3</sup> Von Arx, W. S., Woods Hole Paper in Phys., Oceanog., Meteor., **11** (3) (1960).
- <sup>4</sup> Elman, V. W., *Arkiv. Mat. Astron. Fysik* (Stockholm), **2** (11) (1965).

## MOLECULAR STRUCTURE OF NUCLEIC ACIDS

### A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey<sup>1</sup>. They kindly made their manuscript available to us in advance publication. Their model consists of three interwoven chains, with the phosphates near the axis, and the bases on the outside. In our opinion this structure is unsatisfactory for two reasons: (1) We believe that the material which gives X-ray diagrams is the salt, not the free acid. With the acidic hydrogen atoms it is not clear what force would hold the structure together, especially as negatively charged phosphates near the axis repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate ester groups joining  $\beta$ -D-deoxyfuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's<sup>2</sup> model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the bases near it is close to P<sub>1</sub>' standard configuration, the sugar being roughly perpendicular to the attached base.

This figure is purely diagrammatic. The two ribbons symbolize the two phosphate ester chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis.

is a residue on each chain every 3.4 Å. in the  $\alpha$ -direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 Å. The distance of a phosphorus atom from the fibre axis is 10 Å. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the

738

NATURE

April 25, 1953 VOL 171

King's College, London. One of us (J.D.W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

J. D. WATSON  
F. H. C. CRICK

Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge.

April 2.

<sup>1</sup> Pauling, L., and Corey, R. B., *Nature*, **171**, 348 (1953); *Proc. U.S. Natl. Acad. Sci.*, **38**, 84 (1952).

<sup>2</sup> Furberg, B., *Acta Chem. Scand.*, **6**, 634 (1952).

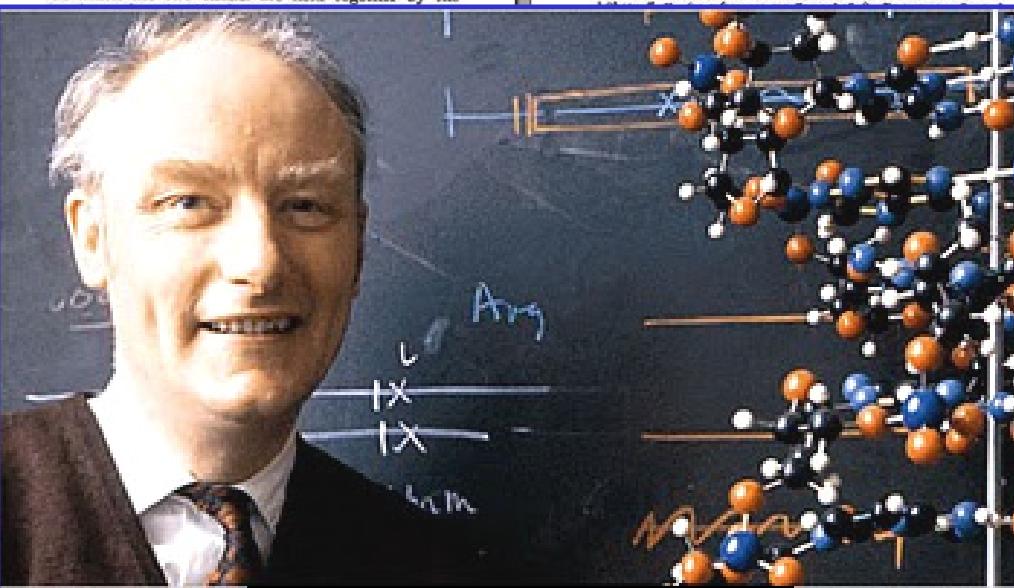


Fig. 1. Fibre diagram of deoxypentose nucleic acid from *E. coli*. Fibre axis vertical.

innermost maxima of each Bessel function and the origin. The angle this line makes with the equator is roughly equal to the angle between an element of the helix and the helix axis. If a unit repeats  $n$  times along the helix there will be a meridional reflexion ( $n$ ) on the  $n$ th layer line. The helical configuration induces side bands on this fundamental frequency, the effect being to reinforce the intensity distribution about the origin around the new origin, on the  $n$ th layer line, corresponding to  $C$  in Fig. 2. We will now briefly analyse in physical terms some of the effects of the shape and size of the repeat unit nucleotide on the diffraction pattern. First, if the nucleotide consists of a unit having circular symmetry about an axis parallel to the helix axis, the whole fraction pattern is modified by the form factor of a nucleotide. Second, if the nucleotide consists of a series of points on a radius at right-angles to the fibre axis, the phases of radiation scattered by the series of different diameters passing through each point are the same. Summation of the corresponding spherical functions gives reinforcement for the inner-

1916-2004

ribose nucleic acid are in agreement with ours. So far as compatible with the experiments, we can regard this as unproven, against more exact results in the following communication of the details of the results of the research group who devised our structure, which rests mainly on published experimental data and stereochemical arguments.

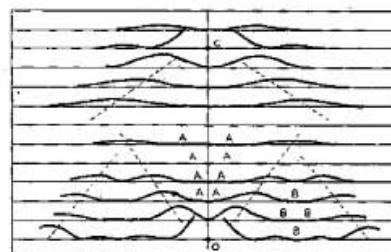
It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published

as a fibre diagram as shown in Fig. 1. Astbury suggested that the meridional reflexions corresponded to the intersections of the fibre axis. The ~34 Å. period is not due to a repetition of a unit, but to the chain conformation, which causes strong diffraction as the nucleotides have higher density than the interstitial water. The absence of reflexions on or near the meridian immediately suggests a helical structure with axis parallel to fibre length.

### Diffraction by Helices

It may be shown<sup>3</sup> (also Stokes, unpublished) that the intensity distribution in the diffraction pattern of a series of points equally spaced along a helix is



3. Diffraction pattern of system of helices corresponding to structure of deoxypentose nucleic acid. The squares of Bessel functions are plotted about 0 on the equator and on the first, third and fifth layer lines for half of the nucleotide mass (10 Å. diameter) and the remainder distributed along a radius, the total a given section being proportional to the square of the radius. The layer lines similar functions are plotted for an outer diameter of 12 Å.

## DNA Model and Experiment

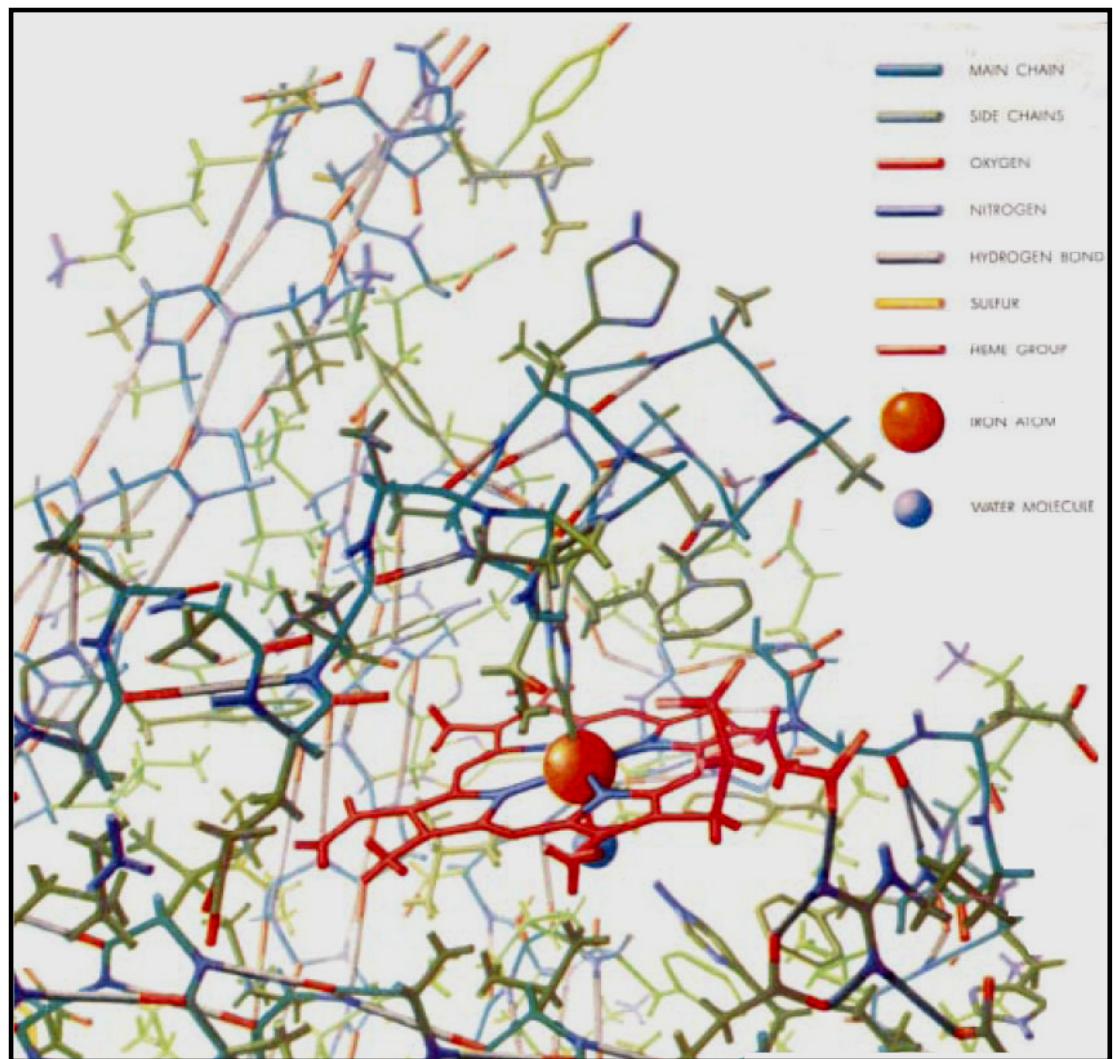
# 1959: KENDREW AND MYOGLOBIN



1917–1997

First protein X-ray  
structure.

Scientific American 1961

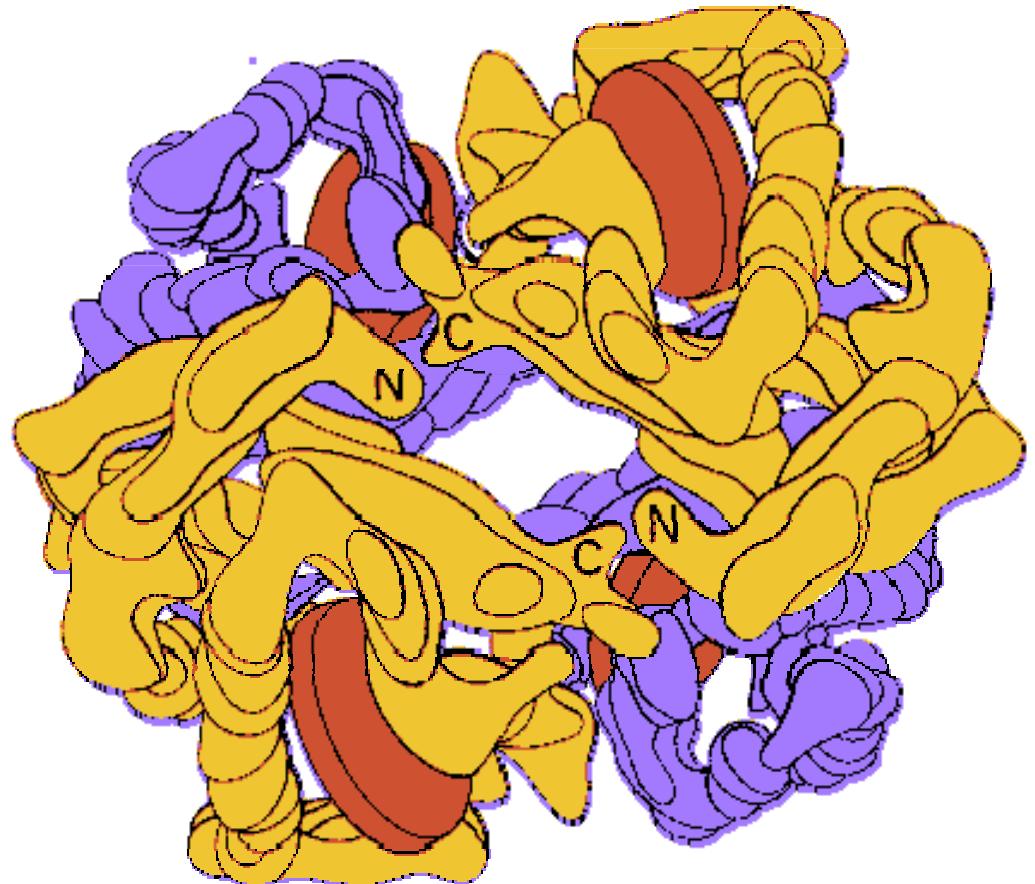


Painted by artist Irving Geis

# 1962: PERUTZ AND HEMOGLOBIN



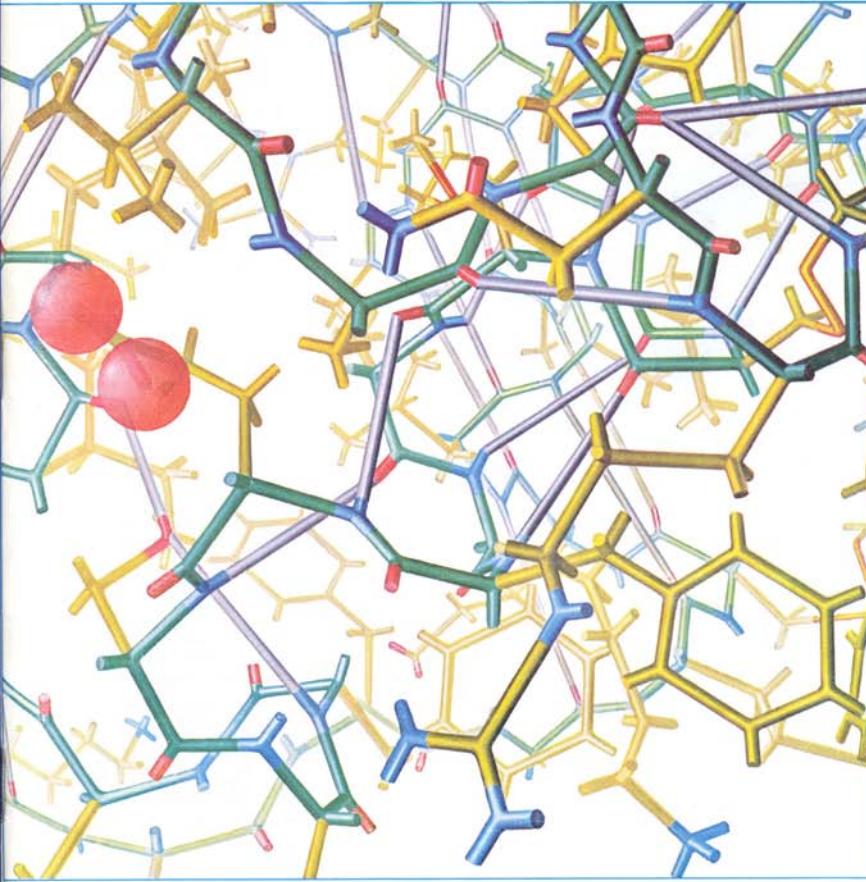
1914-2002



The REAL HERO of  
structural biology.

