

BIRTH & FUTURE OF MULTI-SCALE MODELING OF MACROMOLECULES

Nobel Lectures, Stockholm
8 December 2013

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Structural Biology & Computer Science
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<http://csb.stanford.edu/levitt>

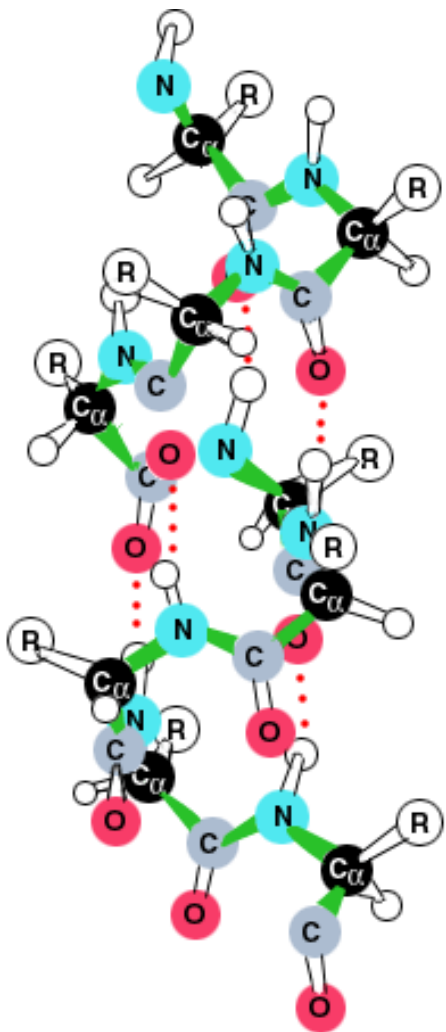
SUMMARY

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

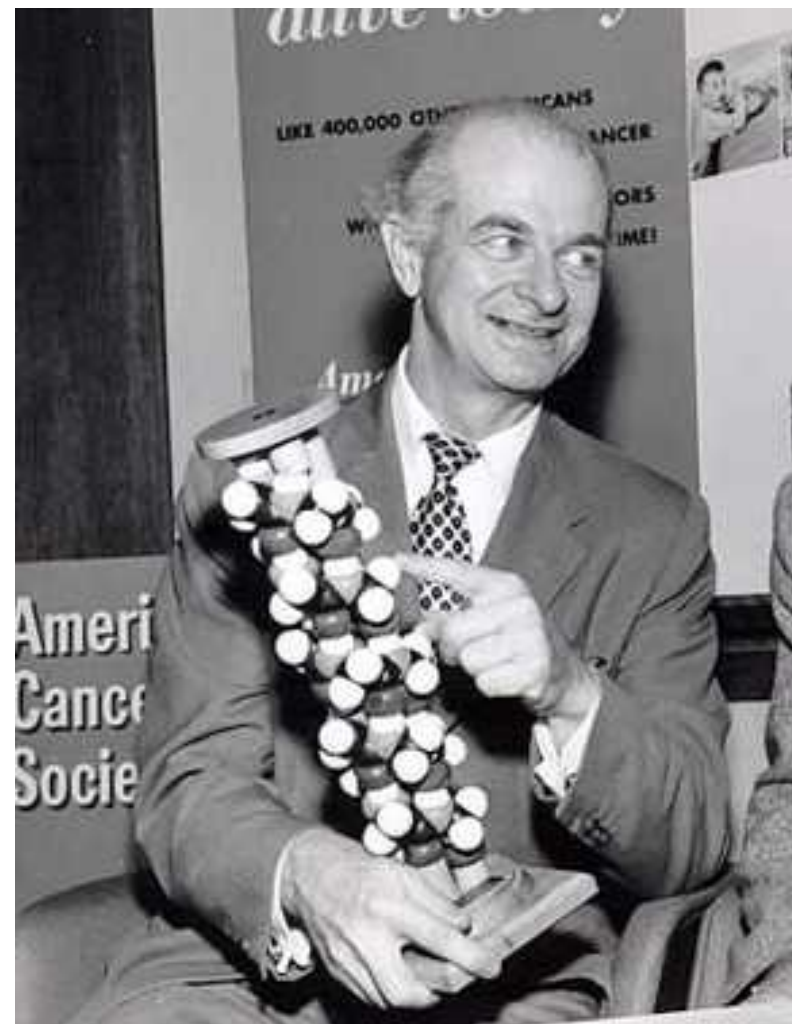
1. HOW IT
ALL BEGAN

STAND ON THE
SHOULDERS OF
GIANTS

1951: PAULING THE GREAT CHEMIST



1951
The alpha-helix



1901-1994

1953: FRANCIS CRICK

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.

- ¹ Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).
- ² Longuet-Higgins, M. S., *Mon. Not. Roy. Astr. Soc., Geophys. Supp.*, **4**, 285 (1949).
- ³ Von Arx, W. S., *Woods Hole Papers in Phys. Oceanog. Meteor.*, **11** (3) (1950).
- ⁴ Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1905).

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 Corey¹. They kindly made their manuscript available to us in advance of its publication. Their model consists of three intertwined 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 rise to the X-ray diagrams is the salt, not the free acid. With the acidic hydrogen atoms it is not clear what would hold the structure together, especially a negatively charged phosphate near the axis which repels 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 a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram).

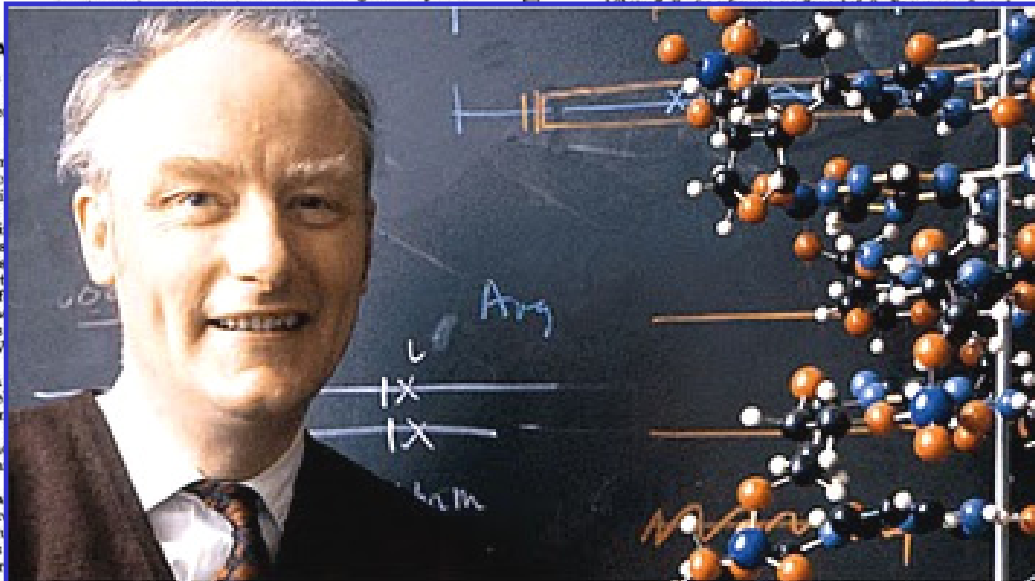
We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β -D-deoxyribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, and owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's² 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 base near it is close to the standard configuration, the sugar being roughly perpendicular to the attached base

This figure is purely diagrammatic. The two ribbons symbolize the two phosphate-sugar 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 z-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



1916-2004

deoxyribose nucleic acid are in line with our structure. So far as is compatible with the experimental data, it can be regarded as unproved against more exact results in the following communication. The details of the results of our structure, which rests mainly though not entirely 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

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.

- ¹ Pauling, L., and Corey, R. B., *Nature*, **171**, 348 (1953); *Proc. U.S. Nat. Acad. Sci.*, **39**, 84 (1953).
- ² Furberg, E., *Acta Chem. Scand.*, **6**, 634 (1952).

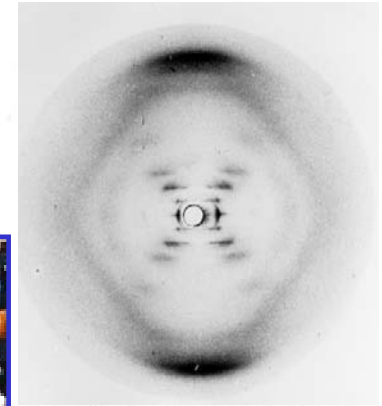


Fig. 1. Fibre diagram of deoxyribose nucleic acid from *E. coli*. Fibre axis vertical.

The innermost maxima of each Bessel function and the angle this line makes with the equator are roughly equal to the angle between an element of a helix and the helix axis. If a unit repeats a times around the helix there will be a meridional reflexion on the n th layer line. The helical configuration produces side bands on this fundamental frequency, the effect being to reproduce 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 diffraction 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 helix axis, the phases of radiation scattered by the points of different diameter passing through each point are the same. Summation of the corresponding Bessel functions gives reinforcement for the inner-

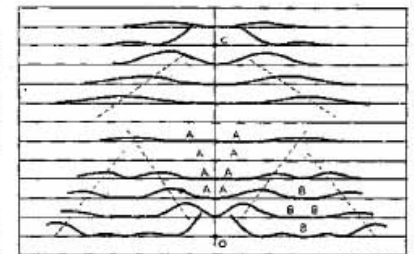


Fig. 2. Diffraction pattern of system of helices corresponding to structure of deoxyribose nucleic acid. The squares of Bessel functions are plotted about 0 on the equator and on the first, second, third and fifth layer lines for half of the nucleotide mean diameter and remainder distributed along a radius, the radius being proportional to the diameter. About a tenth layer line similar functions are plotted for an outer diameter of 15 Å.

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 shown³ (also Stokes, unpublished) that the intensity distribution in the diffraction pattern of a series of points equally spaced along a helix is

DNA Model and Experiment

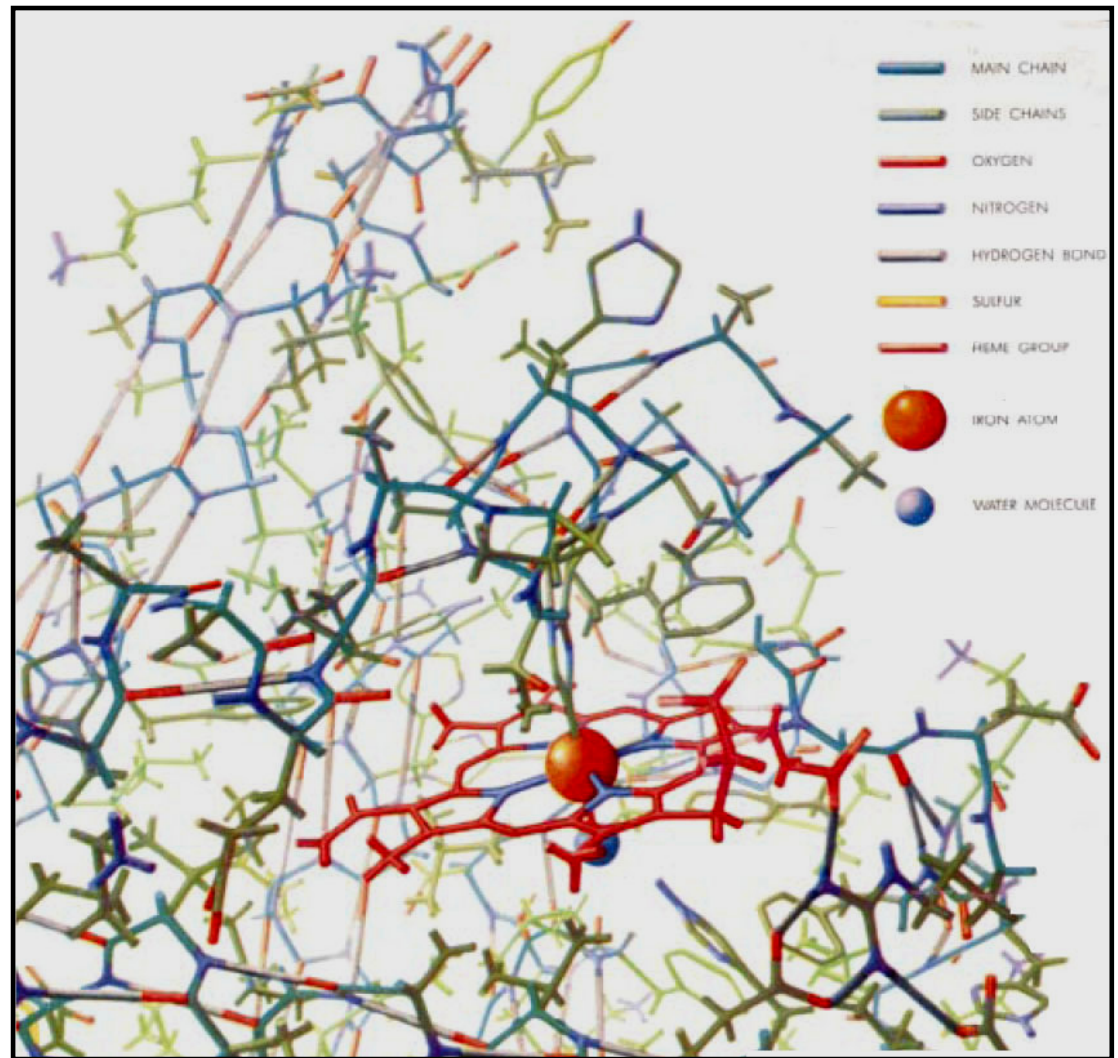
1959: KENDREW AND MYOGLOBIN



1917-1997

First protein X-ray structure.

