Computer simulation of protein folding

GROUP 12TH

Yanmin Chen, Yuwei Wang, Sicheng Ye, Yang Wang, Mengting Liu.

Michael Levitt and his research

Basic review of his early work

Michael Levitt

Education

1964-1967	B.Sc. in Physics, King's College, London, UK
1967-1968	Royal Society Fellow with S. Lifson , Weizmann Institute, Israel
1968-1971	Ph.D. in Biophysics, MRC Laboratory of Molecular Biology and Cambridge University , Cambridge, UK.

Professional Experience

1972-1974	EMBO postdoctoral Fellow, Shneior Lifson Weizmann Institute of Science, Rehovot, Israel.
1974-1979	Staff Scientist, Structural Studies, MRC Laboratory Molecular Biology, Cambridge, England.
1977-1979	Visiting Scientist with Francis Crick, Salk Institute, La Jolla, California.
1979-1987	Associate & Full Professor of Chemical Physics, Department of Chemical Physics, Weizmann Institute of Science, Israel. Chair from 1980-1983, Full Professor from 1984.
1987-	Professor of Structural Biology, Department of Structural Biology, Stanford University School of Medicine, Stanford. Chair from July 1993.

Research Interest

Physical Simulation

Heuristic Structure Prediction

Structural Bio-Informatics

Early research

Levitt's early research interest focused on Energy Minimization to refine Protein Conformation

His representative work during earlier career:

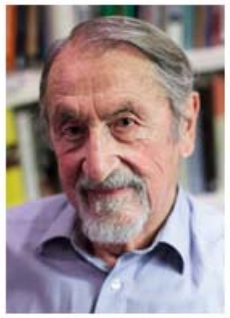
Levitt, M. and S. Lifson. Refinement of Protein Conformations Using a Macromolecular Energy Minimization Procedure. J. Mol. Biol. ***46****, 269-279 (1969).*

It is a First energy minimization of an entire protein molecule.

Research Highlights

"for the development of multiscale models for complex chemical systems"

——The Nobel Prize in Chemistry 2013



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Martin Karplus

Photo: © S. Fisch
Michael Levitt

Photo: Wikimedia Commons
Arieh Warshel

Background

In the early studies, the method of analysis protein structure are X-ray crystallography of crystals or NMR-spectroscopy

Today the focus of chemical research is much more on function analysis

However, chemical processes state is not experimentally accessible

Theoretical modeling is a necessary complement to experiment.

