BIRTH & FUTURE OF MULTI-SCALE MODELING OF MACROMOLECULES

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SUMMARY

1. How It All Began.

2. Birth of Computational Structural Biology.


4. Some General Thoughts.
1. HOW IT ALL BEGAN
STAND ON THE SHOULDERS OF GIANTS
1951: PAULING THE GREAT CHEMIST

The alpha-helix

1901-1994
1953: FRANCIS CRICK

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

We wish to suggest a structure for the deoxyribonucleic acid (DNA) of nucleic acids which is of possible biological interest.

A structure for the nucleic acid has already been proposed by Wilkins and Perutz. They identify their manuscripts available to us in advance publication. Their model consists of three different chains, with the phosphates near the axis and the bases on the outside. In our view, this structure is unsatisfactory for two reasons: (1) We believe that this material which gives X-ray diagrams is the salt, not the free acid. With the free bases, hydrogen bonding is not clear what we would hold the structure together, especially in a way that the phosphates near the axis are placed by hydrophobic bonds. (2) Some of the van der Waals distances appear to be too small.

Another double-strand structure has also been suggested by Verma and in the preface. In his model, each base of the nucleic acid is the base of the inside, linked together by hydrogen bonds. The structure as described is rather ill-defined, and for our purposes we shall not comment on it.

We wish to put forward a different structure for the double-strand nucleic acid. This structure has helical chains each of which is a single-strand material. Each chain contains a helix with a helix on the outside. The chains consist of phosphates and other groups along the length of the chain and the bases at the outside. The two chains may be held together by hydrogen bonds. The chain itself is a double helix, and the two helices are held together by hydrogen bonds. The chain is a double helix, and the two helices are held together by hydrogen bonds. The chain is a double helix, and the two helices are held together by hydrogen bonds. The chain is a double helix, and the two helices are held together by hydrogen bonds.
First protein X-ray structure.

1917–1997

1959: KENDREW AND MYOGLOBIN

Scientific American 1961

Painted by artist Irving Geis

©Michael Levitt 13
1962: PERUTZ AND HEMOGLOBIN

The REAL HERO of structural biology.
1965: PHILLIPS AND LYSOZYME

SCIENTIFIC AMERICAN

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.
LIQUIDS: ARGON & WATER

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.
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2. BIRTH OF COMPUTATIONAL STRUCTURAL BIOLOGY
The Thread of Life: An INTRODUCTION TO MOLECULAR BIOLOGY

**Episodes (BBC TV Winter 1964)**

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Nobel Prize in 1962
Gave TV Series in 1964
Sent me to Israel in 1967
SHNEIOR LIFSON 1914-2001

Weizmann Institute 1967-68
BIOMOLECULES ARE DETAILED
BIOLOGY IS DETAILED INTERACTIONS

Myoglobin 1961

Lysozyme 1966
CONSISTENT FORCE-FIELD 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

\[ U = \sum_{\text{All Bonds}} \frac{1}{2} K_b (b - b_0)^2 + \sum_{\text{All Angles}} \frac{1}{2} K_\theta (\theta - \theta_0)^2 + \sum_{\text{All Torsion Angles}} K_\phi [1 - \cos(n \phi + \delta)] + \sum_{\text{All Nonbonded pairs}} \varepsilon \left[ \left( \frac{r}{r_0} \right)^{12} - 2 \left( \frac{r}{r_0} \right)^6 \right] + \sum_{\text{All partial charges}} \frac{332 q_i q_j}{r} \]

- Simple sum over many terms
- Hooke 1635
- Fourier 1768
- Van der Waals 1837
- Coulomb 1736
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


\[ E = \sum_{b} \frac{1}{2} K_b (b - b_0)^2 + \sum_{\tau} \frac{1}{2} K_\tau (\tau - \tau_0)^2 + \sum_{\theta} \frac{1}{2} K_\theta \left( 1 + \cos (n\theta - \delta) \right) \]

- all bonds
- all bond angles
- all dihedral angles
- all non-bonded pairs
- all atomic co-ordinates

First protein structure refinement

\[ U = \sum_{b} \frac{1}{2} K_b (b - b_0)^2 - \sum_{\phi} \frac{1}{2} K_\phi (\phi - \phi_0)^2 + \sum_{\psi} \frac{1}{2} K_\psi [1 - \cos (n\psi)] + \sum \epsilon [ (\gamma_i - \gamma_i^0)^2 ] + \sum 332 q_i q_j / r \]

- All Bonds
- All Angles
- All Torsion Angles
- All non-bonded pairs
- All partial charges

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COARSE GRAINED MODELS

1975
COMPUTER SIMULATION OF PROTEIN FOLDING

Michael Levitt* & Arieh Warshel*  
Department of Chemical Physics, Weizmann Institute of Science, Rehovoth, Israel

Fold protein with 1000 steps of minimization.  
Escape from local minima with normal modes jumps.

Reduced models
QM/MM MODELS FOR CATALYSIS

1976
THEORETICAL STUDIES OF ENZYMIC REACTIONS


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

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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

In Water

In Vacuo

All-atom rms, Å

Time, ps

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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.

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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.

Move any part of system:
- Atoms
- Nucleotides
- Base Pairs
- Hairpin Helices
- Many Helices together
- All of these
APPLICATIONS TO HUMAN HEALTH
A humanized antibody that binds to the interleukin 2 receptor
(chimeric antibody/antibody affinity/autoimmune disease)

CARY QUEEN*, WILLIAM P. SCHNEIDER*, HAROLD E. SELLICK†, 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.
BREADTH OR LACK OF FOCUS?
SUMMARY SO FAR

1. How It All Began.

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4. SOME GENERAL THOUGHTS
PUSHED AHEAD
BY TECHNOLOGY
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

Ornö Kyrke

Store

“Paradise”

First Beach

Rest Stop

Kayak Rental
IT WAS A PARADISE

BUT

ALSO

VERY

STUPID
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
Miriam Hirshberg
Chris Lee
Britt Park
Dave Hinds
Enoch Huang
Jerry Tsai
Yu Xia
Michael Sykes
Rachel Kolodny
Nizar Batada
Sergio Moreno

Dahlia Weiss
Gaurav Chopra
Adelene Sim

Post Docs
S. Subbiah
Valerie Daggett
Peter David
Mark Gerstein
Steven Brenner
Boris Fain
Chen Keasar

Golan Yona
Ram Samudrala
Tanya Raschke
Patrice Koehl
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Julian Gough
Peter Minary
Gunnar Schroeder
Karine Bastard

Avraham Samson
Xuhui Huang
Julie Bernauer
Alena Shmygelska
Mitul Saha
Andrea Scaiowitz
Jenelle Bray
Marie Brut
Junjie Zhang
Leonid Pereyaslavets
Yana Gofman
Ivan Ufimtsev

Canada
China
France
Germany

Hungary
India
Israel
Pakistan

Russia
Singapore
Spain
Sweden

UK
Ukraine
Uruguay
USA

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NOBEL COMMITTEE IN CHEMISTRY

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

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OUR FIELD IS THE BIG WINNER
My Thanks
To You All