Scientific American 1961

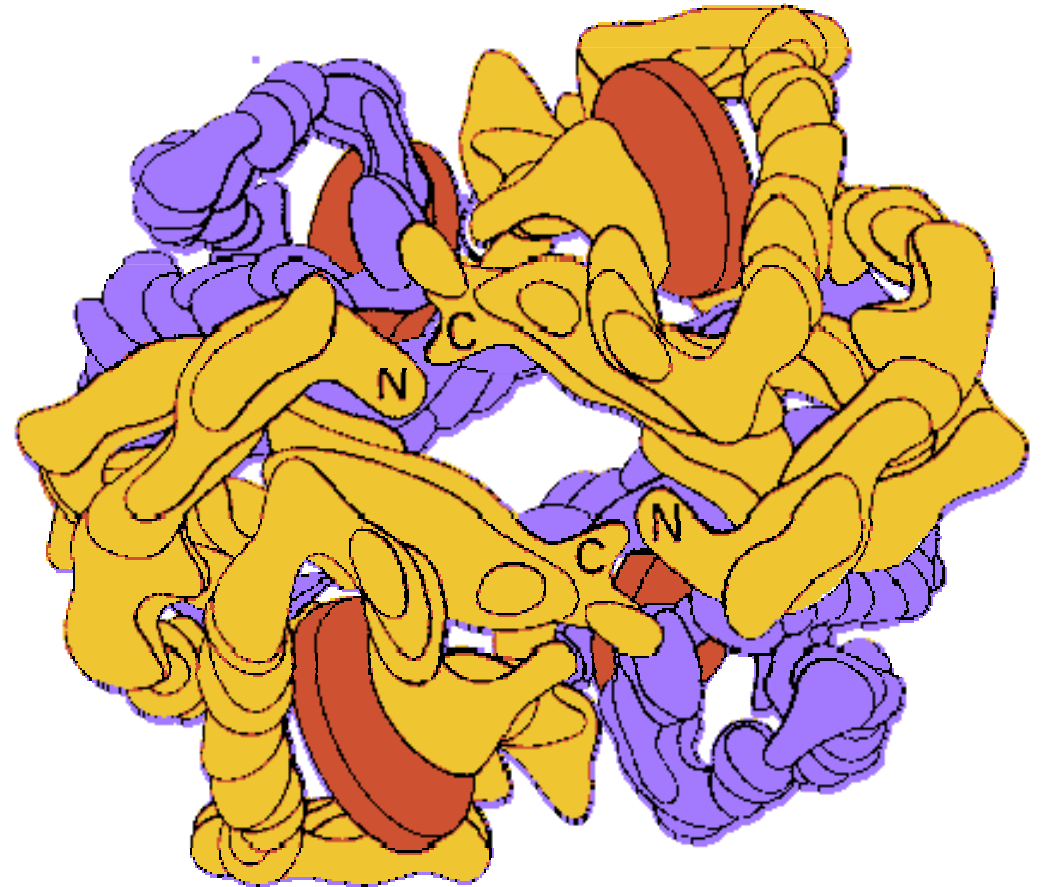


Painted by artist Irving Geis

1962: PERUTZ AND HEMOGLOBIN

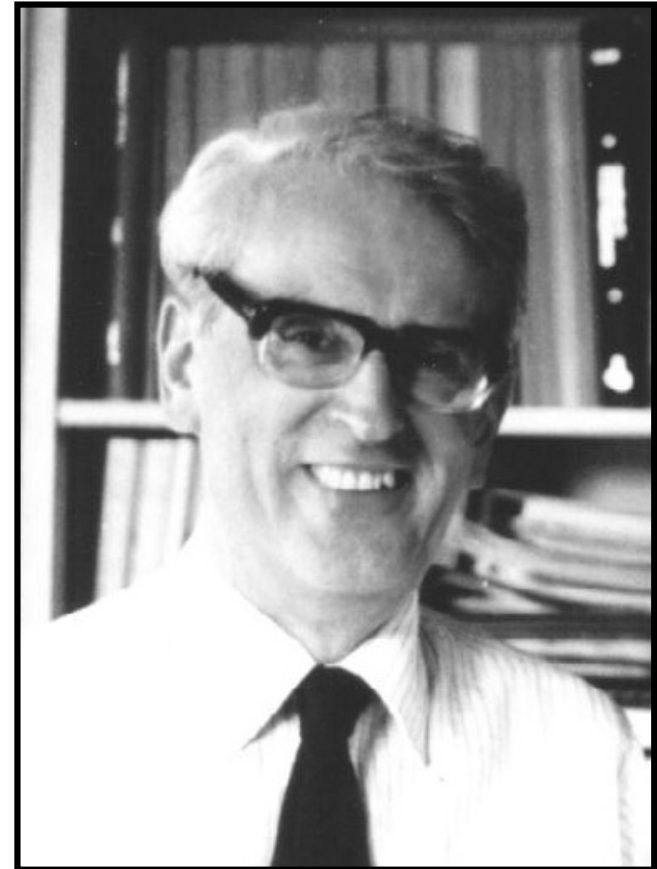
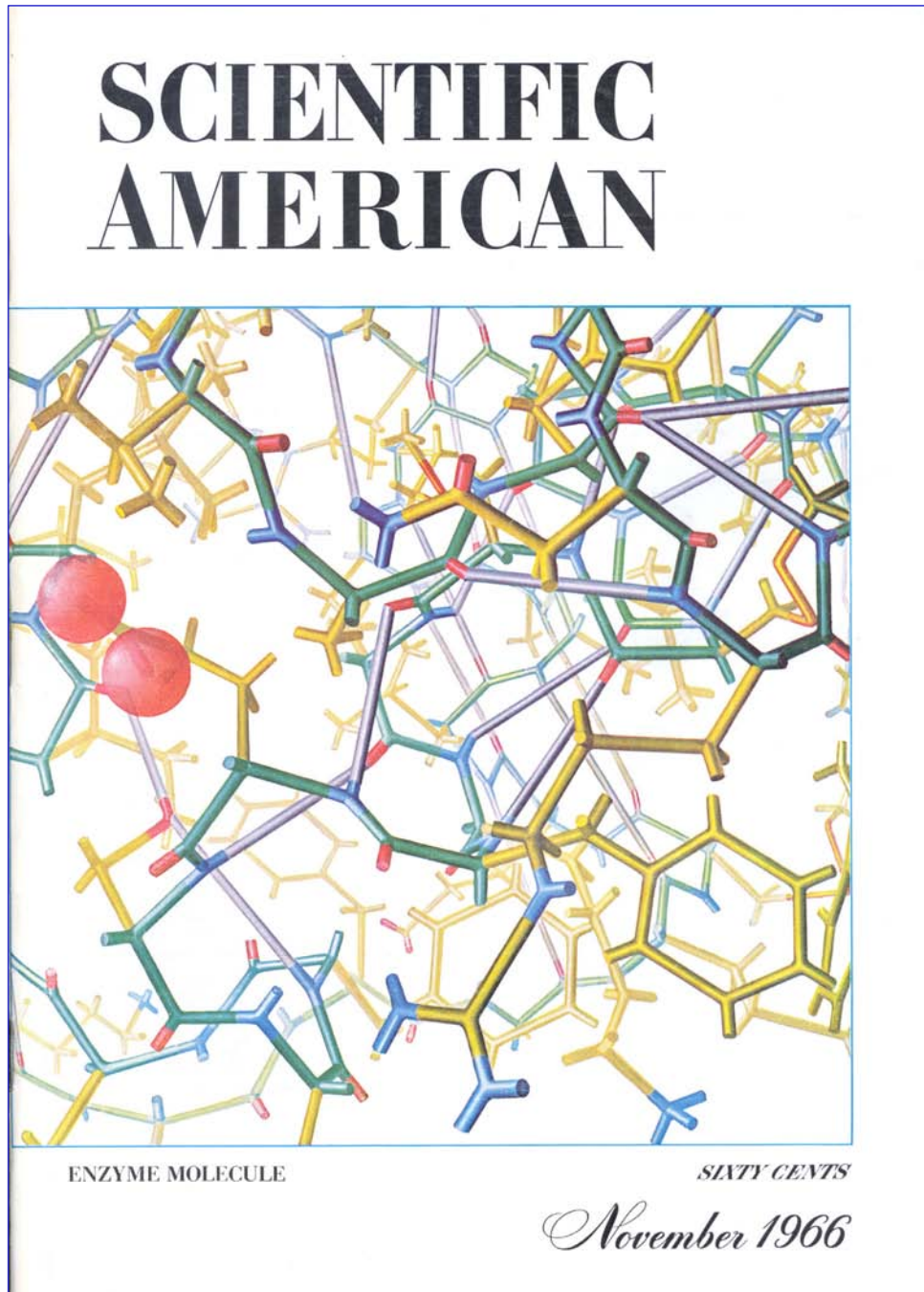


1914-2002



The REAL HERO of structural biology.

1965: PHILLIPS AND LYSOZYME



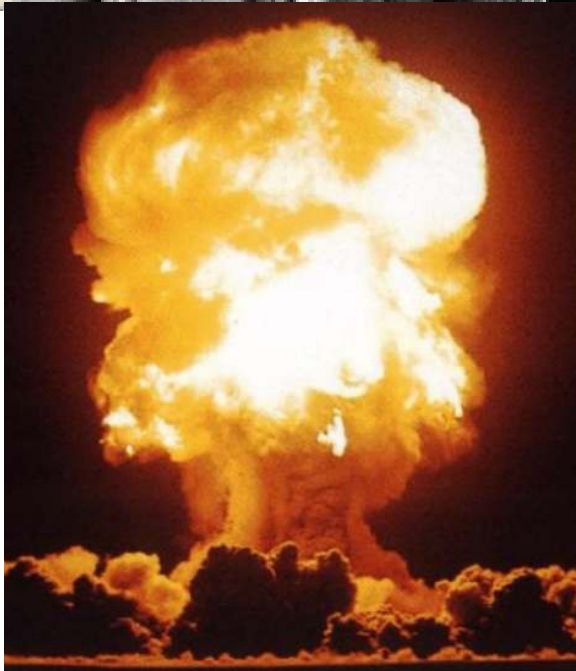
1924-1999

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).

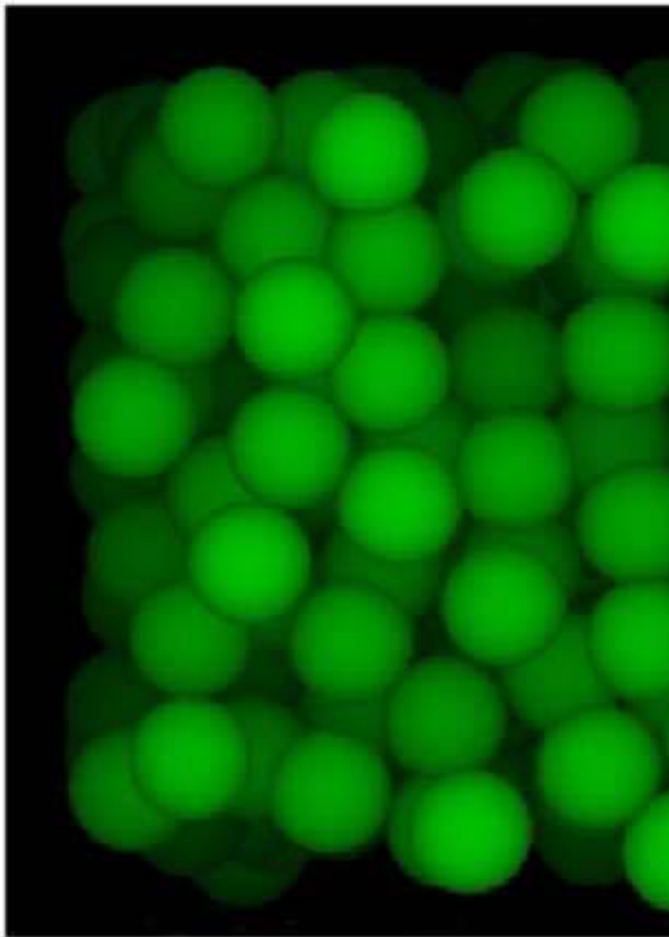


To get around the apparently inevitable incorporation of the random, von Neumann devised a third kind of simulation called the "Monte Carlo" in homage to the games of luck he enjoyed in the gambling capital of Europe. He held that random elements in simulations were unacceptable, a form of contamination 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.

