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Molecular Modelling: All the Way from Atomistic Structure to Function in Complex Systems

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Molecular modelling lies at the nexus of two momentous developments in modern science: it couples the explosive development of computational power with the drive towards molecular-scale understanding and subsequent control of function and properties in complex systems. Indeed, one of the great challenges in modern science involves establishing quantitative relationships between macroscopic function and organization of biological systems and materials on the one hand and the underlying molecular architectures, interactions, and dynamics on the other. Breakthroughs in this challenge are likely to have substantial impacts in the knowledge-based economy in the coming decades, with technologies as crucial yet disparate as the fabrication of new computers and the development of new fluorescent probes for in vivo tissue imaging and medical diagnostics, bringing enormous benefits to Australia's society and its economy.

Computational molecular science is emerging as a critical enabling technology for in-silico approaches to this challenge. Its potential for generating molecular paradigms to rationalize phenomena in biology, materials science, and nanoscience has emerged as a possibility in recent years through the simultaneous development of ever more powerful high-performance-computing hardware, together with new generations of scalable algorithms for solving the equations governing molecular behaviour. In parallel, and equally important, are advances in characterization (e.g. microscopy and high-throughput crystallography) which help contribute to the context in which meaningful computational problems can be formulated and tackled.

This thematic issue of the *Australian Journal of Chemistry* presents a collection of papers associated with contributions to the Molecular Modelling 2009 (MM2009) conference hosted by the Association of Molecular Modellers of Australasia (www.mgms.org.au), which is the Australasian branch of the Molecular Graphics and Modelling Society (www.mgms.org). The MM2009 meeting was held at the Gold Coast in Queensland, 26–29 July, 2009. It was attended by a substantive grouping of Australian as well as international participants, drawn from a wide range of disciplines where computational molecular science has a significant role to play.

We note below a thematic summary of general areas that featured in the conference presentations and discussions, followed by a brief overview of the specific papers contained herein.

Electronic Structure

Atoms and molecules move according to the forces they experience, and these forces are dictated by the way in which the electronic energy changes with position of the nuclei. If the electronic energy possesses a marked minimum for a particular arrangement of the atoms then this will indeed be the equilibrium structure of the system. Molecular structure becomes poorly defined when different arrangements of the atoms result in similar electronic energies, such that thermal energy of motion can allow the atoms to adopt quite different arrangements. Ultimately, structural changes, phase transitions, protein folding, and chemical reactivity are all dictated by the underlying behaviour of the electronic energy as the atomic or molecular configurations change. Small wonder, then, that development of accurate and scaleable solution methods for the electronic

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Scrödinger equation has been and continues to be a major focus of computational chemistry.

Biomolecular Modelling and Design

Computational biology may be considered broadly to cover topics as diverse as gene annotation, protein folding, molecular orbital studies of biomolecules and their natural or synthetic ligands, ADMET modelling, modelling of protein folding, biomimetic design, computational drug, veterinary drug and agrochemical design and complex systems science. The ability to model the interactions of biomolecules at the atomic level using sophisticated computational methods is increasingly underpinning advances in molecular biology, molecular pharmacology, and molecular medicine. Computational methods can increase the efficiency of design, discovery and development of commercially and medically important biomolecules such as drug, vaccines, protein therapeutics, and gene therapies.

Materials and Nanotechnology

The study of structure, function, phase transitions, magnetic and electronic properties, and surface catalytic activity of materials based on their properties at the atomic and molecular scale is an enormous field of endeavour with a vast array of applications. In recent years the dependence of the physical and chemical properties as a function of size at the nanoscale has become a signature question in the field of nanoscience. Computational nanotechnology incorporates all of the traditional branches of activity in computational chemistry and physics. Important links to biomolecular modelling lie in the burgeoning area of biomaterials research – an area of vast application potential for materials and nanotechnology specialists interacting with bioscientists and neuroscientists.

Kinetics and Dynamics in Complex Systems

The development of predictive models which will allow quantitative simulation of the evolution in real time of complex systems is a huge challenge which lies at the forefront of many fields. In the engineering, physical, chemical, biological, and environmental sciences such quantitative modelling requires the input of quality data describing the rates of molecular processes, which are integral to the overall phenomena being observed. Sometimes, as in combustion networks, these elementary chemical reactivities are fed directly into the time integrator algorithm. In other cases, such as neural or biological networks, particle processing models, or climate simulators the individual molecular data must be synthesized into more coarse grained parameters which then feed into models that operate at a larger scale. Ultimately, to predict macroscopic behaviour in such systems a layered, hierarchical approach, often termed multiscale modelling, is necessary.

Papers in this Issue

The current collection of papers begins with the highlight from Chandana Epa and coworkers. The paper presents some of the most significant recent developments in computational modelling studies of the structure of the binding site and reaction mechanisms of reactive oxygen species generation.[1]

Followings are articles on the ground and excited states of four interesting systems. Smith's group present the results of a systematic series of constrained minimum energy pathway calculations on ground state potential energy surfaces for a cluster model of the proton chain transfer that mediates the photocycle of the green fluorescent protein, as well as for a model including the solvated protein environment.[2] An accurate *ab initio* potential energy surface describing the twisting of diethyl disulfide through its three central dihedral angles is described by Haworth and coworkers.[3] Zhang and colleagues report a first-principles study of fluorination effects on atomic hydrogen interactions with fluorinated corannulene radical ($C_{15}H_{10}F_5$). They found that on carbon top site the adsorption is almost barrierless, whereas in the middle bond site there is a barrier for the hydrogen adsorption.[4] In order to gain insight into fundamental aspects of organic photocell materials, Kearley's group study ground and excited, electronic-state structures and molecular vibrations for an isolated HAT6 molecule (hexakis(nhexyloxy)triphenylene).[5]

Several research contributions that broadly span biomolecular modelling, protein and drug design follow. The paper by Hofmann and coworkers illustrates how Visinin-like proteins interaction with phospho-inositides. The molecular modelling results support a binding site for phospho-inositides in the N-terminal area of VILIP-1 (the subcellular membrane localization of neuronal calcium sensor proteins in living cells), and the involvement of the conserved N-terminal lysine residues in binding the phosphoinositol head group, and the results are in consistent with experiment observations.[6] In Manallack and coworkers' study, three methods – molecular docking (*Glide*), shape similarity (*ROCS*) and pharmacophore modelling (*Phase*) – are evaluated for their ability to reproduce the experimentally determined binding mode of 25 PDE4 inhibitors identified by X-ray crystallography.[7] Liu and colleagues report allosteric conformational transition in adenylate kinase. They also suggest a quantitative dynamics criterion for determining the allosteric cooperativity, which may be applicable to other proteins.[8]

Finally, this Research Front features a paper from Reid and coworkers. They apply bi-directional Jarzynski methods to quasi-equilibrium states in order to measuring free energy differences between states which is fundamental importance to understanding and predicting the behaviour of thermodynamic systems.[9]

It is with great pleasure, then, that we commend this collection of papers associated with MM2009 to the reader.

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