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published in

Computational Soft Matter: From Synthetic Polymers to Proteins, Lecture Notes,
Norbert Attig, Kurt Binder, Helmut Grubmüller, Kurt Kremer (Eds.),
John von Neumann Institute for Computing, Jülich,
NIC Series, Vol. **23***, ISBN 3-00-012641-4, pp. 321-322, 2004.*

http://www.fz-juelich.de/nic-series/volume23

Self-Organization of Biomolecular Systems: Simulating the Folding and Aggregation of Peptides, Proteins and Lipids.

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Computer simulations of proteins, lipids and nucleic acids at equilibrium have become largely routine. The basic methodology is well established and has been extensively verified.[1] The challenge for the future is to use such approaches to understand composition and concentration depend phenomena such as those which give rise to spontaneous self-organization in (bio)molecular systems and which by their very nature cannot be readily probed by experiment. Examples of such processes include the folding and aggregation of peptides and proteins,[2,3] the aggregation of lipids and surfactants into micelles[4,5] bilayers[6] and vesicles,[7] as well as the assembly of mixed systems into functional complexes, all fundamental to living cells.

Peptide folding: It is not yet possible to fold complete proteins using atomic models. Nevertheless, dramatic process is being made regarding the folding and aggregation of peptides. For example, in certain cases it is now possible, to simulate the folding of small (10-15 a.a.) peptides under reversible conditions from an arbitrary initial configuration with experimental precision.[2,3] Such work has lead to a reassessment of the nature of the unfolded state and point the way forward to the folding of larger systems.[8–10]

Lipid aggregation: Cell membranes are the archetypal example of a self-organized system which in addition to various types of lipids can contain peptide, proteins and high concentrations of molecules such as cholesterol. Previously it was believed that it was only possible to such collective behavior in such systems using simplified or coarse-grained models. We have recently shown however that it is possible to simulate the self-assembly for a random mixture of lipids (or surfactants) in water into their correct phase in atomic detail. This has proved to be an extremely powerful approach to investigate processes such as the pore formation in bilayers, domain formation in mixed bilayers, and the mechanism of vesicle formation and fusion.[7,11] By performing simulations of the same phenomena using a specifically parameterized course-grained model as well as in atomic detail has also been possible to investigate for what aspects modeling in atomic detail is truly needed.

Assembly of functional complexes: The process of assembly of a membrane-water interface can also provide a powerful driving force to initiate the folding and self-assembly of peptides and proteins. For example the protein hydrophobin SC3 is largely unstructured in solution but rapidly forms extended b-sheet at hydrophobic/hydrophilic interfaces.[12] In the same manner multiple copies of pore forming peptides can be included in simulations leading to spontaneously formed bilayers. This is shedding light on exactly how such

peptides manage to insert, assemble and function within membranes.[13]

Examples illustrating the extent to which simulations both at an atomic level and at a more coarse grained level can be used to understand cooperative phenomena such as those mentioned above will be presented. In particular the lecture focus on to what extent the results we obtain from such simulations are reasonable[14] and how basic traps when simulating biomolecular systems can be avoided.

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