BIRTH & FUTURE OF MULTI-SCALE MODELING OF MACROMOLECULES

Nobel Lectures, Stockholm
8 December 2013

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http://csb.stanford.edu/levitt
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

DNA Model and Experiment
1959: KENDREW AND MYOGLOBIN

First protein X-ray structure.

Painted by artist Irving Geis

1917–1997

Scientific American 1961
1962: PERUTZ AND HEMOGLOBIN

The REAL HERO of structural biology.

1914-2002
1965: PHILLIPS AND LYSOZYME

Early supporter of Computational Biology

1924–1999
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

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.

Aneesur Rahman
1927-1987
SUMMARY SO FAR

1. How It All Began.

2. Birth of Computational Structural Biology.


4. Some General Thoughts.
2. BIRTH OF COMPUTATIONAL STRUCTURAL BIOLOGY
KENDREW, ME & ISRAEL

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)
BIOMOLECULES ARE DETAILED
BIOLOGY IS DETAILED INTERACTIONS

Myoglobin 1961

Lysozyme 1966
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

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

- **All Torsion Angles**
  - Fourier 1768

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

- **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
First protein structure refinement
COARSE GRAINED MODELS

1975
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
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

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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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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 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

Bases Pairs
Bases Pairs & Helices

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APPLICATIONS TO HUMAN HEALTH
A humanized antibody that binds to the interleukin 2 receptor
(chimeric antibody/antibody affinity/autoimmune disease)


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.
4. SOME GENERAL THOUGHTS
PUSHED AHEAD BY TECHNOLOGY
### How Computers Have Changed

<table>
<thead>
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<th>DATE</th>
<th>COST</th>
<th>SPEED</th>
<th>MEMORY</th>
<th>SIZE</th>
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<tr>
<td>1967</td>
<td>$40M</td>
<td>0.1 MH\text{z}</td>
<td>1 MB</td>
<td>HALL</td>
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<tr>
<td>2013</td>
<td>$4,000</td>
<td>1 GH\text{z}</td>
<td>10 GB</td>
<td>LAPTOP</td>
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<tr>
<td>CHANGE</td>
<td>10,000</td>
<td>10,000</td>
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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
### PAST & PRESENT GROUP

<table>
<thead>
<tr>
<th>PhD Students</th>
<th>Post Docs</th>
<th>Avraham Samson</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miriam Hirshberg</td>
<td>Dahlia Weiss</td>
<td>Xuhui Huang</td>
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<tr>
<td>Chris Lee</td>
<td>Gaurav Chopra</td>
<td>Julie Bernauer</td>
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<tr>
<td>Britt Park</td>
<td>Adelene Sim</td>
<td>Alena Shmygelska</td>
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<tr>
<td>Dave Hinds</td>
<td>S. Subbiah</td>
<td>Mitul Saha</td>
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<tr>
<td>Enoch Huang</td>
<td>Valerie Daggett</td>
<td>Andrea Scaiewitz</td>
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<tr>
<td>Jerry Tsai</td>
<td>Peter David</td>
<td>Jenelle Bray</td>
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<tr>
<td>Yu Xia</td>
<td>Mark Gerstein</td>
<td>Marie Brut</td>
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<td>Michael Sykes</td>
<td>Steven Brenner</td>
<td>Junjie Zhang</td>
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<td>Boris Fain</td>
<td>Leonid Pereyaslavets</td>
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<td>Nizar Batada</td>
<td>Chen Keasar</td>
<td>Yana Gofman</td>
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<tr>
<td>Sergio Moreno</td>
<td></td>
<td>Ivan Ufimtsev</td>
</tr>
</tbody>
</table>

**Countries:**
- 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
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- 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