Modeling large complex chemical systems and reactions

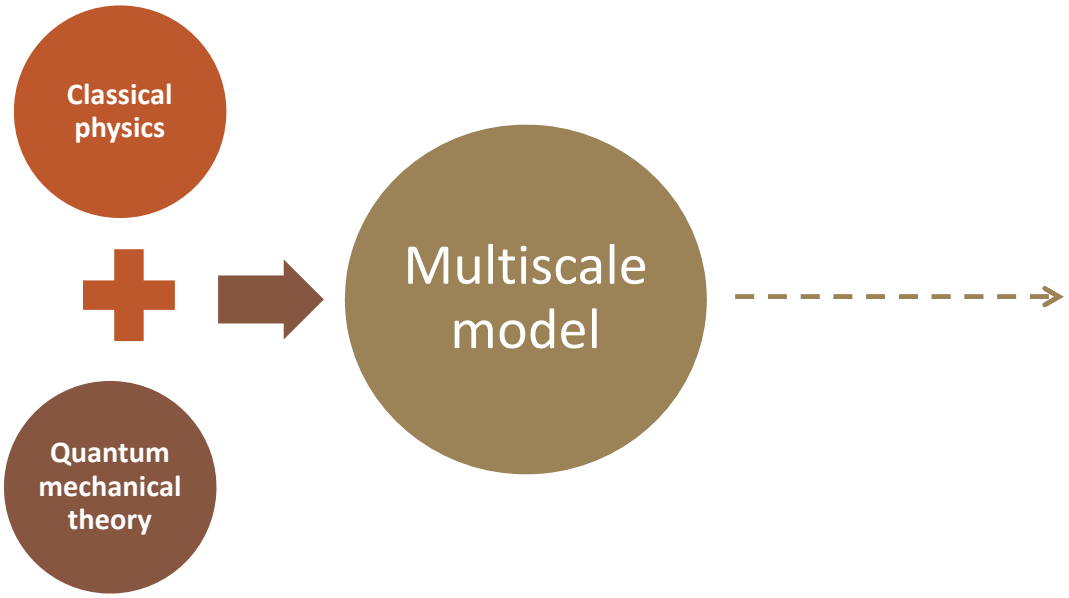


Figure 2. Newton and Schrödinger's cat. Previously, classical physics and quantum chemistry belonged to rivalling worlds. The Nobel Laureates in Chemistry 2013 have opened a gate between those worlds and have brought about a flourishing collaboration.

"The Nobel Prize in Chemistry 2013 – Advanced Information" . *Nobelprize.org.* Nobel Media AB 2013. Web. 23 Oct 2013.

Multiscale models for complex chemical systems

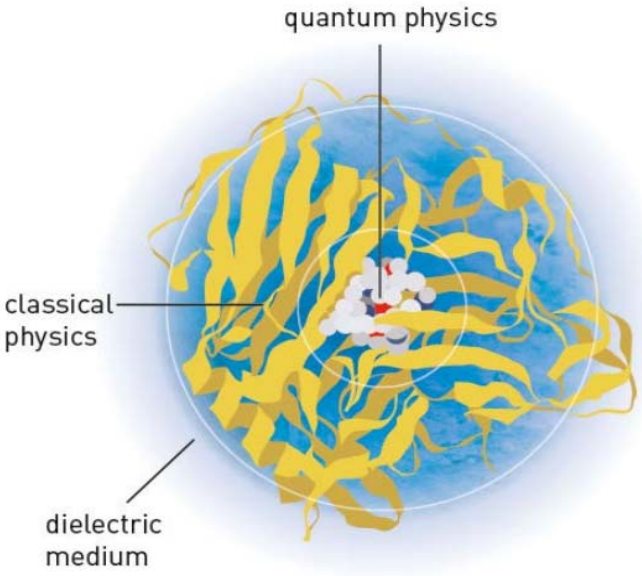


Figure 1

"The Nobel Prize in Chemistry 2013 – Advanced Information" . *Nobelprize.org.* Nobel Media AB 2013. Web. 23 Oct 2013.

Historical Perspective of Multiscale models

1972

The first work to construct Classical theory and Quantum Chemical method to describe complex chemical systems

A.Warshel and M.Karplus , J.Amer.Chem.Soc. 94,5612,1972

1975

The folding of the protein from an open conformation to a folded conformation showed that it is possible to group atoms in a classical system into rigid units and to treat these as classical pseudoatoms

M.Levitt and A.Warshel,Nature 253,694,1975

1976

Constructed a general scheme for a partitioning between electrons that are included in the classical modeling and electrons that are explicitly described by a quantum chemical model

A.Warshel and M.Levitt, J.Mol. Biol.103,227-249,1976

Multiscale modelling today

Complex processes in organic chemistry and biochemistry

Heterogeneous catalysis

theoretical calculation of the spectrum

"The Nobel Prize in Chemistry 2013 – Advanced Information“ . *Nobelprize.org.* Nobel Media AB 2013. Web. 23 Oct 2013.

I thank the 2013 Chemistry Committee selected me and my fellow laureates, Martin Karplus and Arieh Warshel not for the field we pioneered, it is because we were ***brave and daring enough to recognize a new field***.

