BIRTH & FUTURE OF MULTI-SCALE MODELING OF MACROMOLECULES

Nobel Lectures, Stockholm
8 December 2013

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Structural Biology & Computer Science
Stanford

http://csb.stanford.edu/levitt

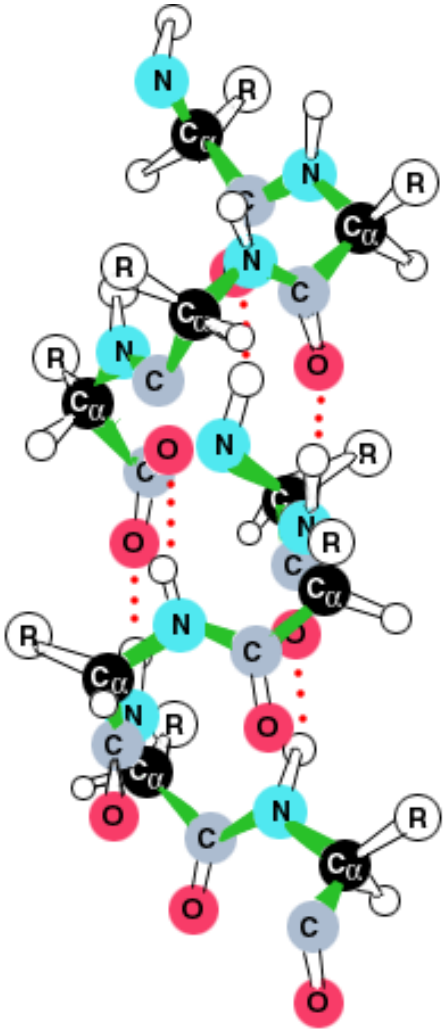
SUMMARY

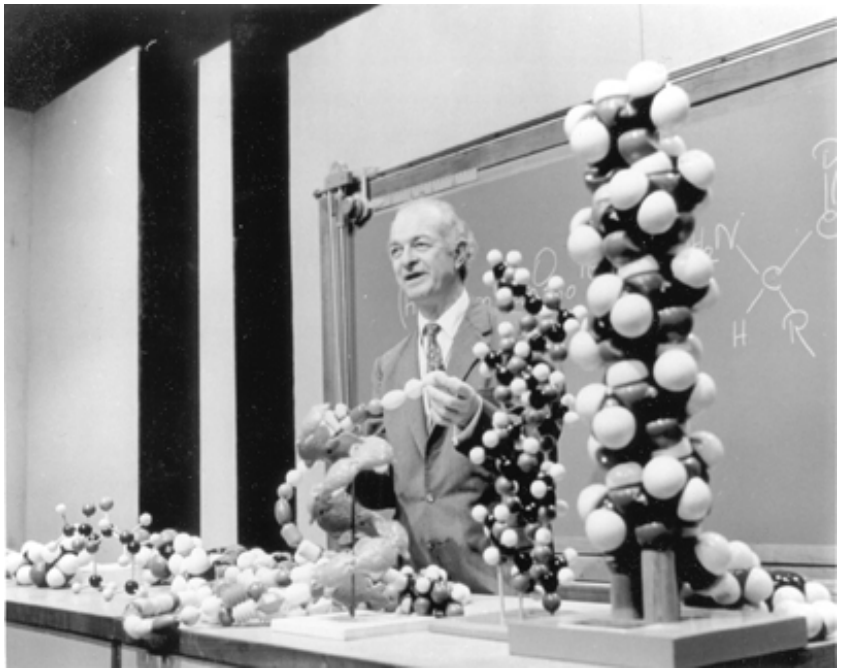
- 1. How It All Began.
- 2. Birth of Computational Structural Biology.
- 3. Future: Multi-Scale Dynamics of Huge Systems.
- 4. Some General Thoughts.

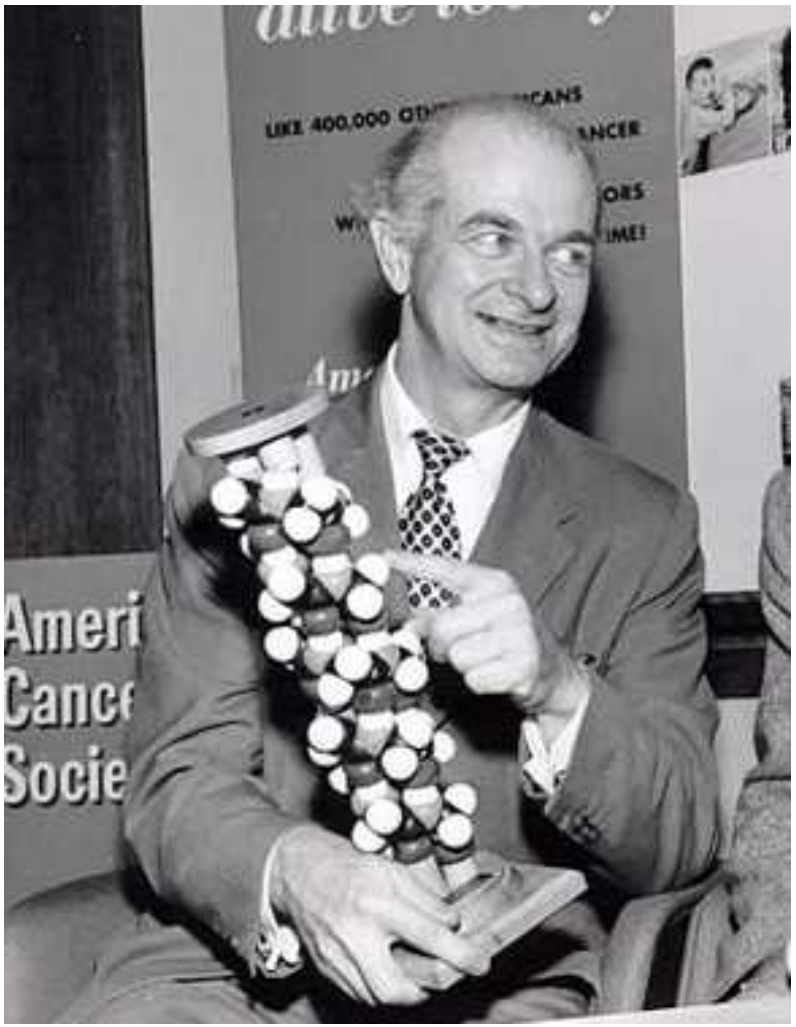
1. HOW IT ALL BEGAN

STAND ON THE SHOULDERS OF GIANTS

1951: PAULING THE GREAT CHEMIST







1951
The alpha-helix

1901-1994

1953: FRANCIS CRICK

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. Astro. Soc., Geophys. Supp.*, **5**, 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 A

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

A structure for nucleic acid has already proposed by Pauling and Corey[1]. They kindly their manuscript available to us in advanc publication. Their model consists of three twined chains, with the phosphates near the axis, and the bases on the outside. In our opi this structure is unsatisfactory for two reas (1) We believe that the material which gives X-ray diagrams is the salt, not the free acid. Wit the acidic hydrogen atoms it is not clear what f would hold the structure together, especially a negatively charged phosphates near the axis repel each other. (2) Some of the van der W distances appear to be too small.

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

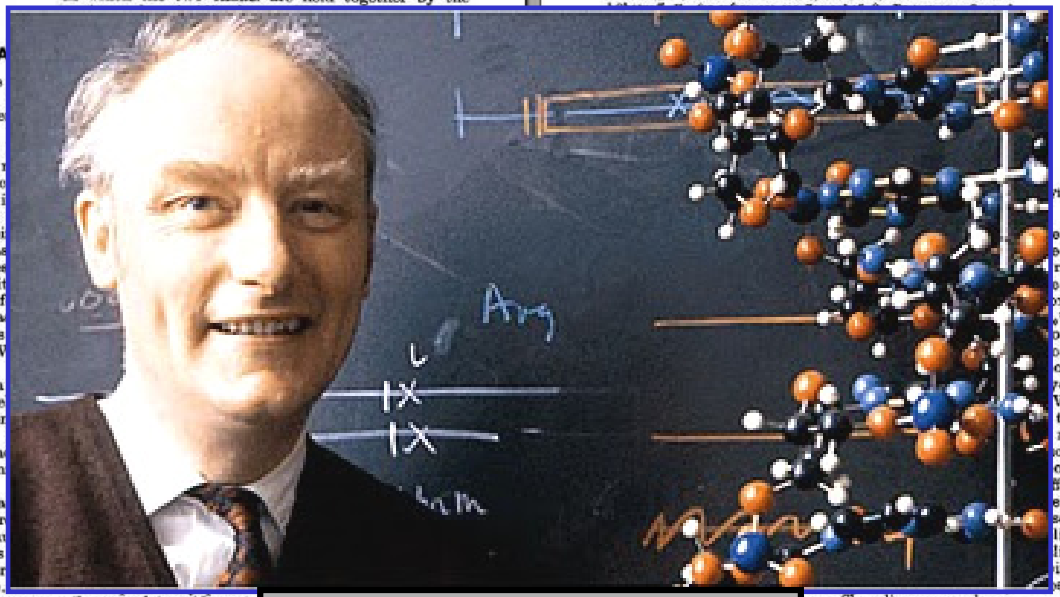
We wish to put forwa radically different structur the salt of deoxyribose n acid. This structure has helical chains each coiled the same axis (see diagram). have made the usual chemical assumptions, namely, that each chain consists of phosphate di-ester groups joining β-D-deoxy-ribofuranose residues 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 Fur-berg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosph the outside. The config of the sugar and the near it is close to F 'standard configuratio sugar being roughly p cular 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 A. 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 A. The distance of a phosphorus atom from the fibre axis is 10 A. 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

ribose nucleic acid are in of our structure. So far compatible with the exp be regarded as unprove against more exact resul in the following commun of the details of the resu devised our structure, w 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**, 346 (1953); *Proc. U.S. Nat. Acad. Sci.*, **39**, 84 (1953).
[2] Furberg, S., *Acta Chem. Scand.*, **6**, 634 (1952).

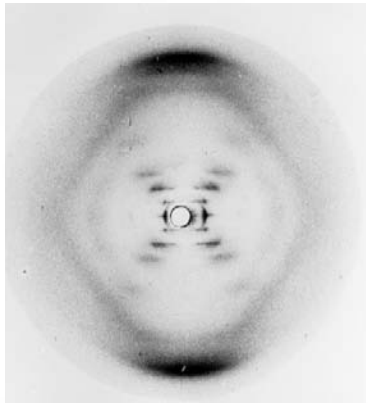


Fig. 1. Fibre diagram of deoxypentose nucleic acid from *B. coli*. Fibre axis vertical

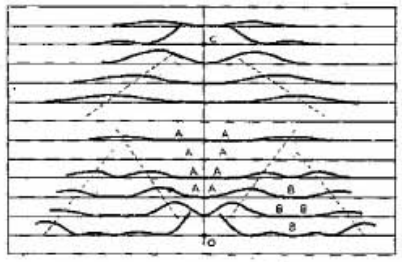
innermost maxima of each Bessel function and origin. The angle this line makes with the equator roughly equal to the angle between an element of helix and the helix axis. If a unit repeats *n* times ng the helix there will be a meridional reflexion on the *n*th layer line. The helical configuration duces side-bands on this fundamental frequency, effect being to reproduce the intensity distribution out the origin around the new origin, on the *n*th er line, corresponding to *C* in Fig. 2.

We will now briefly analyse in physical terms some the effects of the shape and size of the repeat unit nucleotide on the diffraction pattern. First, if the leotide consists of a unit having circular symmetry out an axis parallel to the helix axis, the whole fraction pattern is modified by the form factor of nucleotide. Second, if the nucleotide consists of series of points on a radius at right-angles to the lix axis, the phases of radiation scattered by the lices of different diameter passing through each int are the same. Summation of the corresponding sel functions gives reinforcement for the inner-

es a fibre diagram as shown stbury suggested that the corresponded to the inter-he fibre axis. The ~ 34 A. not due to a repeat of a on, but to the chain con-causes strong diffraction as ve 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[3] (also Stokes, unpublished) that the intensity distribution in the diffraction pattern of a series of points equally spaced along a helix is