# 1965: PHILLIPS AND LYSOZYME

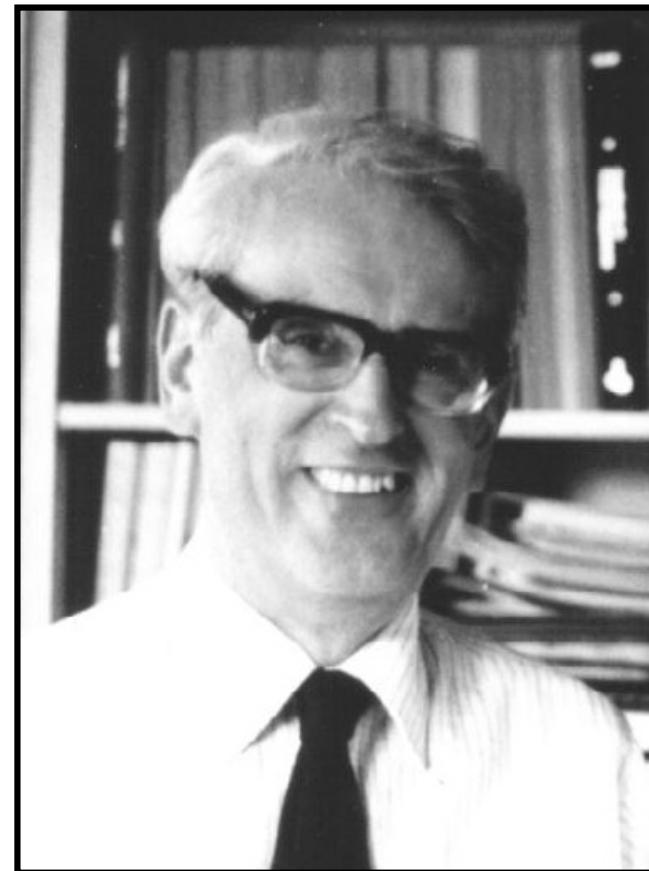
SCIENTIFIC AMERICAN



ENZYME MOLECULE

SIXTY CENTS

November 1966



1924–1999

Early supporter of  
Computational Biology

# 1943-1945: LOS ALAMOS



When any sufficiently large nuclear explosion occurs within a container, unless the radioactive material is properly contained and the timing of triggering explosions perfect, neutrons stream out of one side of the container. This leak causes an asymmetrical, much weaker, and more unpredictable blast. In order to make the most potent blast possible, a series of complex events must be modeled so that the radioactive material explodes symmetrically. This research appears under the hygienic guise of solving the "neutron diffusion problem." Until 1943, when von Neumann and Stanley Ulam worked on the neutron diffusion problem, there were essentially only two sorts of modeling employed by scientists and mathematicians to describe complex events: deterministic methods (which are essentially applied mathematics) and variations on stochastic techniques (which were known simply as simulation).

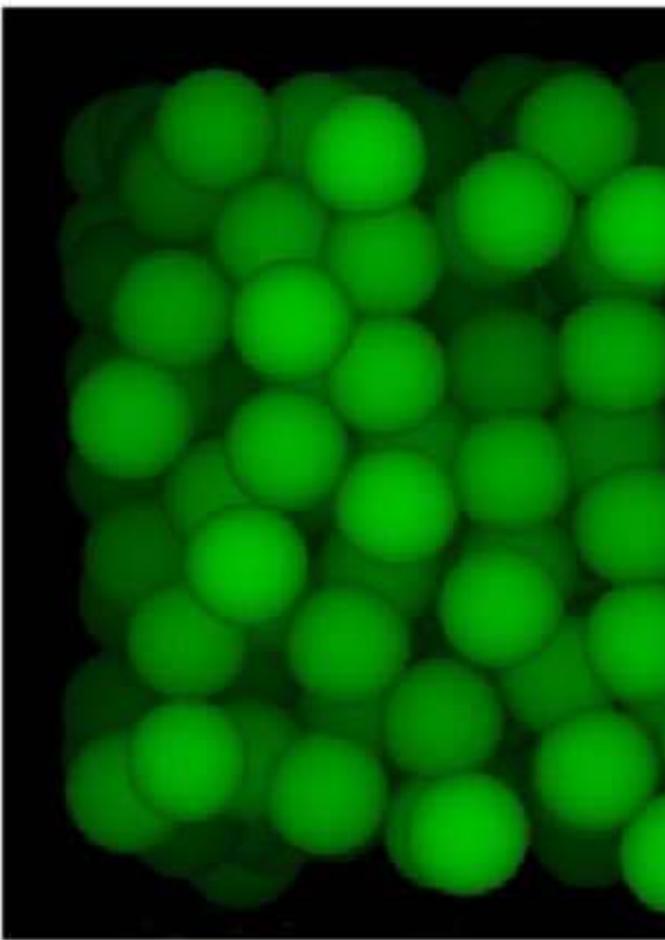
To get around the apparently inevitable incorporation of the random, von Neumann devised a third kind of simulation called the "Monte Carlo" in homage to the games of luck he enjoyed in the gambling capital of Europe. He held that random elements in simulations were unacceptable, a form of contamination tantamount to cheating at cards. Indeed, his aversion to stochastic modeling and his appreciation of rule-based games is at the heart of his epistemology. In the Monte Carlo simulation, Von Neumann devised a non-stochastic formula for approximating the stochastic operators in non-trivial simulations. Essentially, he had found a deterministic way to model random events. At the same time, he had rigged the game in the house's favor. When the Monte Carlo simulation worked, it suggested not only that we could describe nature without relying on randomness or chance, but that nature itself was deterministic.

## The Birth of the Monte Carlo Method.

<http://trace.ntu.ac.uk/frame2/articles/borg/JvN.html>

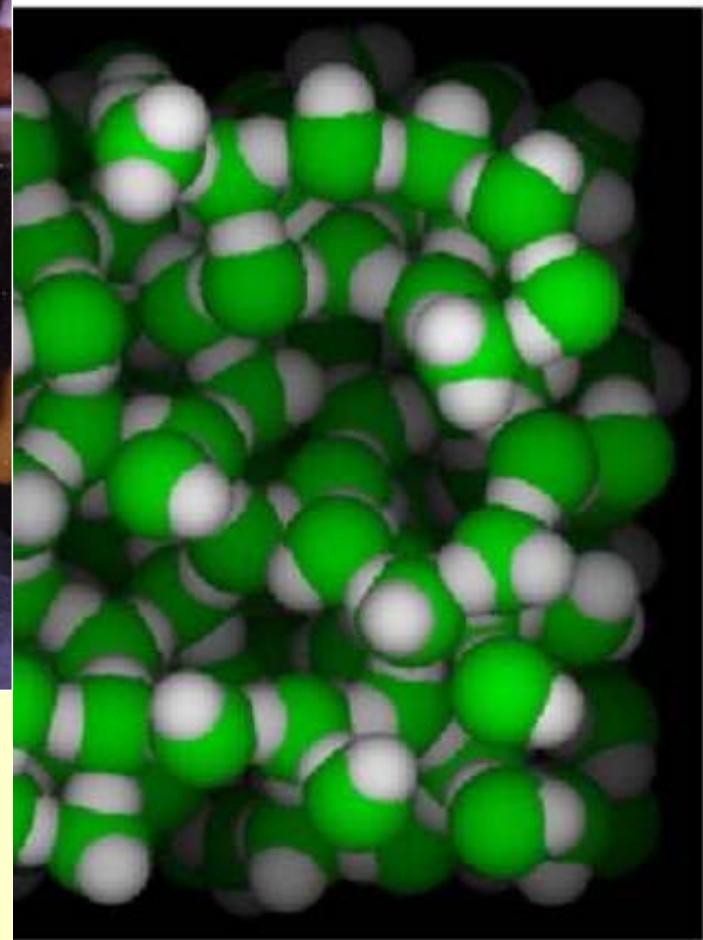
©Michael Levitt 13

# LIQUIDS: ARGON & WATER



Aneesur Rahman

1927–1987



Argon is like a collection of hard spheres. Each Argon has 12 to 14 neighbors.

Water has an open structure. Due to tetrahedral geometry, each water has 4 to 5 neighbors.

Molecular Simulation.

# SUMMARY SO FAR

- ✓ 1. How It All Began.
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# 2. BIRTH OF COMPUTATIONAL STRUCTURAL BIOLOGY

# KENDREW, ME & ISRAEL

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Prime Michael's Amazon.com Books See all 41 Product Categories

**The Thread of Life: an introduction to molecular biology. Based on the series of B.B.C. Television Lectures of the same title (Hardcover)**  
by John C. Kendrew (Author), b/w photos. Illustrated by Diagrams

Nobel Prize in 1962  
Gave TV Series in 1964  
Sent me to Israel in 1967

## **The Thread of Life: An INTRODUCTION TO MOLECULAR BIOLOGY**

### **Episodes (BBC TV Winter 1964)**

**The REVOLUTION IN BIOLOGY (04/01/1964)**

**INSIDE THE CELL (11/01/1964)**

**PROTEINS IN ONE DIMENSION (18/01/1964)**

**PROTEINS IN THREE DIMENSIONS (25/01/1964)**

**REPRODUCTION AND GENETICS (01/02/1964)**

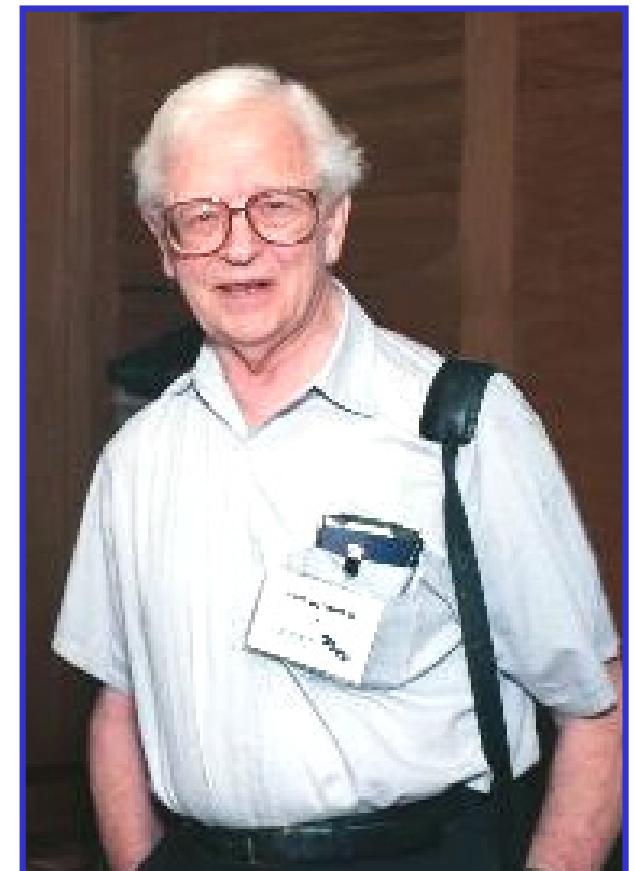
**NUCLEIC ACID The INFORMATION CARRIER (08/02/1964)**

