Multiscale modeling for complex chemical systems: Highlights about the Nobel Prize in Chemistry 2013

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Modelización multiescala de sistemas químicos complejos: Apuntes sobre el Premio Nobel de Química 2013

Modelització multiescala de sistemes químics complexos: Apunts sobre el Premi Nobel de Química 2013

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RESUMEN

Martin Karplus, Michael Levitt y Arieh Warshel recibieron conjuntamente el Premio Nobel de Química 2013 por sus desarrollos de modelos multiescala aplicados a sistemas químicos complejos. Desde la aproximación más simple de la mecánica molecular (MM) hasta la mecánica cuántica (QM), diferentes técnicas computacionales permiten la simulación de una gran variedad de sistemas químicos. Los métodos combinados QM/MM, sin embargo, resultan el mejor consenso para el tratamiento de los sistemas biológicos complejos. Este artículo repasa la base teórica de los métodos QM/MM y sus aplicaciones durante los últimos veinte años.

Palabras clave: QM/MM; Premio Nobel; Modelización Molecular.

SUMMARY

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel for the development of multiscale models for complex chemical systems. From the simplest approximation of molecular mechanics (MM) to quantum mechanics (QM), computational techniques allow simulating a great variety of chemical systems. Combined QM/MM methodologies, however, are the best consensus for treating complex biological systems. Herein we review the theoretical basis of QM/MM methods and their applications during the last twenty years.

Key words: QM/MM; Nobel Prize; Molecular Modeling.

RESUM

Martin Karplus, Michael Levitt i Arieh Warshel van rebre conjuntament el Premi Nobel de Química 2013 pels seus desenvolupaments de models multiescala aplicats a sistemes químics complexos. Des de l'aproximació més simple de la mecànica molecular (MM) fins a la mecànica quàntica (QM), diferents tècniques computacionals permeten la simulació d'una gran varietat de sistemes químics. Els mètodes combinats QM/MM, emperò, són el millor consens per al tractament dels sistemes biològics complexos. Aquest article repassa la base teòrica dels mètodes QM/MM i les seves aplicacions durant els últims vint anys.

Mots clau: QM/MM; Premi Nobel; Modelització Molecular.

INTRODUCTION

For a long time, theoretical chemistry has been trying to understand experimental results, in order to establish a framework that allows simulating and predicting new phenomena. Paul Adrien Maurice Dirac (1902-1984) asserted in 1929 that "the underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble" [1]. Four years later, he shared the Nobel Prize in Physics with Erwin Schrödinger, for the discovery of new productive forms of atomic theory [2].

In 1966 Robert Sanderson Mulliken (1896-1986) was awarded with the Nobel Prize in Chemistry. He replied in his Nobel lecture "I would like to emphasize strongly my belief that the era of computing chemists, when hundreds if not thousands of chemists will go to the computing machine instead of the laboratory for increasingly many facets of chemical information, is already at hand" [3].

Mulliken was visionary, since computers in the 1960s were extremely limited compared with the current ones. With the advent of computational science, simulation became the third pillar of scientific development, together with theory and experiment. Computational simulations permit nowadays to perform fundamental experiments following the laws and hypothesis of current knowledge in a virtual environment, without the intrinsic limitations of the real world. This way, the scientific community is able to study unaffordable problems (due to the number of experiments, cost, hazard or complexity) from an experimental point of view.

To solve a problem (analytically or numerically) or to describe the temporal evolution of a system and predict its response at different conditions, we must know which the actors are (i.e. the study units) and how can we describe the action mathematically, in terms of motion (kinetic energy) and their interactions (potential energy). Obviously, the simulation efficiency is closely related with computational power. Although the remarkable improvements in computers in the last years, they are still not able to solve some of the scientific challenges in a reasonable time. Actually, the computational complexity theory [4] classifies the most challenging computational problems as difficult to solve or even intractable (e.g. NP-complete problems). Within the scope of biochemistry and engineering, protein folding, cellular transport dynamics or cellular recognition are still great challenges; in chemistry, simulations play a key role in new knowledge generation.

On one side, simulation may provide an essential support for the study of chemical reactivity: as chemists, we can use the previous information about the reactants to know which products we will obtain. On the other side, the elucidation of reaction mechanisms may be specially complicated. Different experimental techniques have been already reported in literature in order to follow the behavior of some specific atoms over time. Some examples thereof are isotopic substitution (where one or more atoms are changed by one of its isotopes: using ^{2}D, ^{13}C or ^{15}N instead of ^{1}H, ^{12}C, ^{14}N) or photochemical techniques (which permit the study of high-speed phenomena or chemical species with lifetimes in the femtosecond scale). In contrast to experiment, the simulation of chemical reactions permits to elucidate their mechanism unequivocally, by means of the combination of two formalisms: molecular mechanics and quantum mechanics.

