Guest Editorial

Israel Journal of Chemistry

DOI: 10.1002/ijch.201410011

Computational Molecular Biophysics: 40 Years of Achievements

The Nobel Prize in Chemistry for 2013 was shared by three people in recognition of their seminal work more than 40 years ago, which established the foundations for computational investigations of the dynamics of complex molecules. Martin Karplus (Harvard, University of Strasbourg), Michael Levitt (Stanford) and Arieh Warshel (University of Southern California) played central roles in providing new approaches and techniques for the study and understanding of complex biological molecules. Their revolutionary contributions during the years 1968–1976 created the new field of computational molecular biophysics. The 40 years between the foundation of the field and the announcement of the highest possible recognition by the Nobel committee are reminiscent of the 40 years the people of Israel had to wander in the wilderness before entering to the Promised Land. In both cases, these years were full of refinements, increased understanding and sophistication.

Through the significant contributions of many other talented minds who followed the lead of Karplus, Levitt, and Warshel in the past few decades, the field has flourished and branched out into sub-fields, involving many areas of chemistry and biology. The community of computational biologists viewed this Nobel Prize as the recognition that Computational Biology has come of age; as such it generated great excitement as reflected by several commentaries on the prize.[1–3]

This special volume of the *Israel Journal of Chemistry* focuses on Computational Molecular Biophysics to celebrate the 2013 Nobel Prize awarded to Karplus, Levitt, and Warshel. It has become somewhat of a tradition for the *Israel Journal of Chemistry* to dedicate a special volume to Israeli Nobel Prize laureates in Chemistry. Within the last 10 years, four prizes were awarded to Israeli scientists (Avraham Hershko and Aaron Ceichanover in 2004, Ada Yonath in 2009, Dan Shechtman in 2011). While none of the three current chemistry Nobel laureates is a professor at an Israeli university (with the exception of Michael Levitt who is a visiting scientist at the Weizmann Institute of Science), a substantial fraction of the honored work was done at the Weizmann Institute of Science. Some of these studies were published when Levitt and Warshel were Principal Investigators at the department of Chemical Physics at the Weizmann Institute, and other, earlier but by no means not less important, were completed when they worked under the supervision of Shneior Lifson.[4] Lifson joined the Weizmann Institute in 1949 and started his PhD under the supervision of Prof. Aharon Katzir studying the dynamic properties of large molecules, using the principles of statistical mechanics. He was one of the first to recognize the power of computers to analyze the dynamics of large molecules on the atomic level. Prof. Shneior Lifson died in 2001 at the age of 87.

The contribution of Shneior Lifson for advancing computation of complex and large molecules (e.g., biological macromolecules) was acknowledged by the three laureates on many occasions since the prize was announced. Levitt, who joined the Lifson lab in 1967 while waiting for a position in the lab of Sir John Kendrew at Cambridge University, writes, "Kendrew said that I should spend the intervening period at the Weizmann Institute with Shneior Lifson. Kendrew had just heard of Lifson's initial ideas on the consistent force field (CFF), which was an attempt to simulate the properties of any molecular system from a simple energy potential." Levitt calls Lifson a "towering hero of science who unrelentingly insisted on understanding," and credits Lifson's influence on his work, both scientifically and personally.

Arieh Warshel, who was a PhD student in Lifson's lab when Levitt arrived, called Lifson "a true renaissance man who showed interest and knowledge in fields outside science including music and other art forms, politics and public education. He would require consistent agreement among many experiments, which could, of course, only be obtained with major effort. I also remember that he could be gracious in admitting when he was wrong, after having said that I must be incorrect. Eventually he said: "Don't argue with Arieh; he is always right."

In a review article by Karplus from 2006,[5] his impression from a sabbatical in the Lifson group illustrates the pioneering research done by Lifson and his students Levitt and Warshel: "I was aware of Shneior Lifson's work on polymer theory and his reputation of being an open minded scientist, as well as a marvelous storyteller. I wrote Shneior asking whether I could come for a semester, and he kindly invited me to join his group. The sabbatical gave me the leisure to read and explore a number of areas in which I hoped to do constructive research by applying my expertise in theoretical chemistry to biology.

Discussions with Shneior and visitors to his group helped me in these explorations… Although many persons have contributed to the development of empirical potentials, the two major inputs to our work came from Schneior Lifson's group at the Weizmann Institute and Harold Scheraga's group at Cornell University. As I already mentioned, Warshel had come to Harvard and had brought his CFF program with him. His presence and the availability of the CFF program were important resources for Gelin, who was also aware of Michael Levitt's pioneering energy calculations for proteins."

The study of Levitt and Warshel with Lifson on the development of the CFF for small molecules[6] and later for biological macromolecules[7] has formed the basis for transferable force fields for any biomolecules and paved the way for the common force fields such as AMBER, CHARMM, GROMOS, and OPLS. The development of the force fields was critical for computational understanding of protein structure via minimization and their dynamics via molecular dynamics simulations.