**The MESSENGER OF THE GENES (15/02/1964)**

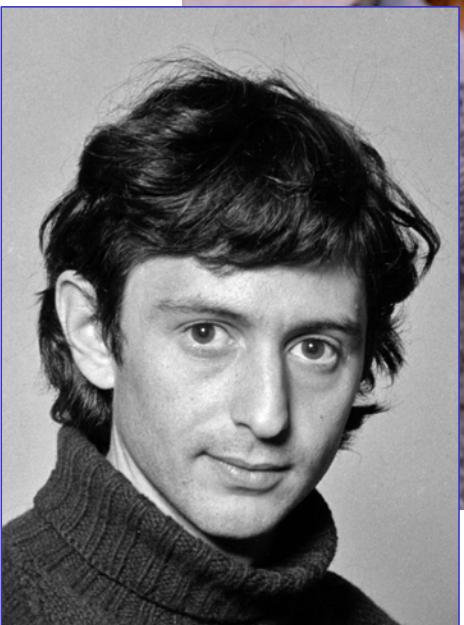
**SOLVING THE CODE (22/02/1964)**

**LIVING ARCHITECTURE The VIRUSES (29/02/1964)**

**The WAY AHEAD (07/03/1964)**



# SHNEIOR LIFSON 1914-2001

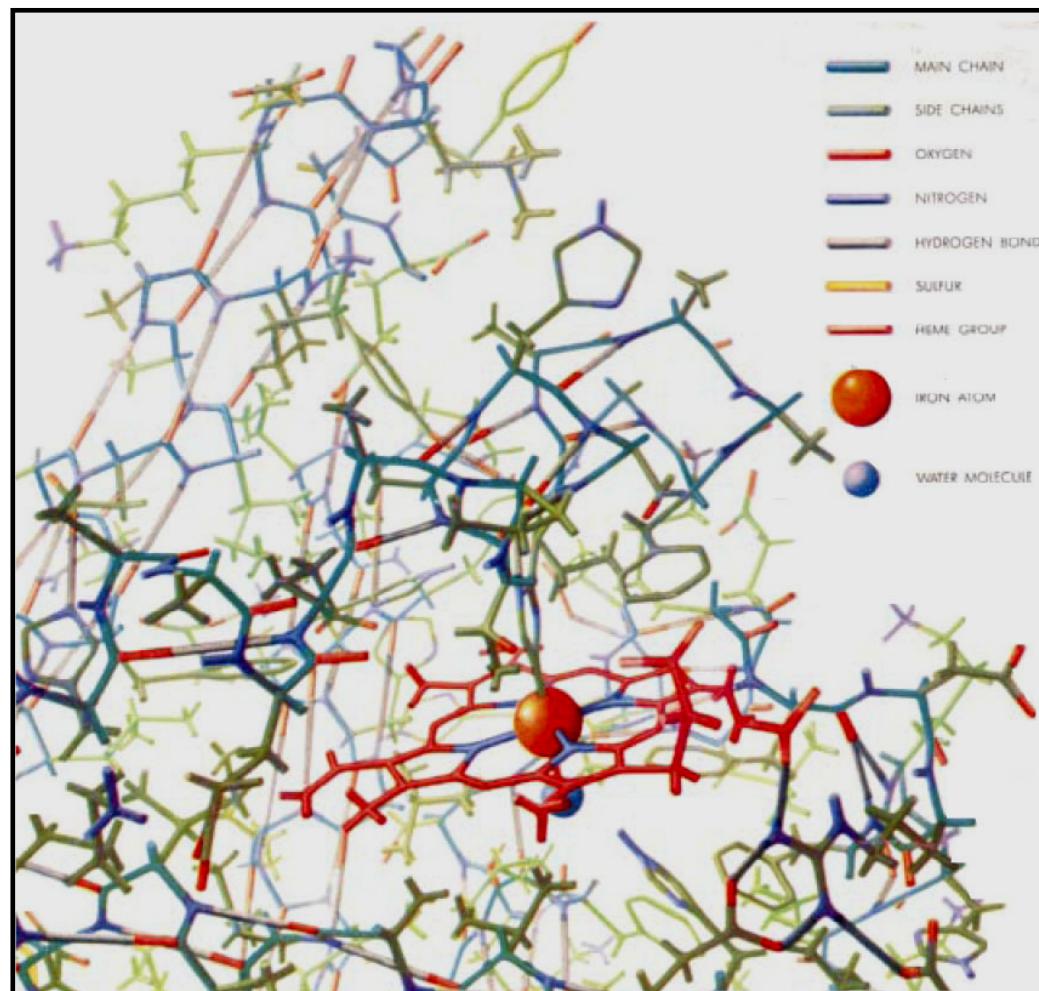


Weizmann Institute 1967-68

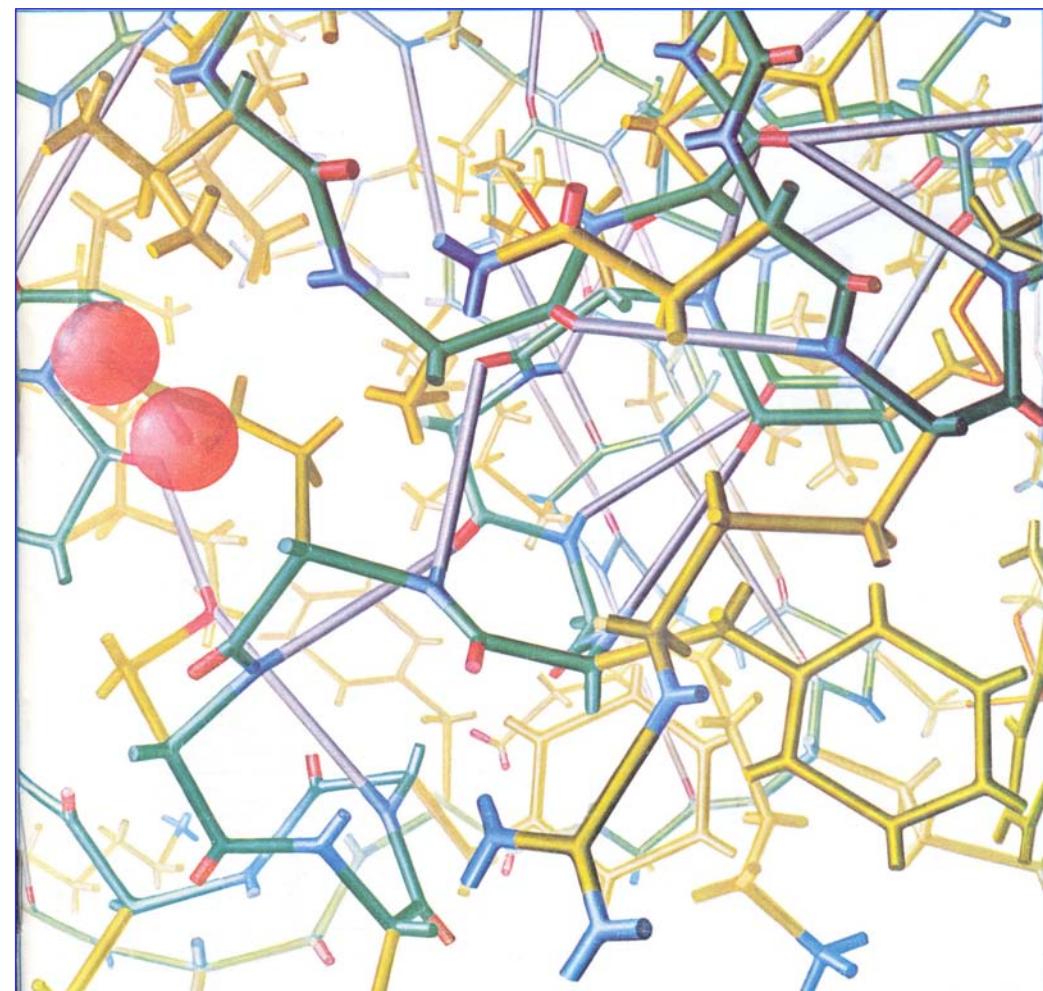
BIMOLECULES  
ARE DETAILED

# BIOLOGY IS DETAILED INTERACTIONS

Myoglobin 1961



Lysozyme 1966

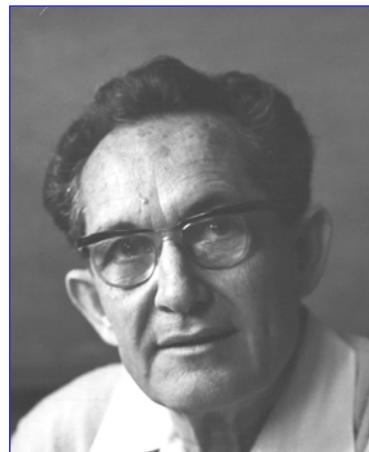


# CONSISTENT



# FORCE-FIELD

1968



THE JOURNAL OF CHEMICAL PHYSICS

VOLUME 49, NUMBER 11

1 DECEMBER 1968

Consistent Force Field for Calculations of Conformations, Vibrational Spectra, and  
Enthalpies of Cycloalkane and *n*-Alkane Molecules

S. LIPSON AND A. WARSHEL

*Department of Chemical Physics, Weizmann Institute of Science, Rehovot, Israel*

(Received 13 May 1968)

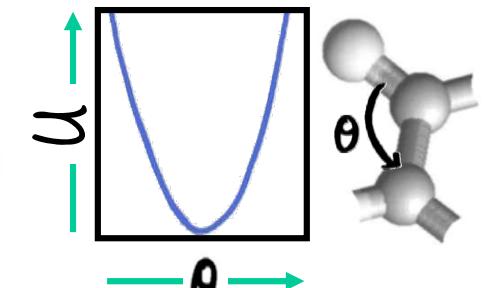
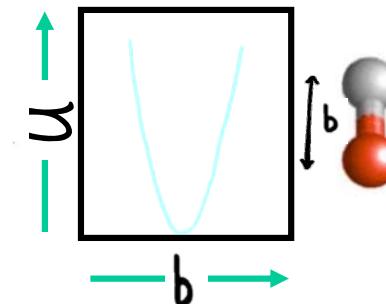
# MOLECULAR POTENTIAL ENERGY

$$U = \sum \frac{1}{2} K_b (b - b_0)^2 + \sum \frac{1}{2} K_\theta (\theta - \theta_0)^2$$

All Bonds

Hooke 1635

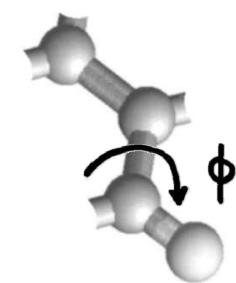
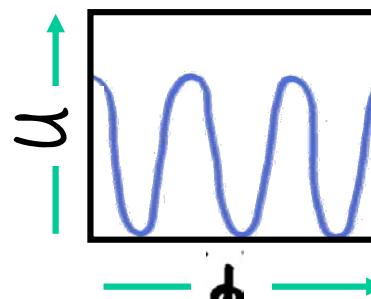
All Angles



$$+ \sum K_\phi [1 - \cos(n\phi + \delta)]$$

All Torsion Angles

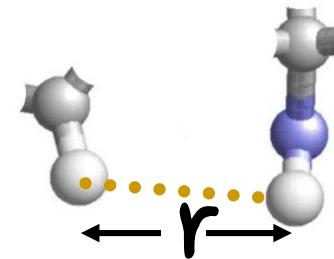
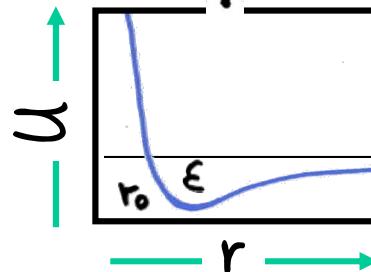
Fourier 1768



$$+ \sum \epsilon \left[ \left( \frac{r_0}{r} \right)^{12} - 2 \left( \frac{r_0}{r} \right)^6 \right]$$

All Nonbonded pairs

Van der Waals 1837

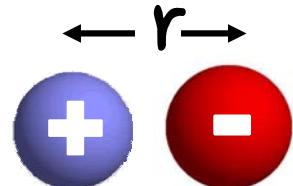
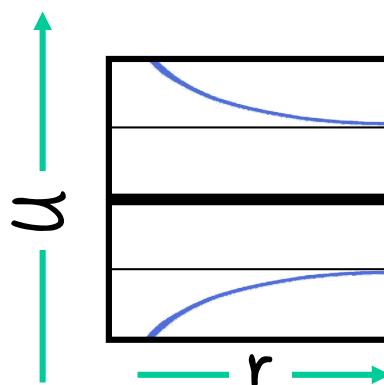


$$+ \sum 332 q_i q_j / r$$

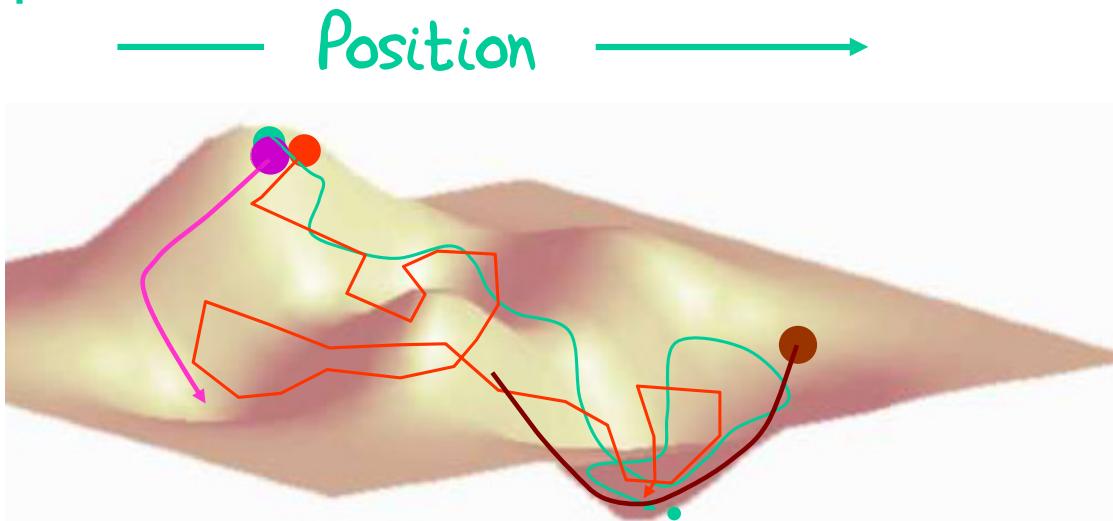
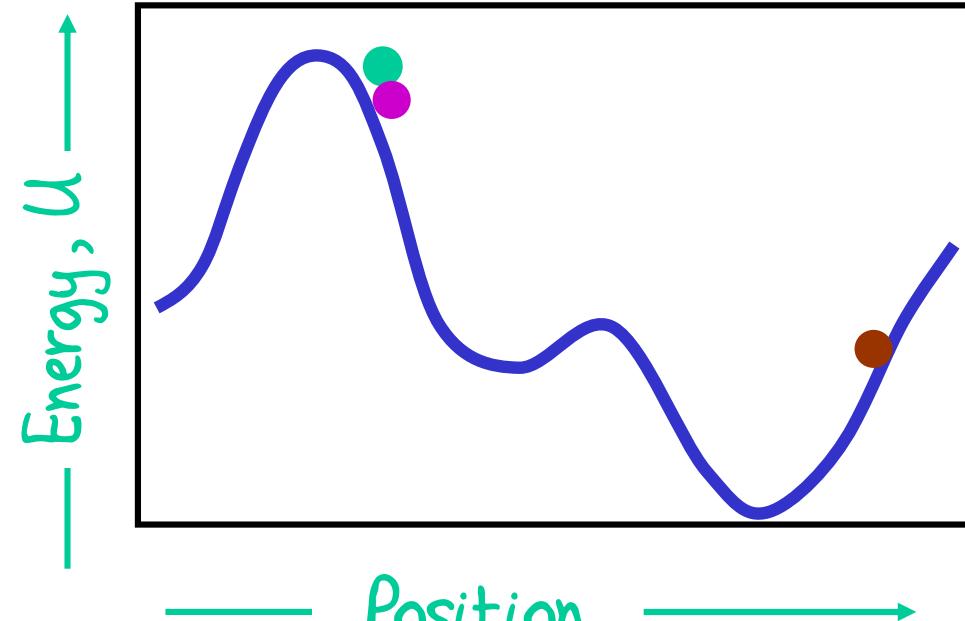
All partial charges