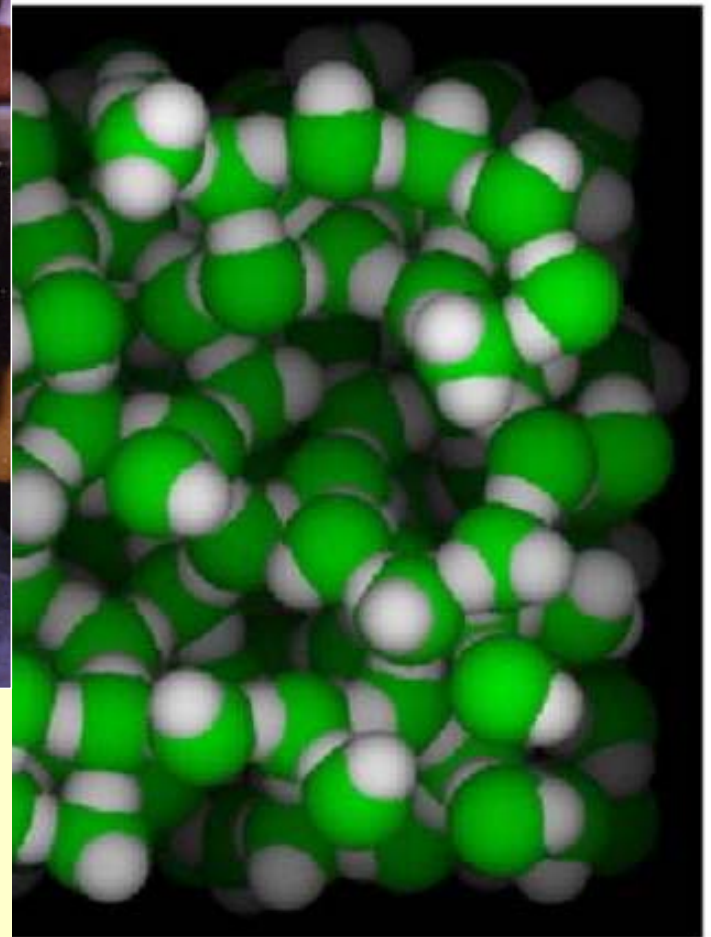
<http://trace.ntu.ac.uk/frame2/articles/borg/JvN.html>

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

amazon.com 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)

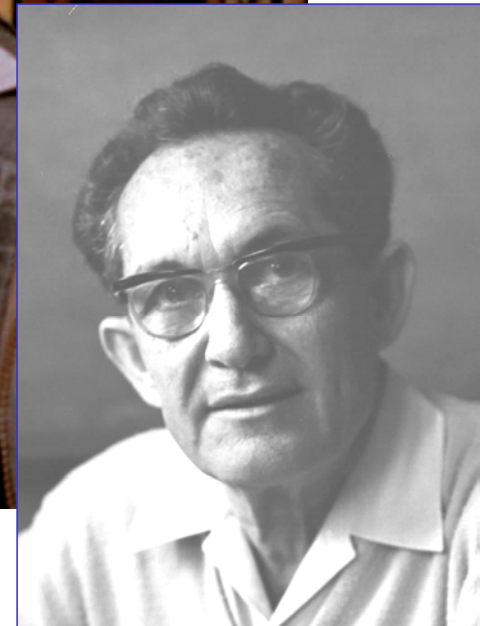
- The REVOLUTION IN BIOLOGY (04/01/1964)**
- INSIDE THE CELL (11/01/1964)**
- PROTEINS IN ONE DIMENSION (18/01/1964)**
- PROTEINS IN THREE DIMENSIONS (25/01/1964)**
- REPRODUCTION AND GENETICS (01/02/1964)**
- NUCLEIC ACID The INFORMATION CARRIER (08/02/1964)**
- The MESSENGER OF THE GENES (15/02/1964)**
- SOLVING THE CODE (22/02/1964)**
- LIVING ARCHITECTURE The VIRUSES (29/02/1964)**
- The WAY AHEAD (07/03/1964)**



SHNEIOR LIFSON 1914-2001



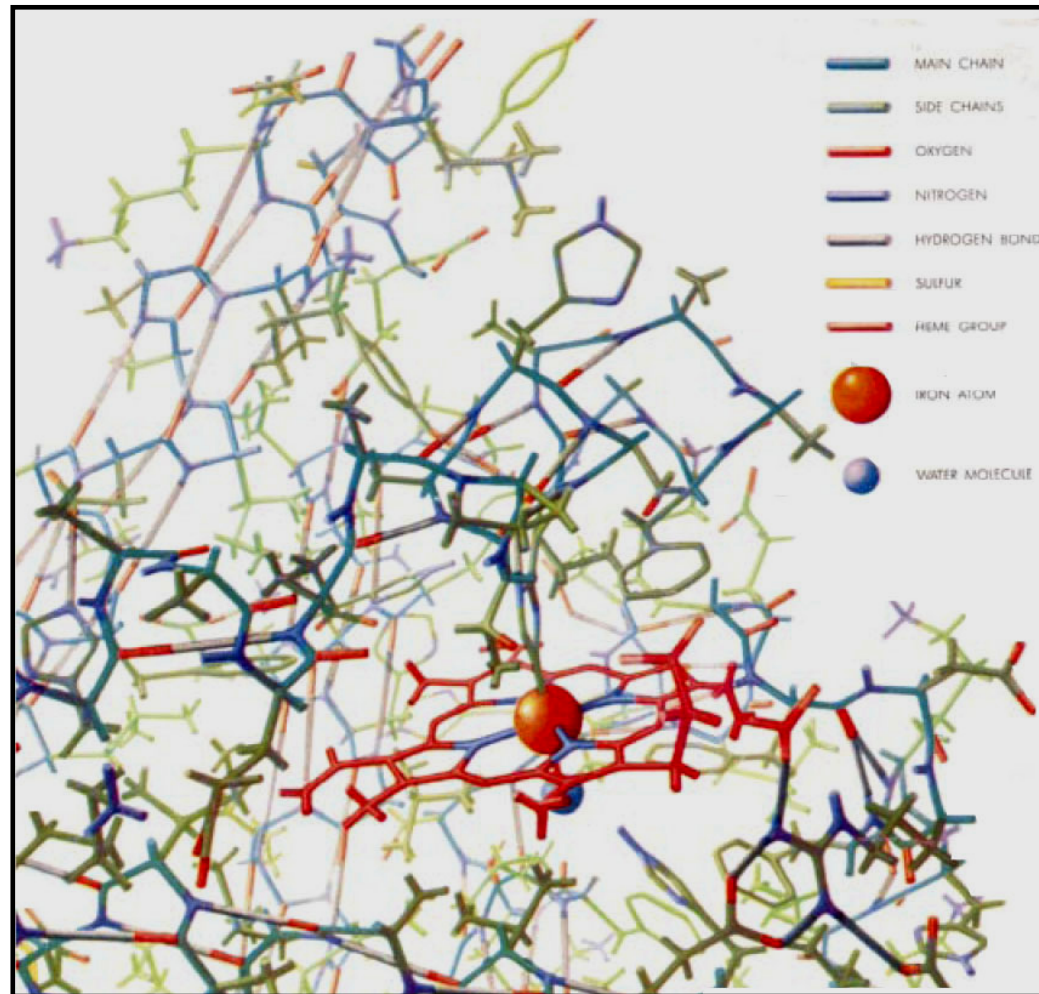
Weizmann Institute 1967-68



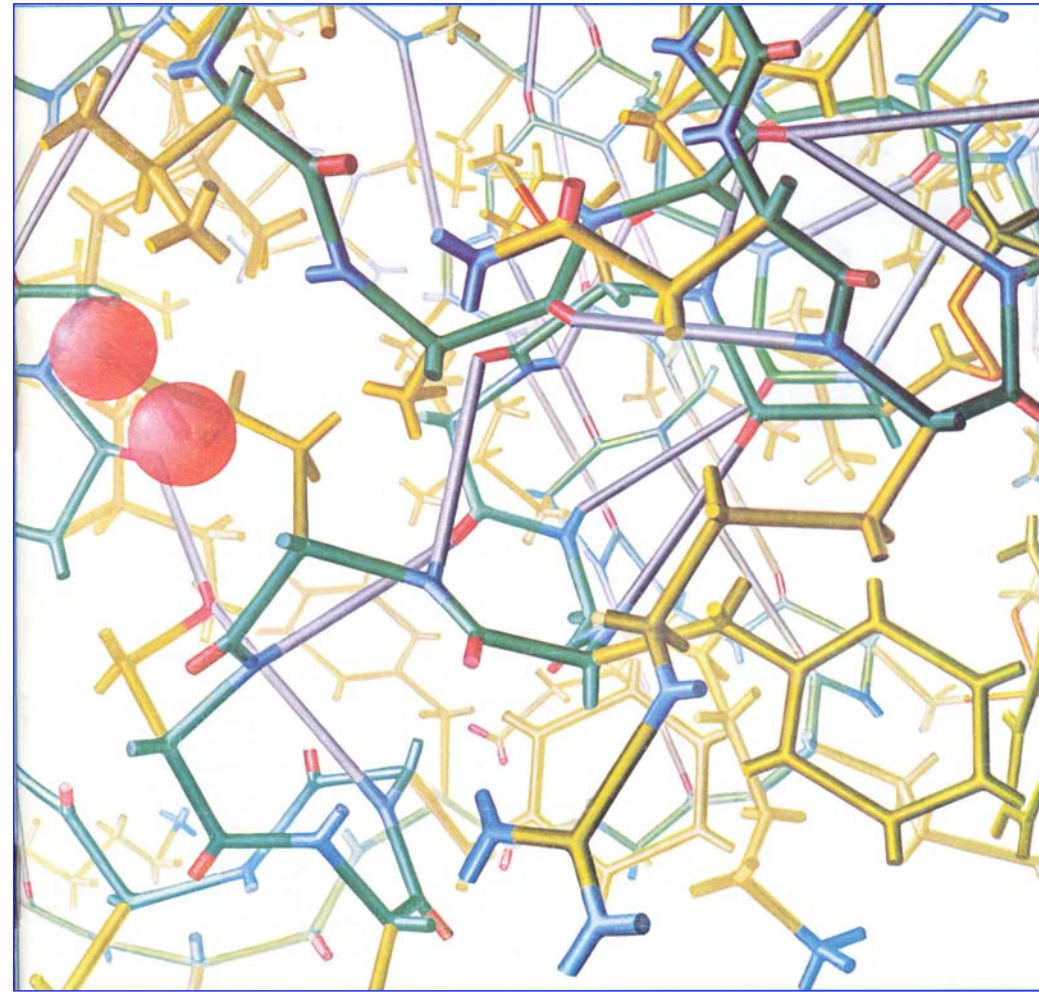
BIOMOLECULES
ARE DETAILED

BIOLOGY IS DETAILED INTERACTIONS

Myoglobin 1961



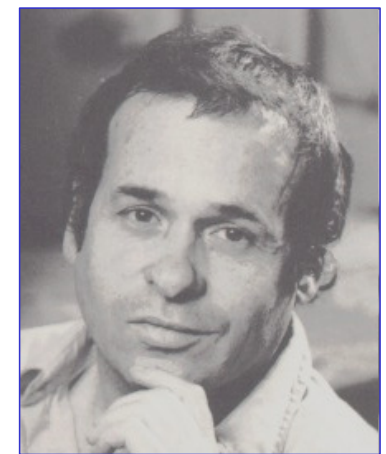
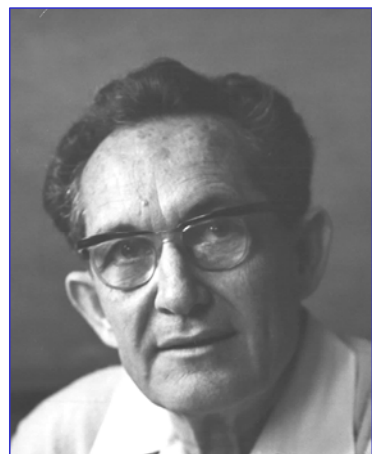
Lysozyme 1966



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. LIFSON AND A. WARSHEL

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

(Received 13 May 1968)

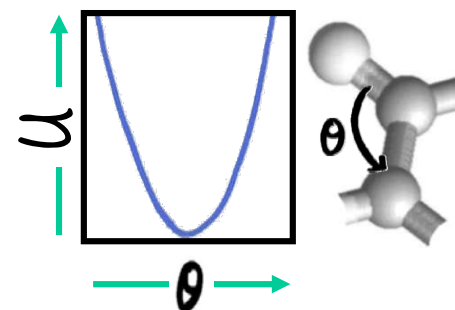
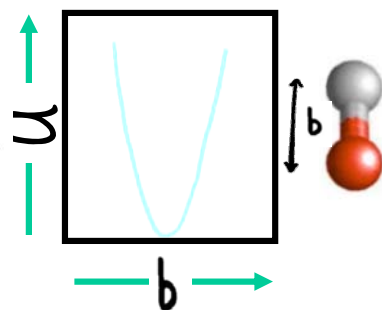
MOLECULAR POTENTIAL ENERGY

