Modeling the structure and the dynamics of peptides and proteins in aqueous solution using novel semiempirical quantum methods

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With the development of high performance computing, it now becomes possible to model larger and larger molecular systems using quantum chemistry tools. In our laboratory, we have developed an approach that combines linear scaling semi-empirical quantum methodology (here the Divide and Conquer approach) with molecular dynamics. Called SEBOMD (SemiEmpirical Born-Oppenheimer Molecular Dynamics), it has been recently introduced in the AMBER software that is specialized in the modeling of biomolecular systems. One of the interests of the SEBOMD approach is that it enables the modeling of condensed phase systems, typically biomolecules in aqueous solution in the nanosecond timescale. In these systems, intermolecular interactions have a strong influence on the dynamical and structural behavior of the molecules therein. Unfortunately, most current available semiempirical methods (e.g., AM1, PM3, PM7, etc.) have trouble in correctly describing these intermolecular interactions. Indeed, as their names suggest, semiempirical methods use experimental data to compensate for the approximations they make compared to ab initio quantum chemical equations. The parameters that they employ mostly come from experimental data extracted from the properties of small molecules in gas phase (e.g., geometries, heats of formation, molecular dipole moments, ionization potentials, etc.). Today is now a crucial moment : computer tools allow us to model by (approximate) quantum chemistry large complex molecular systems for relative long simulation times (e.g., several hundred of atoms in the nanosecond timescale), but existing parameters to chemically describe these systems are not precise enough to obtain relevant physical or chemical answers from these simulations.

The objective of the thesis is to participate in the development of an accurate semiempirical quantum method targeted to model peptides and proteins in aqueous solution. This new "semi-ab initio" approach to be implemented in the AMBER package will allow for the study of the structure, the dynamics, and the reactivity of biomolecules in aqueous solution. Instead of using parameters extracted from experimental data, the new semiempirical parameters will be extracted from ab initio potential energy surfaces that will represent essential interactions in these kind of systems. Among the key points that will be tackled during the thesis, one can

cite :

- — the development and assessment of ab initio potential energy surfaces
- — the assessment of current semiempirical methods in reproducing these ab initio potential energy surfaces
- — the study of the electronic properties of semiempirical wave-functions and of their atomic charge representations
- — the development of new semiempirical (“semi-ab initio”) parameters
- — the assessment of these new parameters in SEBOMD simulations

We are looking for highly motivated candidates with a background in computational chemistry, physics or biology. Experience in programming and numerical analysis are of advantage.

This job announcement corresponds to a doctoral contract that can be awarded by the SESAMES Doctorate Program of the University of Lorraine (http ://sesames.univ-lorraine.fr/). The gross monthly salary for a doctoral contract in France is about 1,685 €. If the PhD candidate is also given a teaching load, the total monthly salary can reach 2,025 €.

Keywords : Quantum chemistry ; Semiempirical methods ; Molecular Dynamics ; Potential energy surfaces ; Parameter development ; Biochemical systems ;