Coulomb 1736

Simple sum  
over many  
terms



# MOVING OVER ENERGY SURFACE



- EM: Energy Minimization drops into local minimum.  
Euclid 325 BC
- NMD: Normal Mode Dynamics vibrates about minimum.  
Galileo 1564
- MD: Molecular Dynamics uses thermal energy to move smoothly over surface.  
Newton 1643
- MC: Monte Carlo Moves are random. Accept with probability  $\exp(-\Delta U/kT)$ .

Metropolis 1915

©Michael Levitt 13

# MULTI-SCALE MODELING OF MACROMOLECULES

# EINSTEIN\* ON SIMPLIFICATION

"Everything Should Be Made As Simple  
As It Can Be, But Not Simpler"

\*Einstein may have crafted this aphorism, but there is no direct evidence in his writings. He did express a similar idea in a lecture but not concisely. Roger Sessions was a key figure in the propagation of the saying. In fact, he may have crafted it when he attempted to paraphrase an idea imparted by Einstein.

<http://quoteinvestigator.com/2011/05/13/einstein-simple/>

# SIMPLIFY REPRESENTATION

All Non-Hydrogen Atoms	1969
Atom Groups	1975
All Atoms & Electrons	1976
All Atoms & Water	1988

# PROTEIN ENERGY

# MINIMIZATION

1969



# MACROMOLECULAR ENERGY MINIMIZATION

## Refinement of Protein Conformations using a Macromolecular Energy Minimization Procedure

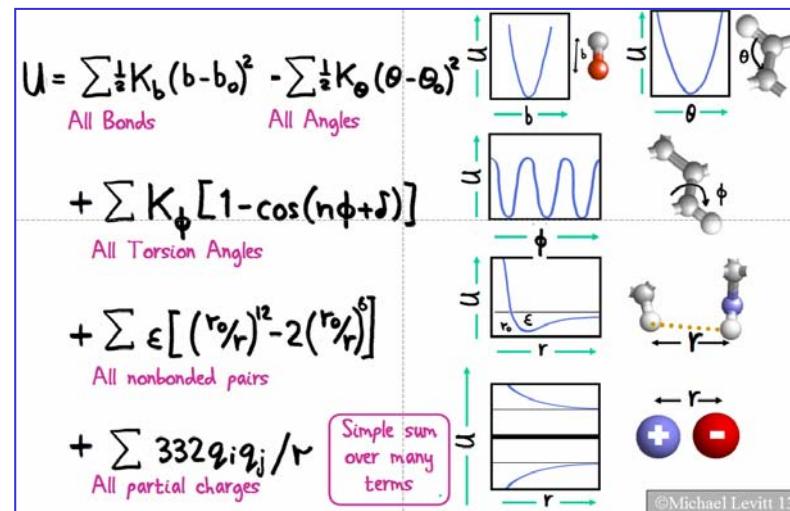
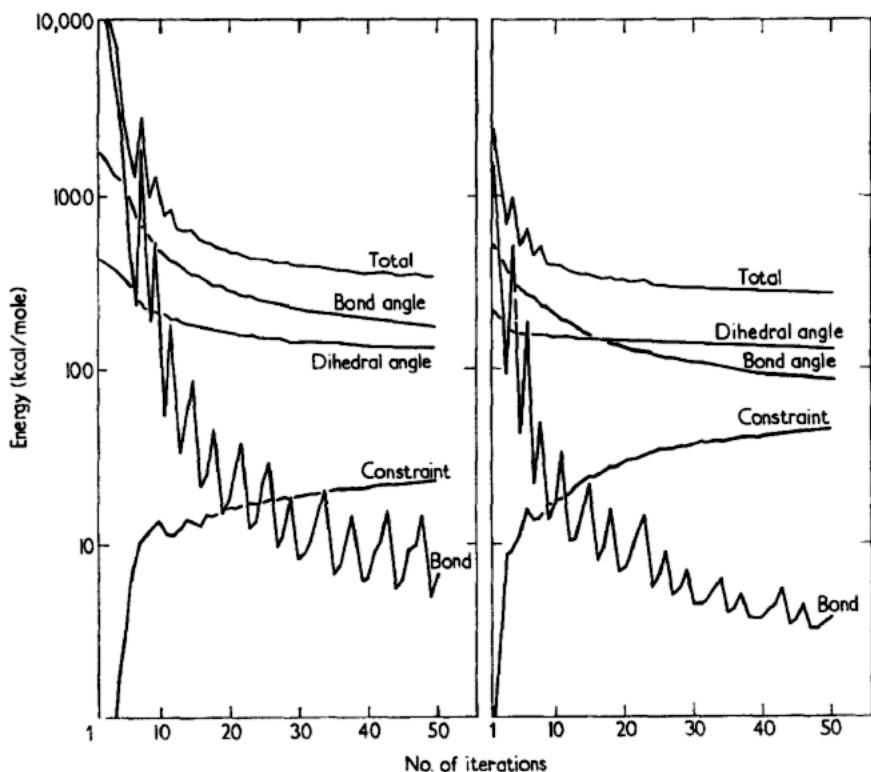
MICHAEL LEVITT<sup>†</sup> AND SHNEIOR LIFSON

Weizmann Institute of Science

J. Mol. Biol. (1969) 46, 269–279



$$E = \sum_{\text{all bonds}} \frac{1}{2} K_b (b - b_0)^2 + \sum_{\text{all bond angles}} \frac{1}{2} K_\tau (\tau - \tau_0)^2 + \sum_{\text{all dihedral angles}} \frac{1}{2} K_\theta \{1 + \cos(n\theta - \delta)\}$$
$$+ \sum_{\text{all non-bonded pairs}} \epsilon_{ij} \left\{ \left( \frac{r_{ij}^0}{r_{ij}} \right)^{12} - 2 \left( \frac{r_{ij}^0}{r_{ij}} \right)^6 \right\} + \sum_{\text{all atomic co-ordinates}} \frac{1}{2} w (x_i - x_i^0)^2$$



First protein structure refinement

# COARSE GRAINED MODELS

1975

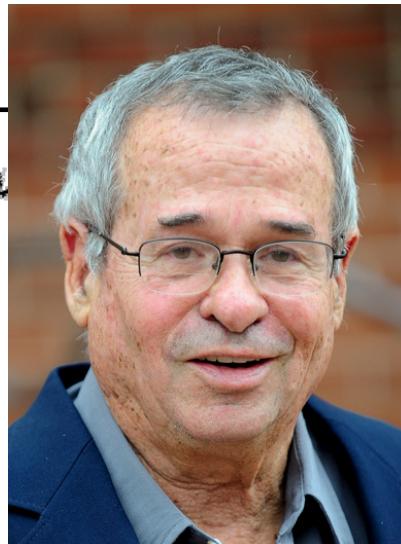
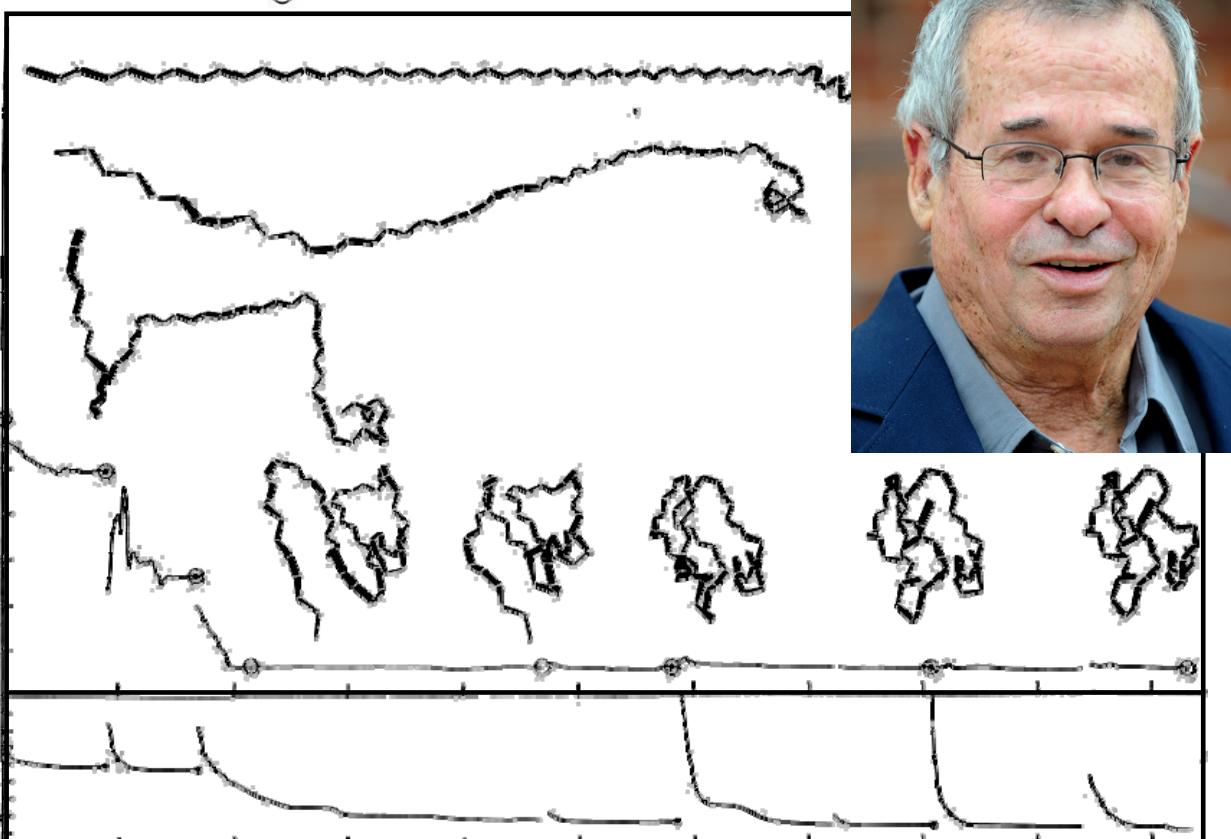
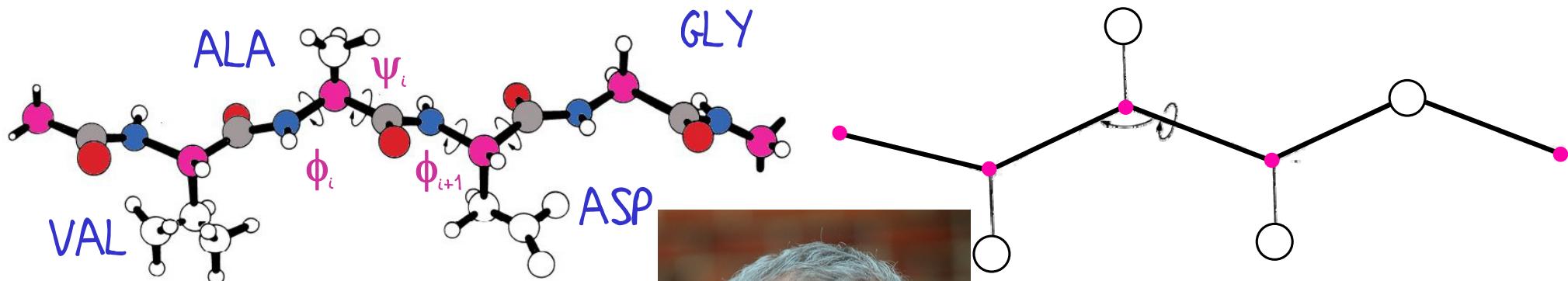


# COMPUTER SIMULATION OF PROTEIN FOLDING

Michael Levitt\* & Arieh Warshel\*

Nature Vol. 253 February 27 1975

Department of Chemical Physics, Weizmann Institute of Science, Rehovoth, Israel



Reduced models

Fold protein with 1000 steps of minimization.

Escape from local minima with normal modes jumps.