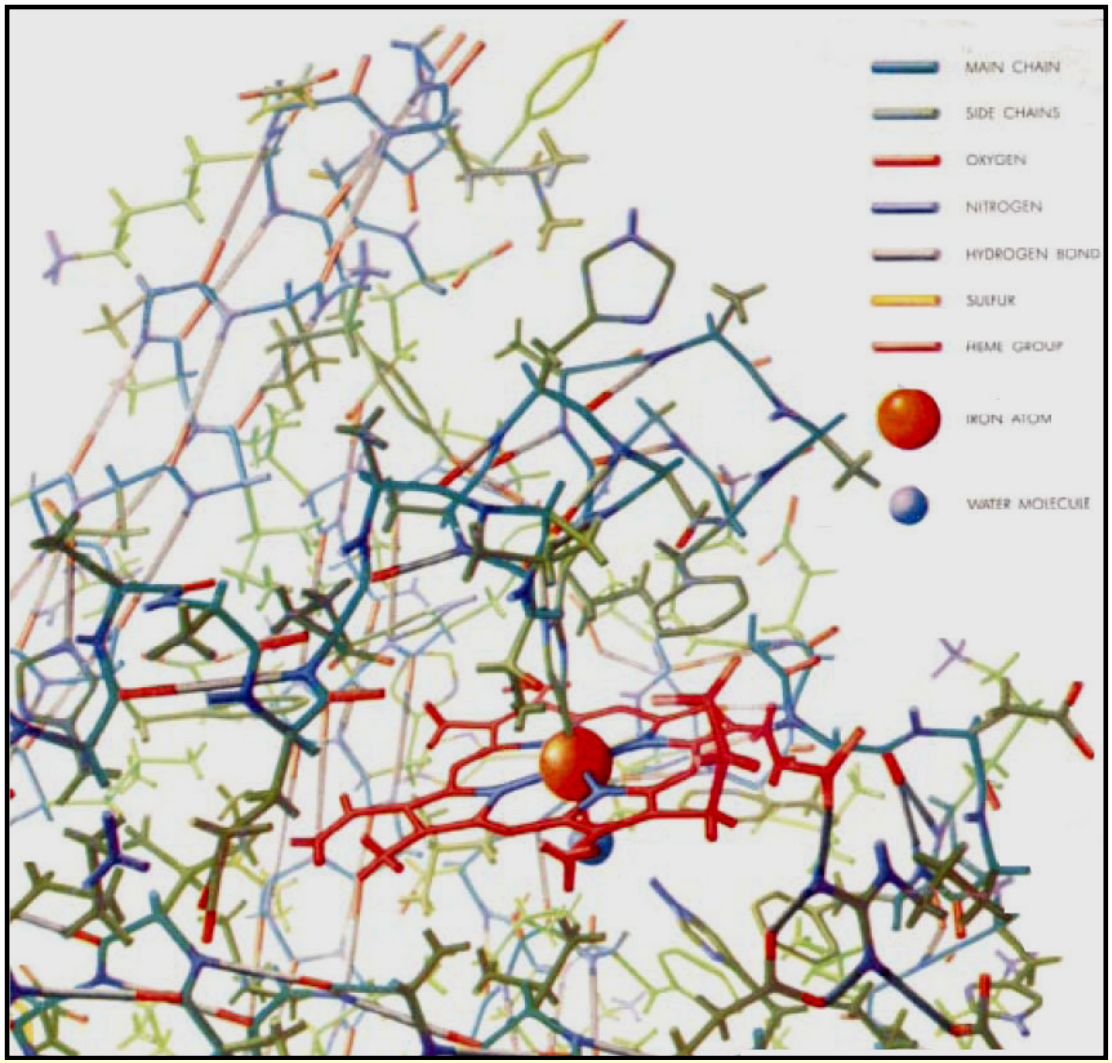
3. Diffraction pattern of system of helices corresponding to ture of deoxypentose nucleic acid. The squares of Bessel tions are plotted about 0 on the equator and on the first, nd, third and fifth layer lines for half of the nucleotide mass 0 A. diameter and remainder distributed along a radius, the s at a given radius being proportional to the radius. About n the tenth layer line similar functions are plotted for an outer diameter of 12 A.

DNA Model and Experiment

1959: KENDREW AND MYOGLOBIN

1917-1997

Scientific American 1961



Painted by artist Irving Geis

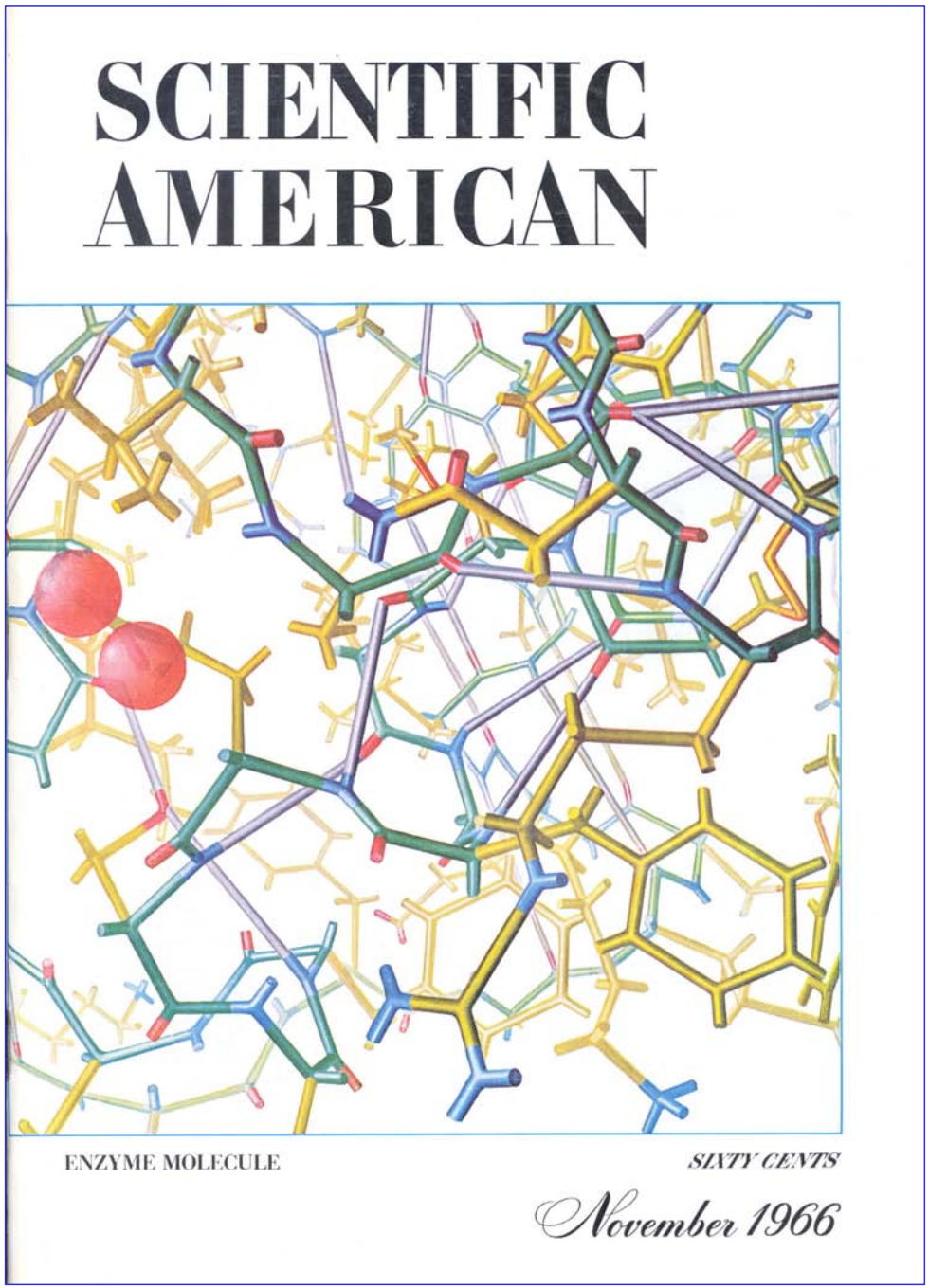
First protein X-ray structure.

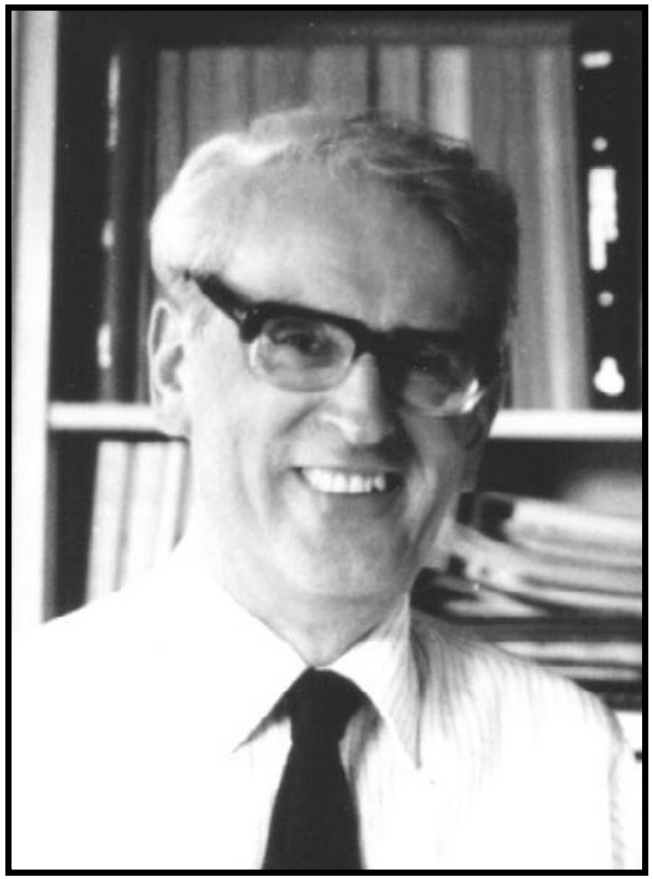
1962: PERUTZ AND HEMOGLOBIN

1914–2002

The REAL HERO of structural biology.

1965: PHILLIPS AND LYSOZYME



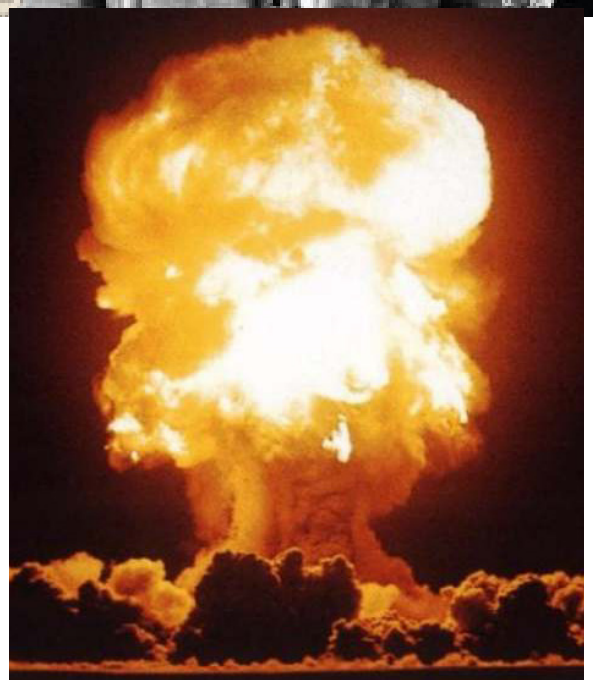


1924–1999

Early supporter of Computational Biology

1943-1945: LOS ALAMOS

Equation of State Calculations by Fast Computing Machines



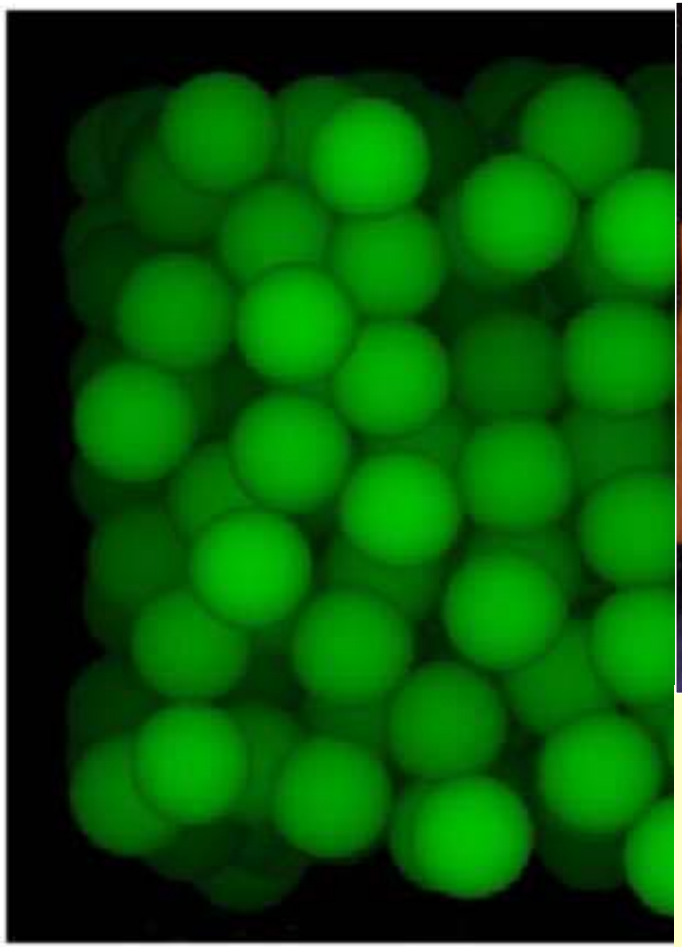
When any sufficiently large nuclear explosion occurs within a container, unless the radioactive material is properly contained and the timing of triggering explosions perfect, neutrons stream out of one side of the container. This leak causes an asymmetrical, much weaker, and more unpredictable blast. 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.