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

All Bonds

Hooke 1635

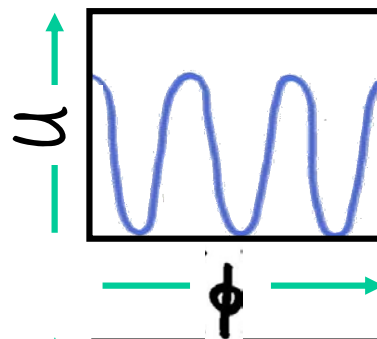
All Angles



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

All Torsion Angles

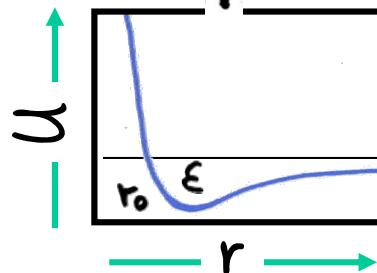
Fourier 1768



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

All Nonbonded pairs

Van der Waals 1837

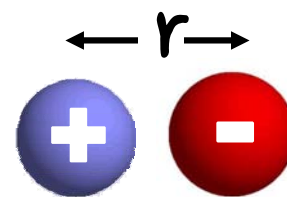
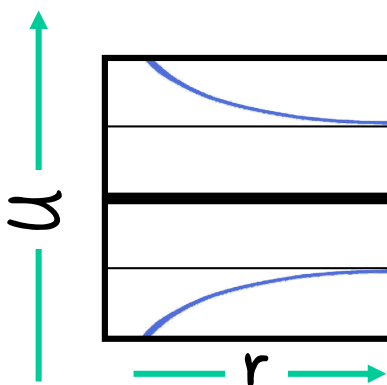


$$+ \sum \frac{332 q_i q_j}{r}$$

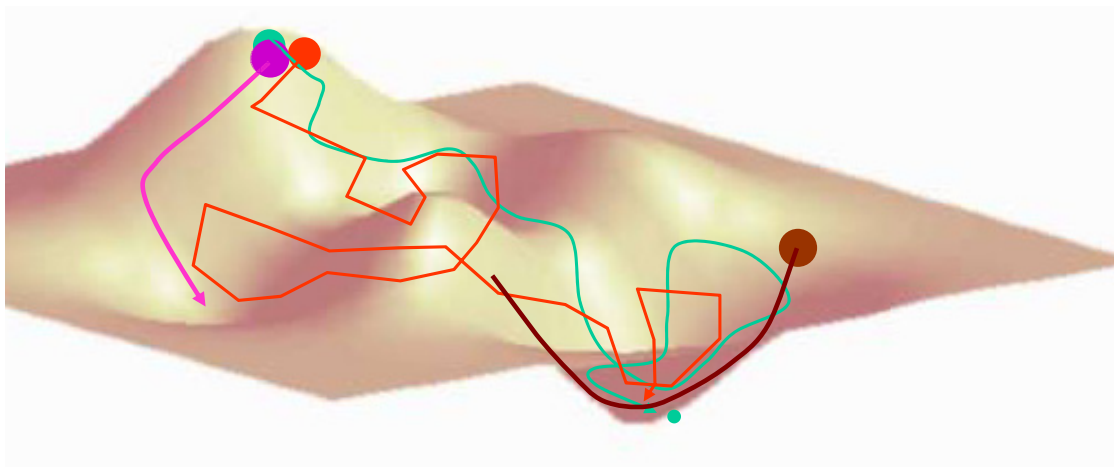
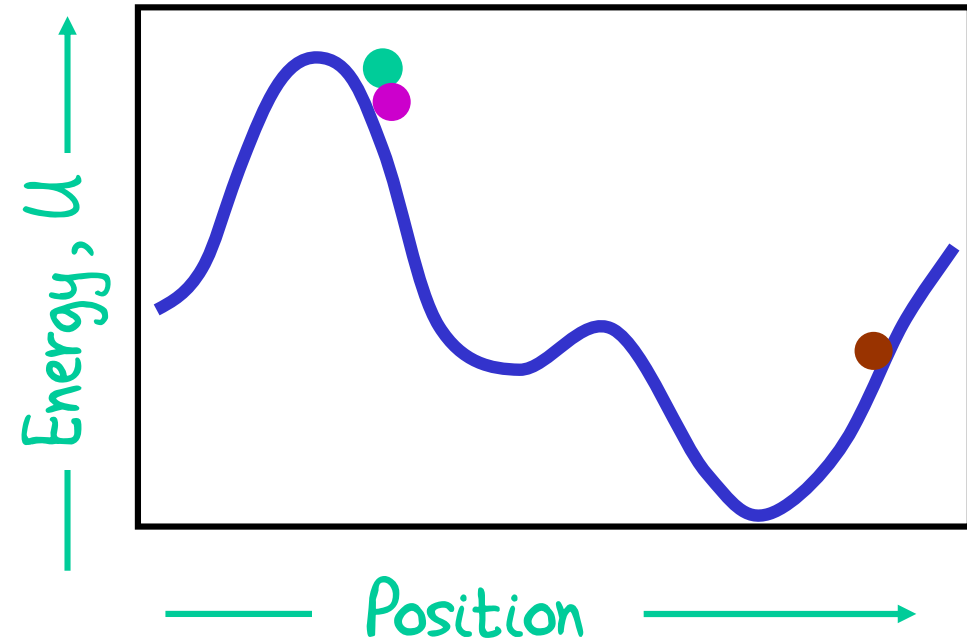
All partial charges

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

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

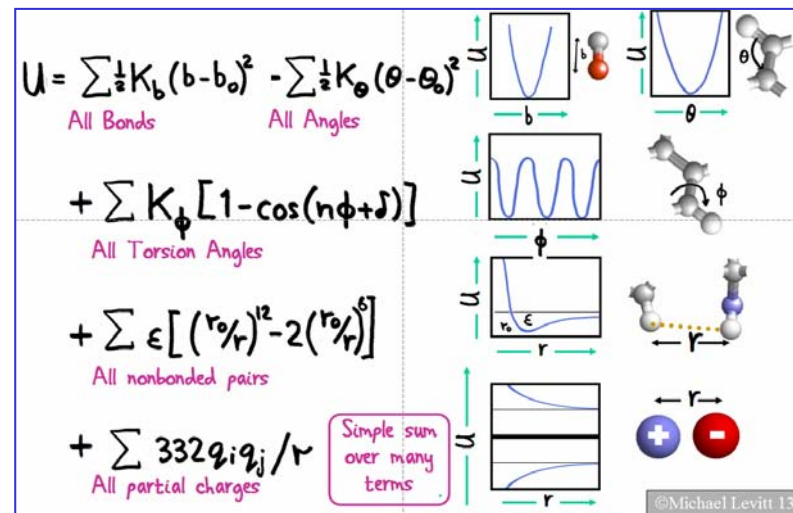
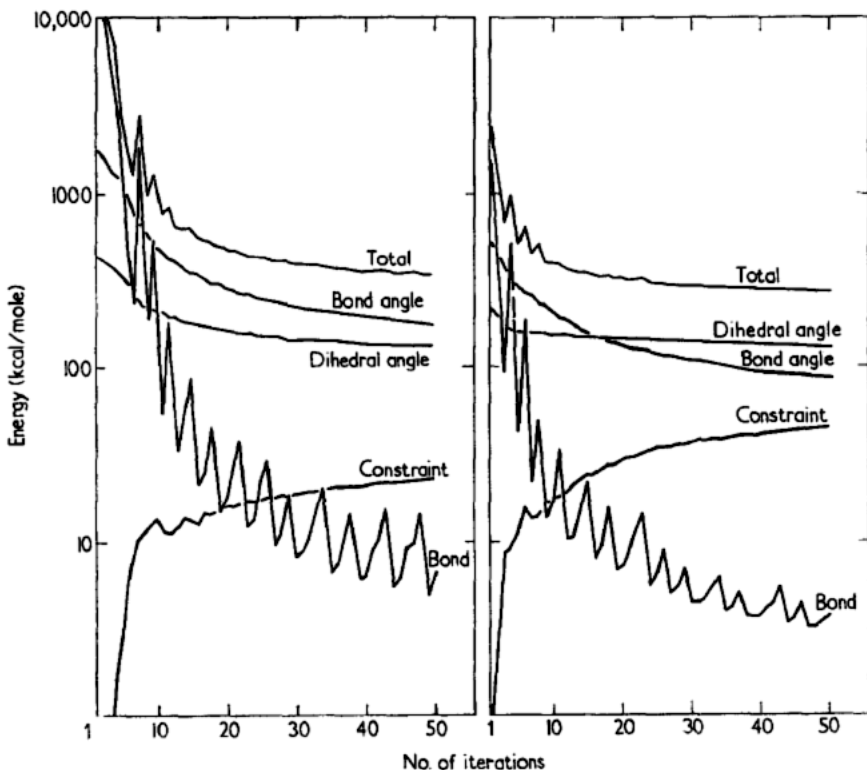
MICHAEL LEVITT† AND SHNEIOR LIFSON

Weizmann Institute of Science

J. Mol. Biol. (1969) **46**, 269-279



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



First protein structure refinement

COARSE GRAINED MODELS

1975

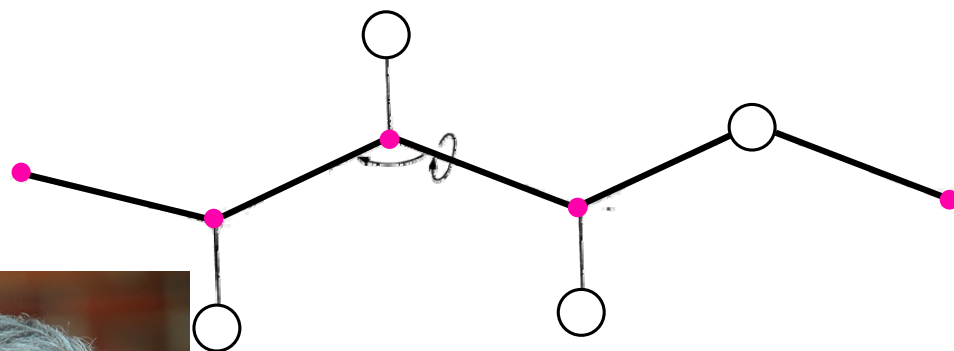
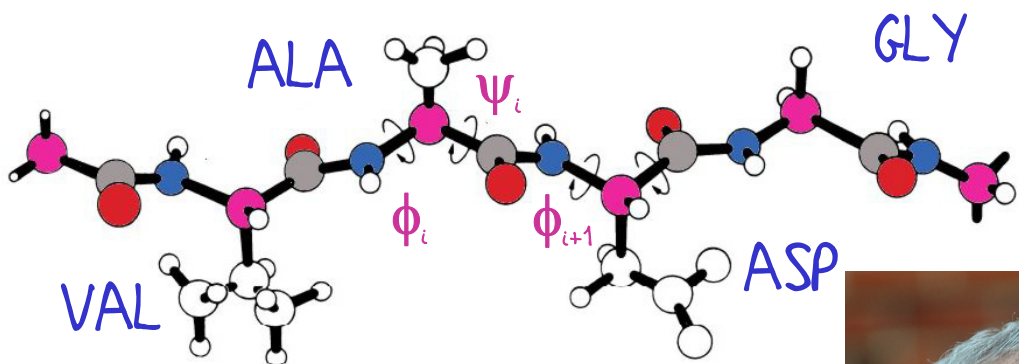