# QM/MM MODELS FOR CATALYSIS

1976



# THEORETICAL STUDIES OF ENZYMIC REACTIONS

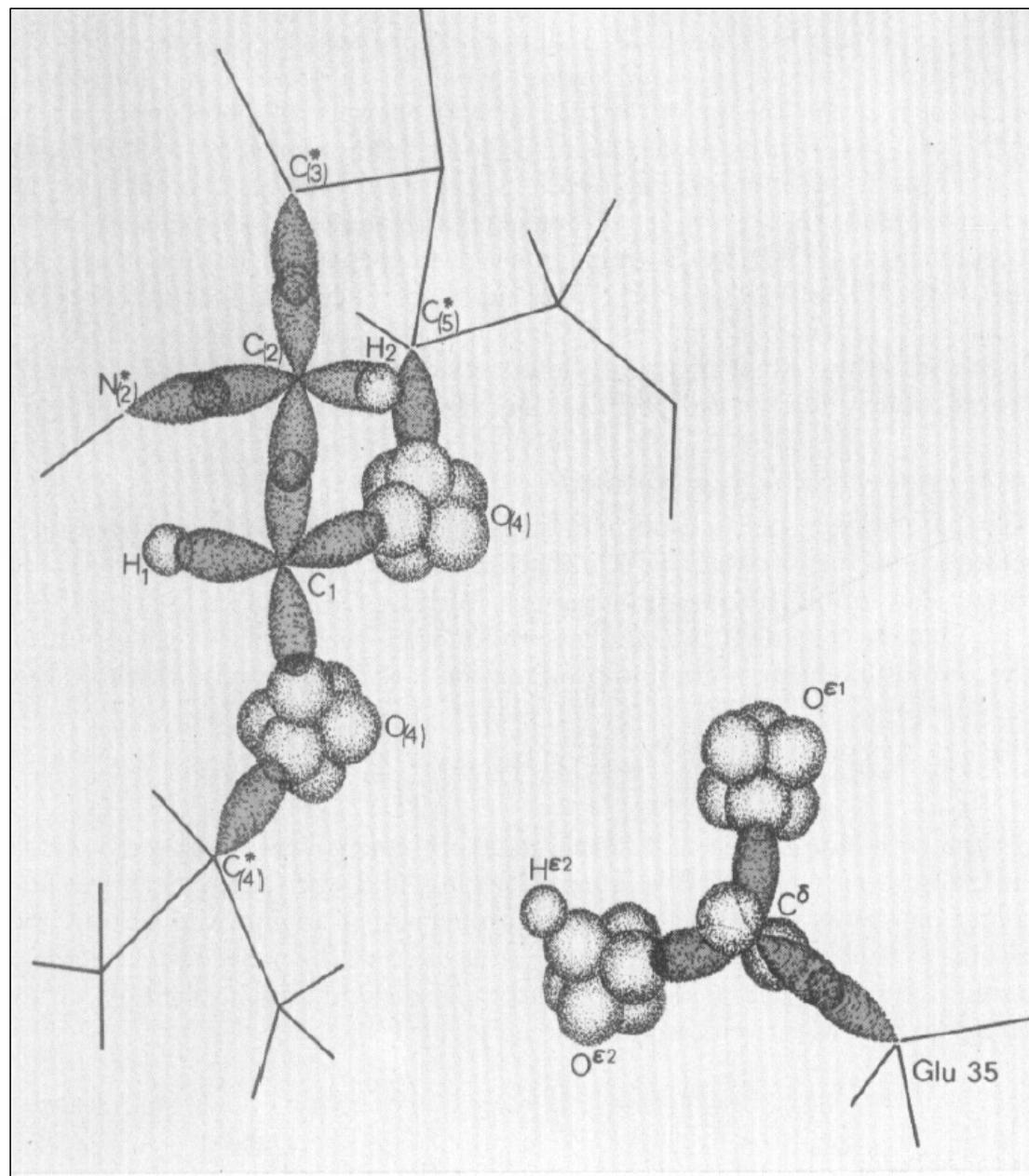
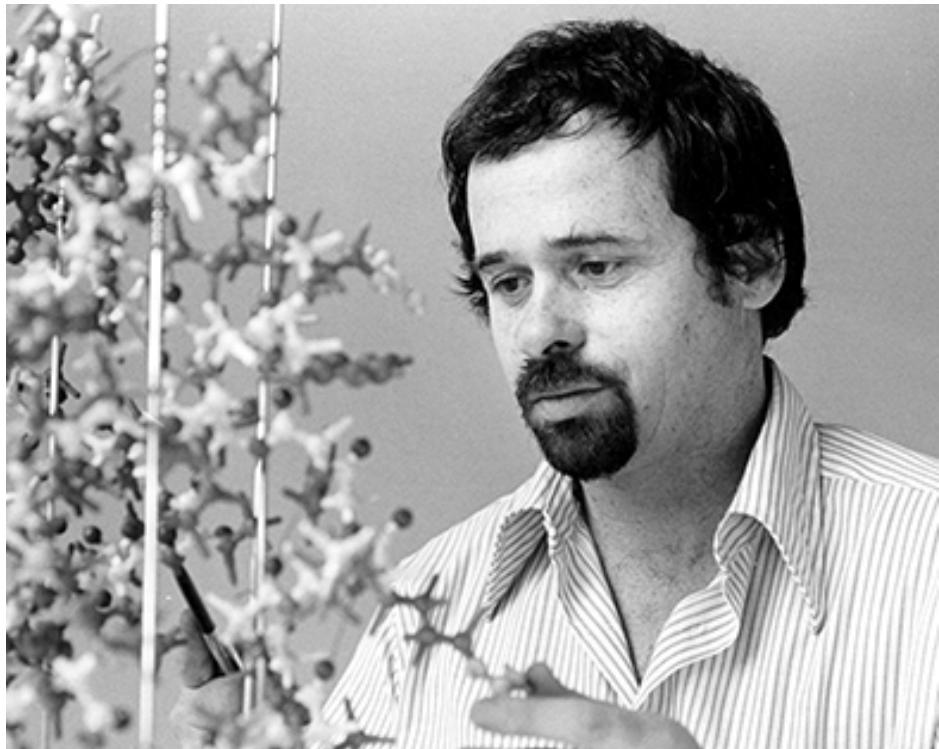
*J. Mol. Biol.* (1976) **103**, 227–249

A. WARSHEL AND M. LEVITT

Medical Research Council Laboratory of Molecular Biology  
Hills Road, Cambridge CB2 2QH, England

and

Department of Chemical Physics  
The Weizmann Institute of Science  
Rehovot, Israel



FIRST MD

MOVIE

1979

**Filming by**

**Richard J. Feldmann  
National Institutes  
of Health  
Bethesda, Maryland**

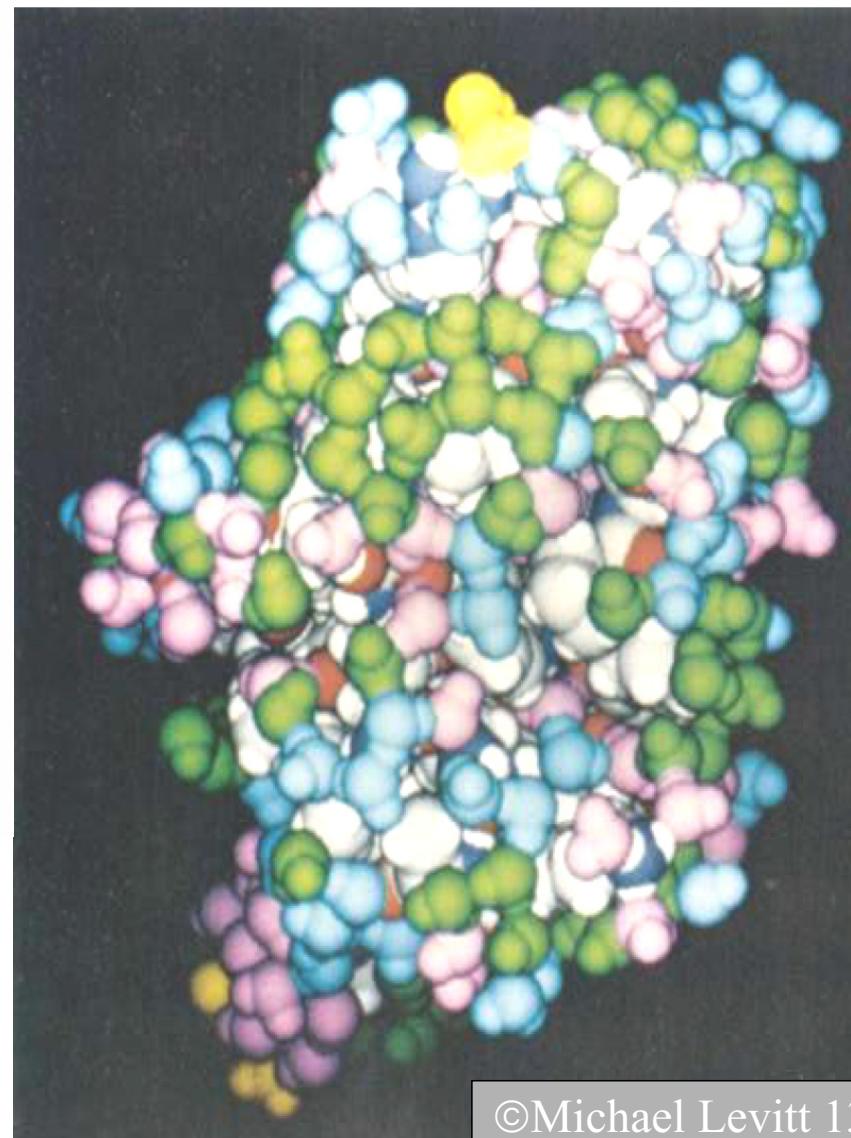
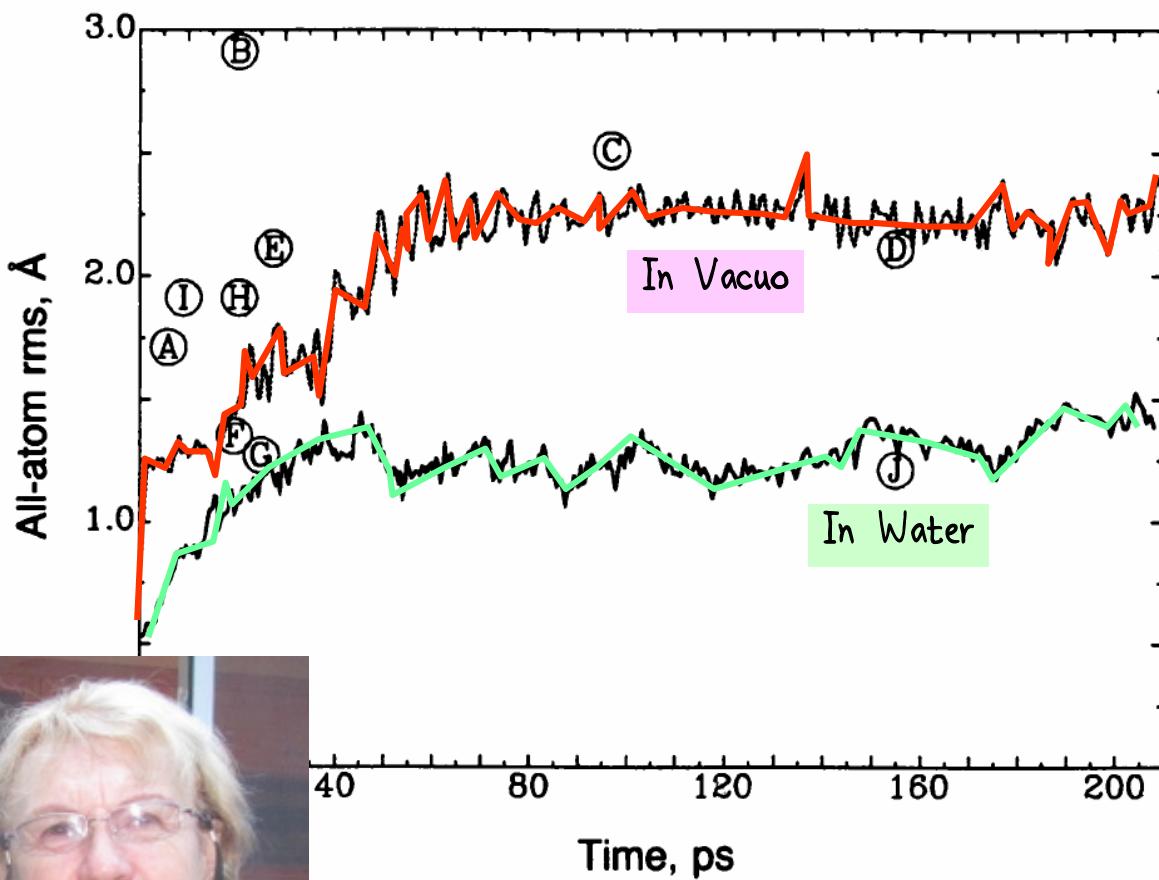
# PROTEIN MOLECULAR DYNAMICS IN WATER 1988