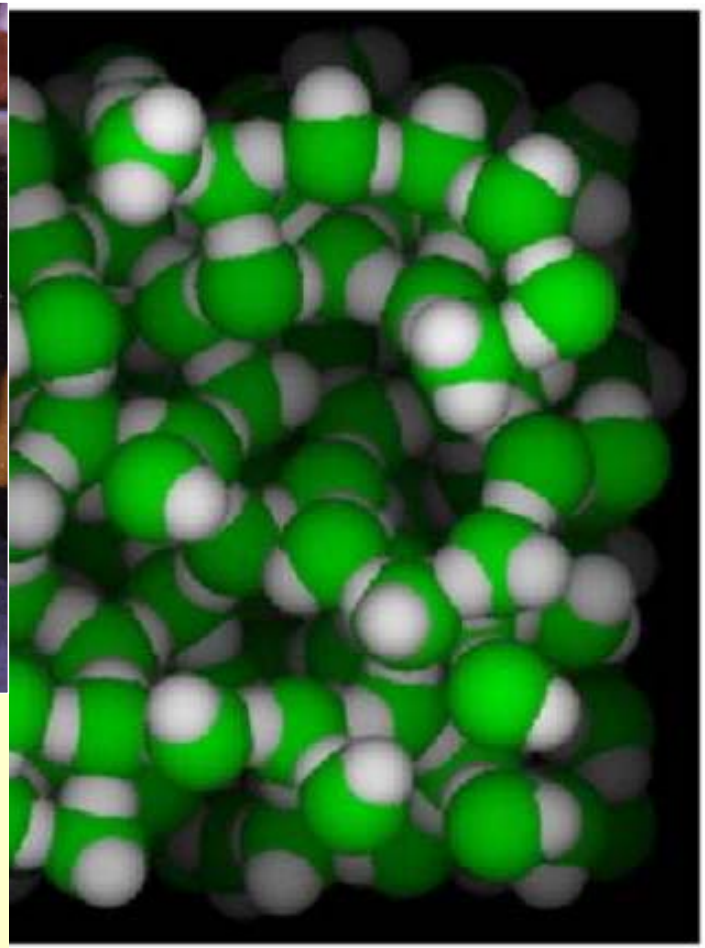
http://trace.ntu.ac.uk/frame2/articles/borg/JvN.html

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

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

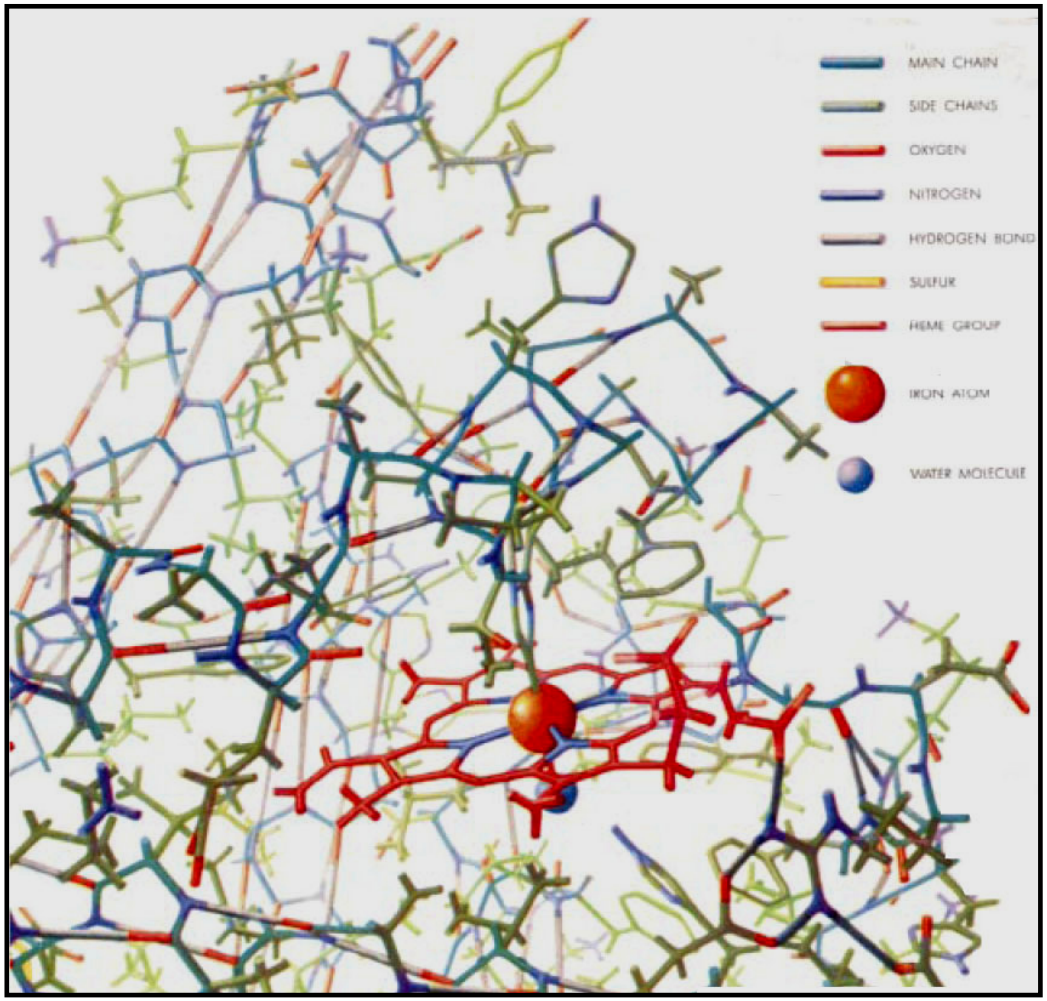
Weizmann Institute 1967-68

BIOMOLECULES

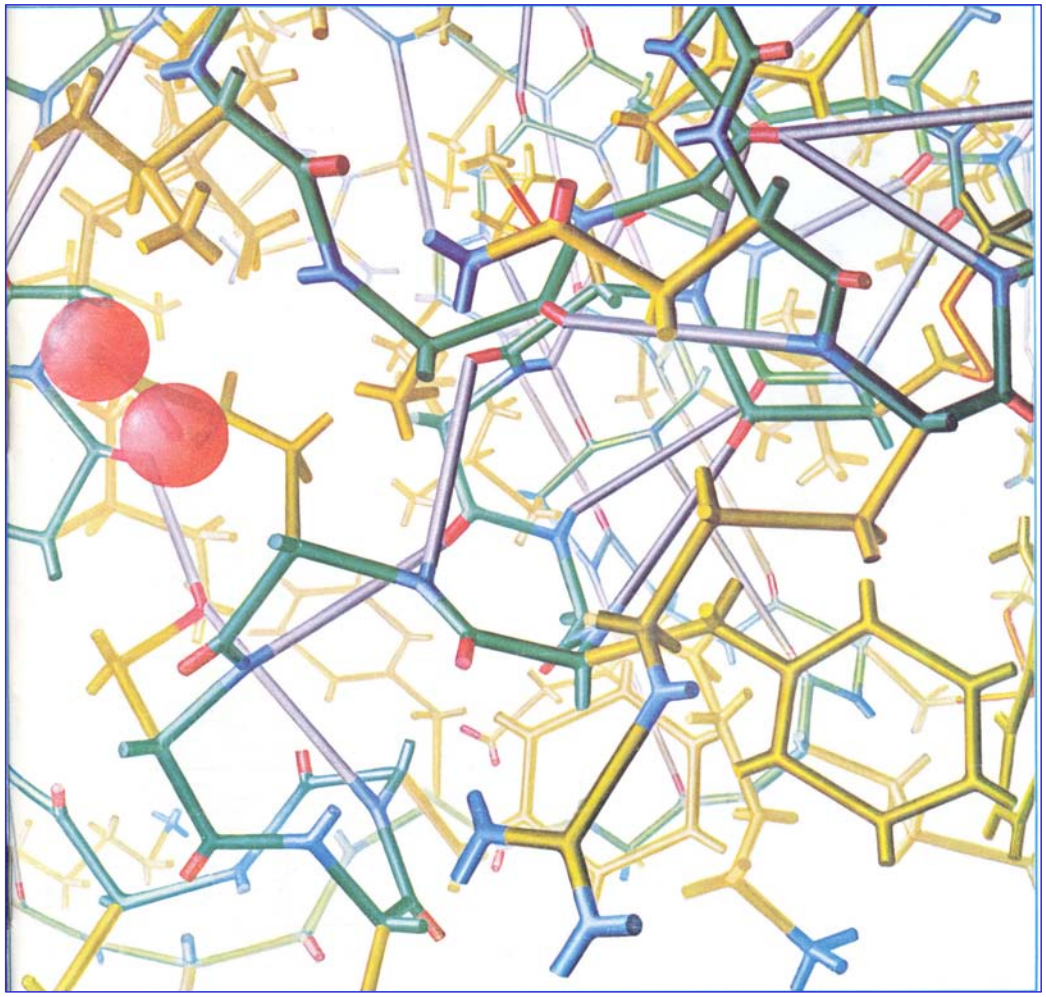
ARE DETAILED

BIOLOGY IS DETAILED INTERACTIONS

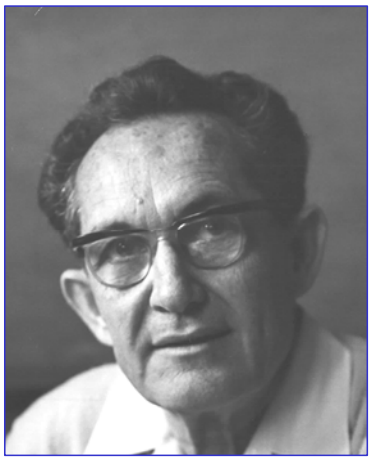
Myoglobin 1961

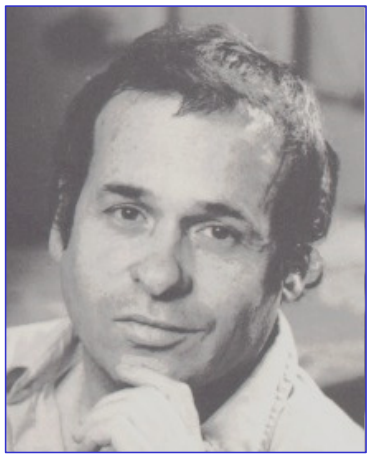


Lysozyme 1966



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

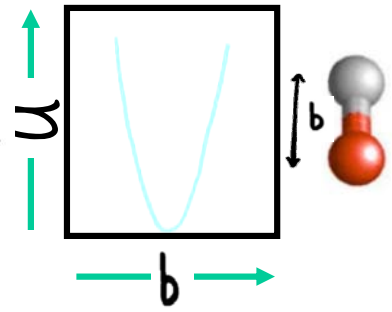
(Received 13 May 1968)

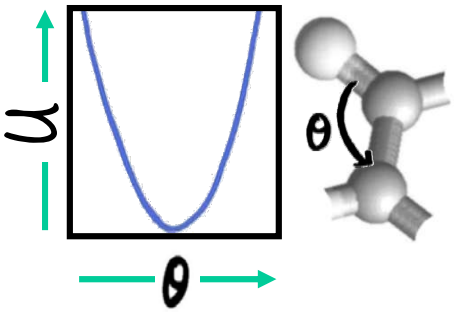
MOLECULAR POTENTIAL ENERGY

$$U = \sum \tfrac{1}{2} K_b (b - b_o)^2 + \sum \tfrac{1}{2} K_\theta (\theta - \theta_o)^2$$

All Bonds — All Angles

Hooke 1635

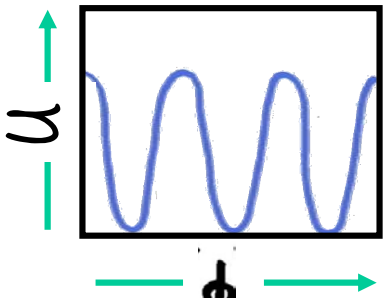


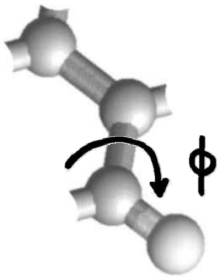


$$+ \sum K_\phi [1 - \cos(n\phi + \delta)]$$

All Torsion Angles

Fourier 1768

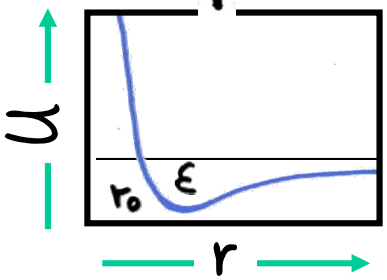


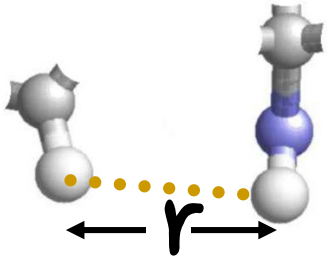


$$+ \sum \varepsilon \left[\left(r_o / r \right)^{12} - 2 \left(r_o / r \right)^{6} \right]$$

