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## PREFACE

Computer aided modeling of polyatomic molecular systems is one of the leading consumers of processor time and computer memory nowadays. Despite tremendous progress in both computer hardware and molecular modeling software, the complete quantum mechanics-based numerical study of a realistic model of any, say biologically or technologically, relevant system is out of the reach of the workers in the field. The problem, however, is not only the enormity of computational resources required for conducting such a study, but the absence of any clear proof “by construction” of the validity of the employed calculation methods and a lack of real understanding of the result. These two problems are related to each other and the situation may be described as follows: even if we get an answer by a quantum mechanical (QM) or quantum chemical (QC) modeling package, we are almost never able to say what the physical reasons are for it to be that or something else. We cannot add anything to that last number printed in the output. Chemists, however, generally think differently. They need more trends than numbers. The reason is of course that in many cases exact experimentally derived numbers are missing. This situation is by no means a new one. Yet at the dawn of numerical quantum chemistry, C.A. Coulson [1] made a point about the importance of qualitative understanding and commented that accuracy of quantum chemical calculation is “purchased very dearly” since “ab initio-ists abandon all conventional chemical concepts and simple pictorial quality in their results”.

This situation, well known to the workers in the field, has occurred due to a factor external to quantum chemistry itself, namely the intense development of computational hardware during the past few decades. The numerical point of view, which reduces the subject of Quantum Chemistry to obtaining certain numbers, has thus become predominant. It might be acceptable, but the situation changes completely when we find ourselves in the realm of complex systems (for which, as we shall see, hybrid modeling is basically necessary): obtaining numerical results for the complex systems or their subsequent interpretation in the frame of the standard procedures becomes too costly if at all possible and the answer obtained numerically becomes unobservable (if some one does not understand just *one* number to be the answer

e.g. the energy). Therefore hybrid QM/MM (QM is Quantum and MM is Molecular Mechanics) modeling requires development of the relevant concepts which could help to achieve decision making while singling out the relevant quantum and classical parts and establishing the adequate construction of the interface between them on a rational basis. This can be done by finding an alternative to pure numerics – the qualitative and theoretical approach, paying attention to the development of adequate concepts related to hybrid modeling and learning to perform the calculations using theoretical concepts relevant to the system under study.

The very possibility of hybrid modeling is intimately related to the idea of dividing the problem to be solved or the object to be studied into parts formalized in various techniques of separating variables. Dividing into parts is the most general method of studying the reality. As a philosophical maxim it was first formulated by René Descartes in his “Discours de la Méthode” [2] (“to divide each of the difficulties under examination into as many parts as possible, and as might be necessary for its adequate solution”). Separation of a complex system into parts has two aspects: the technical aspect, aimed at simplifying calculations by separating the variables describing the system under study, and the conceptual aspect, having as a purpose the development of qualitative concepts i.e. identifying the ideas which would describe the system in adequate, comprehensible terms. Clearly, the description of a system comprising numerous strongly interacting components in terms of some almost independent parts and/or variables describing these parts will be inevitably approximate and the art here is to select these parts and variables in such a way that the description of their terms is acceptable. One may be pretty sure that in the case of the complex problem that requires hybrid modeling, there will be no chance to “invent” adequate parts into which the modeled system has to be divided “from one’s head”. Fortunately, the quantum mechanical paradigm itself provides sufficient requirements, which allow the reasonable identification of the parts the system can and has to be divided into. The adequate parts must be observable. This very general requirement allows one to establish a relation between hybrid modeling and the rest of theoretical chemistry. Yet at the early stage of the development of chemical theory the idea of “chromophores” – some specific parts of the molecule responsible for the *color* of the substance – was proposed. This approach was not that naive as it can seem nowadays since it helped to make the problem tractable by significantly reducing the number of variables (those related to the chromophore only) and to take its environment as a weak perturbation. Particularly remarkable in this context however is the observability of the chromophore.

Regarding the problems of the electronic structure of molecular systems, we notice that in the past, the importance of the qualitative concepts and explanations has been stressed many times. In this context, V.A. Fock [3, 4] discussed the (basically meta-physical) problem of interrelation between “exact solution” and “approximate explanation”. His point was that any approximation (more precisely, the general form of the trial electron wave function i.e. an *Ansatz* used for it) sets the system of qualitative concepts (restricted number of variables), which can only be used for interpreting the calculation results and for describing the experiments. A characteristic example

for QC is provided by the orbital energies and the MO expansion coefficients coming from the Hartree-Fock-Roothaan (HFR) approximation. Although in a great number of cases they can be related to the observed ionization potentials, they are nevertheless only mental constructs, having a definite sense only within the HFR realm, becoming invalid beyond its scope.

The chromophores are obviously observable entities. Are there others? This question has been addressed by Ruedenberg who suggested a kind of extension of the standard quantum mechanical definition of observability from the *quantities* to the *entities*. The example he used had a rather unhappy destiny in quantum chemistry although it relates to the fundamental chemical concept – that of chemical bond. At quite an early stage it was decided that chemical bonds are not observable as “there is no quantum mechanical operator for the bond”. This argument is, however, not acceptable as the “bond” is not assumed to be a quantity, but an entity and to deduce nonobservability of bonds from the fact that there is no operator for the bond is equivalent to concluding that there is no atomic nuclei as there are no operators for them. Nevertheless, something had to be done about the observability of entities and K. Ruedenberg [5] proposed the following definition: “fragments in a molecular system can be singled out if these latter are observable, so that they manifest a reproducible and natural behavior; if for a series of molecules variations of fragments fit to that or another curve and its parameters can be found empirically by considering enough of the series members this proves that singling out the fragments makes sense”. This definition allows us to single out numerous fragments which can be two-center two-electron bonds, or conjugate  $\pi$ -systems, open *d*-shells, atomic cores, etc. An adequate theory must be constructed in terms of such observable objects. At first glance the current situation in quantum chemistry is in sharp contradiction to this requirement. However, as we show in Chapter 2, the real constructs of quantum chemistry rely heavily upon the above-mentioned observable objects. This allows us to consider the whole of quantum chemistry from the hybrid perspective. As a result the hybrid methods, instead of being an isolated and specific area of how to program junctions between classically and quantally<sup>1</sup> treated parts of complex systems, shift to the center of the theory. This allows us to talk about the usual QM/MM methods, as of the hybrid methods, in a narrow sense.