# ACCURATE SIMULATION OF PROTEIN DYNAMICS IN SOLUTION

MICHAEL LEVITT\* AND RUTH SHARON

*Proc. Natl. Acad. Sci. USA*  
Vol. 85, pp. 7557–7561, October 1988

Department of Chemical Physics, Weizmann Institute of Science, Rehovot 76100



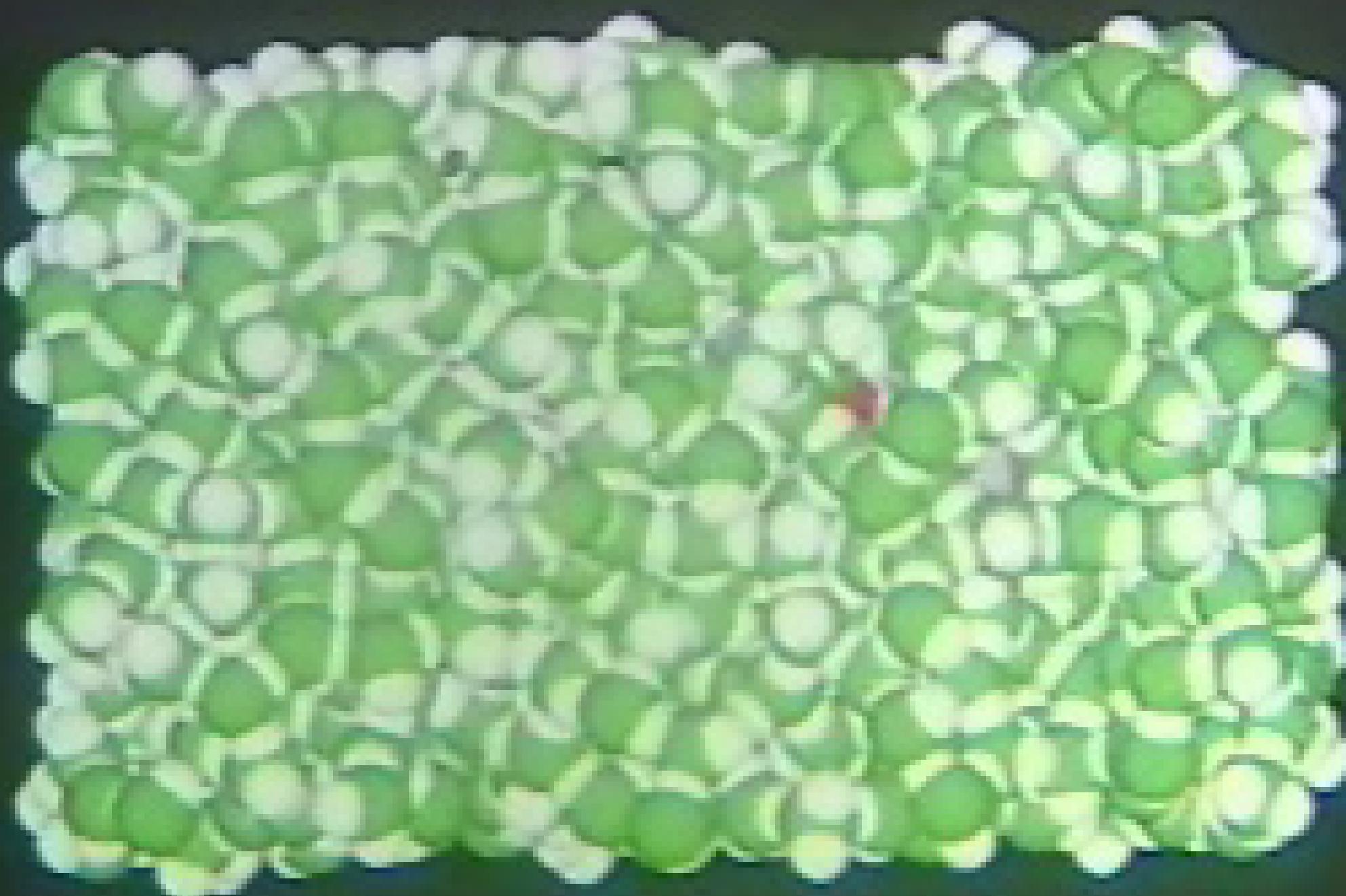
# $\alpha$ -HELIX MOLECULAR DYNAMICS IN WATER 1990



**Molecular Dynamics Simulations of Helix Denaturation**

**Valerie Daggett and Michael Levitt**

*J. Mol. Biol.* (1992) **223**, 1121–1138



Alpha-Helices Unfolding in Solution

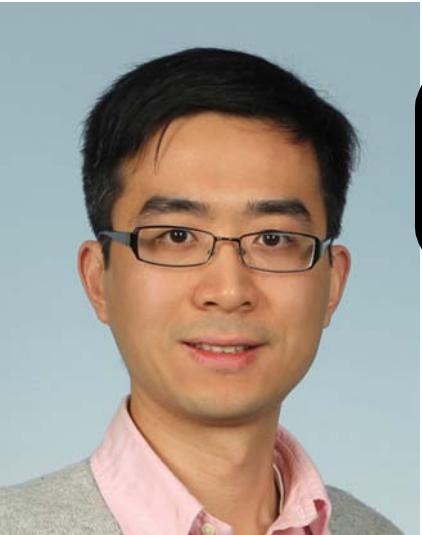
# SUMMARY SO FAR

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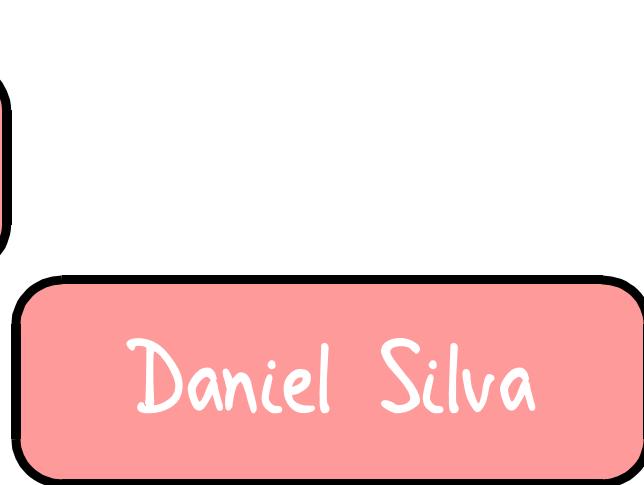
# 3. FUTURE: MULTI- SCALE DYNAMICS OF HUGE STRUCTURES

REDUCED DEGREES  
OF FREEDOM

# MARKOV STATE DYNAMICS OF RNA POLYMERASE II



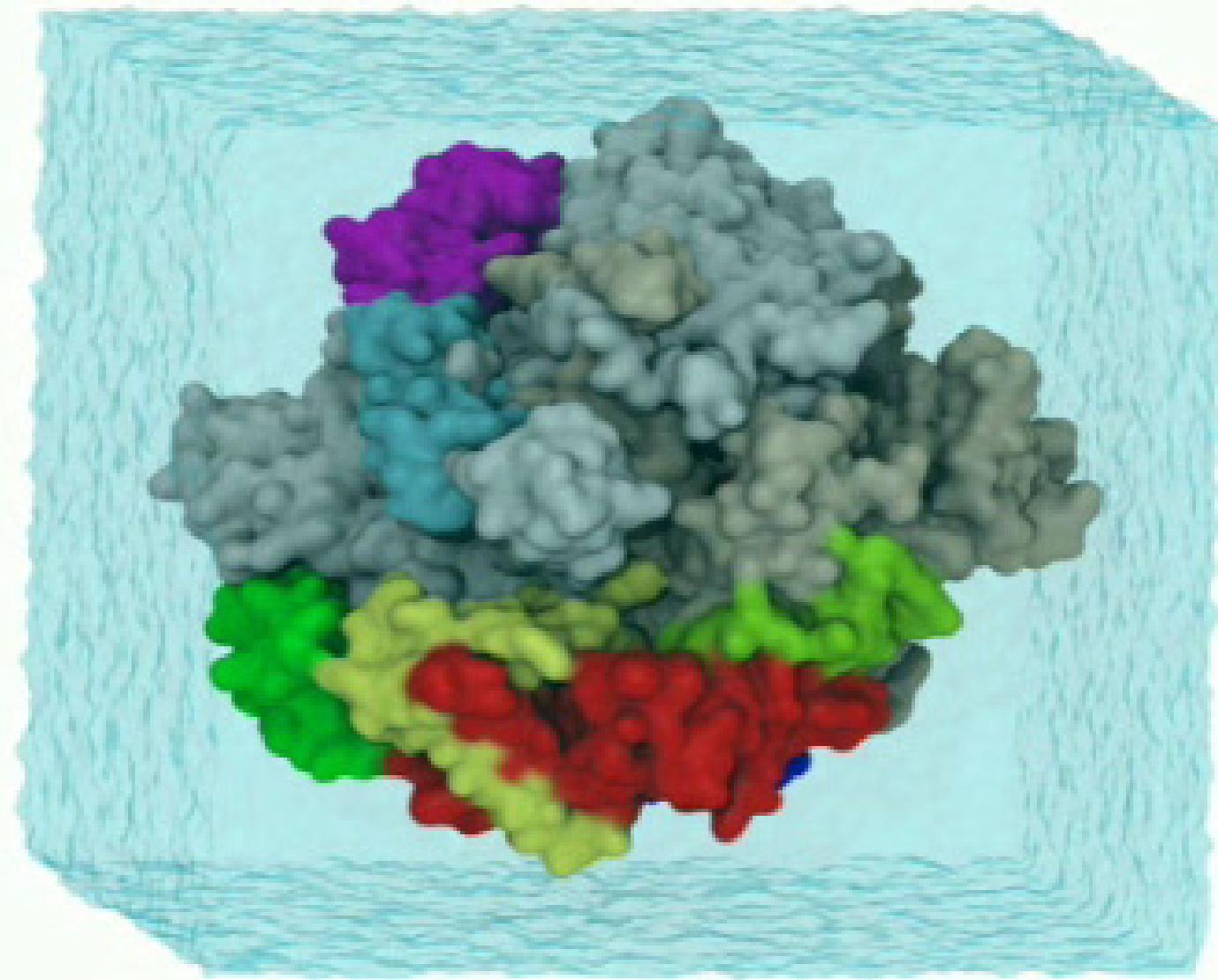
Xuhui Huang



Daniel Silva

*RNA Polymerase II*  
(10 subunits, ~422 kDa)

*Explicit water solvent*  
(~122,000 molecules)



