
Editorial: Current Developments in Computational Studies of Peptides

The first two seminal reviews on computational studies of peptide conformation were published in 1968 by H. A. Scheraga in *Advances in Physical Organical Chemistry*, and by G. N. Ramachandran and V. Sasisekharan in *Advances in Protein Chemistry*. More than three decades later, computational approaches have become an integral part of peptide science, complementing the tremendous success of experimental methods, such as x-ray crystallography, NMR-, IR-, EPR- and fluorescence spectroscopy.

Generally, computational approaches are more important in the studies of peptides than in studies of their larger counterparts, proteins. The main reason is that the level of peptide conformational flexibility is greater and conformational ensembles must be considered. In this respect, peptides occupy a position between proteins that possess a single main conformer, and low molecular compounds, like bioamines that, in fact, have no unique three-dimensional structure in solution. In other words, most peptides exist under physiological conditions as a mixture of more or less well defined, interconverting conformers, and specific receptors select "receptor-bound" (or "biologically active") conformers from among those already present in solution. The interconversion rate is such, that, for instance, NMR spectroscopy cannot distinguish unique conformers of linear peptides of the kilodalton range in solution (with an exception of *cis/trans* peptide bond isomers). On the other hand, x-ray crystallography provides only a single specific "snapshot" of the structure of a peptide in a crystalline lattice that may be nonrelevant to the biologically active conformer. Computational studies that are able

to elucidate thermodynamically stable peptide structures, therefore, became indispensable in any rational search for potential pharmaceuticals based on peptide leads. Currently, such computational studies are being performed on a massive scale using readily available software modeling packages as SYBYL, DISCOVER, QUANTA, etc.

However, the scale of application per se does not mean that computational approaches in peptide science are mature enough to ensure a complete understanding of the physics of peptide behavior, either individually, or in complexes with their receptors. New ideas and algorithms are welcomed nowadays even more than thirty years ago as the practicality of the computational approach becomes more self-evident. This issue of *Peptide Science* has been initiated as a collection of original papers showing current cutting-edge developments in computational approaches to peptide studies.

The first paper of the issue by Liwo and his associates focuses on the problem of conformational averaging of peptide conformations in solution. More specifically, the authors interpret experimental NMR data in terms of an ensemble of conformers rather than a unique structure. They then address the problem of experimental data gathered in organic solvents where thermodynamic solvation data are scarce. Finally, the manuscript presents a method in which the Boltzmann statistical weights of the ensemble of conformers are used to fit the solvation parameters. Obviously, such an approach is very valuable in the analysis of NMR data from organic solvents.

Conformational analysis from the rigorous viewpoint of statistical mechanics is the main emphasis of

the paper by Okamoto and his colleagues. This paper reviews generalized-ensemble algorithms to characterize a potential energy surface. Among the approaches are the multicanonical algorithms, simulated tempering and replica-exchange methods; both strengths and weaknesses of each approach are indicated in the paper. The authors suggest a hybrid approach in which one method is used to scan the surface and the another one used to more fully characterize the local minima found; this approach seems to be more and more useful as the size of the system increases. An application to the folding of short peptides is given in the paper to demonstrate the utility of the approach.

The next two papers discuss somewhat less general, but still extremely important problems of describing peptide structure in solution. Totrov and Abagyan have developed a novel approach for rapid evaluation of contribution of electrostatic forces in peptide solvation (the REBEL method). The conformation of a 23-residue peptide is optimized in this paper with and without the solvation electrostatic term. An ensemble of conformations similar to the experimental $\beta\beta\alpha$ -structure of the peptide was found when the solvation term was included. The paper by Marlow and Pettitt describes a sensitivity analysis of the parameters used for representing solution ions in the simulation of the opioid peptide DPDPE in NaCl solution. These pioneering studies are of great interest

to researchers who must find appropriate means to account for the ionic nature of biological fluids during simulations. Besides, since DPDPE has been studied previously with a variety of techniques, both computational and experimental, the results of the paper can be easily validated.

The last paper of the issue (Galaktionov, Nikiforovich, and Marshall) may formally belong not to peptides, but rather to protein folding. However, the loops on the protein surfaces behave much like peptides, being both flexible and, to a high extent, individually independent. The authors suggest different computational procedures to deal with the loops in proteins depending on their size. Their most impressive result is restoring of large loops (up to 60 residues) by a novel approach utilizing the residue-residue contact matrices.

We hope that the issue as a whole fairly reflects many of the current developments in the “computational peptide science” in the beginning of the 21st century. We are fully aware also that the rapid progress in this field may surpass some of these developments even as we reflect upon them in this exciting issue of *Peptide Science*.

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