It also allows us to reach multiple goals. First, it allows sensible and natural interpretation of the result in chemical terms, and with the use of chemical concepts. Second, estimates of the correction (error) to the energy (or any other quantity) coming from the use of the approximate form of the wave function in this calculation

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<sup>1</sup>Trying to find an adverb to be a counterpart to ‘classically’ the author faced certain problem: no adequate antonym had been designed so far. Merriam-Webster suggests ‘quantal’ as an adjective derived from ‘quantum’. So we decided to use an adverb ‘quantally’ already used in the required meaning in *Handbook of Solvents (Chemicals)* by George Wypytch, Noyes Publications 2001 (p. 21), in *Modern Electrochemistry 2A: Fundamentals of Electrodics* by John O’M. Bockris, Amulya K.N. Reddy, and Maria E. Gamboa-Aldeco, Springer 2001 (p. 724), and in *Introduction to Computational Chemistry* by Frank Jensen, John Wiley & Sons 1998 (p. 393).

can be obtained. And last, but not the least, this approach allows us to carry out the entire calculation with relatively low computational costs using *effective electron Hamiltonians* for the important (i.e. observable) parts of the system – the “chromophores” – and leaving the defects of the restricted form of the trial wave function to be taken into account by renormalized matrix elements of these effective Hamiltonians.

From the above the reader may conclude that this book is largely devoted to the theory of hybrid methods. This is true to a large extent. Nevertheless, the author could not (and did not want to) ignore the existing hybrid QM/MM methods described in the literature and widely used for describing various aspects of the behavior of the complex molecular systems. The key practical problem when applying the QM/MM methodology, namely, the substantiated construction/selection of the junction between the parts of the system described at the QM and MM levels, respectively, is thoroughly discussed here. The author’s feeling is that the “Sturm und Drang” period of the hybrid QM/MM modeling has come to an end and that it is time now to give an evaluation of the state-of-the-art reached during this period and to present a theory of this family of methods, capable of giving a general view of the field, to identify the fundamental problems characteristic of it and to propose physically better based and mathematically more sound approaches to these problems. In this context the theory is useful also because it allows us to introduce some order into the diversity of the junction forms present in the literature, which otherwise resembles the famous classification of animals given by J.-L. Borges [6].

This book offers a step by step derivation of the consistent theoretical picture of hybrid modeling methods and the thorough analysis of the underlying concepts. This forms a basis for classification and analysis of current practical methods of hybrid molecular modeling, including the narrow meaning of this term. Historical remarks are important here since they put the current presentation in a general context and establish a relation with other areas of theoretical chemistry. It presents its material paying attention both to the physical soundness of the approximations used and to mathematical rigor, which are necessary for the practical development of the robust modeling code and for a conscious use of either existing or newly developed modeling tools. The reader should have a knowledge of the basic concepts of quantum and computational chemistry and/or molecular modeling. Familiarity with vector spaces, operators, wave functions, electron densities, second quantization and other tools is also necessary. Short discussions of these topics are given only to establish the relation between the standard presentation of these items in the literature and their specific form as required in the context of the theory of hybrid modeling described in this book.

This book is intended both for practicing experts and students in molecular modeling and to those in related areas, such as Materials Science, Nanoscience, and Biochemistry, who are interested in making an acquaintance with the conceptual basis of hybrid modeling and its limitations, which possibly enables them to make educated decisions while choosing a tool appropriate for solving their specific problem and for interpreting the results of the modeling. It also contains a self-sufficient example of

developing a targeted hybrid method designed for molecular modeling of transition metal complexes with open  $d$ -shells. This presentation allows the reader to specify on the spot all the significant elements of the general theory and to see how they work.

The theory described here was originally developed by the author, as also the specific targeted application of the theory to molecular modeling of the transition metal complexes. This and other original methods of molecular modeling described here have been implemented in FORTRAN program suits. They are a kind of “research software” available for use to other researchers through the Net Laboratory access system which provides sample input files and minimal reference information to start with, at <http://www.qcc.ru/~netlab>.

Some of the results presented in this book have been published in original research papers and in two reviews in the Springer series of Progress of Theoretical Chemical Physics based on materials of the Congress on Theoretical Chemical Physics and of the European Conference on Physics and Chemistry of Quantum Systems both edited by Prof. J. Maruani and Prof. S. Wilson. When the material was presented at these conferences, Prof. J. Maruani and Prof. S. Wilson suggested that I extend and reorganize it into a book. Without their kind suggestion and constant encouragement and support, this book would never have appeared. Prof. I. Mayer kindly agreed to read the manuscript and give his valuable comments. I am very grateful to him for his help in improving the manuscript significantly. All the errors are of course the author's fault.

The process of rearrangement and of translation into English of some results available only in Russian took somewhat longer time than originally planned. I beg pardon and hope on understanding of all those whom I promised to do something during this period and failed to perform it on time. I am particularly thankful to Ms Laura Chandler of Springer Verlag for her kind patience.

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