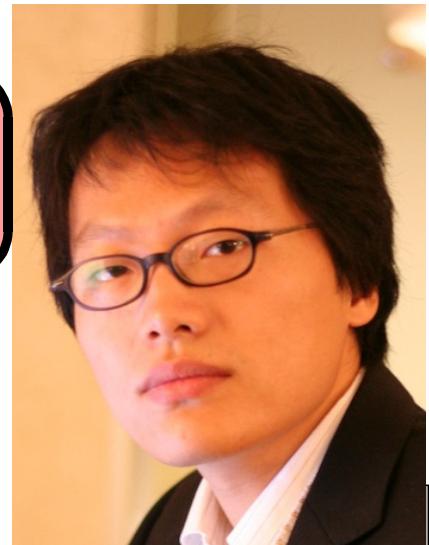
*Simulation of a ~426,000 atom system*

# NORMAL MODES OF ENTIRE RIBOSOME

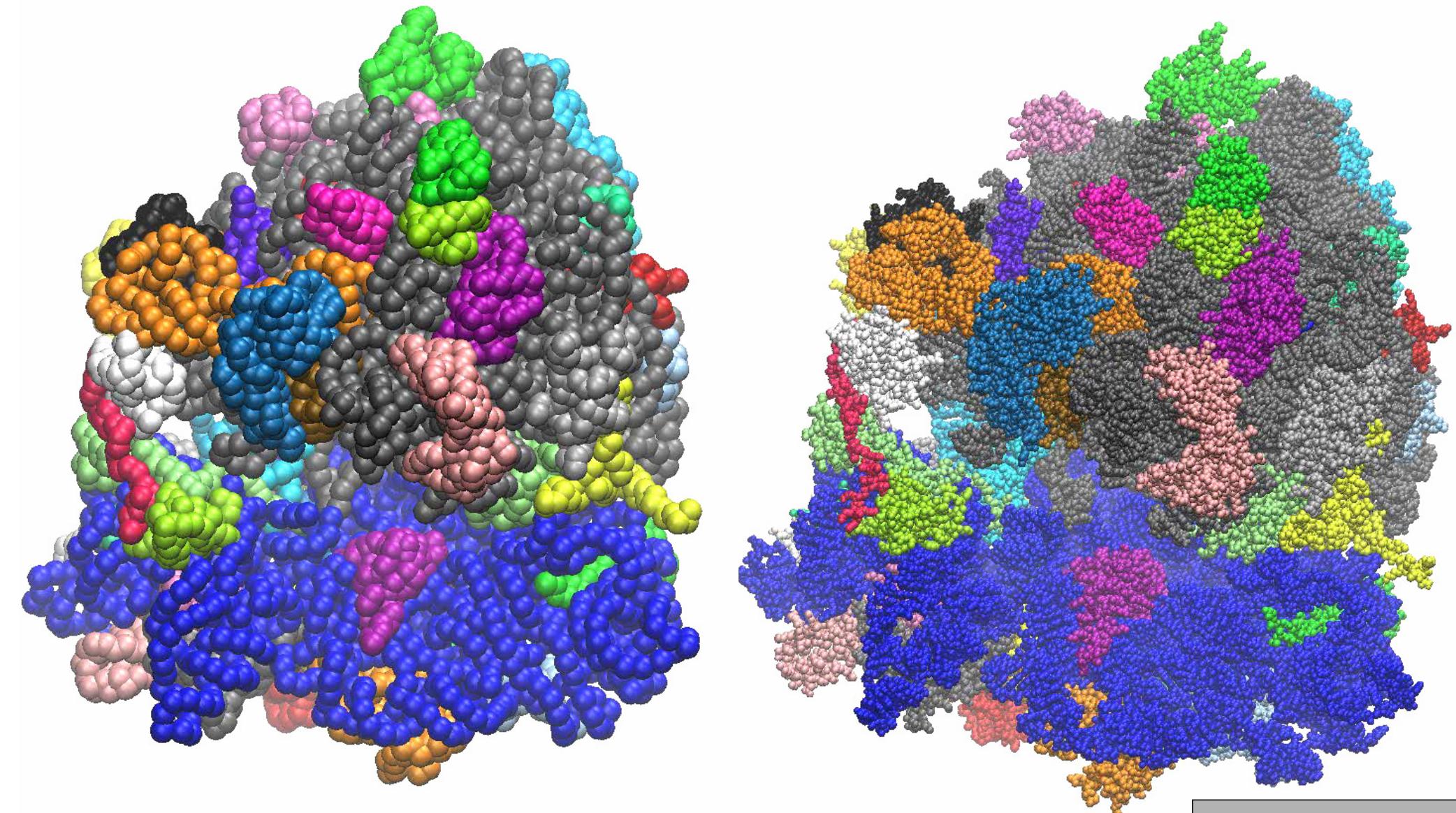


Jenelle Bray

Junjie Zhang



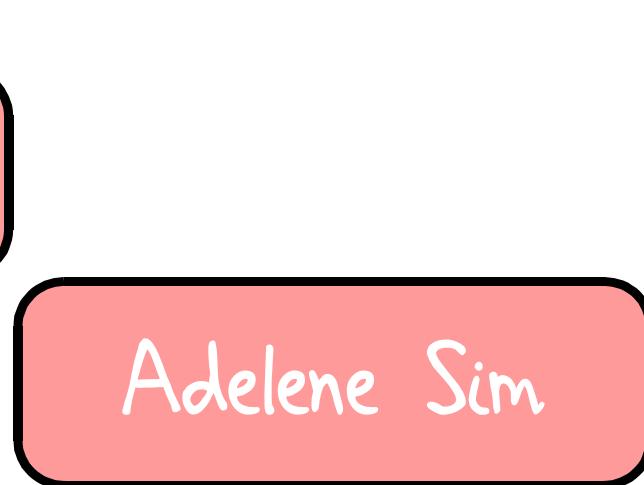
# COARSE-GRAINED & ALL-ATOM NORMAL MODE DYNAMICS OF ENTIRE RIBOSOME



# NATURAL MOVE MONTE CARLO OF RNA



Peter Minary



Adelene Sim

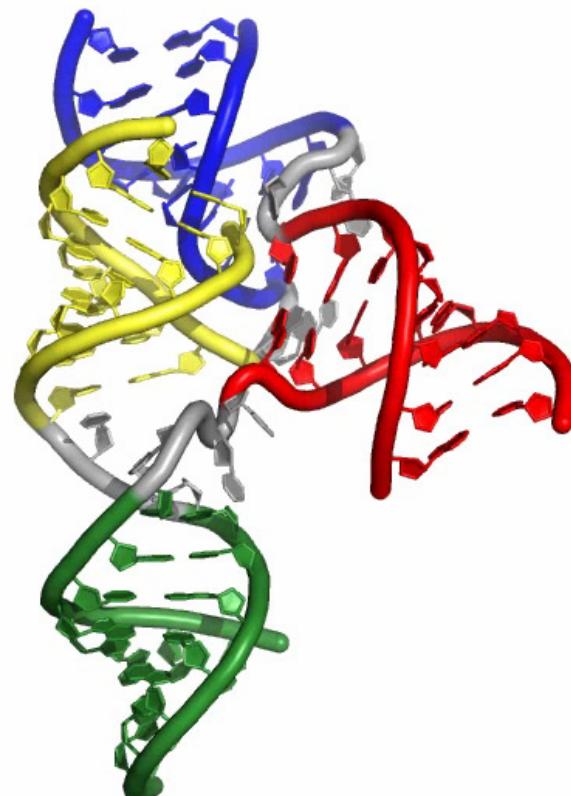
# NATURAL MOVE MONTE CARLO



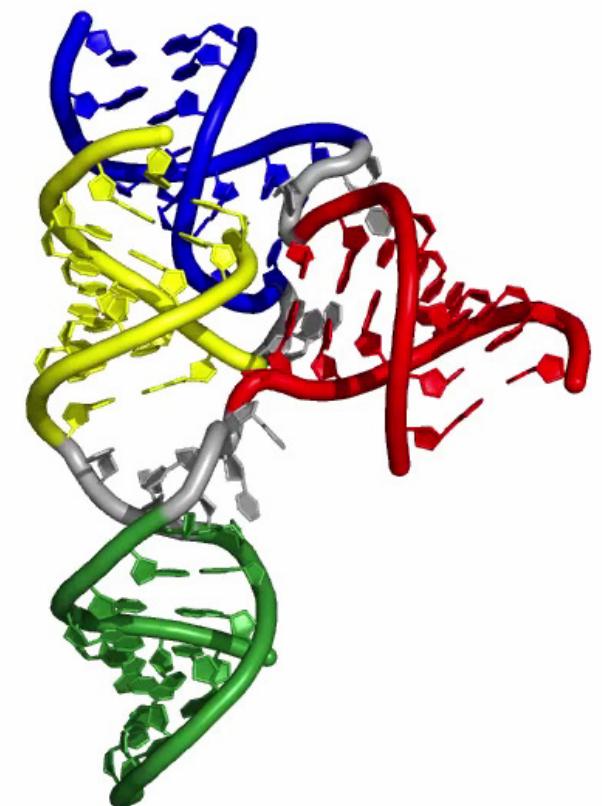
Natural Moves allow a hierarchy of moves.

One calculation can combine all the different scales.

Bases Pairs



Bases Pairs & Helices



Move any part of system:

Atoms

Nucleotides

Base Pairs

Hairpin Helices

Many Helices together

All of these

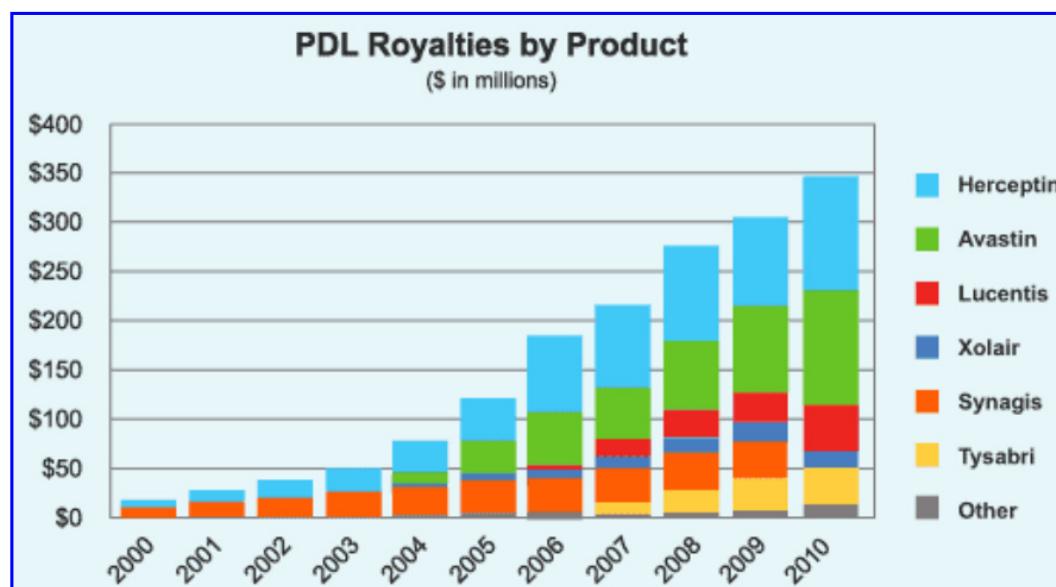
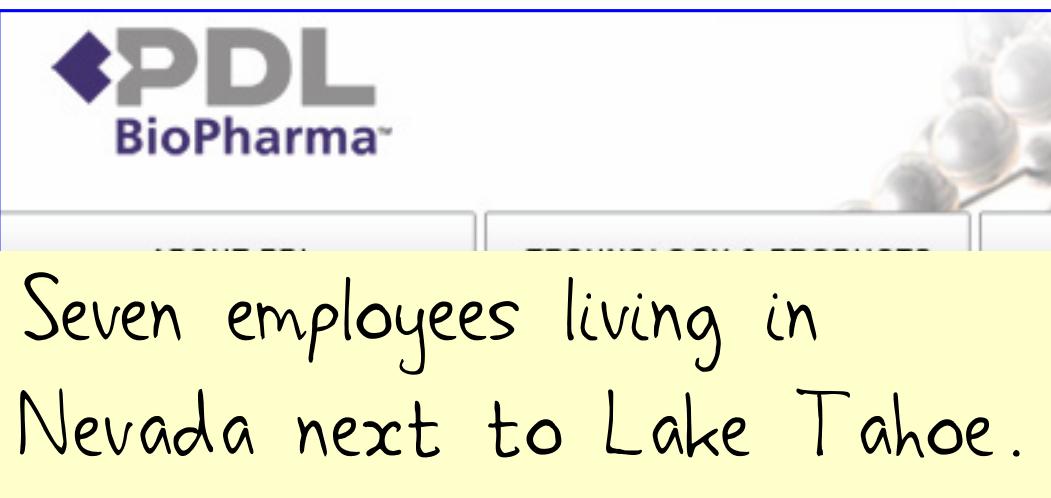
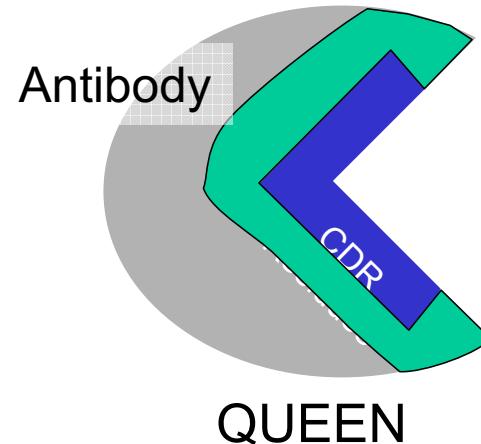
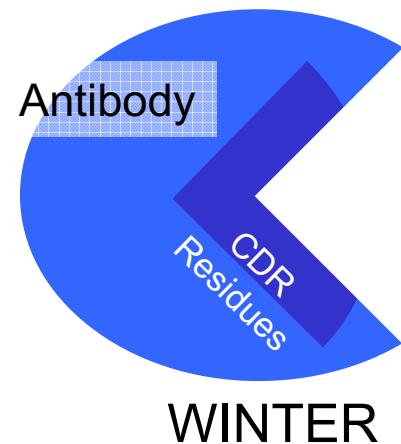
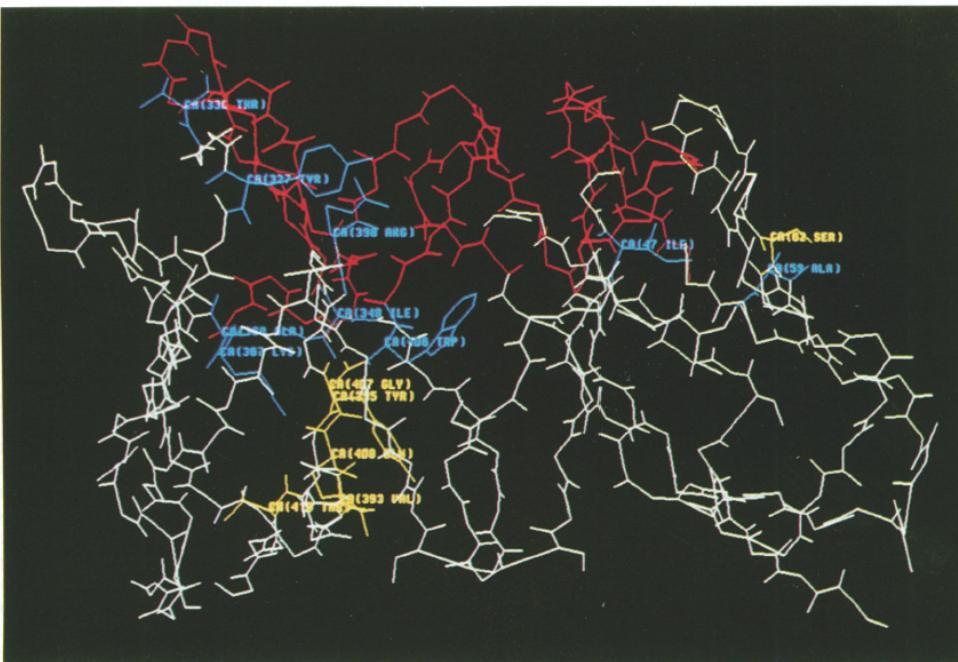
# APPLICATIONS TO HUMAN HEALTH

# ANTIBODY HUMANIZATION

## A humanized antibody that binds to the interleukin 2 receptor

(chimeric antibody/ antibody affinity/ autoimmune disease)

CARY QUEEN\*, WILLIAM P. SCHNEIDER\*, HAROLD E. SELICK\*†, PHILIP W. PAYNE\*,  
NICHOLAS F. LANDOLFI\*, JAMES F. DUNCAN\*‡, NEVENKA M. AVDALOVIC\*, MICHAEL LEVITT§,  
RICHARD P. JUNGHANS¶, AND THOMAS A. WALDMANN¶



Compare  
Genomes.

Andrea Scaiewicz

Ivan Ufimtsev

X-Ray Phase  
Problem.



# BREADTH OR LACK OF FOCUS?



Large  
Complexes.

