Chemical theory and computation

Highlighting this issue of PNAS is a special feature comprised of 7 Perspectives and 24 research articles on the topic of chemical theory and computation, the field of study that has progressed to the point of being able to address important questions in the core areas of the chemical sciences, including questions lying on the interface among chemistry, physics, biology, and engineering. These interdisciplinary areas include biomolecular chemistry, the chemistry of materials, and the emerging field of nanochemistry. In addition, many developments in this field overlap with the emerging field of computational biology.

The theoretical pillars of theoretical chemistry are molecular quantum mechanics and classical and quantum statistical mechanics. Computational quantum chemistry has developed to the point where the electronic structure of many-atom molecules and nanomolecular assemblies can be readily and accurately computed. Computational chemistry is based also on the development and use of powerful computational tools such as molecular dynamics and Monte Carlo sampling to predict structural, thermodynamic, and dynamical properties of many-body ordered and disordered systems. These methods have been used for more than four decades to simulate the behavior of liquids, glasses, liquid crystals, simple solutions, and aqueous biomolecular systems, systems for which classical mechanics is a good approximation. To go beyond the classical approximation for atomic motions, computational methods based on Feynman's (1) path integral formulation of quantum mechanics and quantum statistical mechanics have proven very useful; however, it is very difficult to treat many-electron systems computationally by using path integrals. Moreover, because of the notorious sign problem, it is difficult to treat the real-time dynamics of many-body quantum systems by path integrals. There have been several interesting efforts to bypass the sign problem, including semiclassical propagation methods, wave-packet dynamics, centroid dynamics, and Bayesian methods for analytical continuation of imaginary time propagation. An important outgrowth of quantum chemical methods and molecular dynamics is the mixed quantum mechanics in molecular mechanics, or QM/MM, method in which one part of the system is treated quantum mechanically and the other part is treated classically. Examples are ligands bound to active sites of enzymes. The ligand and active site are treated quantum chemically whereas the rest of the system is treated classically.

New methods have been devised to speed up molecular dynamics and Monte Carlo sampling. Examples are methods to treat systems with multiple time scales and long-range electrostatic forces in molecular dynamics and new methods for speeding up the Monte Carlo sampling of systems with rough energy landscapes.

Most molecular dynamics and Monte Carlo simulations are based on the use of force field models, and considerable effort has therefore been expended toward designing accurate force fields. Unfortunately, it is very difficult to devise force fields that are chemically accurate, yet chemical accuracy is required in such applications as rational drug design. In recent years, polarizable force fields have been devised for aqueous solutions of amino acids and proteins with considerable promise. A different approach is to calculate the forces "on-the-fly" quantum mechanically and use them to advance the system classically by molecular dynamics. In this scheme, called *ab initio* molecular dynamics, the forces are computed, the system is advanced one time step, the forces are recomputed, etc. *Ab initio* molecular dynamics has proven useful for studying complex systems such as nanotubes, proton transfer in water, etc. The method is computationally expensive, and only small systems can be studied at the present time. This approach should improve in the future as density functional methods for the computation of quantum electronic structure are improved.

The powerful tools of molecular dynamics and Monte Carlo sampling allow for the prediction of the thermodynamic, structural, and transport properties of materials too complex to calculate by analytical means. These tools are used in two different ways. On the one hand, they allow one to compute the "exact" properties of "model systems" and to test theoretical approximations. The models often are designed to incorporate essential features of realistic systems but might be minimalist with respect to other features. Examples are liquids or glasses with model pair potentials or simple force fields. Such applications are designed to provide insight into the physical behavior of chemical and physical systems rather than to provide a means for making *ab initio* predictions with chemical accuracy. This approach has a rich tradition in enabling scientists to perform "thought experiments" on complex systems. On the other hand, there is a real need to use these tools to predict physical properties with chemical accuracy. This is required for rational drug and materials design and for understanding such things as the mechanisms of enzyme catalysis. It should be recognized that there is an intermediate level of computation that treats part of a complex system with great precision and other parts more approximately. Such applications can be extremely useful for studies of complex systems not fully amenable to highly accurate methods. Current computations on complex systems are not yet at chemical accuracy, but they still can be extremely useful for gaining insight into important physical and biological processes and for guiding future experimental efforts.

Recent progress in chemical theory and computation has been impressive and encourages faith that the holy grail of computational chemistry—the development of accurate and efficient methods for computer-aided drug design, computer-aided materials design, and protein structure and function prediction—may one day be found.

For several years PNAS has published special feature issues on many cutting edge research topics. Some of the themes of past special features have included: Astrobiology, Social and Behavioral Sciences, Asymmetric Catalysis, Science and Technology for Sustainable Development, Long-Range Electron Transfer, and, most recently, Gene Regulatory Networks. Scheduled for future issues of the journal are special features on Molecular Electronics, Demography, and Supramolecular Structure and Dynamics. One objective of these special features is to advance the journal's ongoing initiative to expand its coverage of the physical and social sciences and mathematics. PNAS continues to encourage and welcome research articles in all areas of the natural and social sciences and mathematics.

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1. Feynman, R. P. & Hibbs, A. R. (1965) *Quantum Physics and Path Integrals* (McGraw–Hill, New York).