Review of: "Kirchhoff Coupling Generates ATP, the Chemical Energy of Life"

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In this brief communication, Eisenberg presents the essence of three papers that he has authored or co-authored, as referenced. The manuscripts have been published as preprints in 2022 and form the basis of his note, and I believe that his contribution to Queios can neither be fully appreciated nor understood without an in-depth study and discussion of this work. Until acceptance of the manuscripts this is, however, a task of the editors and referees of the journals in which publication is intended, and I will consequently comment on the note to Queios considering it basically as stand-alone work.

The manuscript presents the idea to model non-equilibrium, dynamically coupled proton and electron flow in the respiratory chain of mitochondria by a replacement circuit. This is only vaguely motivated by Maxwell's governing equations of electromagnetism, but not detailed in any way (the preprints do a much better job). Introducing the subject, the author briefly touches the biochemical and biophysical basis of cellular respiration, but does so in a way that intends to underline the maverick character of the work. Instead, it would be helpful to the readers to reference some of the work in structural biology, experimental biophysics or molecular dynamics that had addressed the problem of biological charge transfer in the past, rather than referring to Youtube, as impressive as e.g. Junge's animation of the ATPase may be. In addition, an appropriate terminology also adds to verisimilitude and to the acceptance of new concepts by scientists working in these fields, e.g. 'ATPase' or 'ATP synthase' rather than 'another protein device', and a word like 'periplasm' should feature in figure 1. Reference should also be given to the vast body of literature addressing static dielectric phenomena like protonation, proton transfer or electron transport by a field equation originating from Maxwell's, viz. that of Poisson or its statistical mechanics extension, the Poisson-Boltzmann equation, via numerical solutions. Some of the long and successful history of replacement circuits in biophysics should also be touched.

To some extent, I share the authors' skepticism about a stand-alone all-atom molecular dynamics perspective on systems exhibiting charge transfer due to the underlying time and length scales. Some of the claims made in the discussion section do, however, not reflect the state of the art of these approaches and the underlying algorithms: a current of one nanoampere – as typically observed e.g. in patch-clamp experiments - is equivalent to the passage of an elementary charge - e.g. through a channel - in 100 picoseconds, permitting a very effective sampling. This statement even holds for electrons using techniques that model quantum mechanical degrees of freedom, see e.g. a simulation of hole transfer in DNA (Steinbrecher et al., J. Phys. Chem. B 112, 16935 (2008)). In addition, free energy methods like thermodynamic integration or umbrella sampling can address the energetics of these processes once brute-force simulations fail. From an

algorithmic point of view, molecular dynamics scales as n to n^2 rather than n! or n^n– as claimed by Eisenbart - due to the short-range nature of most of the forces and the effective treatment of the long-range Coulomb forces using multipole expansion, lattice and Fourier transform techniques. Atomically resolved Coulomb interactions ARE pairwise additive, even in a nonhomogeneous polarizable dielectric environment (D. Gnandt, T. Koslowski, PCCP 34, 18595 (2019)). At the risk of getting needlessly philosophical, let me note that the resistors, capacitors, diodes and electron pumps of replacement circuits are, of course, also coarse-grained versions of multiatomic units, albeit on a different (and much smarter) functional level than just arbitrarily lumped atoms.

I acknowledge the originality and novelty of the ideas outlined in the note, but I believe that they should be detailed and put into the context of the vast body of experimental, theoretical and computational work on respiratory chain bioenergetics. Ideally, they could help to bridge atomistic information and the macroscale, but I do not consider them as a pure field theory alternative detached from an atomistic perspective.