All Nonbonded pairs

Van der Waals 1837



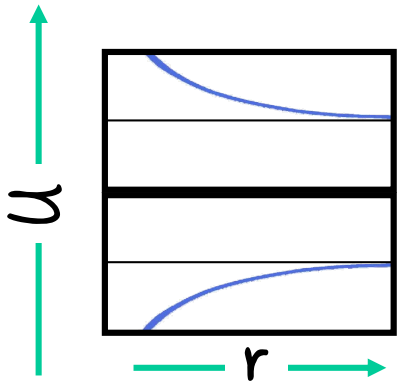


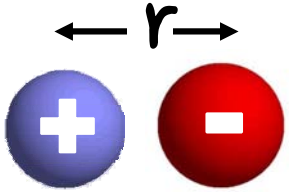
$$+ \sum 332 q_i q_j / r$$

All partial charges

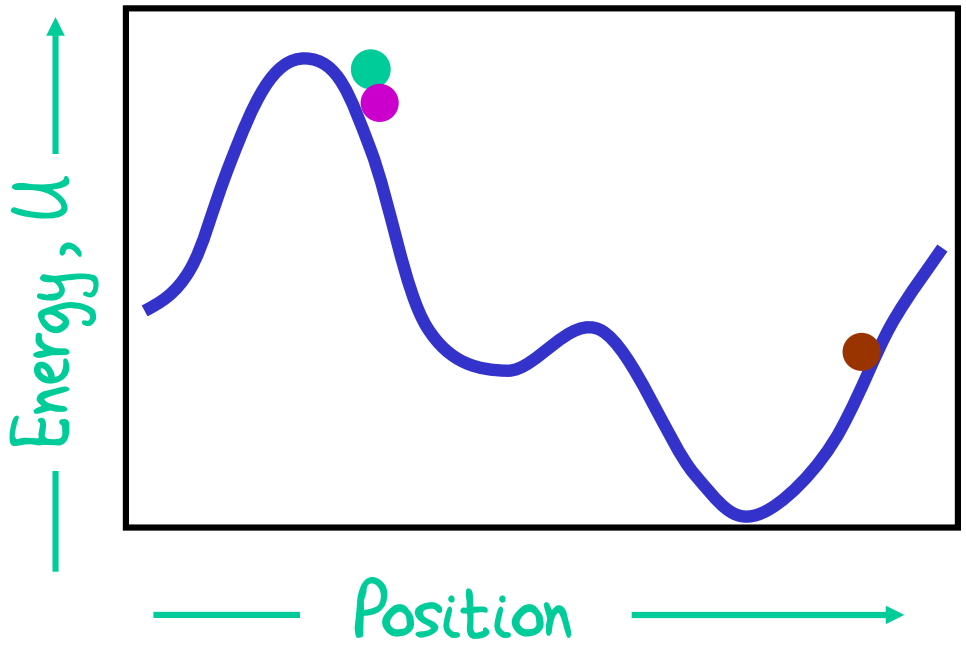
Coulomb 1736

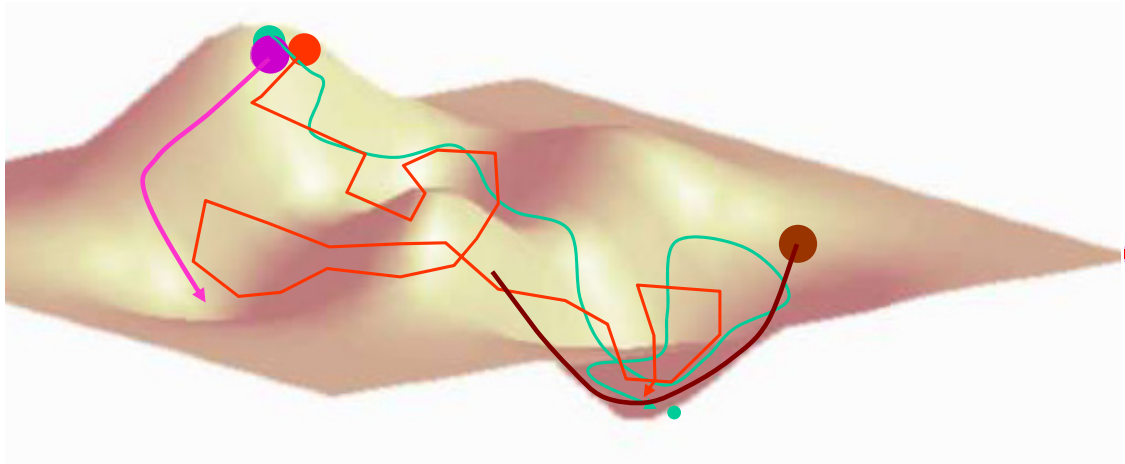
Simple sum over many terms





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

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

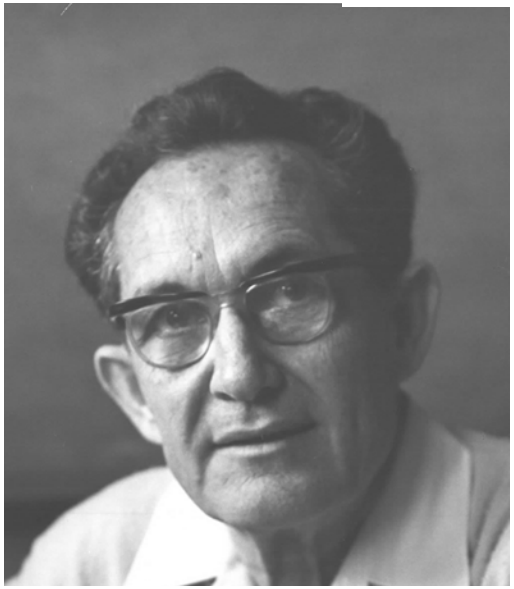
Refinement of Protein Conformations using a Macromolecular Energy Minimization Procedure

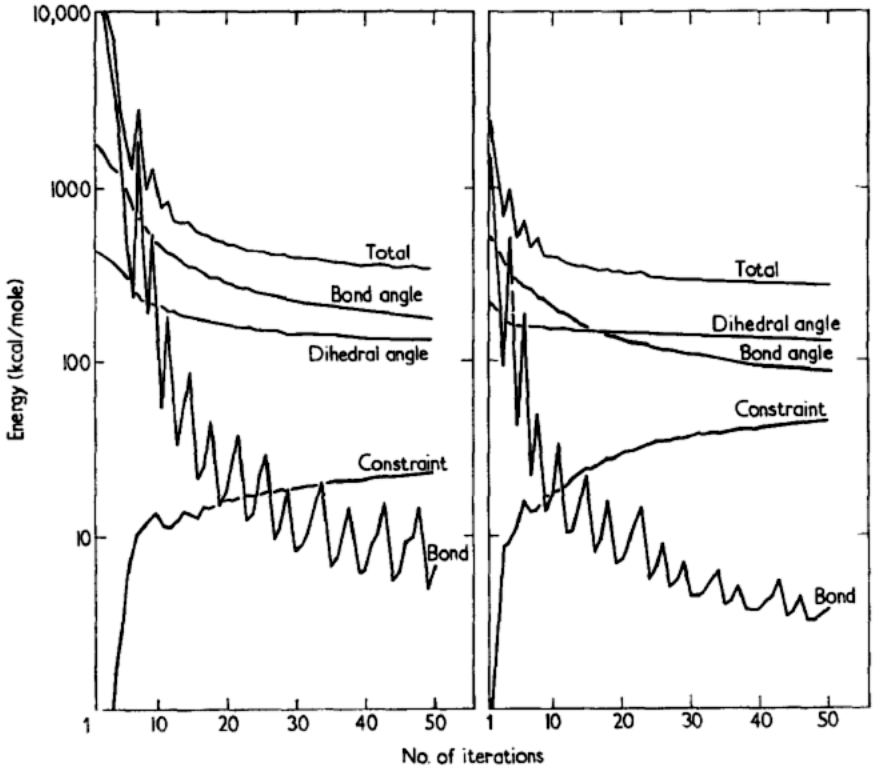
MICHAEL LEVITT† AND SHNEIOR LIFSON

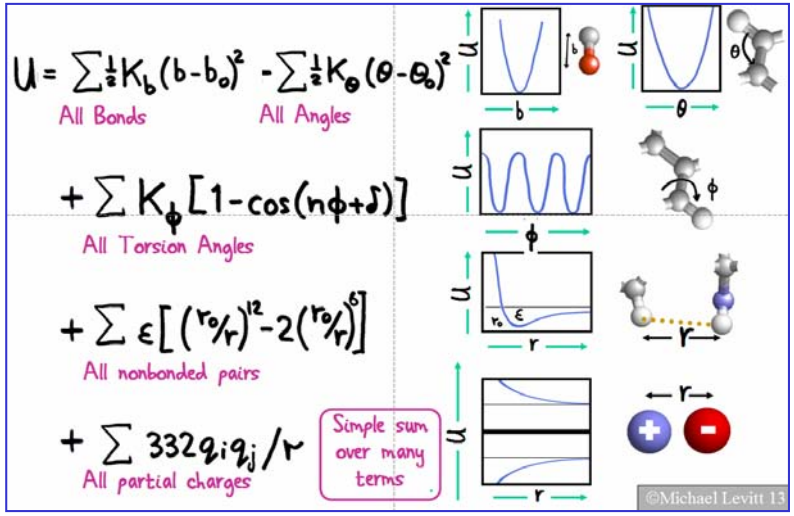
Weizmann Institute of Science

J. Mol. Biol. (1969) **46**, 269–279

$$E = \underset{\text{all bonds}}{\Sigma \tfrac{1}{2} K_b (b - b_0)^2} + \underset{\text{all bond angles}}{\Sigma \tfrac{1}{2} K_\tau (\tau - \tau_0)^2} + \underset{\text{all dihedral angles}}{\Sigma \tfrac{1}{2} K_\theta \{1 + \cos(n\theta - \delta)\}} + \underset{\text{all non-bonded pairs}}{\Sigma \epsilon_{ij} \{(r^0_{ij}/r_{ij})^{12} - 2(r^0_{ij}/r_{ij})^6\}} + \underset{\text{all atomic co-ordinates}}{\Sigma \tfrac{1}{2} w (x_i - x^0_i)^2}$$