COMPUTER SIMULATION OF PROTEIN FOLDING

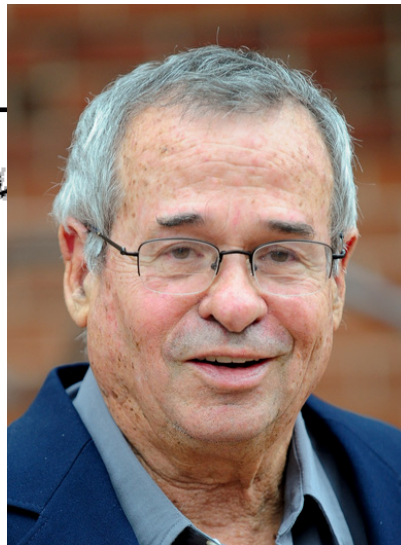
Michael Levitt* & Arieh Warshel*

Nature Vol. 253 February 27 1975

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

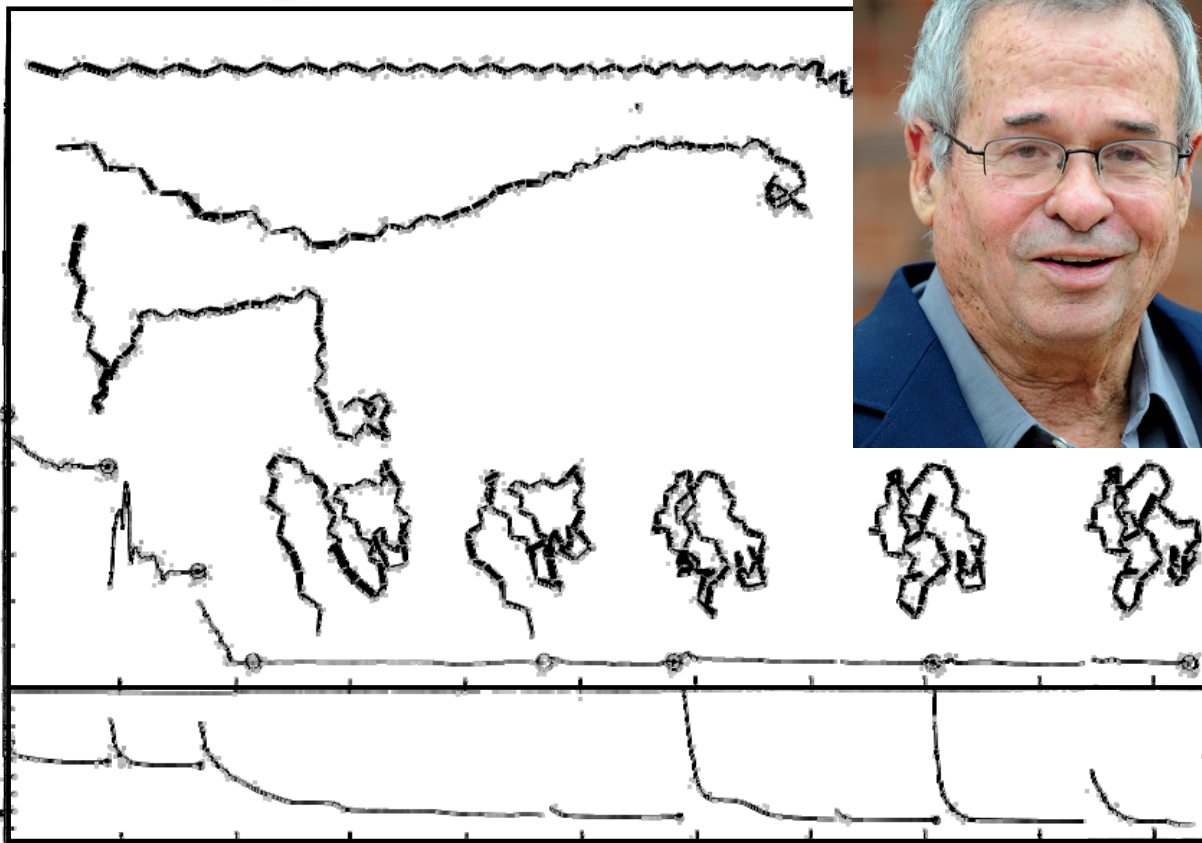


Reduced models



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

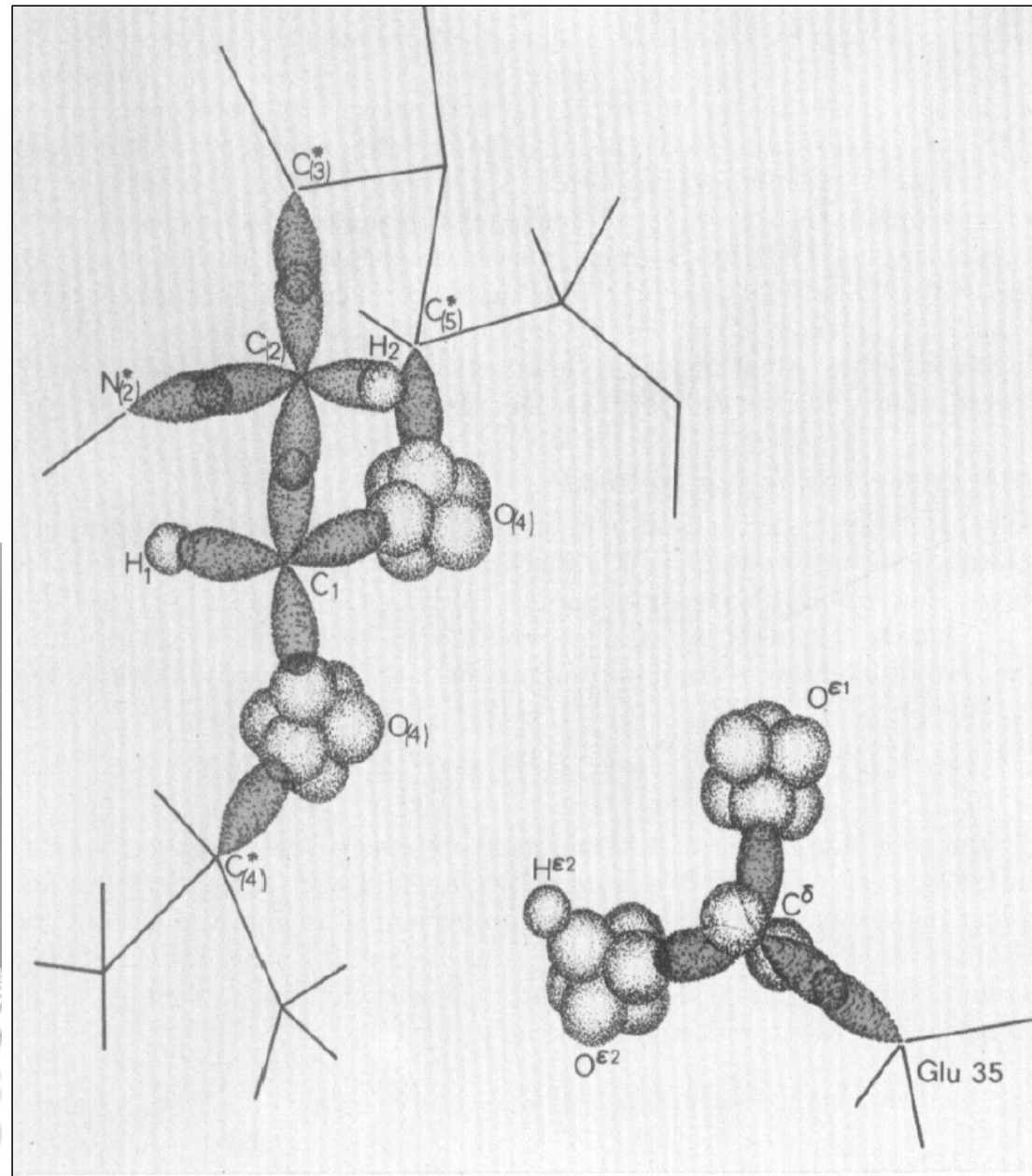
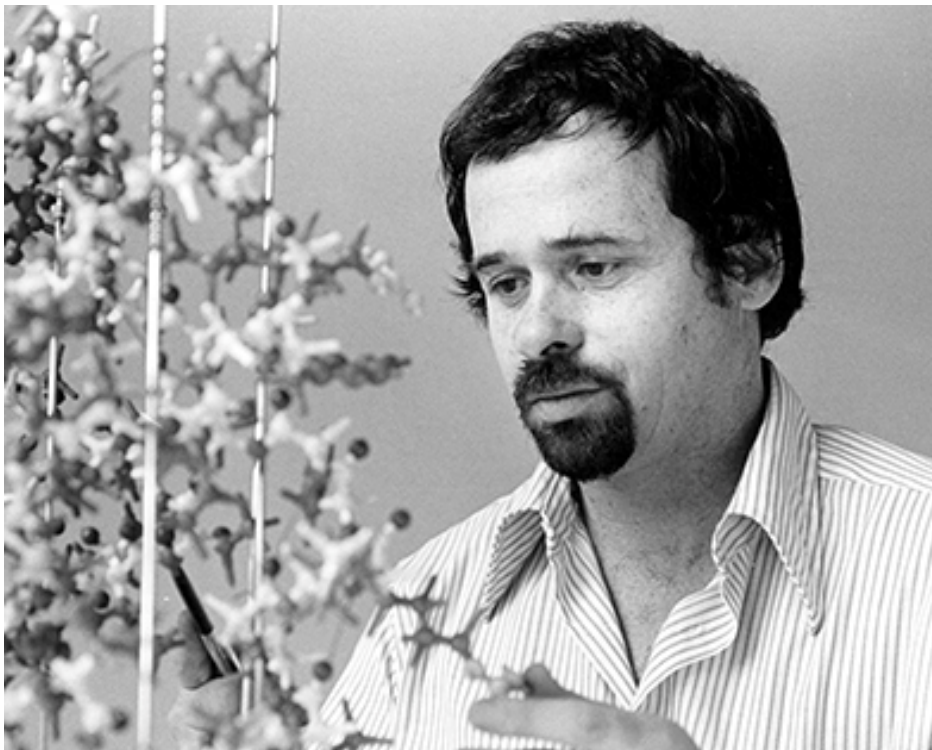
J. Mol. Biol. (1976) **103**, 227–249

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**

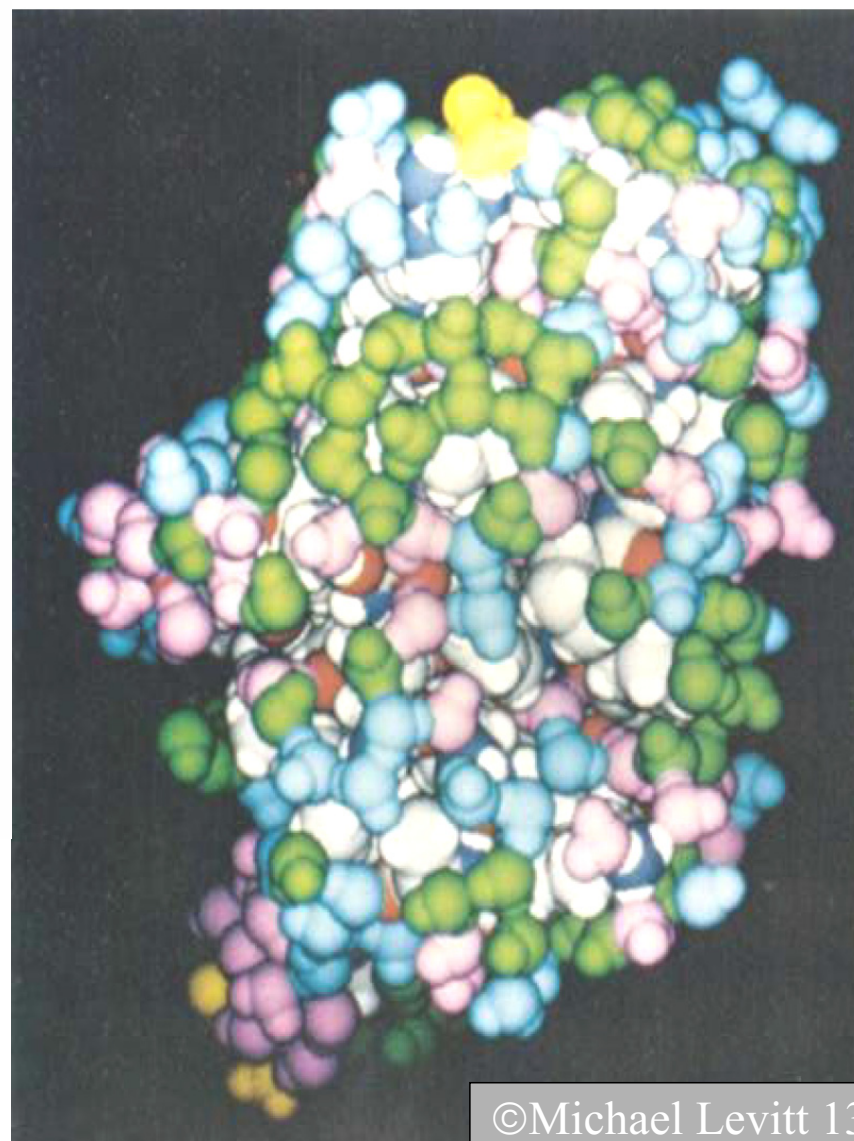
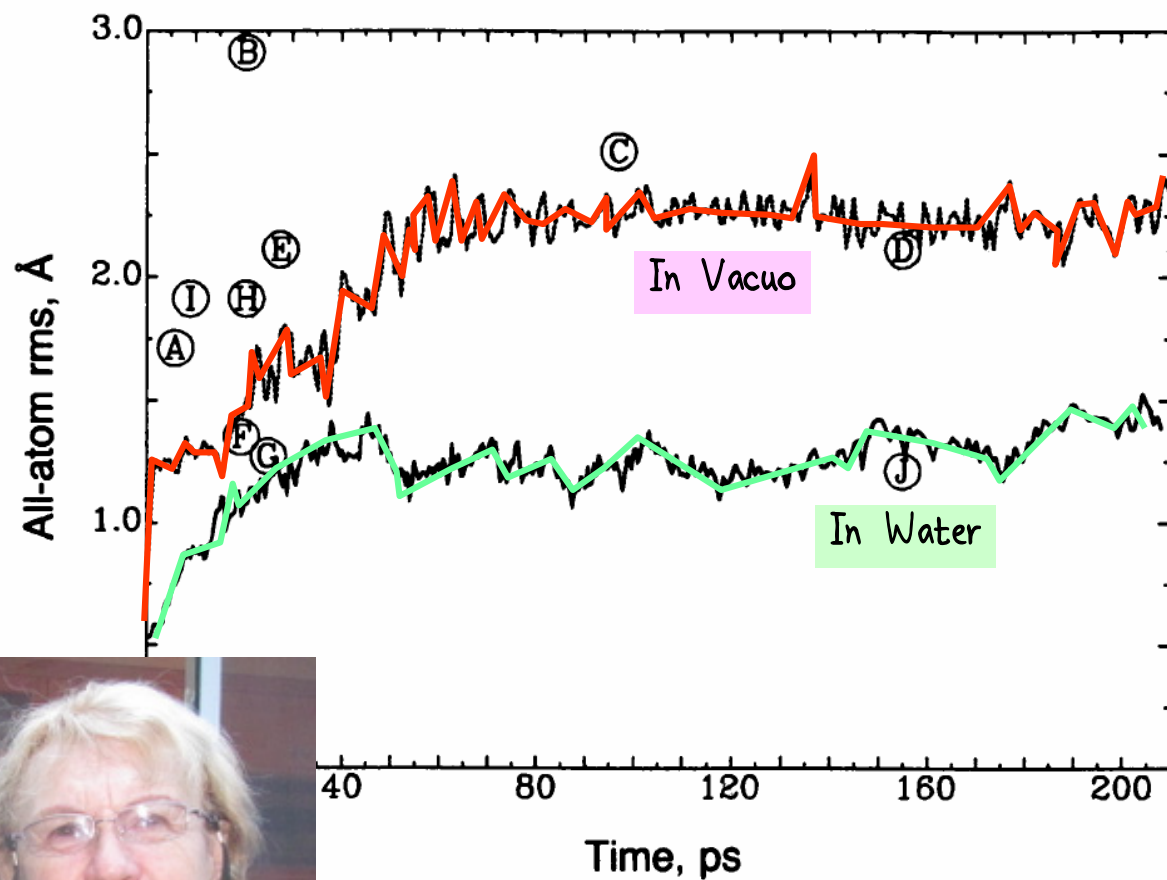
PROTEIN MOLECULAR
DYNAMICS IN
WATER 1988