——Michael Levitt

Some Bio-informatic research of M.Levitt

- **First use of structural information in sequence alignment.**

*Lesk, A. M., M. Levitt and C. Chothia. Alignment of the Amino Acid Sequences of Distantly Related Proteins Using Variable Gap Penalties. Protein Engineering, **1**, 77-78 (1986)*

- **Simple method for simultaneous alignment and three-dimensional superposition of protein structures.**

*Subbiah, S., D. V. Laurents and M. Levitt. Structural Similarity of DNA-binding Domains of Bacteriophage Repressors and the Globin Core. Current Biol. **3**, 141-148 (1993)*

- **Automatic structural alignment with structural is able to recognize similarity objectively.**

*Gerstein, M. and M. Levitt. Comprehensive Assessment of Automatic Structural Alignment against a Manual Standard, the SCOP Classification of Proteins. Protein Science, **7**, 445-456 (1998).*

- **Present a closed form equation giving the chance that a particular sequence or structure alignment score will occur at random.**

*Levitt, M and M. Gerstein. A Unified Statistical Framework for Sequence Comparison and Structure Comparison. Proc. Natl. Acad. Sci., **95**, 5913-5920 (1998).*

Michael Levitt and his research

Basic review of his early work

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

Refinement of Protein Conformations using a Macromolecular Energy Minimization Procedure

MICHAEL LEVITT AND SHNEIOR LIFSON

Weixmann Institute of Science
Rehovot, Israel

-SER-ALA-LEU-LEU-SER-ALA-ASP-ILE-THR-ALA-SER-VAL-ASN7CIS-ALA-LY3-LY1-ILE-VAL-SER

-ALA-GLY-ASP-GLY-MET-ASN-ALA-TRY-AL1-ALA-TRY-AR1-ASN-ARG5CIS-LYS-GLY-THR-ASP-VAL
-AL1-ALA-TRY-ILE-ALA-GLY4CIS-ALA-LEU

(a)

GLY	NCAO	ALA	NC(C)AO
VAL	NC(C(C)C)AO	ILE	NC(C(C)CC)AO
LEU	NC(CC(C)C)AO	SER	NC(CO)AO
THR	NC(AOC)AO	PRO	*NC(CC*C)AO
CIS	NC(C=S)AO	MET	NC(CC.SC)AO
LYS	NC(CCCCN)AO	ARG	NC(CCCNB(N)N)AO
ASP	NC(CAOO)AO	ASN	NC(CAON)AO
GLU	NC(CCAOO)AO	GLN	NC(CCAON)AO
HIS	Nc(c*BNBN*B)a0	PHE	NC(C*BBBBB*B)AO
TYR	NC(C*OBBBOO*B)AO	TRY	NC(C*BBN$BBBBB$*B)AO
AL1	NC(CC)AO	LY1	NC(CCCC)AO
TR1	NC(C*BBNB*B)AO	MT1	NC(CC.S)AO
AR1	NC(CCCN)AO		

The total molecule potential energy:

$$E = \sum \frac{1}{2} K_b (b - b_0)^2 + \sum \frac{1}{2} K_\tau (\tau - \tau_0)^2 + \sum \frac{1}{2} K_0 \{1 + \cos(n\theta - \delta)\}$$