First protein structure refinement

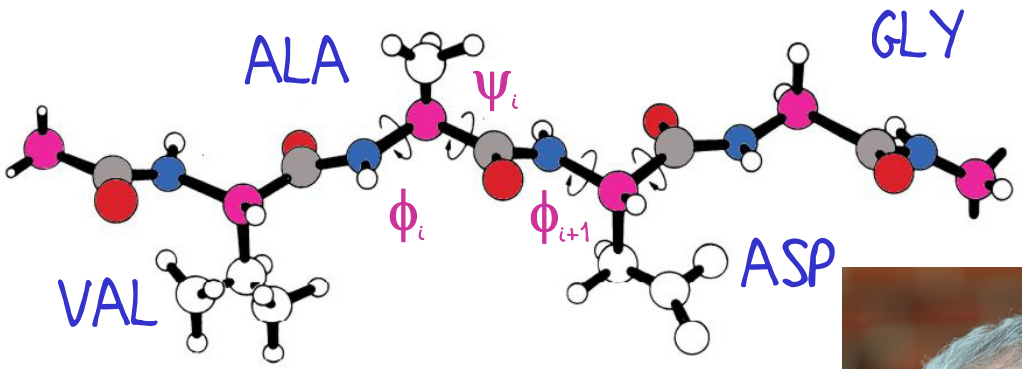
COARSE GRAINED MODELS 1975

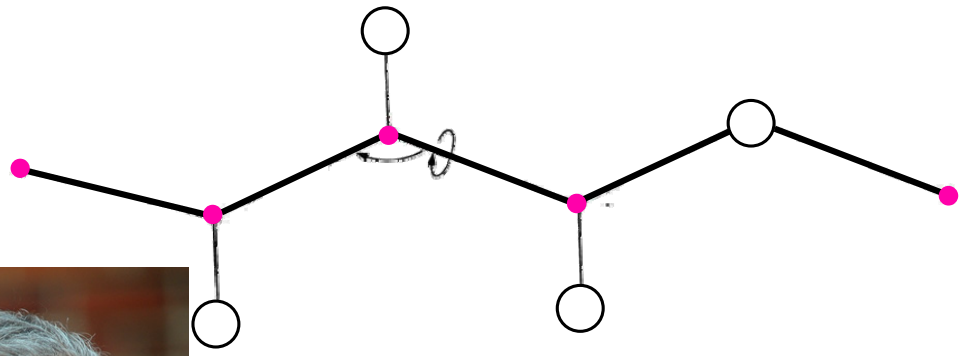
COMPUTER SIMULATION OF PROTEIN FOLDING

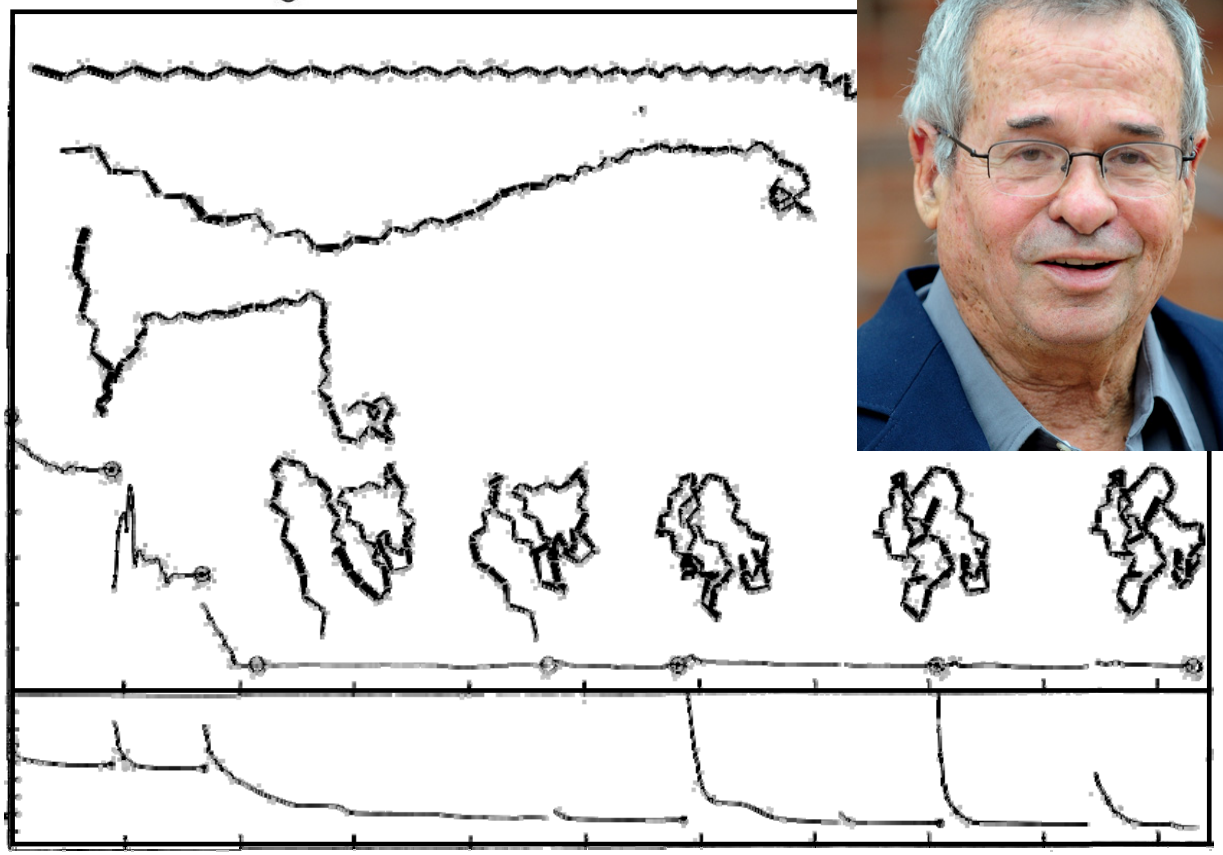
Michael Levitt* & Arieh Warshel*

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

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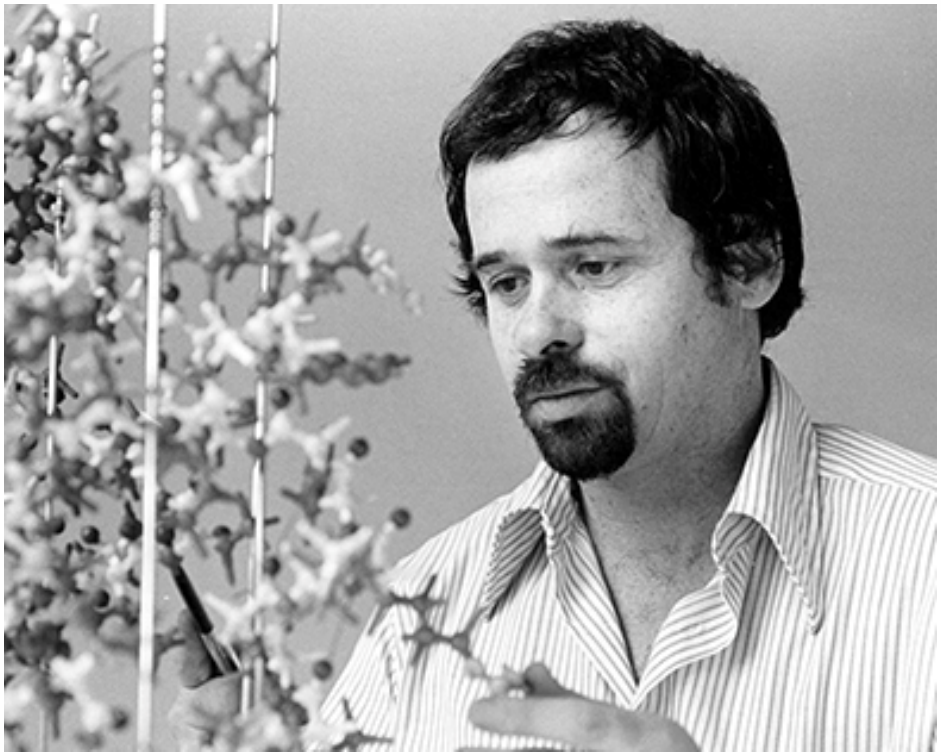
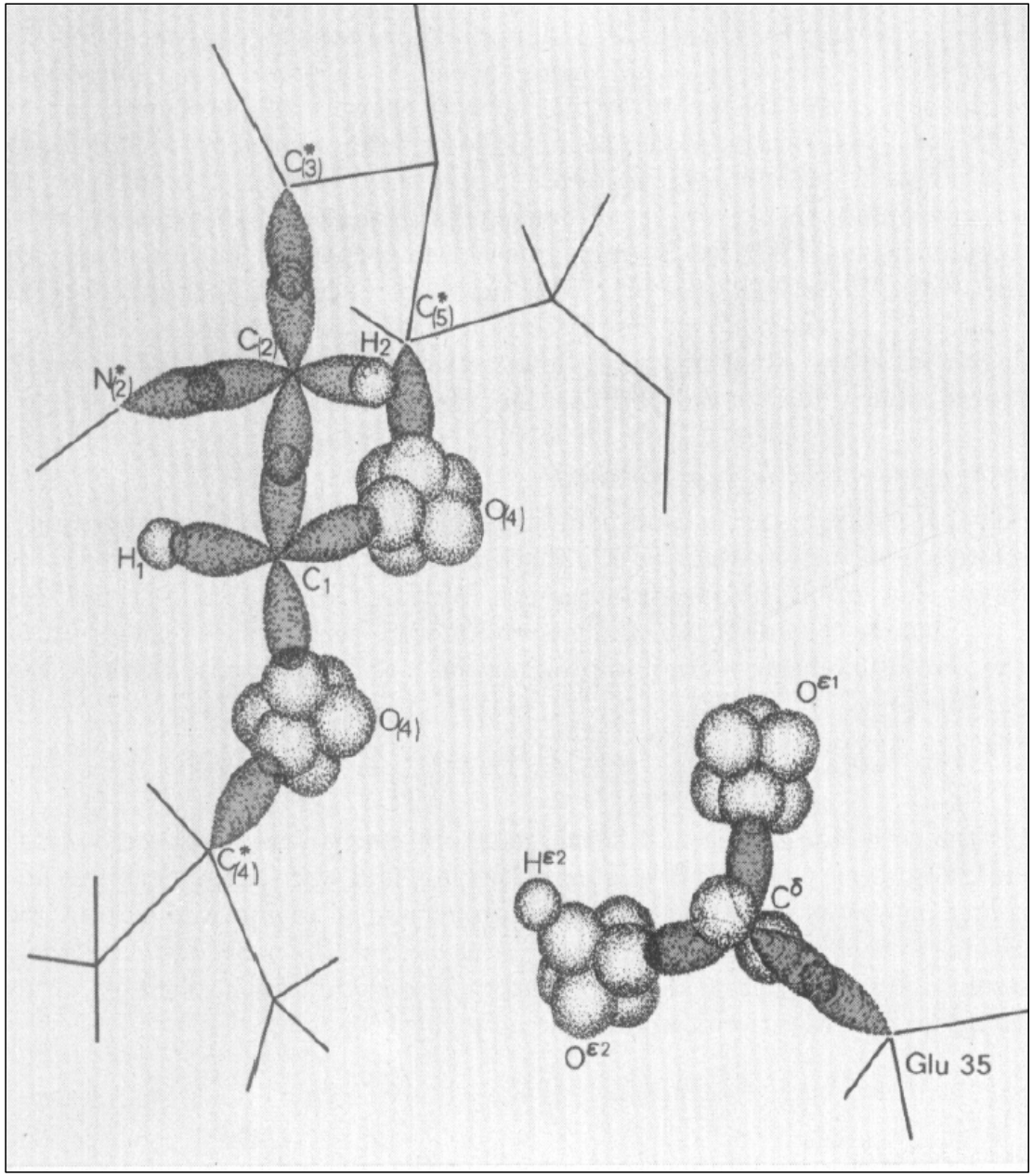
Department of Chemical Physics
The Weizmann Institute of Science
Rehovot, Israel





FIRST MD

MOVIE

1979

Filming by

Richard J. Feldmann
National Institutes
of Health
Bethesda, Maryland

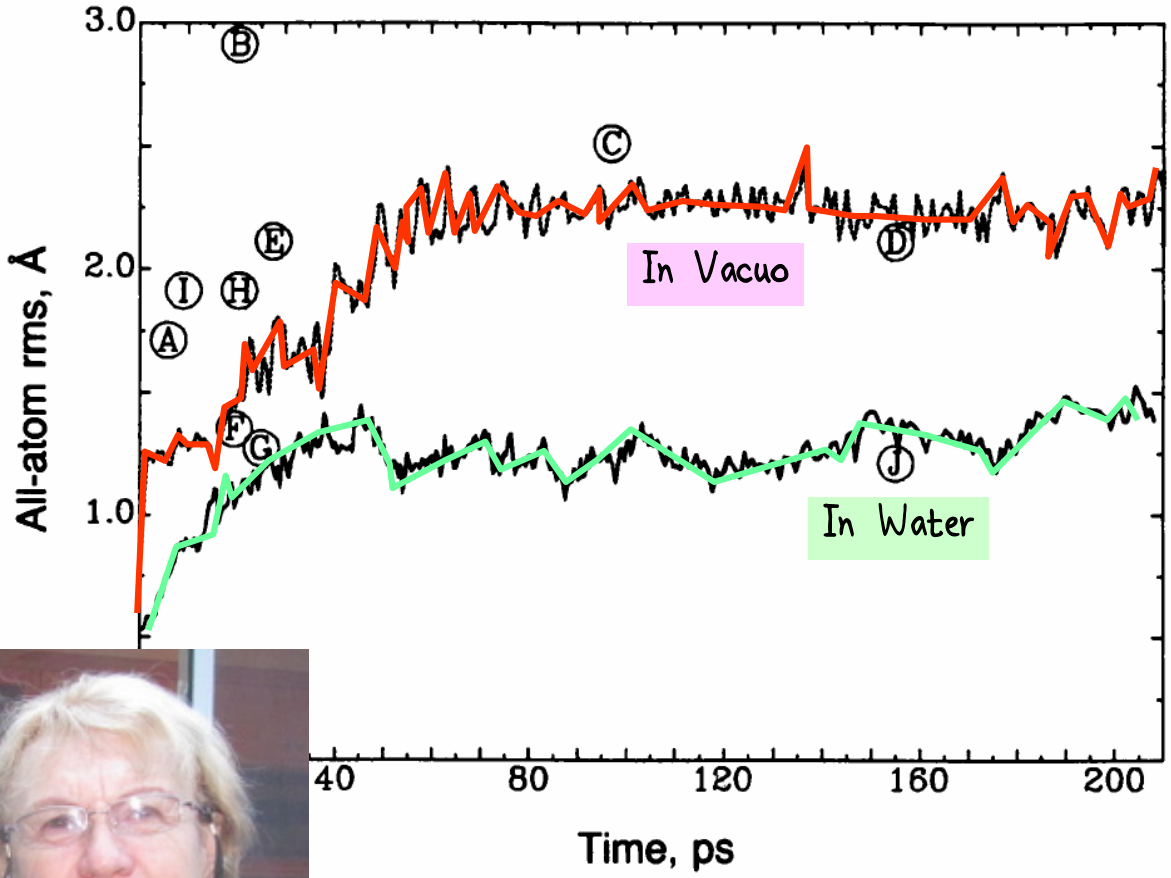
PROTEIN MOLECULAR DYNAMICS IN WATER 1988