Molecular mechanics

Molecular mechanics (MM) defines chemical systems through its geometric description and the energetic parameters that contribute to the internal energy of the molecule. Considering molecules as billiard balls (atoms) connected by helical spring (bonds), the whole system is governed by springs force constants and atom types. Molecular interactions are therefore described by a combination of the classical forces (e.g. van der Waals, electrostatics or hydrogen bond) according to a mathematical function known as *force field*. This function must include all information related to atomic distances, angles, bond torsions and spring force constants responsible of bond stretching, openings, etc. (Table 1).

Table 1. *Energetic terms considered in the definition of a general force field (MM)*

$E_{MM} = E_{str} + E_{ben} + E_{tor} + E_{oop} + E_{non}$	
E_{str}	*Bond stretching energy*, due to a change in the length of a bond. Morse's curve is usually used, since the bond stretching fits to harmonic motion around the equilibrium position and it correctly describes the atomic dissociation at large interatomic distances.
E_{ben}	*Bond bending energy*, due to a change in the angle between two bonds. It is simulated as a variation of Hooke's law.
E_{tor}	*Torsion energy*, due to a change in the torsion angle between three bonds. Energy profiles are usually defined by Fourier series, to reflect periodical intramolecular rotations.
E_{oop}	*Out of plane bending* penalizes the modification of planar regions (such as double bonds).
E_{non}	*Non-bonded interactions* include electrostatic and van der Waals interactions, and hydrogen bonds.

This simple approach must be validated experimentally for its later usage. Due to the broad diversity of chemical systems, it is almost impossible to define a universal force field suitable for any molecule. According to the validation set, the parameterization and the nature of equations used, force fields can be specially designed for the study of a specific family of compounds (i.e. proteins, nucleic acids or different kind of small molecules).

Mathematical resolution of these equations allows the description of the molecular geometry of a system by finding a local minimum in its potential energy surface. If we are instead interested in tracking the temporal evolution of the system under different conditions, Newton's equations of motion may be integrated to study the dynamic behavior of the system or to describe the potential energy surface. This way, macromolecular interactions involving proteins and/or nucleic acids are described nowadays in high detail, and this procedure is routinely applied for the comprehension of subcellular processes whose dysfunction is responsible for a variety of diseases.

Quantum mechanics

Mathematical complexity of QM methods contrasts with the simplicity of the MM formalism. Although correctly simulating chemical entities, MM unfortunately cannot simulate chemical reactions successfully, since they involve the reorganization of chemical bonds to create a new chemical entity. The description of electronic rearrangements belongs to quantum mechanics, by which it

is possible to simulate chemical reactivity, calculate more complex molecular properties than geometry optimization, define excited states or predict spectroscopic data (e.g. IR, UV).

In order to describe the electronic behavior of small molecules, QM methods postulate that calculating the wave function (Ψ) is necessary to define the state of a molecular system in a given time. Wave function can be calculated through solving the time-independent Schrödinger equation for a conservative non-relativistic system (eq.1).

$$\mathbf{H}\,\Psi = \mathbf{E}_{\mathbf{QM}}\,\Psi \quad \textit{(eq.1)}$$

The Hamiltonian operator (**H**) owes its name to Hamilton's equations of motion for the description of systems consisting in a high number of particles [5,6]. It is the quantum operator responsible for describing the energy of the given system, defined by the Ψ wave function, including not only the kinetic and potential energies but also other energetic contributions as spin-orbit coupling or electromagnetic interactions. At the same time, these terms can be decomposed in nuclear and electronic components. Since nuclear momentum is higher than electron's one, the Born-Oppenheimer approach establishes that electronic wave function fits instantaneously to a small variation in the nuclear coordinates. Thus, the movement of nuclei and electrons can be uncoupled. This means that solving the electronic Schrödinger equation is enough to study the potential energy surface of a molecular system, but it is necessary to solve both (electronic and nuclear equations) to describe molecular vibrational states.

Determination of the wave function (although the electronic one) is not simple, and it only has analytical solution for monoelectronic systems. In those cases where electronic repulsion plays an important role, it is necessary to find Ψ numerically. This can be done by using a broad range of computational methods (e.g. Hartree-Fock, Density Functional Theory, Môller-Pleset), according to the mathematical definition adopted in the calculation of the system's energy. Nevertheless, these time-consuming procedures are commonly applied iteratively to find the best possible solution (albeit approximate), with the limitation of molecules with few tens of atoms.

This way, QM has been used for many years to describe the underlying mechanisms of fundamental chemical reactions satisfactorily, but it is still impossible to apply those methods in complex biochemical systems. Consequently, a new methodology that permits the description of the structure of biomolecules and the mechanism of enzymatic reactions is necessary.