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



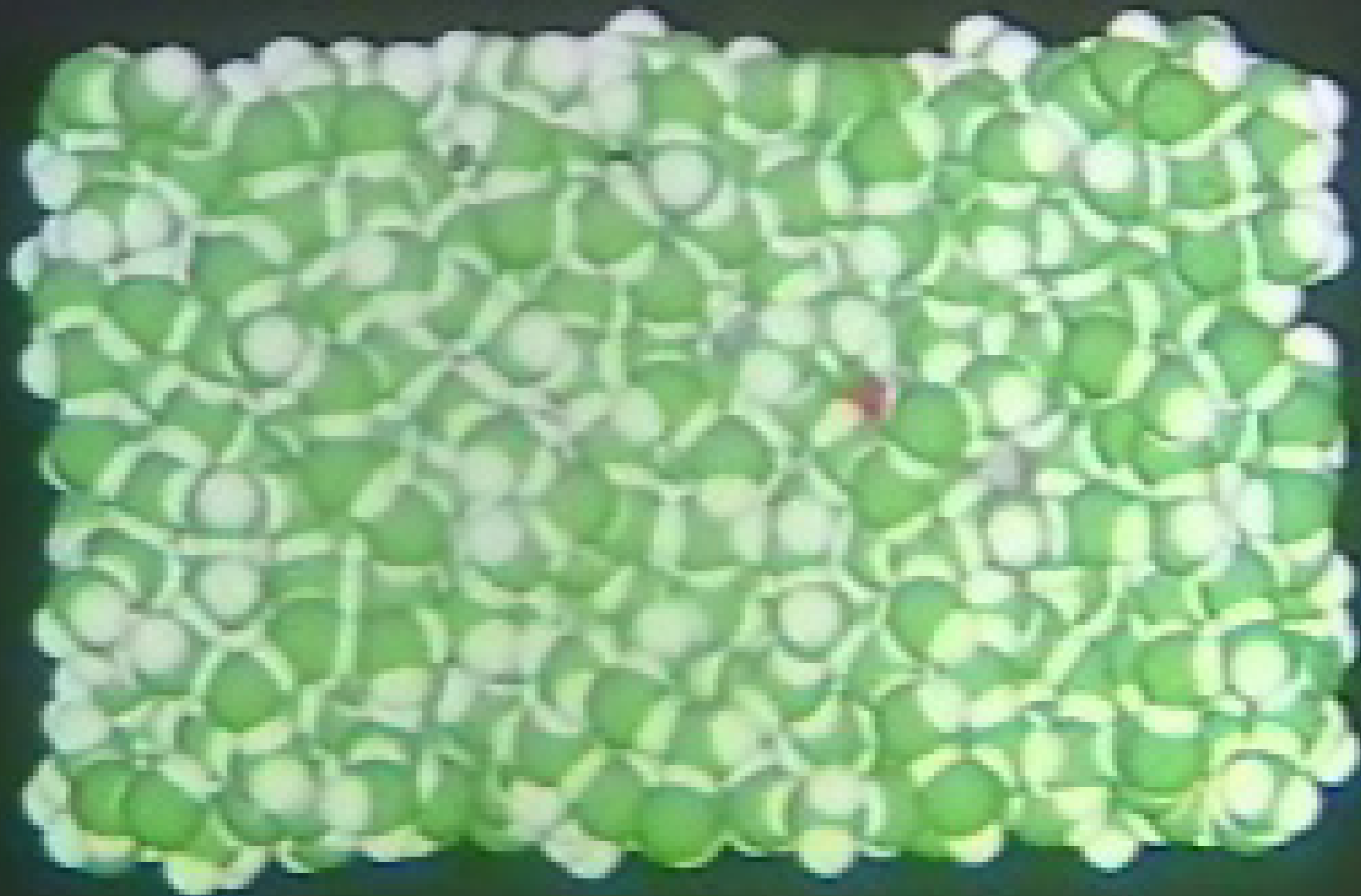
α -HELIX MOLECULAR DYNAMICS IN WATER 1990

Molecular Dynamics Simulations of Helix Denaturation

Valerie Daggett and Michael Levitt

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





Alpha-Helices Unfolding in Solution

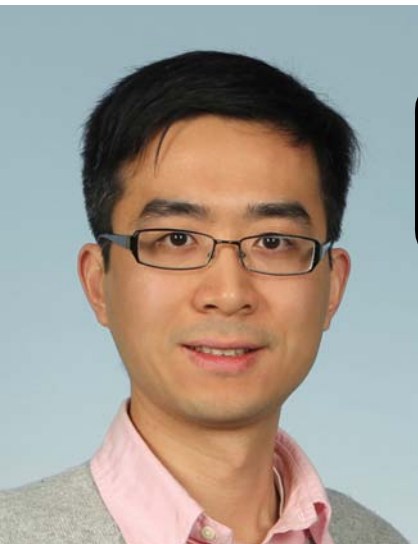
SUMMARY SO FAR

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3. FUTURE: MULTI-
SCALE DYNAMICS OF
HUGE STRUCTURES

REDUCED DEGREES OF FREEDOM

MARKOV STATE DYNAMICS OF RNA POLYMERASE II



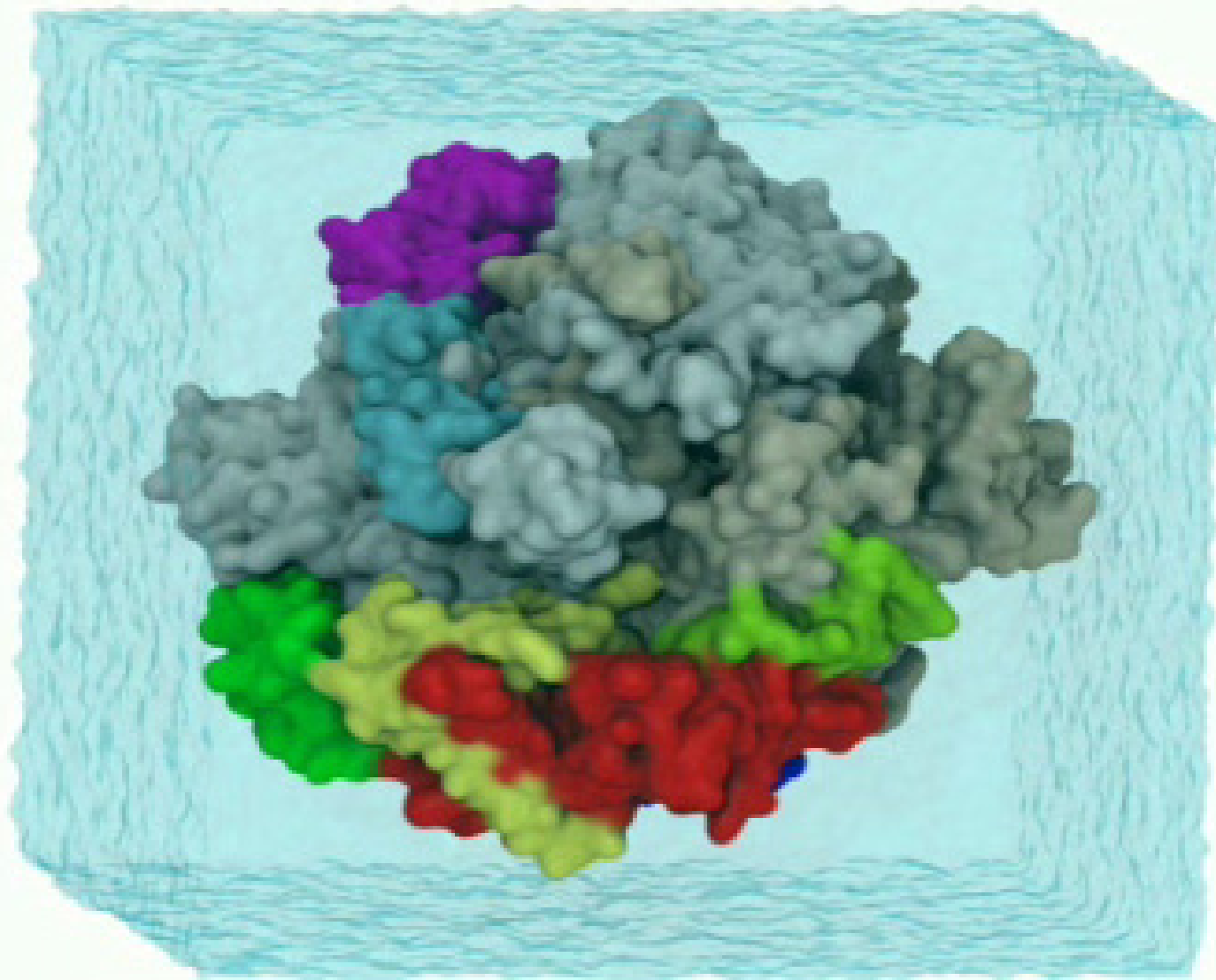
Xuhui Huang



Daniel Silva

RNA Polymerase II
(10 subunits, ~ 422 kDa)

Explicit water solvent
(~ 122,000 molecules)