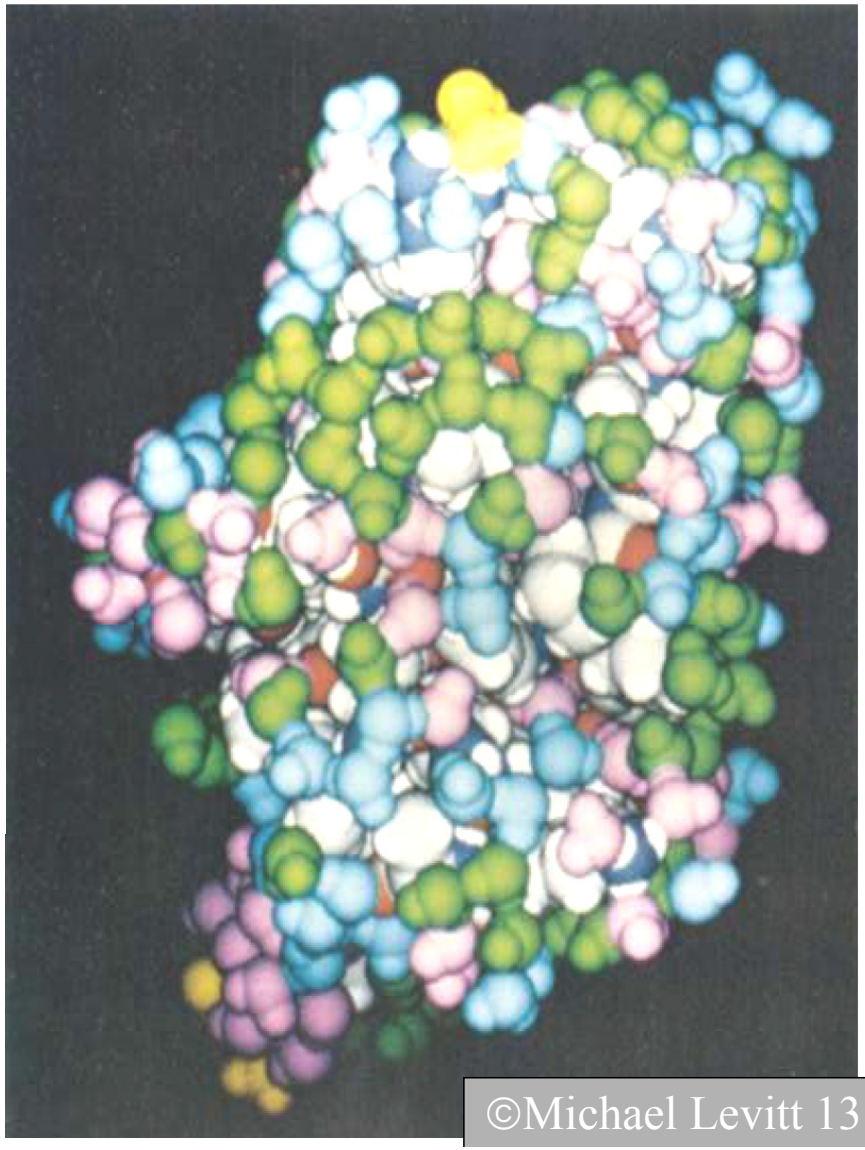
ACCURATE SIMULATION OF PROTEIN DYNAMICS IN SOLUTION

MICHAEL LEVITT* AND RUTH SHARON

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

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



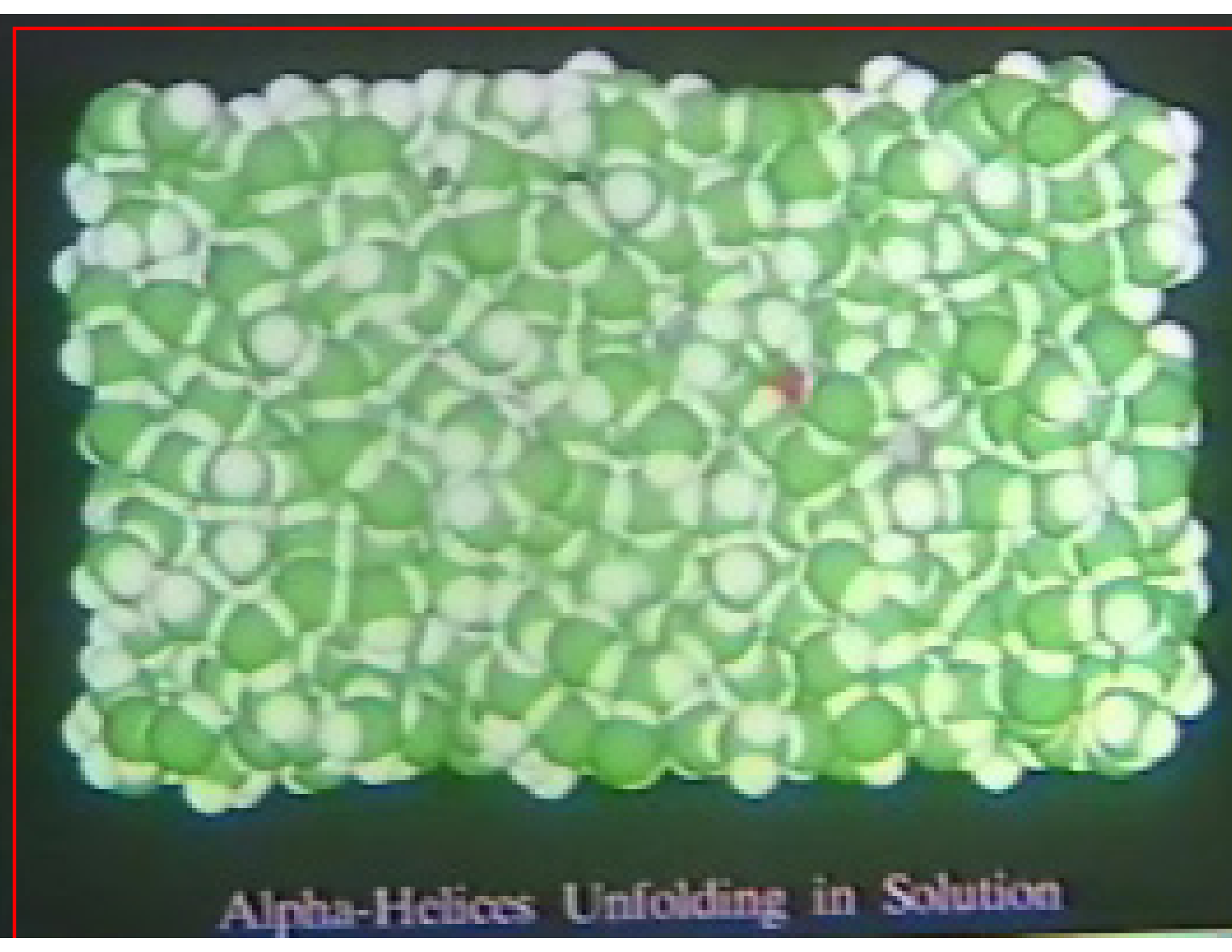


α-HELIX MOLECULAR DYNAMICS IN WATER 1990

Molecular Dynamics Simulations of Helix Denaturation

Valerie Daggett and Michael Levitt

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


Alpha-Helices Unfolding in Solution

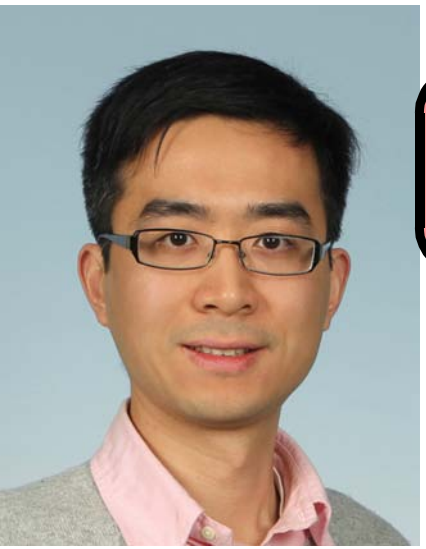
SUMMARY SO FAR

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

3. FUTURE: MULTI-SCALE DYNAMICS OF HUGE STRUCTURES

REDUCED DEGREES OF FREEDOM

MARKOV STATE DYNAMICS OF RNA POLYMERASE II

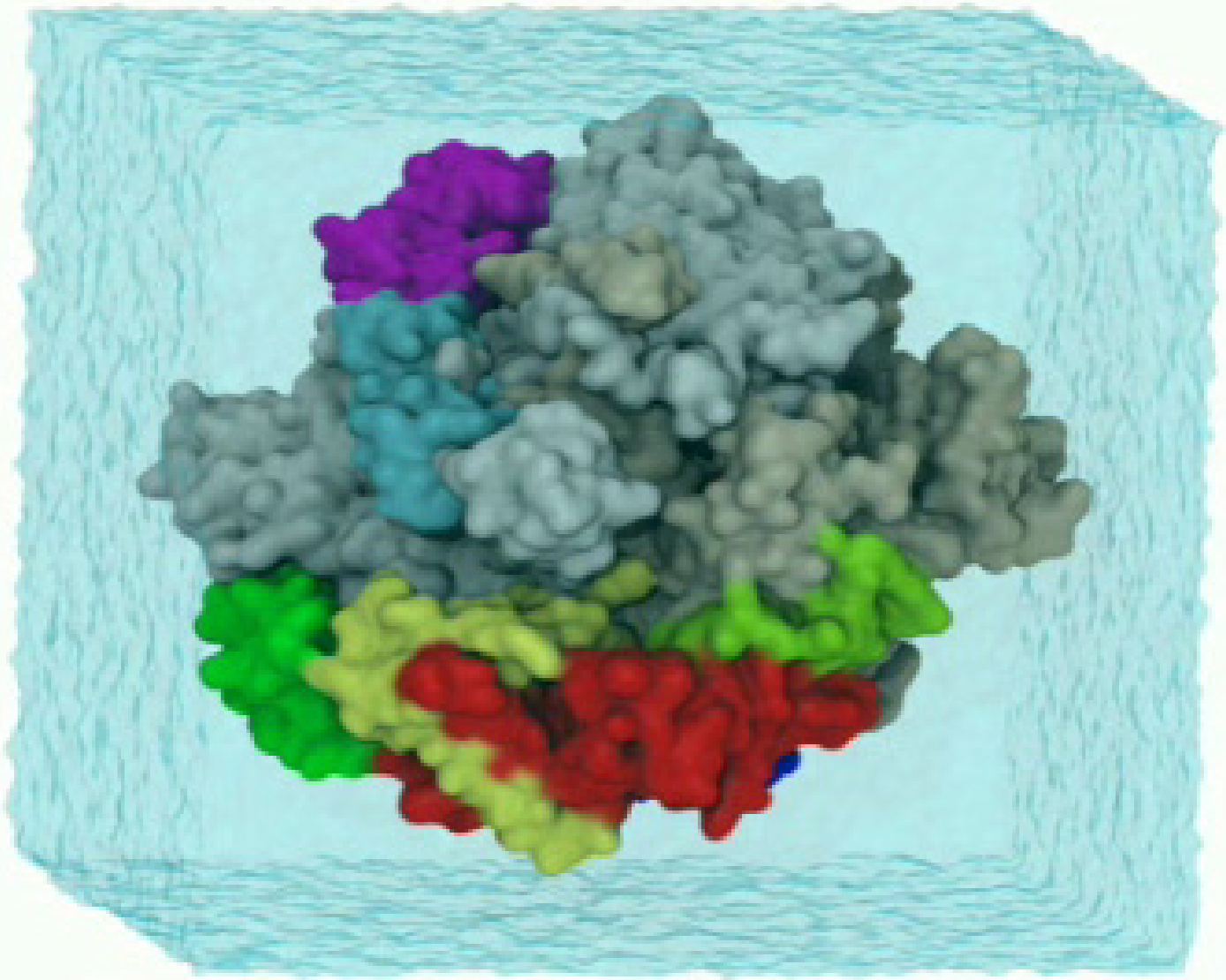


Xuhui Huang

Daniel Silva

RNA Polymerase II
(10 subunits, ~ 422 kDa)

Explicit water solvent
(~ 122,000 molecules)