Nir Kalisman

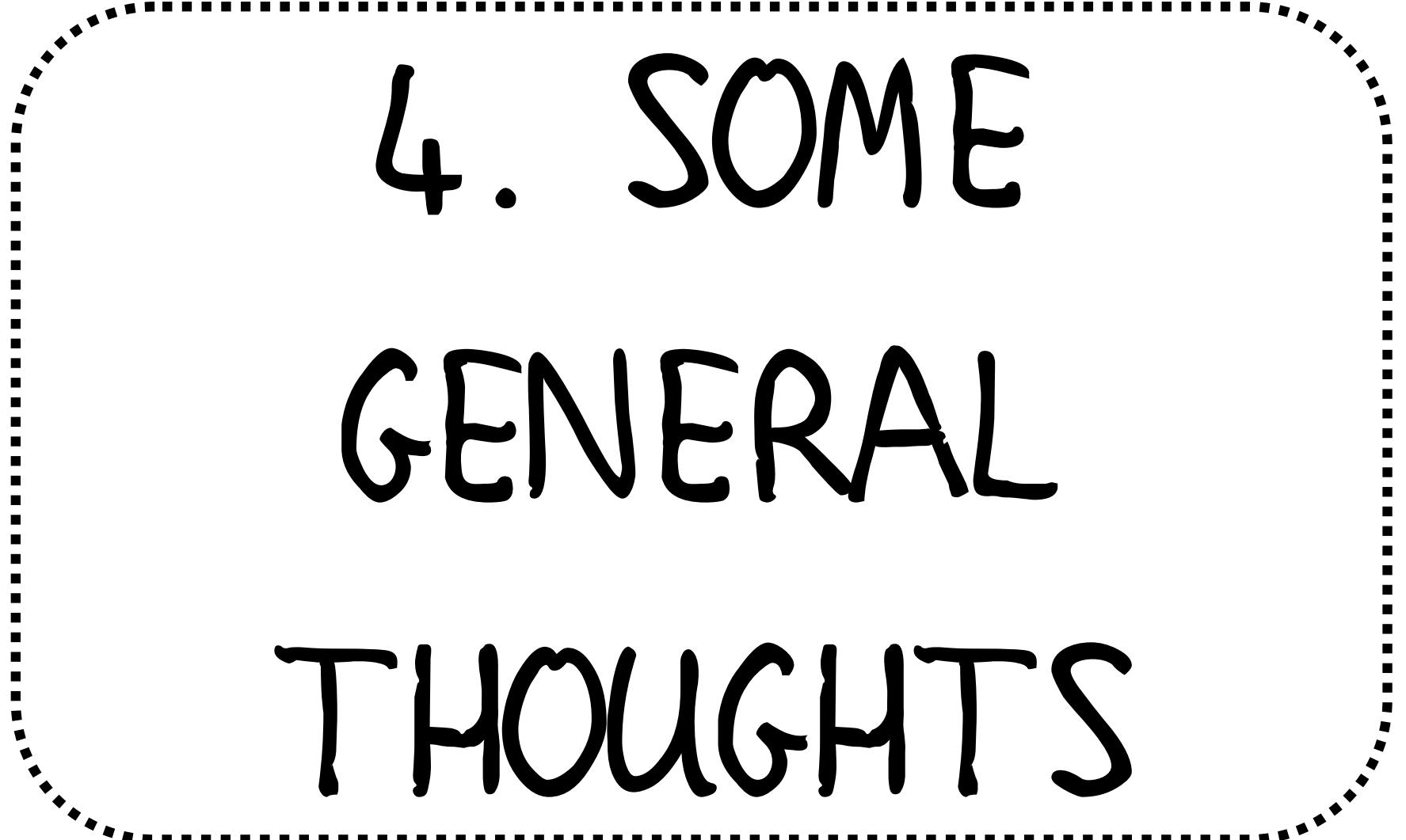


Membrane  
Proteins.

Yana Gofman

# SUMMARY SO FAR

- ✓ 1. How It All Began.
- ✓ 2. Birth of Computational Structural Biology.
- ✓ 3. Future: Multi-Scale Dynamics of Huge Systems.
- 4. Some General Thoughts.



# 4. SOME GENERAL THOUGHTS

PUSHED AHEAD  
BY TECHNOLOGY

# HOW COMPUTERS HAVE CHANGED

DATE	COST	SPEED	MEMORY	SIZE
1967	\$40M	0.1 MH <sub>z</sub>	1 MB	HALL
2013	\$4,000	1 GH <sub>z</sub>	10 GB	LAPTOP
CHANGE	10,000	10,000	10,000	10,000

If cars were like computers, then a new Volvo would cost \$3, would have a top speed of 1,000,000 Km/hr, would carry 50,000 adults and would park in a shoebox

FAMILY  
SUPPORT

# MY MOTHER, MY WIFE



You know the old saying?

"Behind every successful man

there is a

surprised wife"



TAKE CHANCES

TAKE CHANCES,  
BUT DO NOT BE  
TOO STUPID...

# BEGINNER SEA-KAYAKING ALONE



Ornö Kyrke  
Store

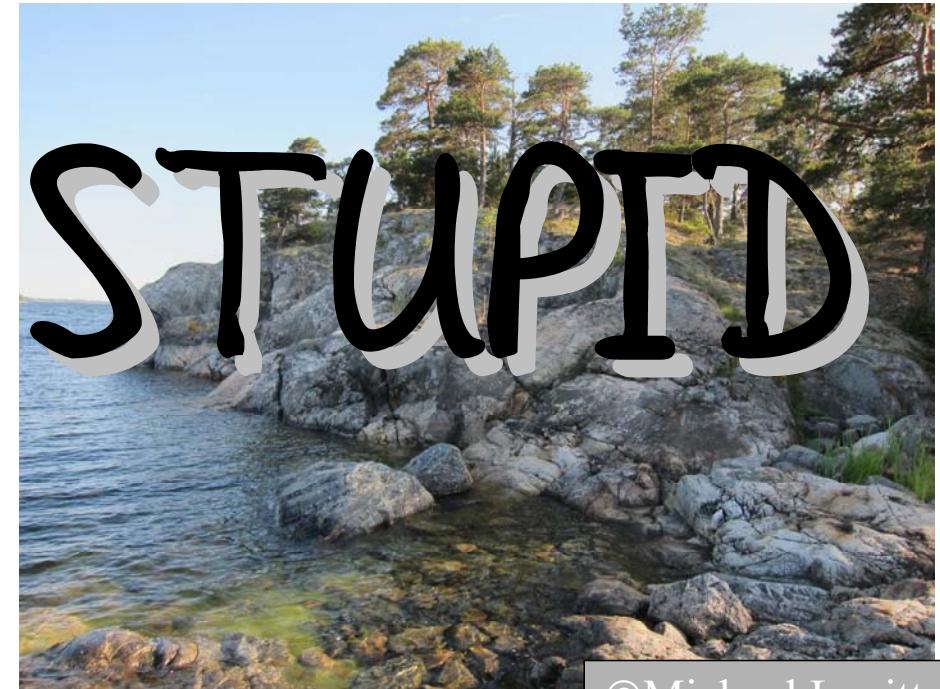
"Paradise"

First Beach

Rest Stop

Kayak Rental

# IT WAS A PARADISE



# ADVICE TO THE YOUNG

- BE PASSIONATE
- BE PERSISTENT
- BE ORIGINAL
- BE KIND & GOOD

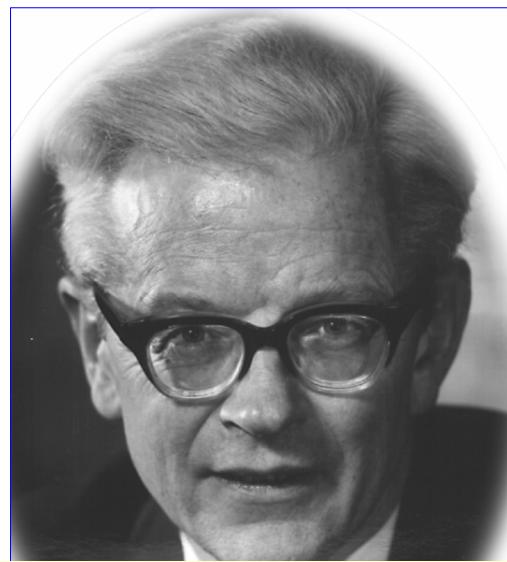
THANKS TO  
MY TOWERING  
HEROES OF SCIENCE

# MENTOR IN ISRAEL

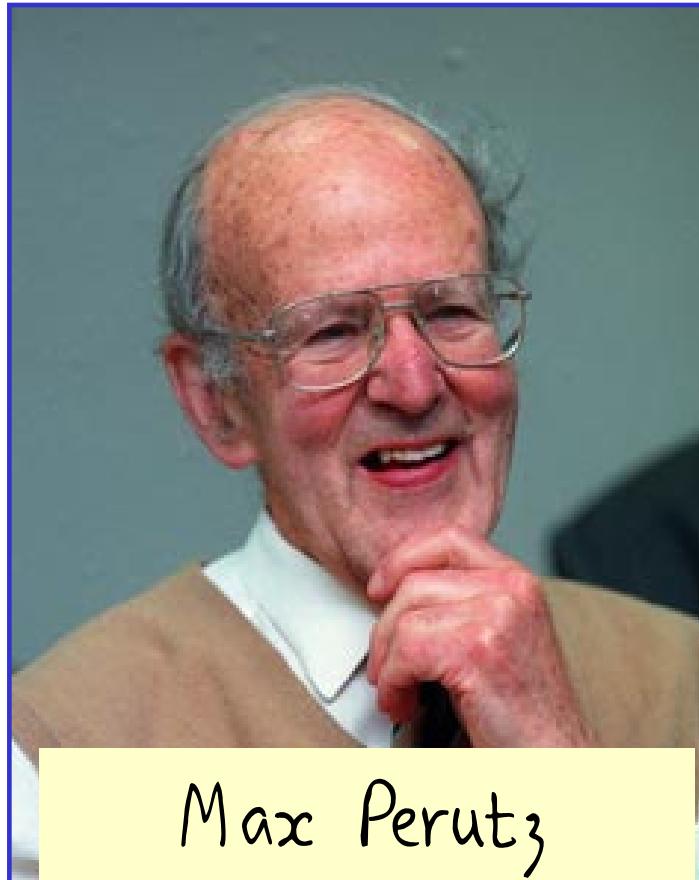


Shneior Lifson

# MENTORS IN CAMBRIDGE



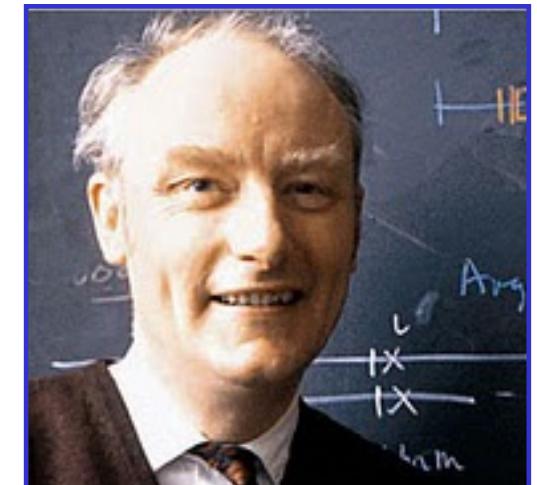
John Kendrew



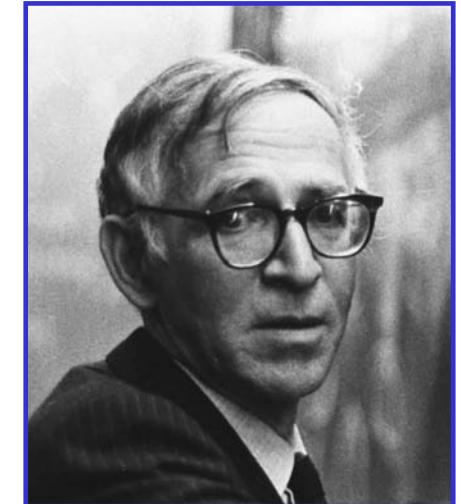
Max Perutz



Bob Diamond



Francis Crick



Aaron Klug

# PAST & PRESENT GROUP

## PhD Students

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Dave Hinds  
Enoch Huang  
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Yu Xia  
Michael Sykes  
Rachel Kolodny  
Nizar Batada  
Sergio Moreno

Dahlia Weiss  
Gaurav Chopra  
Adelene Sim

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Peter David  
Mark Gerstein  
Steven Brenner  
Boris Fain  
Chen Keasar

Golan Yona  
Ram Samudrala  
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Chris Summa  
Erik Lindahl  
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Karine Bastard

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Junjie Zhang  
Leonid Pereyaslavets  
Yana Gofman  
Ivan Ufimtsev



Recent Research Support: NIH, NSF, HFSP

# NOBEL COMMITTEE IN CHEMISTRY

- Sven Lidin



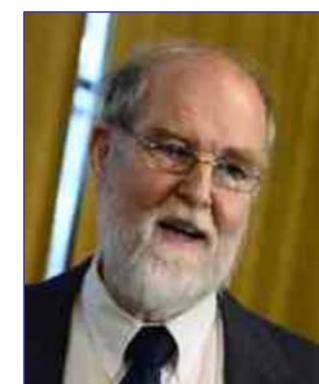
- Måns Ehrenberg



- Jan-Erling Bäckvall



- Gunnar Karlström



- Sara Snogerup Linse



- Astrid Gräslund



A photograph of a man and a young boy cheering on a football field. The man, wearing a red t-shirt with 'STANFORD' and 'NATION' on it, has his arms raised in excitement. The young boy, also in a red shirt, is smiling and pointing upwards. They are standing on a green grassy field with white yard lines. In the background, there are many spectators in the stands under a clear blue sky. A large scoreboard above the stands displays 'STANFORD CARDINAL'.

OUR FIELD IS  
THE BIG  
WINNER

My Thanks  
To You All