Summary of QBtopIC 5, October 27, 2021
Accurate calculations of redox potentials in proteins

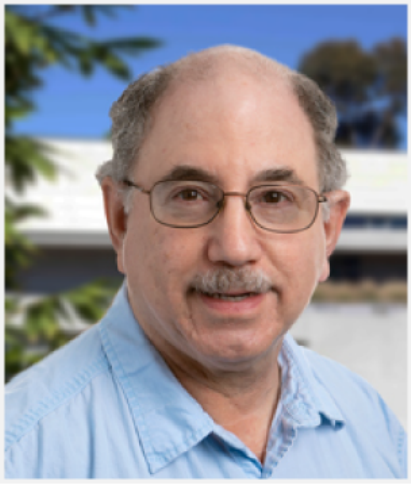
Many biochemical processes involve the transfer of electrons and the driving force of such reactions are determined by the redox potential. In biological systems, three types of metal sites are used for direct electron transfer, viz. cytochromes, blue copper protein and iron–sulfur clusters.[1] Numerous computational studies of redox potentials have been published.[2–7] The calculations are in principle simple, because it involves only the addition of a single electron; thus it is enough to estimate the ionisation potential and the solvation energy of the reduced and oxidised states. However, since the reaction involves a change in the net charge of the system, the change in the solvation free energy is large and very sensitive to the surroundings. If absolute potentials are estimated, a correction term, relating the results to the standard hydrogen electrode is needed. This term has been much discussed.[8]

Three main approaches for calculations of redox potentials have been used: quantum mechanical (QM) cluster calculations in a continuum solvent, continuum-solvent calculations including the entire protein, employing numerical solutions to the Poisson–Boltzmann (PB) equation or other continuum or lattice-based methods, and explicitly solvated simulations with energies calculated using free-energy perturbation (FEP) methods. Continuum-solvation methods describe the considered system by a set of atomic radii and the solvent by a dielectric constant (ε) or alternatively, by matching the so called σ-profiles of the solute and solvent in a more elaborate, but a more accurate COSMO-RS (conductor-like screening model for realistic solvation) method of Klamt.[9] With PB methods, you can assign different values of ε to different points in space (often ε = 1 in the QM system, ε = 4 in the protein and ε = 80 in water). However, the theory considers a homogeneous solvent, which is problematic when treating a protein, with a mixture of hydrophobic and hydrophilic parts.[10] Atomistic FEP simulations avoid such problems, but they instead face problems of convergence and by the change in the net charge of the system.

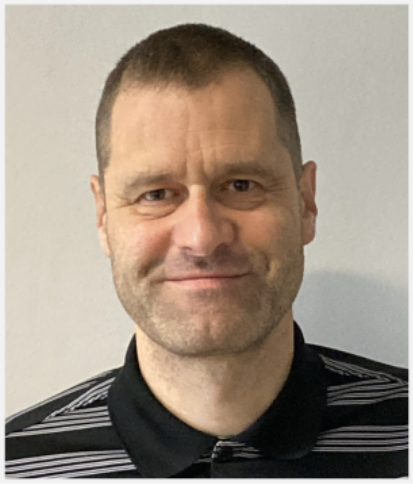
For metal complexes in solvents, rather accurate redox potentials can often be obtained with QM-cluster calculations,[2,11–14] although sometimes effects like spin–orbit coupling and explicit second-shell solvation, need to be considered.[13,15] For complexes with a high charge, the variable temperature H-atom addition approach has been shown to give improved results.[12] With such approaches, a MAD of 0.17 V can be obtained.[16] With a larger benchmark study, a MADs of 0.22 V for organic molecules and 0.33 V or organometallic complexes was obtained for the best DFT methods.[17]

For metal sites in proteins, QM-cluster calculations of different metal sites a mean absolute deviation of ~0.2 V for absolute potentials and 0.1 V for relative potentials for sites of the same type.[18–21] Large QM models and high values of ε seem to improve the results. Calculations with PB- or lattice-based solvation typically give errors of 0.2–0.6 V for the absolute potentials but 0.03–0.11 V in relative potentials for the same site in different proteins or mutants.[3,4,6,22–27] The results can often be improved by combining with QM calculations of the cluster charges with a self-consistent reaction field approach.[28] Methods based on FEP calculations, have serious problems to reach a similar accuracy.[29,30] In fact, even for all-atom QM/FEP simulations, the accuracy of redox potentials is not better than ~0.3 V.[31] Finally, it should be noted that reduction reactions are often coupled protonation, which should also be considered.[24,32]

Panel members:



invited expert
Lou Noodleman



invited expert
Lubomír Rulíšek

discussion leader
Ulf Ryde

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