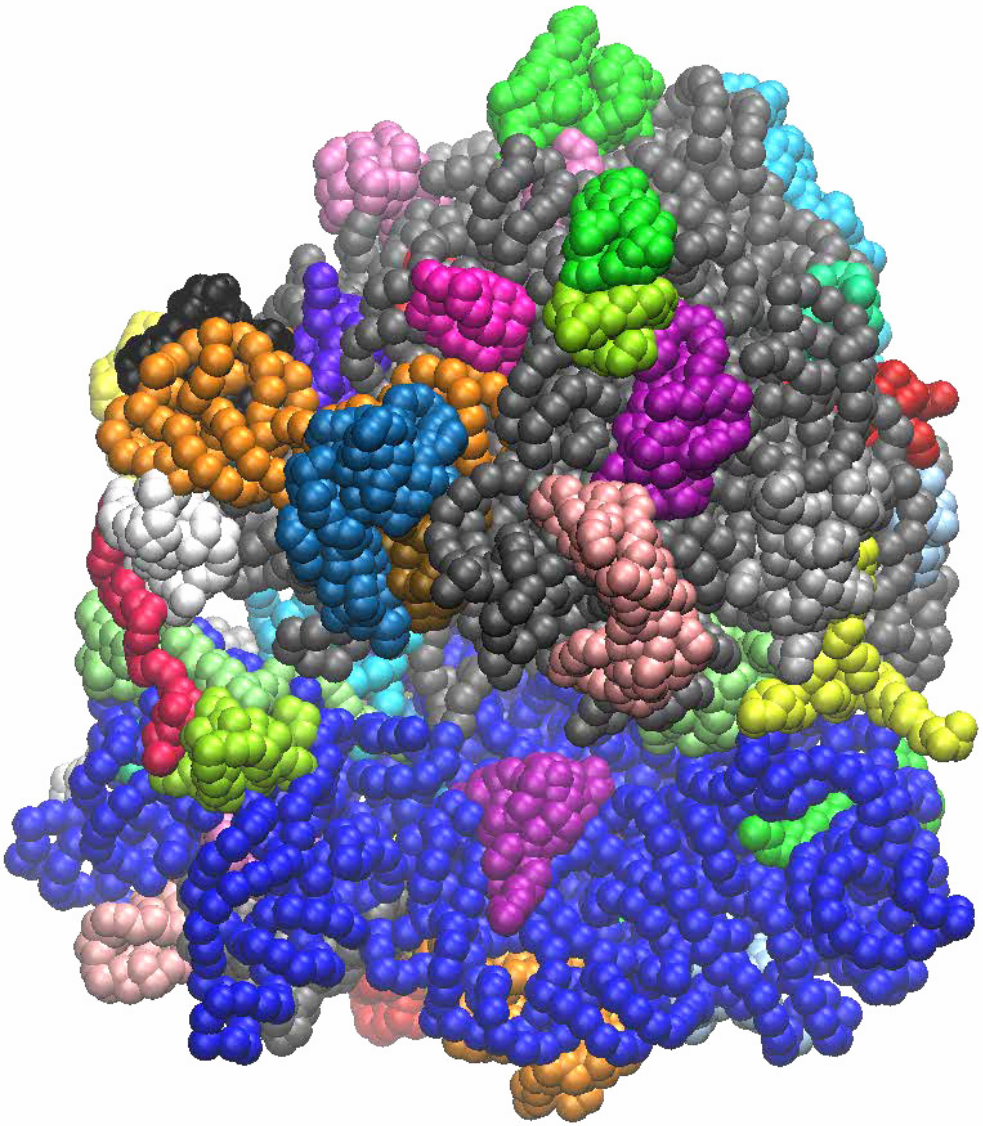
Simulation of a ~ 426,000 atom system

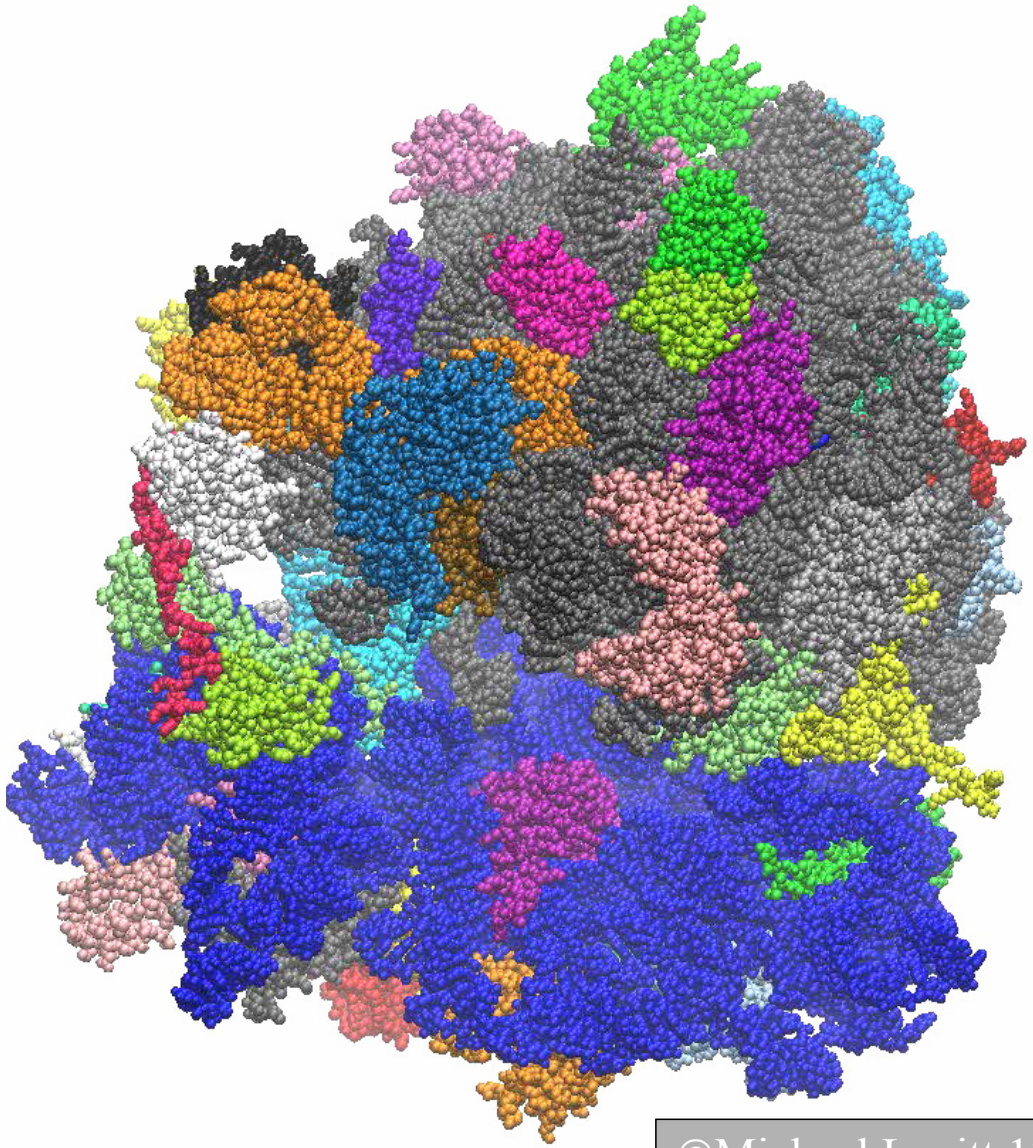
NORMAL MODES OF ENTIRE RIBOSOME

Jenelle Bray

Junjie Zhang

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



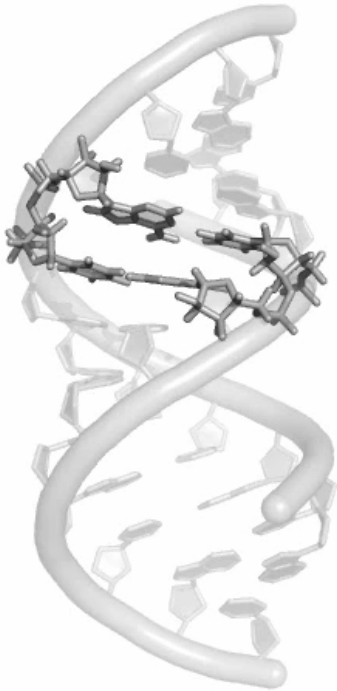


NATURAL MOVE MONTE CARLO OF RNA

Peter Minary

Adelene Sim

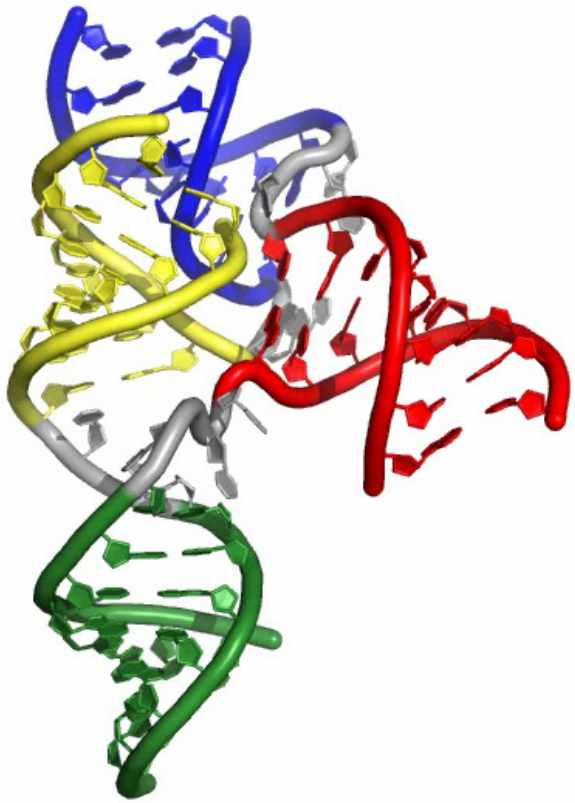
NATURAL MOVE MONTE CARLO



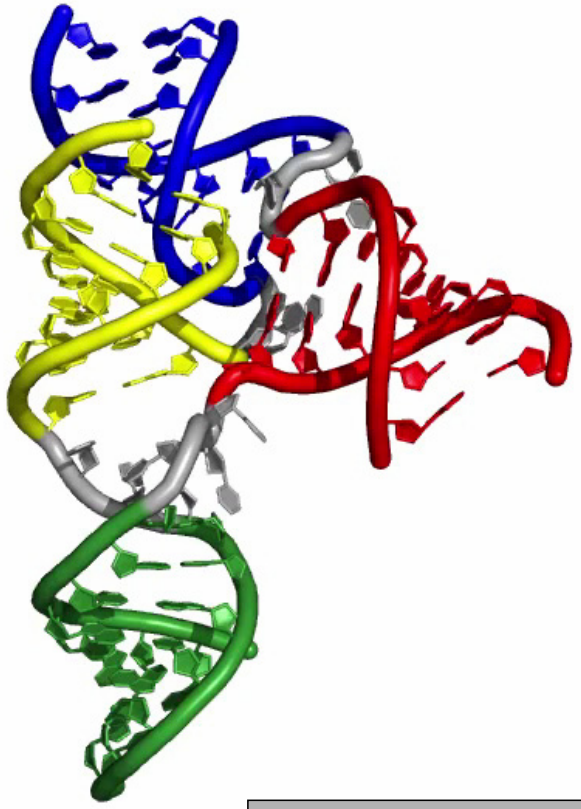
Natural Moves allow a hierarchy of moves.

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

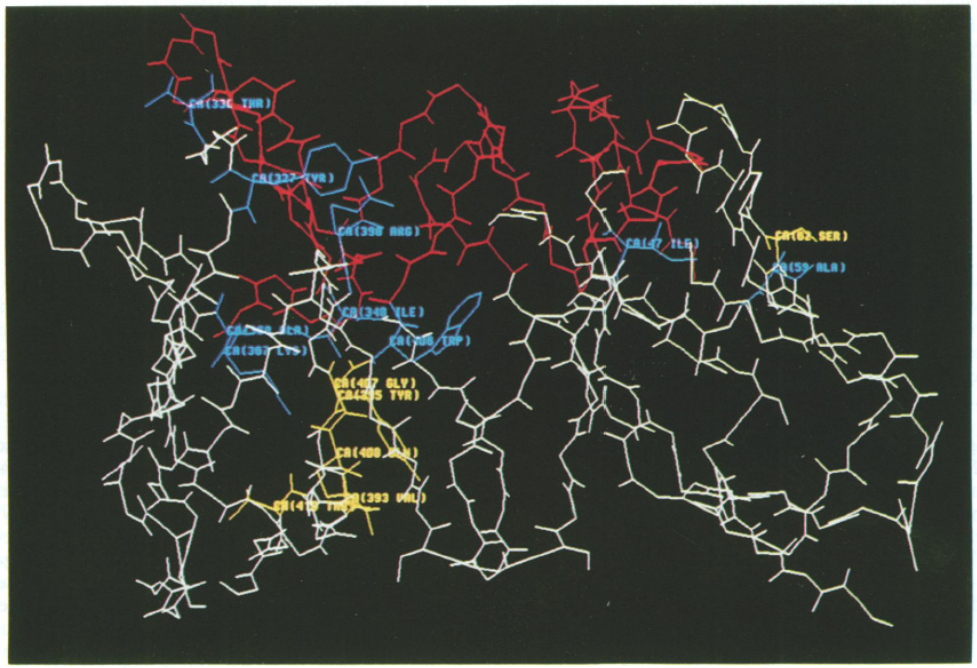
APPLICATIONS TO HUMAN HEALTH

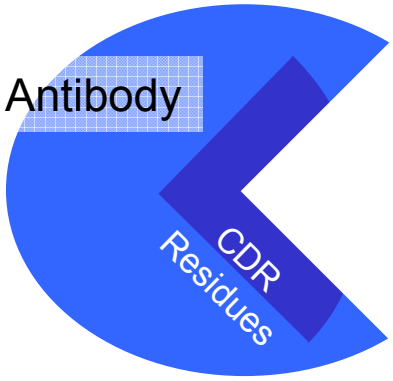
ANTIBODY HUMANIZATION

A humanized antibody that binds to the interleukin 2 receptor

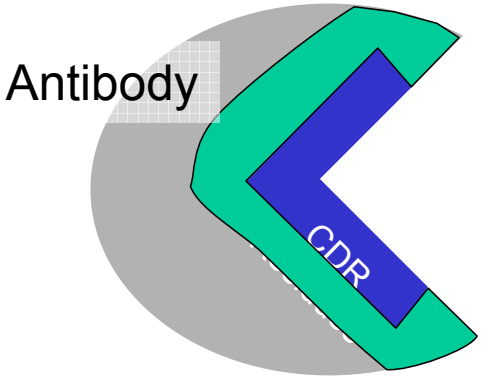
(chimeric antibody/antibody affinity/autoimmune disease)

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¶





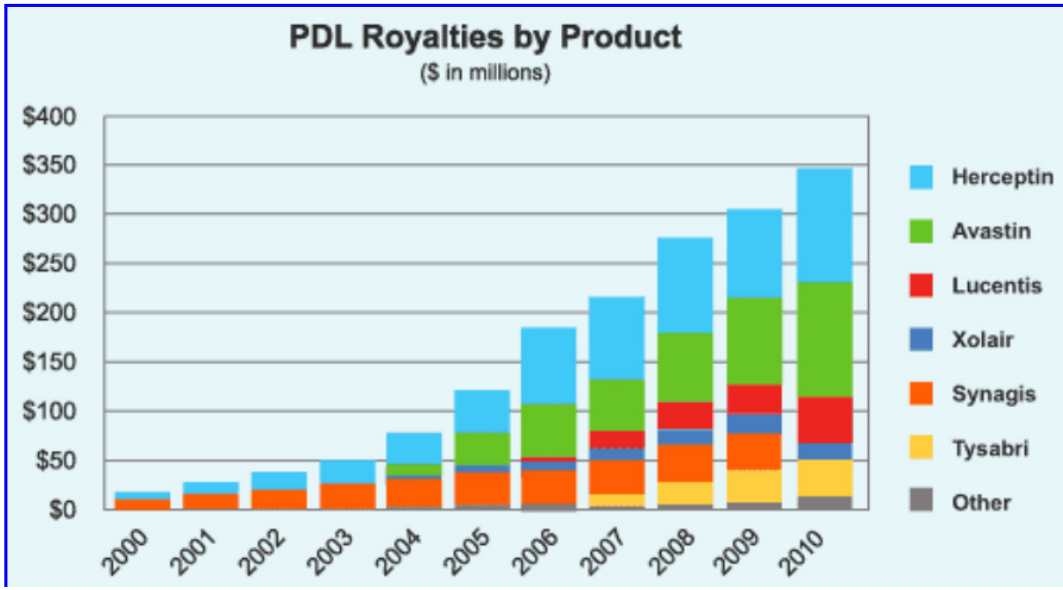
WINTER



QUEEN

PDL BioPharma

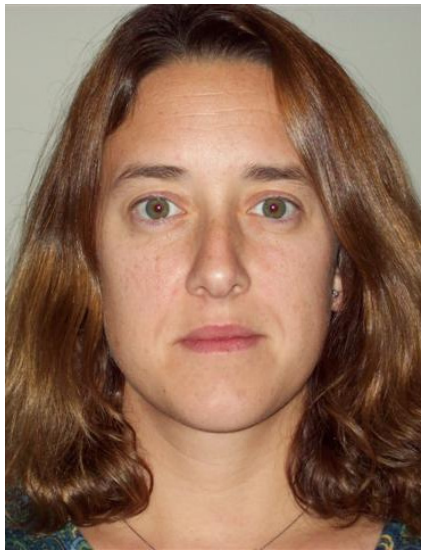
Seven employees living in Nevada next to Lake Tahoe.