QM/MM METHODS: AN OVERVIEW

Progress of scientific knowledge has triggered the interest in using simulation of large biomolecular systems, for getting deeper insight in the molecular basis of biochemical and pathogenic processes. In many cases, pathways involved in the activation or inhibition of a key component in the development of a cellular response (usually a protein) imply bond formation or breaking. Thus, QM methods are required for their correct description.

Furthermore, the biological activity of a protein is usually directly related to some few amino acids of the active site (where electronic rearrangement takes place). One of the very first proposed strategies was the simultaneously application of both QM and MM methodologies for the description of a single macromolecular system. Conceptually, the active site of a protein can be fully described by QM, whereas MM is used to describe the amino acids not involved in its activity. The so-called QM/MM combined methods are based in this strategy, but they have underlying problems related to the description of the frontier atoms. Martin Karplus, Michael Levitt and Arieh Warshel were awarded with the 2013 Nobel Prize in Chemistry for the development of multiscale models for complex chemical systems. They reported crucial works for the application of combined methods, particularly with a novel mathematical description for the interactions between QM and MM molecular regions (fig.1).

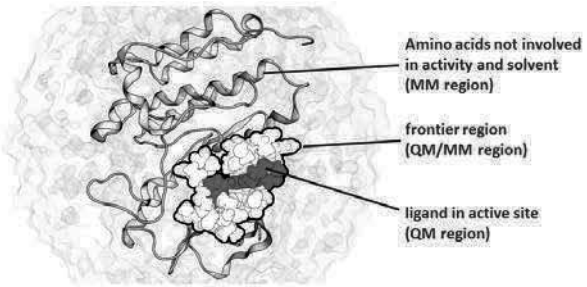

Fig.1 *Computational treatment of a ligand-protein complex by QM/MM methods*

The first references regarding combined QM and MM methods appeared in the 1970s. Lewitt and Warshel published in that time what is considered the first published article about QM/MM methods. In the scope of lysozymes enzymatic reactions, the authors proposed a new methodology that describes bond breaking and the redistribution of charge density at different levels of theory, including electrostatic interactions and steric effects [7].

Handling of the QM/MM embedding

The use of such different formalism as molecular and quantum mechanics simultaneously in one system has an inherent problem when describing the frontier region (often intramolecular), which must guarantee the continuity of the energy definition from one region to the other. Each region contributes in an additive way in the mathematic description of the system's energy, including bonding and non-bonding interactions (eq.2).

$$E = E_{MM} + E_{QM} + E_{QM/MM} \quad \textit{(eq.2)}$$

Since it is not possible to establish a direct relationship between the energy obtained by atom-based MM methods (represented in eq.2 as E_{MM}) and the one defined by Ψ wave function (E_{QM}), it is necessary to take under consideration the energetic contribution of the frontier region ($E_{QM/MM}$). The different possibilities in treating interactions within the frontier region (see fig.1) give rise to different kinds of combined methods.

On one hand, description of non-bonding interactions between MM and QM regions requires to define the electronic coupling between them. Obviously, the most simple strategy is to neglect this effect (**mechanical embedding**), in which non-bonding interactions are treated at MM level. However, this approximation is insufficient in most cases and it is necessary to find a way to correlate the electro-

nic density of the QM region with the atomic charges of the MM force field. One possibility is to include the atom-based MM charges into the Hamiltonian definition, as an external potential, and even including polarization terms (**electronic embedding**, eq.3).

$$E_{QM/MM} = \sum_k^{N_{MM}} \int \frac{\rho_{QM}(r) Q_k}{|r - R_k|} dr + \sum_j^{N_{QM}} \sum_k^{N_{MM}} \varepsilon_{jk} \left[\left(\frac{\sigma_{jk}}{R_{jk}} \right)^{12} - \left(\frac{\sigma_{jk}}{R_{jk}} \right)^{6} \right]$$

(eq.3)

On the other hand, with the existence of an intramolecular frontier (when the ligand is covalently bounded to the receptor), the introduction of complex binding terms is required in order to match the structural parameters of the force field with the behavior of the QM region.

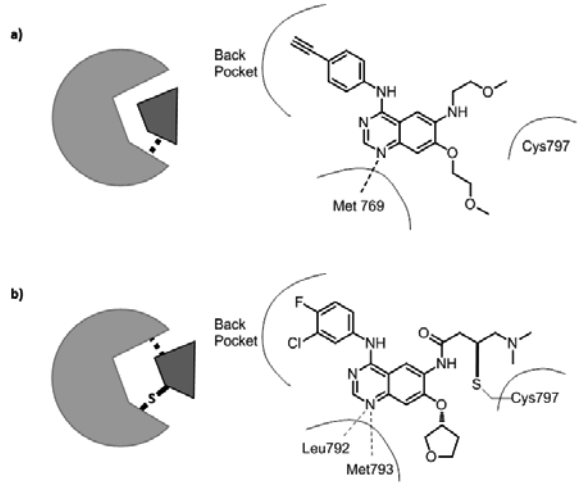

***Fig.2** Ligand interactions with EFGR **a)** Erlotinib presents non-bonding interactions with EFGR **b)** Afatinib acts as an irreversible inhibitor of EGFR due to its bonding interaction with Cys797 through a sulfur bond*

Nowadays, these methods are available for the most frequently used force fields in molecular dynamics, e.g. AMBER [8] or CHARMM [9] (developed at Karplus' laboratory, Harvard University).

