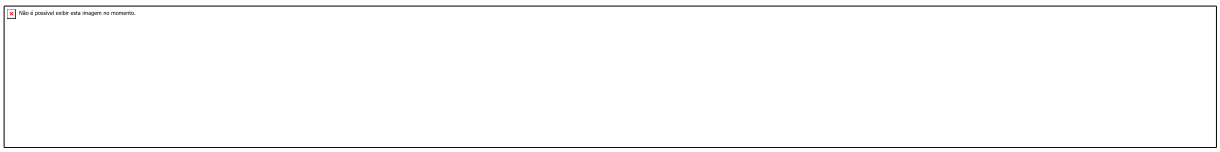

On the calculation of redox potentials in iron-sulfur proteins

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INTRODUCTION. Biological redox processes are orchestrated by metalloproteins containing iron-sulfur clusters. Here, we studied a simple iron-sulfur protein, rubredoxin, which has only one iron center tetra-coordinated by four cysteine residues. **OBJECTIVES:** We seek a reliable computational strategy to estimate redox potentials of metalloproteins. **MATERIAL AND METHODS:** We performed molecular dynamics (MD) simulations of wild-type (WT) and mutant *Clostridium pasteurianum* (Cp), *Pyrococcus furiosus* and *Desulfovibrio vulgaris Hildenborough* rubredoxins in salt-neutralized cubic water boxes. All initial protein configurations were extracted from the Protein Data Bank. Vertical ionization gaps were calculated along the trajectories and used with several variations of the linear response approximation to estimate free-energies of reduction. Pure molecular mechanics and hybrid quantum chemical / molecular mechanical forcefields were tested. Calculations were conducted with the GROMACS 4.6.7 program and the pDynamo 1.8.0 library. **RESULTS AND DISCUSSION**: As predicted by the linear response theory, calculated gaps have gaussian distributions. For example, the calculated redox potential differences between Cp-WT and mutants are 66mV for Cp-V44A and 12mV for Cp-L41A, in agreement with experimental values of 86 and 28mV, respectively. However, the average and standard deviation of vertical gap distributions are highly dependent on forcefield, simulation time, and treatment of long-range electrostatics. **CONCLUSION:** Molecular dynamics and the linear response approximation are useful tools to estimate redox potentials in biological systems, but its sensibility to computational parameters is a matter of concern and should be carefully checked in order to perform reliable and reproducible calculations.

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