In addition to developing the foundations of protein structure prediction and protein dynamics *in silico*, two major breakthroughs are associated with the 2013 Nobel Prize in Chemistry. These two breakthroughs involve elegant "shortcuts" to address difficult problems in biomolecular systems by reducing their high complexity. The first creative "shortcut" is related to their innovative idea to study enzymatic reactions by dividing a complex system into two regions: a small region that is studied quantum mechanically and a larger one that is studied using molecular mechanics. The mixing of quantum and molecular mechanical calculations as introduced by Warshel and Karplus[8] and by Warshel and Levitt[9] was specifically honored by the Nobel committee. The second "shortcut" deals with discriminating between the many degrees of freedoms of the macromolecules and studying their dynamics by using a smaller subset of atoms while ignoring the others. Such an approach was applied by Levitt and Warshel to bovine pancreatic trypsin inhibitor (BPTI), where each of the 58 amino acids of the protein was represented by only two beads.[10] This simplified representation allowed sequential rounds of energy minimization and heating using normal modes to study the collapse transition from unfolded conformations to folded ones. The approach applied by Levitt and Warshel to study the folding transition of BPTI was followed by the first molecular dynamics simulations performed by McCammon, Gelin, and Karplus in which the folded state dynamics of BPTI was studied by solving Newton's equation of motion.[11] This simple representation of the polypeptide chain can be viewed as the first coarse-grained model. Coarse-graining is widely used today because it expands the possibilities to study biomolecular systems. This trend in molecular computational biology to use low resolution models is justified by numerous studies that show the power of such models to reproduce experimental results. Clearly, coarse-grained models, if they are not too crude, may be powerful for several reasons: they allow studying large systems, they allow addressing *in vivo* questions, and they allow studying systems for longer timescales that approach the physiological relevance. Coarse-grained models, which can be very diverse and suited to the question at hand, were shown to be powerful in providing quantitative understanding as well as to test hypotheses; nevertheless comparison to detailed models with accurate representation of the systems and its surrounding (e.g., the water molecules) is essential to obtain a fuller understanding.

In May 2013 a conference was organized at the Weizmann Institute by Yaakov (Koby) Levy and Tamar Schlick on "Computational Biology: Then and Now". To acknowledge the pioneering work on biomolecular modeling started at the Weizmann Institute, the first session was dedicated to Shneior Lifson and to a historical perspective on the field. Levitt and Warshel both gave lectures in this session. A year later, in May 2014, another conference was organized at the Weizmann Institute that had two objectives: to commemorate the 100th anniversary of the birth of Shneior Lifson and to honor the Nobel Prize in Chemistry of his two students (see Figure 1).

This special volume of the *Israel Journal of Chemistry* focuses on Computational Molecular Biophysics in honor of the 2013 Nobel Prize. It includes about 30 review and original articles contributed from scientists in this vast field of biomolecular simulations. In particular, the volume includes contributions from the participants that

Figure 1. Michael Levitt (right) and Arieh Warshel (left) with Gilad Haran (middle, the Dean of the Faculty of Chemistry, Weizmann Institute of Science). The photo was taken during a symposium commemorating the anniversary of the 100th birthday of Shneior Lifson in May 2014 at the Weizmann Institute of Science. A photo of Shneior Lifson is seen in the poster shown at the back.

Israel Journal of Chemistry

attended the meeting that took place in May 2013. This impressive collection of articles illustrates how the field of biomolecular simulations has become diverse, vibrant, and mature. While the articles demonstrate that many biomolecular systems have been successfully studied over the past 40 years since the seminal contributions by Karplus, Levitt, and Warshel, they also clearly indicate how much potential there is for yet greater advancements in this multi-faceted field.

Yaakov Levy
Weizmann Institute of Science, Rehovot, Israel
Guest Editor

Jeffrey Skolnick
Georgia Institute of Technology, Atlanta, USA
Guest Editor

References

[1] J. C. Smith, B. Roux, *Structure* **2013**, *21*, 2102–2105.
[2] W. L. Jorgensen, *Cell* **2013**, *155*, 1199–1202.
[3] A. R. Fersht, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 19656–19657.
[4] M. Levitt, *Nat. Struct. Biol.* **2001**, *8*, 392–393.
[5] M. Karplus, *Annu. Rev. Bioph. Biom.* **2006**, *35*, 1–47.
[6] S. Lifson, A. Warshel, *J. Chem. Phys.* **1968**, *49*, 5116.
[7] M. Levitt, S. Lifson, *J. Mol. Biol.* **1969**, *46*, 269.
[8] A. Warshel, M. Karplus, *J. Am. Chem. Soc.* **1972**, *94*, 5612.
[9] A. Warshel, M. Levitt, *J. Mol. Biol.* **1976**, *103*, 227–249.
[10] M. Levitt, A. Warshel, *Nature* **1975**, *253*, 694–698.
[11] J. A. Mccammon, B. R. Gelin, M. Karplus, *Nature* **1977**, *267*, 585–590.