It is important to note that further computational methodologies (e.g. semi-empirical or coarse-grained) can be used to define other regions besides QM and MM regions. Including more than two regions has allowed developing new methods, like ONIOM, implemented in Gaussian software [10]. ONIOM has been successful applied for the study of different properties of biochemical systems, such as light absorption by bacteriorhodopsine chromophore [11].

Recent Biomolecular QM/MM Studies

In the first years, the application of multiscale methodologies were restricted to developing more accurate algorithms [12-14] or to study fundamental chemical properties such as molecular acidities [15], studies related to solvent polarization effect [16] or Diels-Alder reactions [17]. It should be noted that the hybrid functional B3LYP, which is nowadays routinely used in DFT calculations, was initially described in 1993 [18]. Thus, it is not surprising that early studies of QM/MM applied on biochemical systems did not appear until 1990s. They were mainly conducted in order to understand the reaction mechanism of enzyme-catalyzed reactions [19-22] and their interaction with known ligands in the binding site of different proteins such as dihydrofolate reductase [23], papain [24] or human fibroblast collagenase [25].

An exhaustive list of biomolecular QM/MM studies published in the first decade of XXI century is available in literature [26]. During this time, QM/MM methods were widely applied for the description of biochemical systems, including enzymatic reactions of different metabolic pathways, such as hydrolysis activity of hepatitis C virus proteases [27] or the study of protein-ligand interaction of cyclin-dependent kinase 2 (CDK2) [28]. The number of scientific reports published involving multiscale modeling during the first decade of 2000s almost exceeds 10 times the number of papers since they appeared.

Even though biochemical systems under study have been essentially the same during the last ten years, computational methods were gradually improved by the incorporation of new theories. In this sense, Warshel and coworkers introduced in 1997 a novel strategy to embed DFT description of the high-level region (known as frozen density functional theory approach) [29]. Most of the computational chemistry methods are nowadays implemented in specialized software for the description of QM (i.e. HF, DFT and semiempirical AM1 or PM3 algorithms) and MM regions (basically AMBER and CHARMM forcefields); and all their combinations can be found in literature [26]. The use of semiempirical methods for the description of QM region could be surprising because of their limitations in contrast to HF o DFT methods. Nevertheless, their use was entirely justified since they were applied in the description of the early molecular dynamic simulations involving QM/MM [30], e.g. in the study of chemical reaction paths [31]. Despite first-principle QM/MM molecular dynamics simulations are still high computationally demanding, they are actually possible to perform [32,33], applying in most cases Car-Parrinello molecular dynamics (CPMD) standards [34]. CPMD have been described for the study of protein-ligand interactions [35], the study of the electronic structure of proteins [36] or to analyze the molecular structure of DNA [37].

The latest advances in computational science have helped to the study of dynamic behavior of large molecular systems with QM/MM [38], but they still remain challenging. The improvement in computing power, nevertheless, has speed up the use of these techniques in broad areas of applications such as enzymology [39] or catalytic activity of ribozymes [40] and has promoted the emergence of new software [8,41]. Progress also allows the incorporation of new protocols such as replica-exchange MD or umbrella sampling [42].

QM/MM techniques will continue to be a benchmark in coming years, since we are still far from achieving a QM description of a whole macromolecular system. Nowadays, QM/MM methods are widely generalized: only in the first months of 2014 lots of papers applying above-mentioned strategies have been published in a variety of research fields. Methods first described by the 2013 Nobel laureates have been recently used in the study of excited-states (electronic structure of polyphenyl derivatives by TD-DFT [43] or absorption spectra of proteins [44], among others), as well as the role of coordinated metals cofactors in metalloenzymes (e.g reaction mechanism of homoprotocatechuate 2,3-dioxygenase (HPCD) [45], ribonuclease H1 [46], nicotinamidases [47] or cytochrome P450 [48]). They have also been used for the prediction of hydration

free energies at different solvation models [49] or the role of key residues in catalytic mechanisms of enzymes [50,51]. Furthermore, at the Molecular Design Lab at IQS we are nowadays using QM/MM methodologies for getting deeper insight into myotonic dystrophy type 1 and cancer pathways, to develop new small molecules that can help fighting against these diseases in the next future.

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