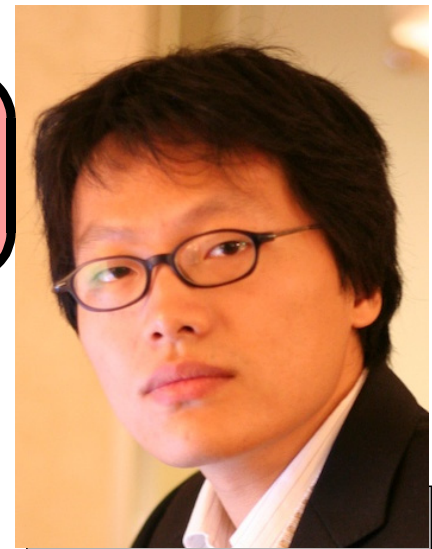
Simulation of a ~ 426,000 atom system

NORMAL MODES OF ENTIRE RIBOSOME

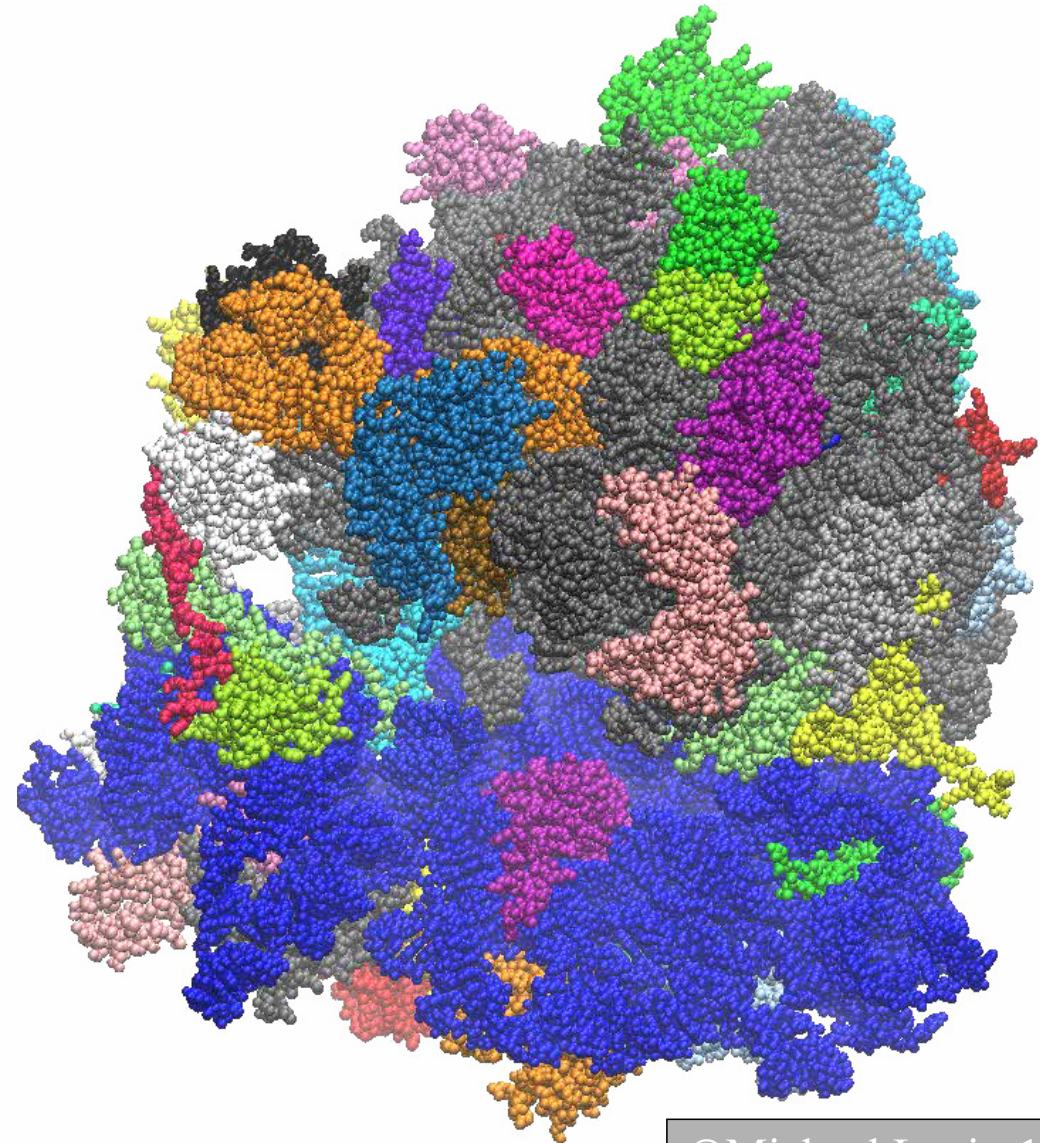
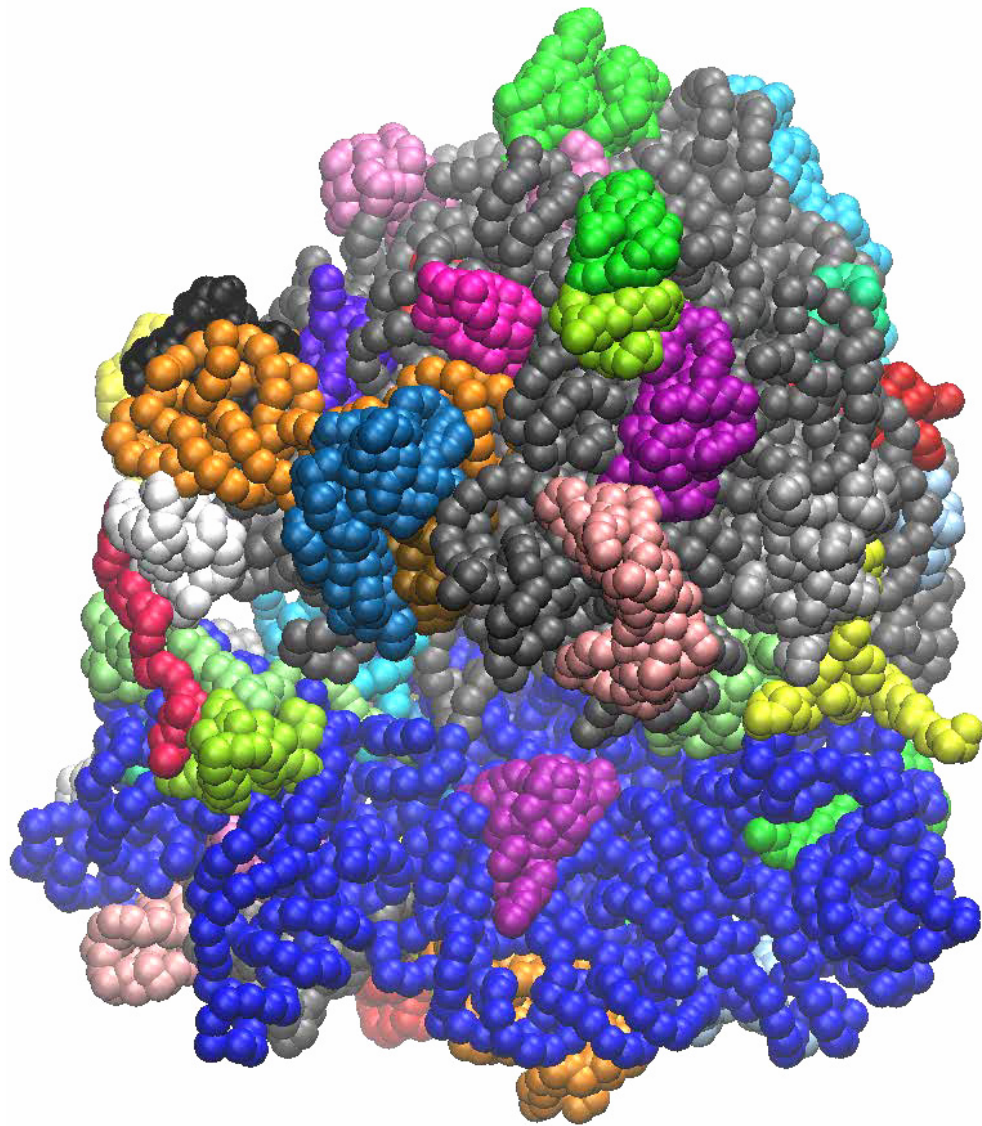


Jenelle Bray

Junjie Zhang



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



NATURAL MOVE MONTE CARLO OF RNA



Peter Minary



Adelene Sim

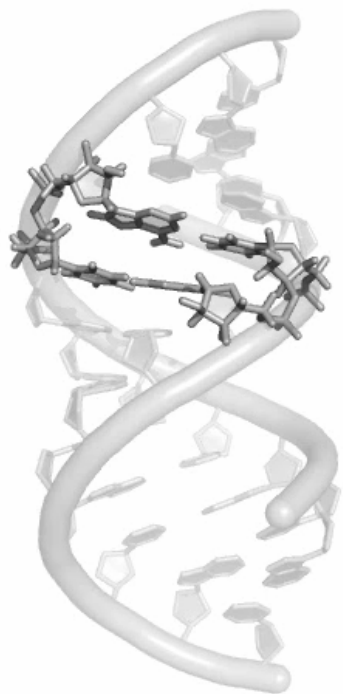
NATURAL MOVE MONTE CARLO

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

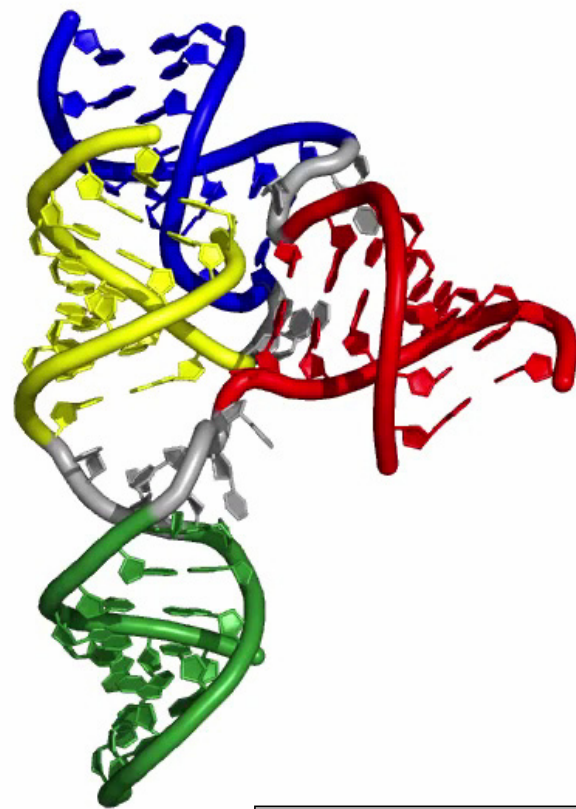
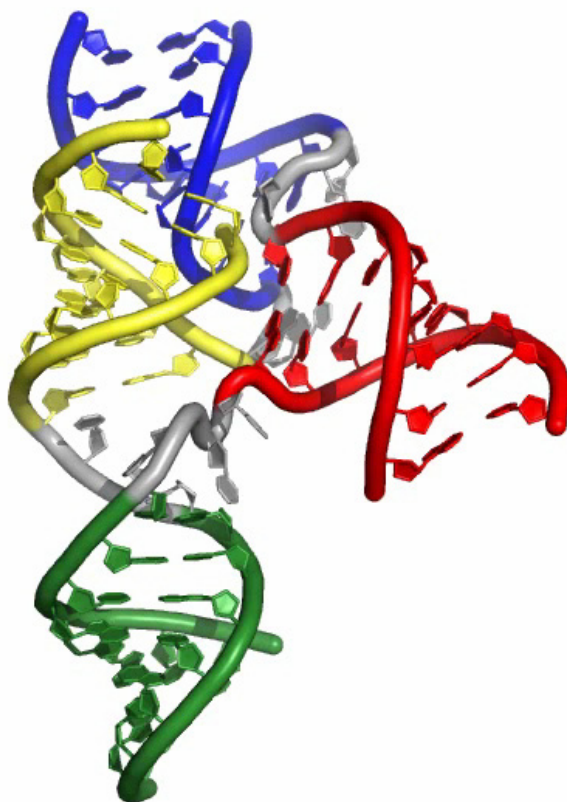
Nucleotides

Base Pairs

Hairpin Helices

Many Helices together

All of these



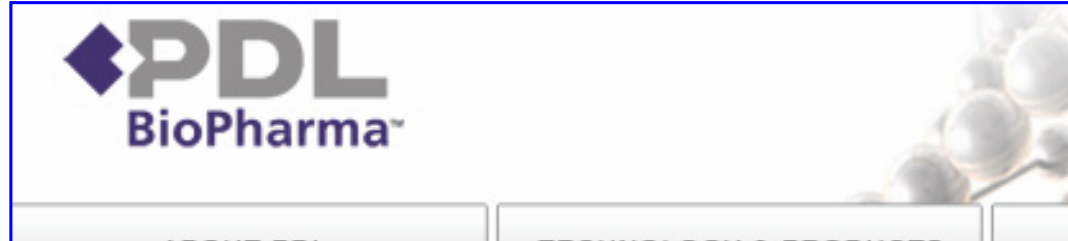
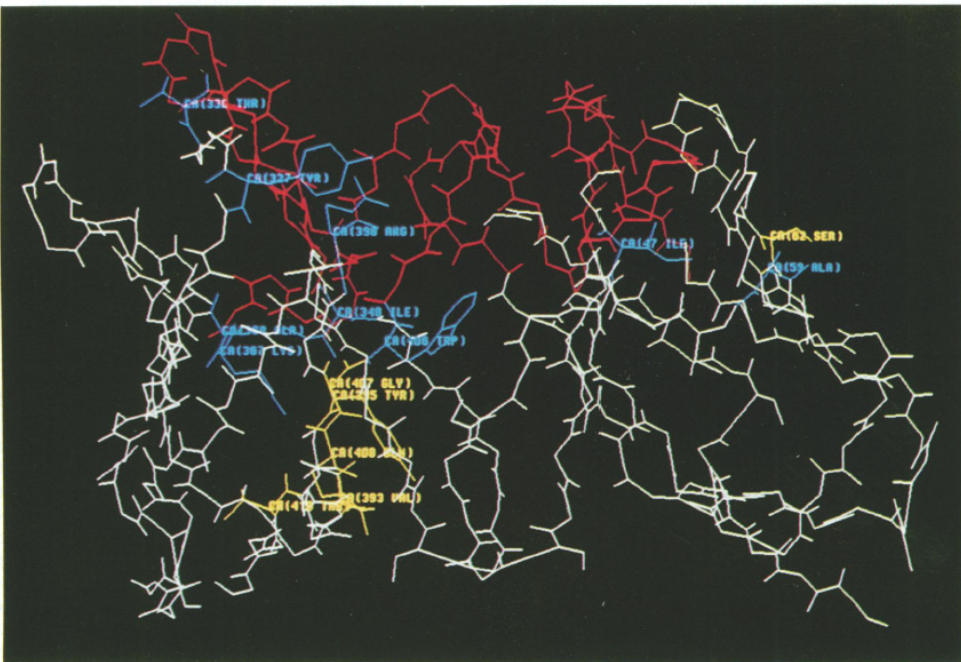
APPLICATIONS TO HUMAN HEALTH