All bonds

All bond angles

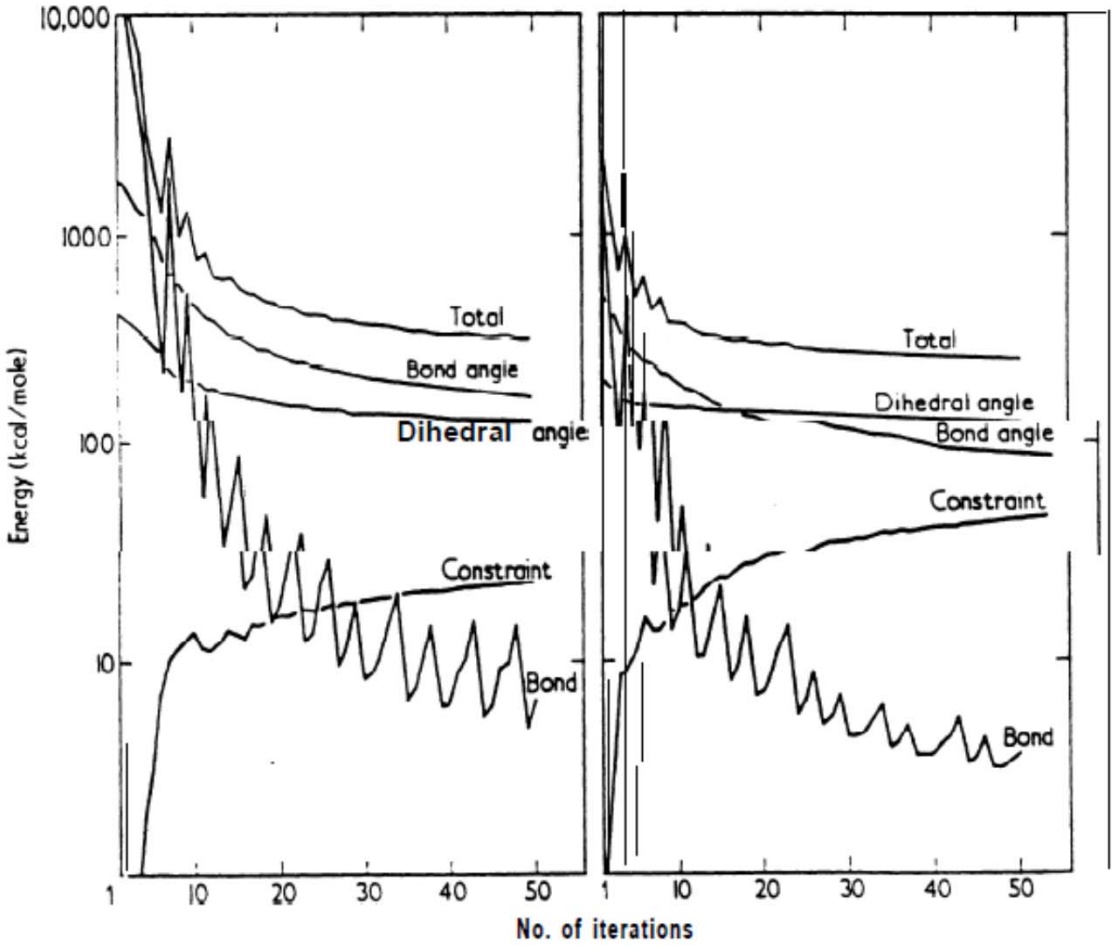
All dihedral angles

$$+ \sum_{\epsilon_{ij}} \{(r_{ij}^0 / r_{ij})^{12} - 2(r_{ij}^0 / r_{ij})^6\} + \sum \frac{1}{2} \omega (x_i - x_i^0)^2$$

All non-bonded pairs
Lennard-Jones potential

All atomic co-ordinates

Iteration history of lysozyme and myoglobin



(Reprinted Nature, Vol. 253, No. 5494, pp. 6 94-6 98, February 2 7, I9 75)

Computer simulation of protein folding

Michael Levitt* & Arieh WarsheI*

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

Question raised

the relationship between
protein sequence and conformation

Problem solving

Simplify the representation of a protein by averaging over the fine details.

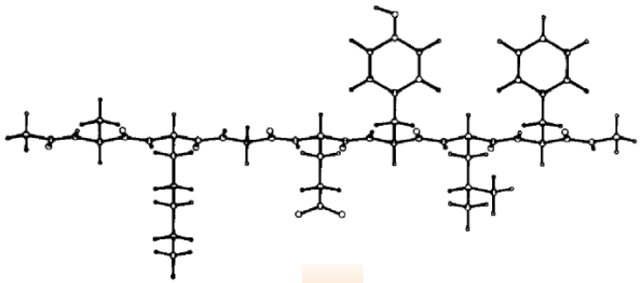
Simulate the folding of this simple structure by the combined use of convergent energy minimization and normal mode thermalization.

