**Coupling Enforced by Continuity of Current**

**Letter to the Editor**

**submitted to**

***Biotechnology and Bioengineering***

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**February 17, 2015**

The eloquent review of Nath and Villadsen (“Oxidative phosphorylation revisited” [15])reminds us of a central unsolved issue in bioenergetics, the coupling between flows in oxidative phosphorylation.

**Continuity of current produces coupling of fluxes.** I write because an important unavoidable source of coupling seems to have been left out, namely coupling of flows of charge produced by “Kirchoff’s current law”, i.e., conservation of current. Flows of charge can be coupled ***independent of the chemical nature of the coupling*** by the physical properties of current flow.

In any system involving electrical charge, current flow is conserved. Charge can accumulate but only as a source of displacement current which carries away ***exactly*** as much charge as is accumulated, within an error of one part in 1018 [13, 17], even in a perfect vacuum. Textbooks of electricity and magnetism discuss these matters at great length, because they form the foundation of Maxwell’s equations and our understanding of the propagation of light and radio waves. The consequences of continuity of current flow for chemical systems seem to be less well known. (As a neophyte I plead guilty of ignorance of the proud literature of oxidative phosphorylation and apologize to those whose work I have not read and so cannot cite.)

What is striking to a biophysicist/physicist is that continuity of current is not included as a constraint in the models and discussion of Nath and Villadsen.

**Continuity of current flow is a separate constraint.** It seems to me that Kirchoff’s current law should be included as a ***separate*** constraint that will always be obeyed **NO MATTER WHAT ATOMIC AND MOLECULAR EVENTS ARE NEEDED TO ENFORCE IT**, no matter what is carrying the current. Couplings that will result from this additional constraint then become an ***output*** of the model. It is easy to compare fluxes in a model that includes Kirchoff’s current law with fluxes in a model that does not. The differences in the fluxes computed as outputs of the two models show the coupling produced by continuity of current flow itself, independent of specific local chemistry.

A complete model of oxidative phosphorylation of course includes chemical detail (I am personally too ignorant to specify). It also includes the separate constraint of Kirchoff’s current law in form appropriate for the geometry of the system. Kirchoff’s current law is of course global in the sense that it involves current flow throughout the system not just in the channels and transporters of oxidative phosphorylation. The chemistry is local. The overall model joins local with global just as it does in the analysis of electrical properties of nerve cells, that we now discuss.

**Precendents.** Analysis starting with continuity of current has productive precedents in membrane biophysics. The classical analysis of Hodgkin et al [10-12] of voltage and space clamped squid axons [6, 8] depended on Kirchoff’s current law in the form



where  are all the currents carried by particles of any species that flow and have mass (e.g., including protons, electrons, and all chemical species), *V* is the potential across the membrane of a spherical like cell or organelle (i.e., one in which the potential is approximately uniform in space), and  is the capacitance of the membrane that includes both the displacement current found in a vacuum and the dielectric (polarization) currents produced by rearrangements of charge within the membrane lipids (mostly) and proteins (to some extent).

In the steady state, this version of Kirchoff’s law becomes



In a long thin axon, without the applied constraints of space or voltage clamp, Kirchoff’s current law becomes the cable equation (called the telegrapher’s equation in the mathematical literature) that couples the atomic properties of individual channels (both the opening of individual channels and also the movement—permeation—of ions through the individual channels) with the macroscopic electric field and thus produces propagation of the nerve signal



where is the resistance of the axoplasm per unit length,  is the current carried by particles (including ions, protons and electrons) across the membrane, per unit length,  is the capacitance of the membrane per unit length. The original reference [7] uses operator methods to solve the differential equation more difficult to follow than modern methods [1].

**Coupling of fluxes in independent channels of nerve.** There are strong couplings indeed of current flow in the action potential mechanism described by eq. & . In the voltage clamp experiments of [3, 9], for example, the flow of sodium and potassium ions are equal. But this coupling is ***not*** produced by chemical interactions of proteins (i.e., sodium and potassium channel proteins), or sodium and potassium ions. The channels are far apart in the axon membrane and single channel measurements show they open and close independently [14, 16]. The coupling of fluxes in the squid voltage clamp experiments are the ***inevitable*** unavoidable consequence of eq. .

Without the coupling of sodium and potassium fluxes produced by Kirchoff’s current law, the analysis of Hodgkin et al would have been impossible. Coupling of sodium and potassium fluxes which cross the membrane in different proteins quite far apart in the squid axon would be mysterious, since no chemical source of coupling could be found: there is none. Chemical processes are not involved in the coupling or in the propagation of the action potential (as shown by Hodgkin as a student [4, 5], in contrast to the views of Nobelist AV Hill [2]).

**Conculsion.** I suggest that oxidative phosphorylation and the couplings of flows that produce it could be much easier to understand if Kirchoff’s current law, in appropriate form for the experiments, usually steady state, were always imposed as an additional constraint.

The couplings imposed by enforcing Kirchoff’s current law are a global property of the entire system (e.g., all channels and transporters and the structure of the system). These couplings are not a local chemical property. Seeking a local chemical explanation of couplings seems unlikely to be more successful than it was in studying the action potential. The coupling agent is a physical law too global, general (and intangible) to grasp as a specific chemical interaction.

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