BREADTH OR LACK OF FOCUS?

Compare Genomes.

Andrea Scaiewicz



Ivan Ufimtsev

X-Ray Phase Problem.

Large Complexes.

Nir Kalisman

Yana Gofman

Membrane Proteins.

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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

TAKE CHANCES,

BUT DO NOT BE

TOO STUPID...

BEGINNER SEA-KAYAKING ALONE

Ornö Kyrke

Store

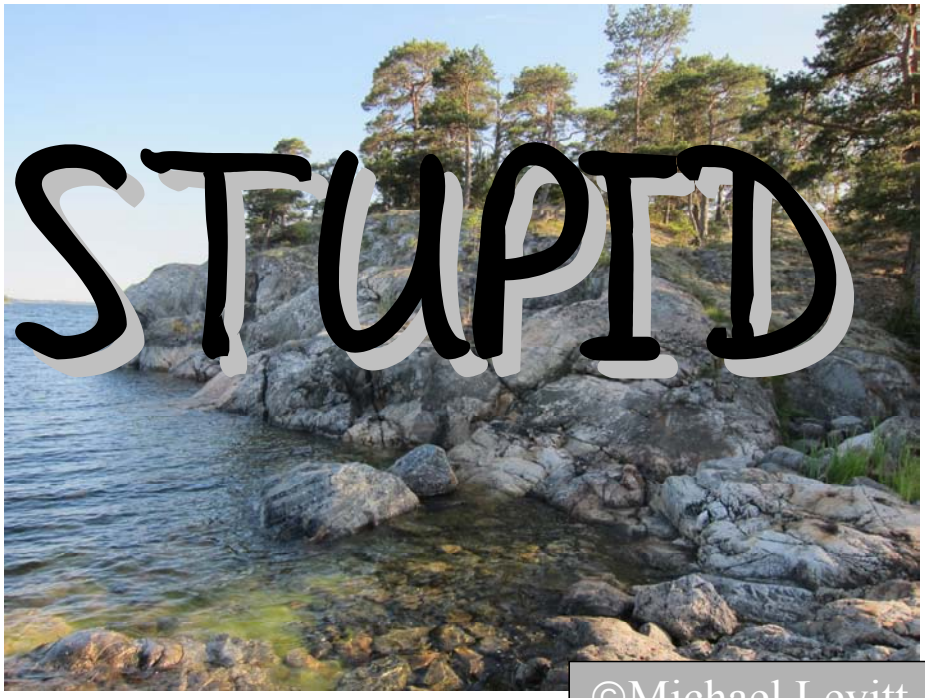
“Paradise”

First Beach

Rest Stop

Kayak Rental

IT WAS A PARADISE

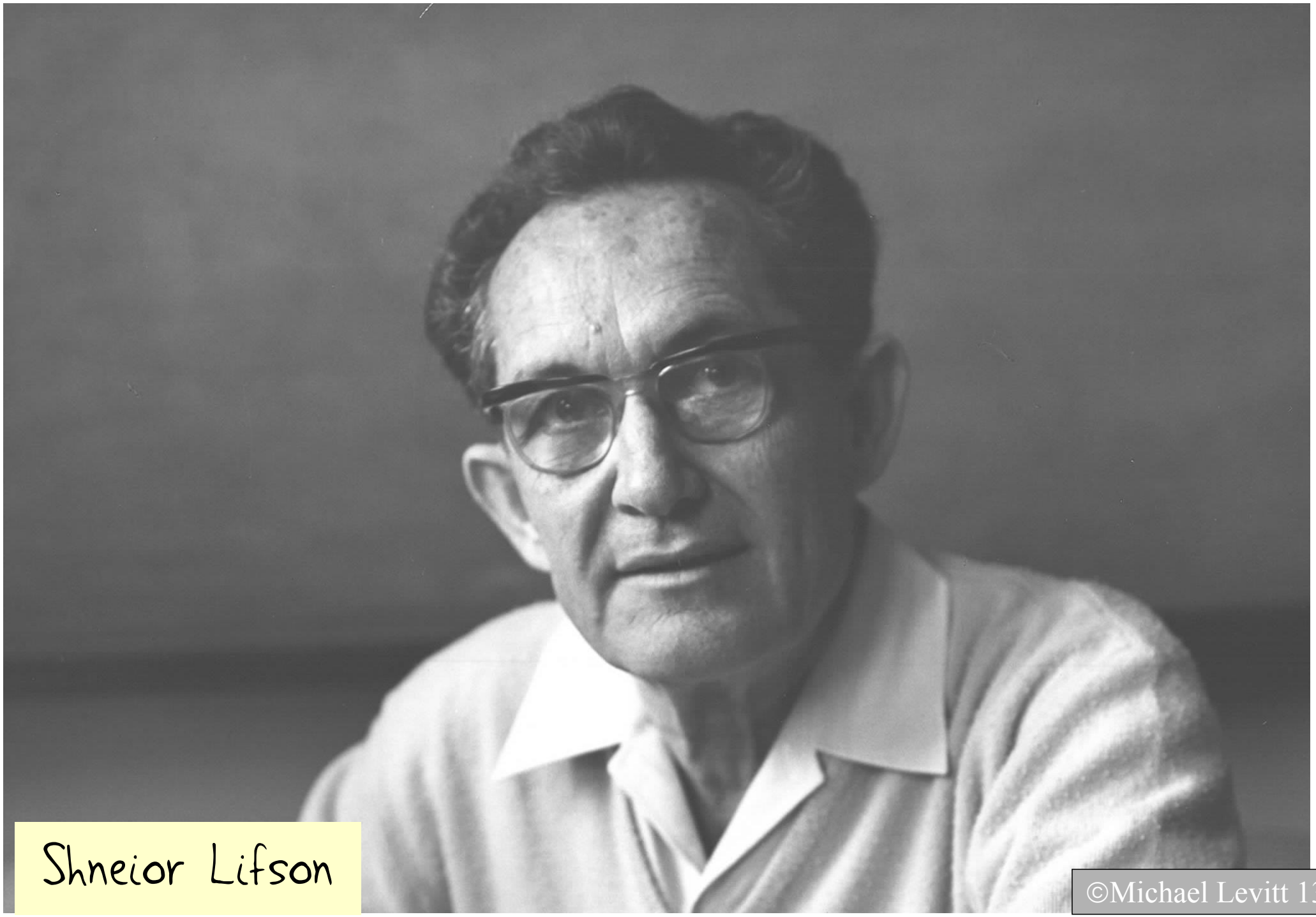


ADVICE TO THE YOUNG

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

THANKS TO MY TOWERING HEROES OF SCIENCE

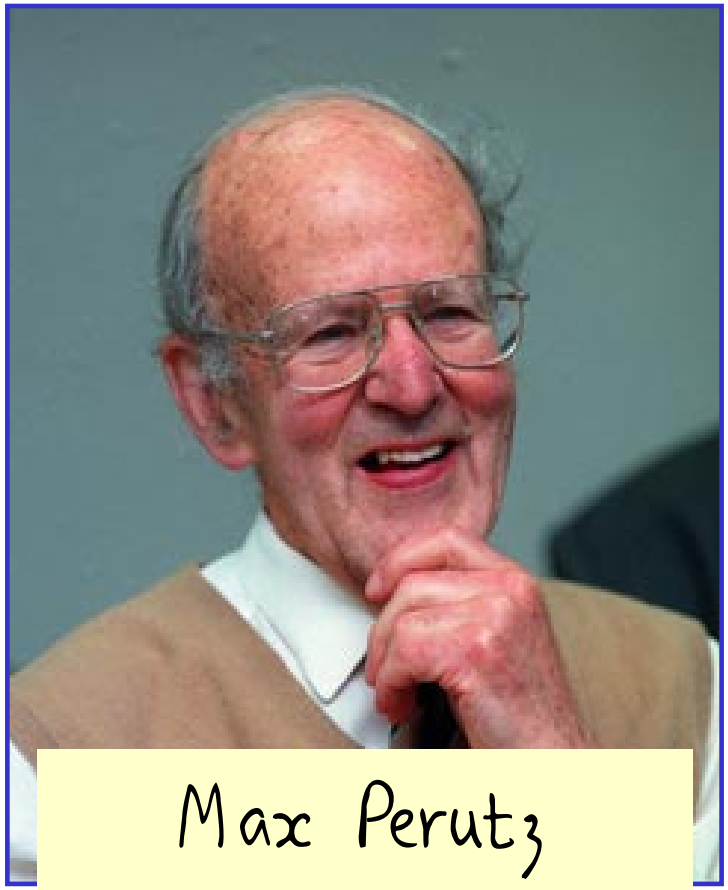
MENTOR IN ISRAEL



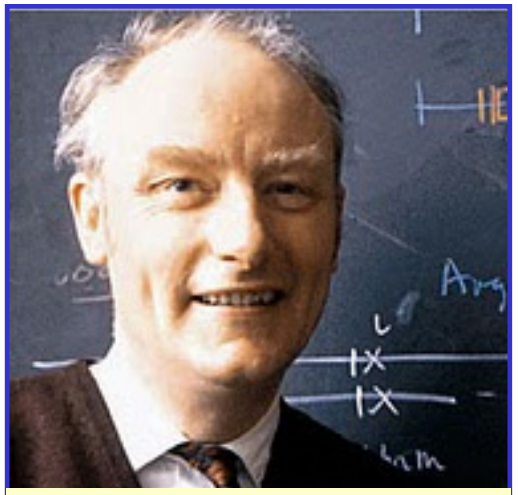
Shneior Lifson

MENTORS IN CAMBRIDGE

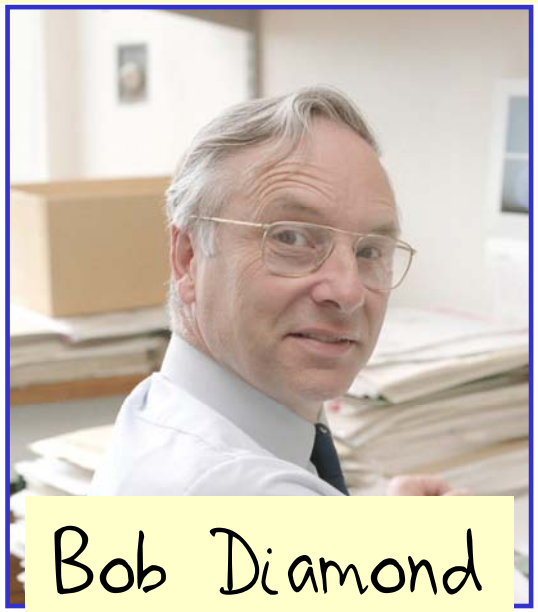
John Kendrew



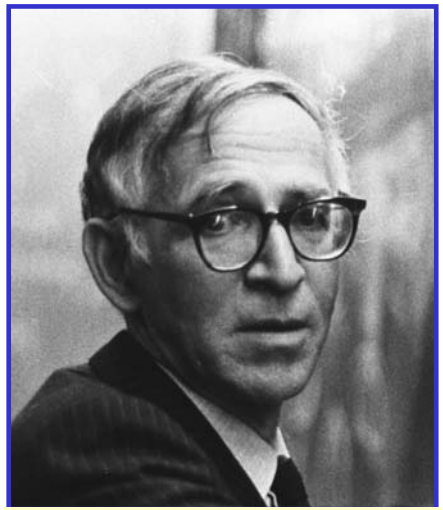
Max Perutz



Francis Crick



Bob Diamond



Aaron Klug

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Boris Fain
Chen Keasar

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Spain

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Ukraine

Uruguay

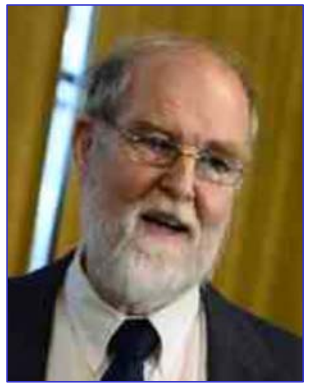
USA

Recent Research Support: NIH, NSF, HFSP

NOBEL COMMITTEE IN CHEMISTRY

- Sven Lidin
- Måns Ehrenberg
- Jan-Erling Bäckvall
- Gunnar Karlström
- Sara Snogerup Linse
- Astrid Gräslund



My Thanks To You All