

First-Principles and Mixed quantum classical QM/MM Simulations of Biological Electron Transfer
(Project acronym: BET)

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Electron-transfer (ET) proteins are crucial for the life of organisms. They serve as electron carrier and/or as catalyst in biochemical ET reactions. As such they are responsible, for instance, of the respiration and the photosynthesis. A detailed understanding of the involved molecular mechanisms is thus of prominent interest from a fundamental point of view as well as for the potential design of highly efficient bio-inspired optoelectronic devices and solar cells.

The study of ET proteins at full atomic and electronic level represents a new challenge for computational biochemistry. These proteins contain one or more metal ions in the active site, such as iron and copper. During the ET process the metal changes oxidation state (*i.e.*, Fe(III/II) and Cu(II/I)) and this is usually accompanied by a reorganization of the environment surrounding it. It has been largely recognized for a long time the importance of a molecular description of the solvent and the proper inclusion of the polarization medium around the metal center. As yet, these effects limited the applicability of standard computational schemes.

We have used state-of-the-art first-principles electronic-structure techniques to perform the first *ab initio* investigation of entire electron-transfer proteins in aqueous solution. We exploited a combined approach, which used empirical force field based molecular dynamics coupled to full quantum mechanics (linear scaling density functional theory) and hybrid quantum mechanics/molecular mechanics (QM/MM) calculations, to get insights on the nature of the drastic decrease of reorganization energy for metal ions in the protein frame and to calculate the tendency of these proteins to acquire electrons (*i.e.*, the redox potential) [*J. Phys. Chem.* 122 (2005) 234505].

We focused on a copper protein (azurin from *Pseudomonas Aeruginosa*) and two iron-sulfur proteins (rubredoxin from *Clostridium Pasteurianum* and from *Pyrococcus Furiosus*). The calculations were carried out at Idris Centre in Paris and at CINECA in Bologna with the codes CPMD [www.cpmc.org] and CP2K [cp2k.berlios.de]. The full *ab initio* (mixed Gaussian and Plane Waves) CP2K calculations performed on rubredoxin, which represented the most expensive part of our study, took explicitly into account the entire protein, 700 water molecules, and 9 counter ions, for a total of 2825 atoms (the Gaussian basis set for the wave functions included 11334 primitives). For this system, each electronic wave function optimization required 4.5 hours on 128 processors of the IBM-

SP4 at the Idris Centre. To have reliably converged quantities, hundreds of such calculations were required.

Our study shows that full *ab initio* calculations on bio-molecules at physiological conditions are now possible by exploiting modern quantum chemistry protocols and today's large-scale supercomputing facilities, like those made available through the DEISA initiative, effectively .

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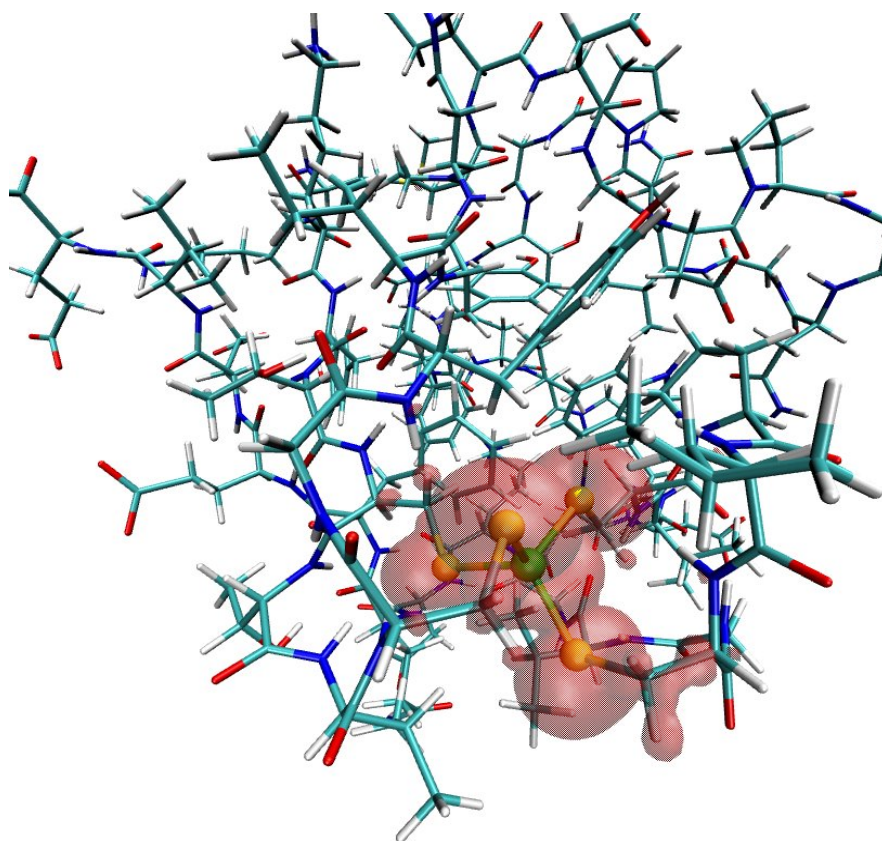


Figure. Isosurface enclosing the 95% of the total spin density (difference of the up and down electron densities) in the oxidized form of the rubredoxin from *Clostridium Pasteurianum*. The iron center is represented by a green sphere, whereas the four sulphur ligands (four cysteines) are drawn as yellow spheres. All of the other atoms are represented as colored sticks (carbon: cyan; oxygen: red; nitrogen: blue; hydrogen: grey). The *ab initio* (DFT) calculation of the electronic wave function explicitly took into account all of the atoms and their valence electrons (included those of the solvent and of the counterions which are not show for sake of clarity) were explicitly taken into account at *ab initio* (DFT) calculation of the electronic wave function.