ANTIBODY HUMANIZATION

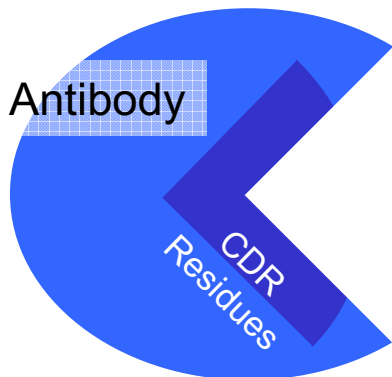
A humanized antibody that binds to the interleukin 2 receptor

(chimeric antibody/antibody affinity/autoimmune disease)

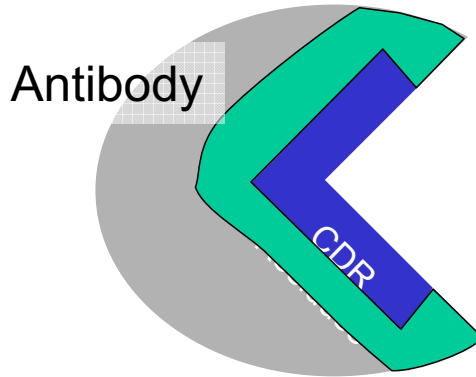
CARY QUEEN*, WILLIAM P. SCHNEIDER*, HAROLD E. SELICK*†, PHILIP W. PAYNE*,
 NICHOLAS F. LANDOLFI*, JAMES F. DUNCAN*‡, NEVENKA M. AVDALOVIC*, MICHAEL LEVITT§,
 RICHARD P. JUNGHANS¶, AND THOMAS A. WALDMANN¶



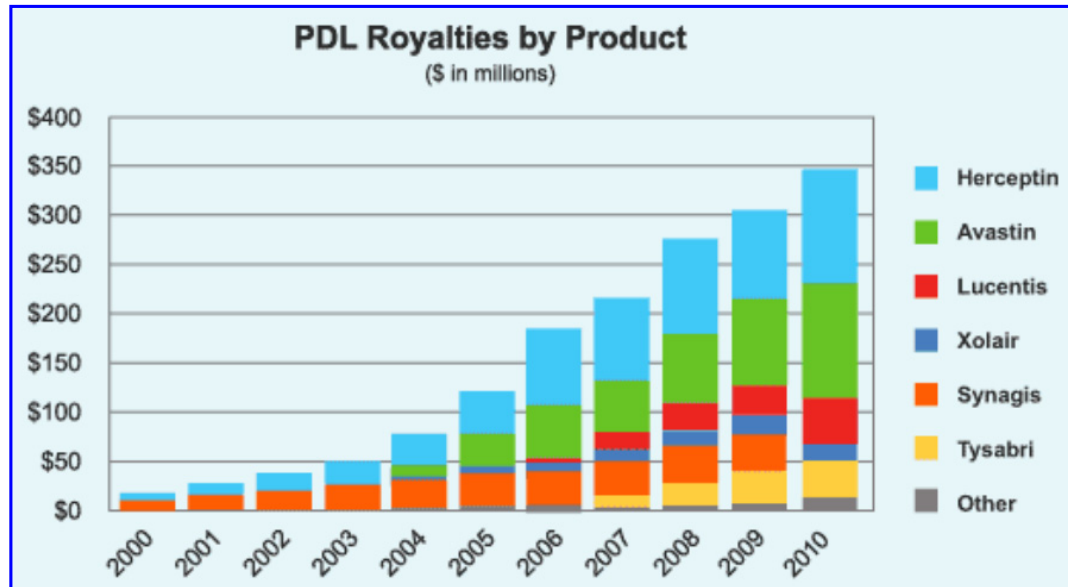
Seven employees living in Nevada next to Lake Tahoe.



WINTER



QUEEN



Compare
Genomes.

Andrea Scaiewicz

Ivan Ufimtsev

X-Ray Phase
Problem.



BREADTH
OR LACK
OF FOCUS?



Large
Complexes.

Nir Kalisman

Yana Gofman

Membrane
Proteins.

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 MHz	1 MB	HALL
2013	\$4,000	1 GHz	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,
BUT DO NOT BE
TOO STUPID...

BEGINNER SEA-KAYAKING ALONE



Ornö Kyrke
Store

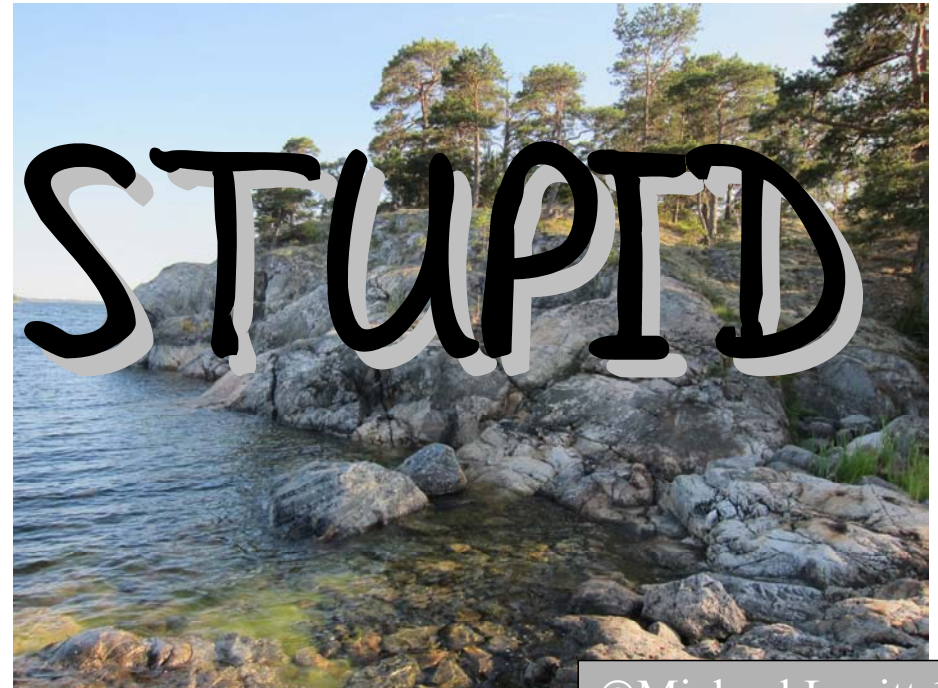
“Paradise”

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

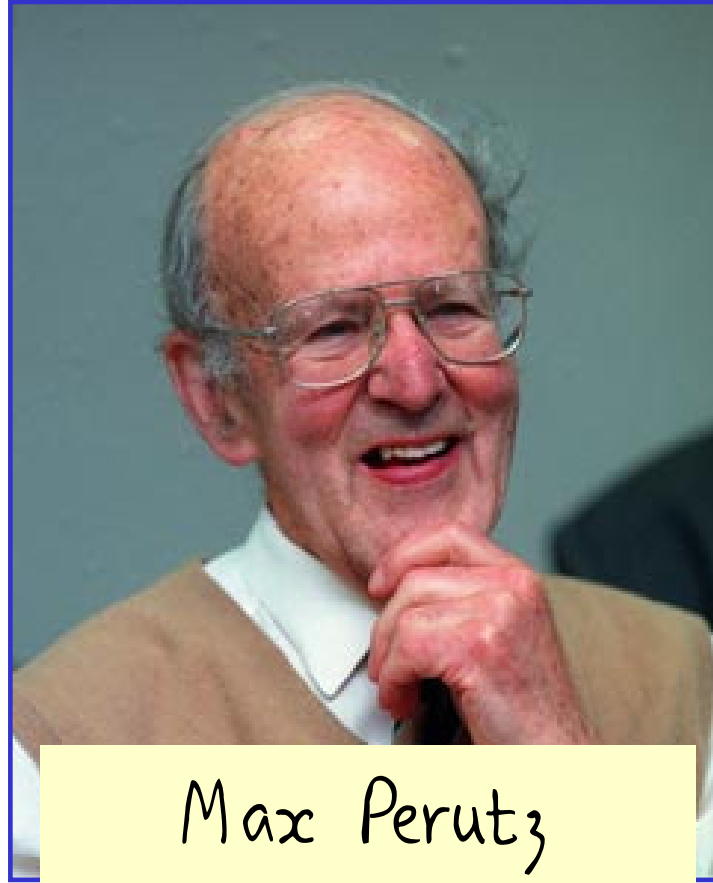


Shneur Lifson

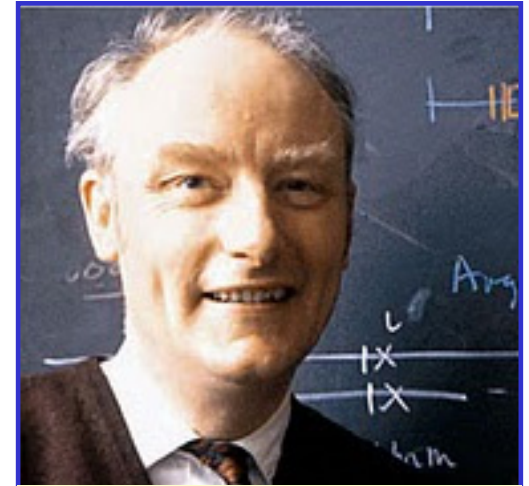
MENTORS IN CAMBRIDGE



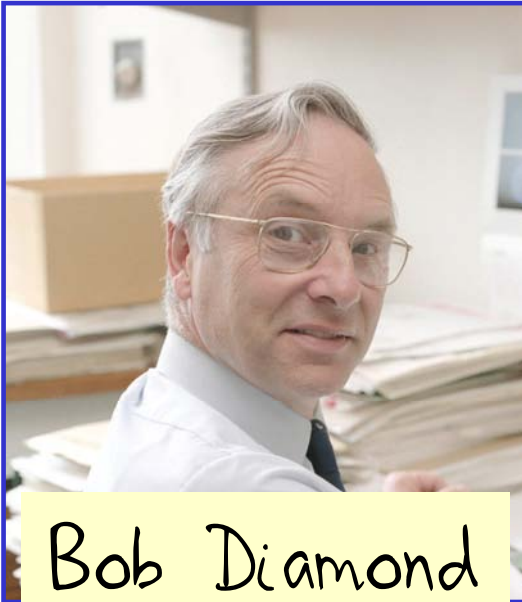
John Kendrew



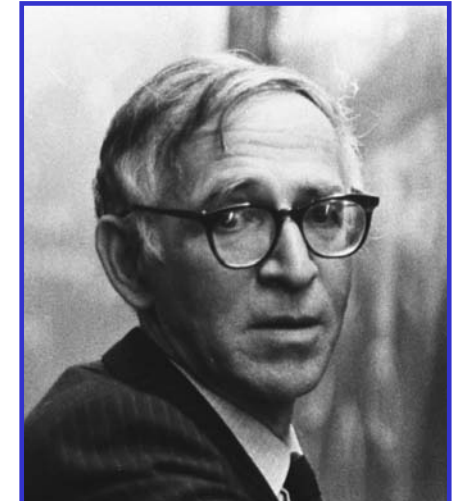
Max Perutz



Francis Crick



Bob Diamond



Aaron Klug

PAST & PRESENT GROUP

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Chris Lee
Britt Park
Dave Hinds
Enoch Huang
Jerry Tsai
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Yana Gofman
Ivan Ufimtsev



Canada



China



France



Germany



Hungary



India



Israel



Pakistan



Russia



Singapore



Spain



Sweden



UK



Ukraine



Uruguay

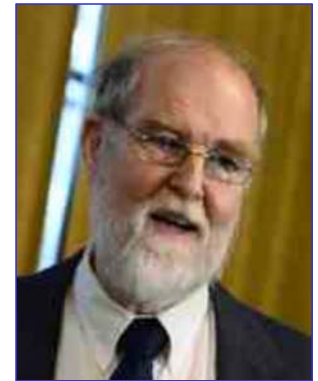


USA

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 girl celebrating on a football field. The man, in the center, is wearing a red t-shirt with a Stanford logo and has his arms raised in a 'V' shape. He is smiling broadly. To his right, a young girl in a red shirt is also smiling and has her right arm raised, holding a small card. The background shows a large stadium filled with spectators under a clear blue sky. A scoreboard in the distance displays 'STANFORD' and 'CAROLINA'.

OUR FIELD IS

THE BIG

WINNER

My Thanks
To You All