Basic Assumptions

Much of the protein's fine structure can be eliminated by averaging

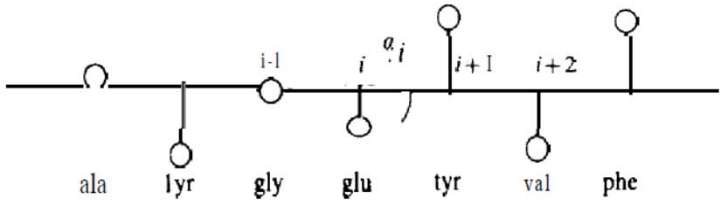
The overall chain folding can be obtained by considering only the effective variables.

Simplified model of protein structure



real all-atom structure of proteins

Simplify



simplified model of protein structure

so simple a model can represent the stable conformation of a folded protein

simulate the actual process of folding

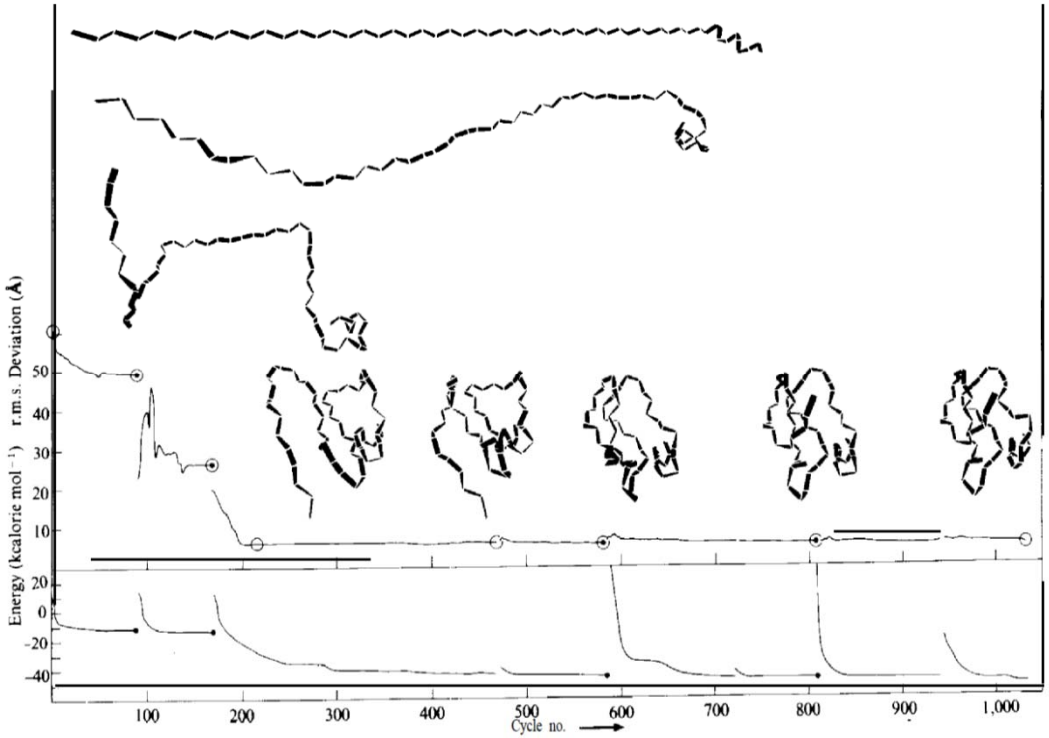
Computing Details

- Method: Molecular Dynamics at sufficient small time intervals.
- Medium: Water (Viscous medium)
- Motion : Brownian Motion.
- Equations : Langevin equations.
- For greater efficiency :

1) neglect these thermal fluctuations while the chain folds.

2) the end points of the trajectory is the potential energy minimum accessible from the starting conformation.

Simulation of pancreatic trypsin inhibitor (PTI) folding from an extended starting conformation with the terminal helix



Summary

A model based on time averaged forces can account for the stability and folding of a molecule as complicated as a protein.

Folding must depend on a very rare random fluctuation that happened to bring the right residues close together with sufficient precision for the short-range forces to take effect.

Acknowledgement

The group members are grateful for the help from Professor Ge Gao and Liping Wei.

We also appreciate the hard work and the patience of the teaching assistant group.

Thanks for your attention