Supporting Information

"Water-mediated electron transfer between protein redox centers"

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It is stated in the main text that the few (due to the computational burden) MD snapshots selected for the *ab initio* calculations of the transfer integrals were chosen by analyzing the *empirical* results affordable on a large collection of snapshots taken at regular time intervals, obtained by the proto-version of the Empirical Pathways (EP) method[1] published in 1987, without comprising H atoms. A more refined EP method[2] was introduced later. Whereas the former EP version distinguishes only between *non-bonded* and *covalently-bonded* steps in the best electron transfer (ET) path, the latter version treats hydrogen-bonds as a distinct class, thus counting separately *covalently-bonded*, *hydrogen-bonded* and *non-bonded* steps. We checked the robustness of our findings against the use of the refined EP model. The figures below show: (S1) that the choice of (water) conformations made on the basis of the EP proto-version complies also with the refined EP version; (S2) that the absence of correlation between the transfer integrals computed *ab initio* and those computed by the EP model is found also with the refined EP version. From these tests we conclude that the inadequacy of the single-pathway picture for treating electron transfer in our water-protein system does not depend on the details of the paths explored to find the dominant ET pathway. Rather, a separate treatment of hydrogen bonds can be crucially important within the empirical multiple pathways model,[3,4] which takes into account the (quantum) interference between different paths.

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[1] Beratan, D. N.; Onuchic, J. N.; Hopfield, J. J. *J. Chem. Phys.* **1987**, *86*, 4488-4498.

[2] Betts, J. N.; Beratan, D. N.; Onuchic, J. N. *J. Am. Chem. Soc.* **1992**, *114*, 4043-4046.

[3] Balabin, I. A.; Onuchic, J. N. *Science* **2000**, *290*, 114-117.

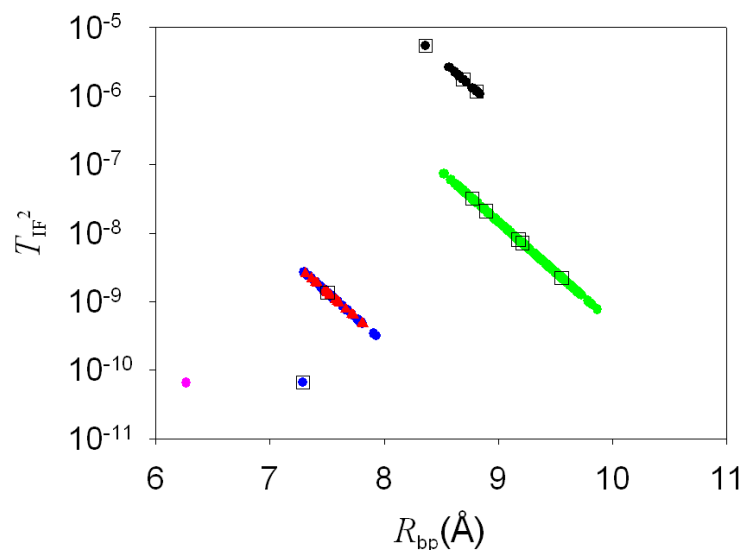[4] Lin, J.; Balabin, I. A.; Beratan, D. N. *Science* **2005**, *310*, 1311-1313.

Figure S1. Vertical axis: The quantity T_{IF} computed by the EP model[1,2] is proportional to the transfer integral and is obtained as the pathway product[5] of the decay factors along the steps of the dominant ET pathway between the donor and acceptor groups; the values reported in this plot were obtained with the refined EP model[2]. Horizontal axis: R_{bp} is the through-space length of the best ET path. The plot was obtained with 250 snapshots from the MD simulation, separated into dots and triangles of different colors according to the specific pattern of tunneling steps, namely whether the best ET pathway involves no interfacial water molecule (pink), one water molecule (blue spheres and red triangles for the donor and acceptor water molecule, respectively), both water molecules with two (green) or three (black) hydrogen bonds. The snapshots selected for our *ab initio* analysis are denoted with squares. Although the different patterns of tunneling steps with the refined EP model give origin to separated "branches" in this plot (compare to Figure 4b in the main text), it is evident that the selected snapshots are correctly distributed on the various branches, thus assuring a good sampling.

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[5] Jones, M. L.; Kurnikov, I. V.; Beratan, D. N. *J. Phys. Chem. A* **2002**, *106*, 2002-2006.
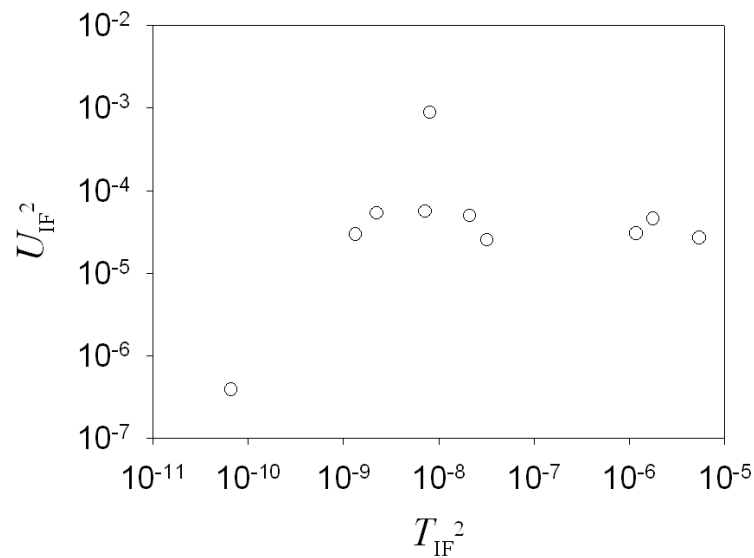
Figure S2. *Ab initio* square transfer integrals (U_{IF}^2) vs square EP products (T_{IF}^2). This plot confirms the general mismatch between the relative values of the *ab initio* transfer integrals and the pathway products. Note also that the absence of significant correlation between the two sets of values is strengthened by the largest T_{IF}^2, which are the most important in determining the ET rate according to the EP picture.