Coupling Enforced by Continuity of Current

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The eloquent review of Nath and Villadsen ("Oxidative phosphorylation revisited" [26]) reminds us of a central unsolved issue in bioenergetics, the coupling between flows in oxidative phosphorylation so electron movement can make ATP.

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. Current flow is continuous. 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 10^{18} [21, 33], even in a perfect vacuum. Voltages and forces change as conditions change to accommodate continuity of current. Indeed, voltages can become large enough to change the physics of the system, which we notice as sparks.

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. Daily experience shows that interrupting current flow in systems connected in series stops current flow in all of them. Interruption of current meters away from a battery stops the chemical reaction in the battery even on the nanometer scale of the metal/electrolyte interface.

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 [26]: The consequences of continuity of current flow for chemical systems seem to be less well known than they might be [6, 7]. Of course, there may be discussion somewhere in the literature that I do not know about. As a neophyte, I am only acquainted with the citations of Nath and Villadsen [26] who could not possibly refer to the entire proud literature of oxidative phosphorylation.

Continuity of current flow is a separate constraint. It seems to me that Kirchoff's current law should be included in models of oxidative phosphorylation as a ***separate*** constraint that will always be obeyed **NO MATTER WHAT ATOMIC AND MOLECULAR EVENTS ARE NEEDED TO ENFORCE IT**, no matter what kind of charge is carrying the electrical current. There should be no ambiguity here. Continuity of current flow (including displacement current) is an absolute requirement of physics that the local chemical reactions must accommodate. Indeed, the local chemical reactions accommodate a far distant interruption of current flow (in a series circuit including a battery) by stopping! In general, voltages and forces change so that Kirchoff's current law is exactly satisfied.

Couplings that will result from the additional constraint of continuity of current then become an ***output*** of the model of oxidative phosphorylation as a whole, not an input. Of course, there may also be chemical couplings occurring on a local scale. 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 the local chemistry.

To say the same thing in other words: a complete model of oxidative phosphorylation of course includes chemical detail. 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. It must include all pathways of current flow across the membrane just as it does in the analysis of electrical properties of nerve cells, that we now discuss.

Precendents. Analysis starting with continuity of current is not new in membrane biophysics. It has productive precedents in the analysis of the action potentials of nerve and muscle fibers.

The classical analysis of Hodgkin et al [18-20] of voltage and space clamped squid axons [14, 16] depended on Kirchoff's current law in the form

$$\sum I_i = C_m \frac{\partial V}{\partial t} \tag{1}$$

where I_i are all the currents carried by particles of any species that flow and have mass (e.g., including protons, electrons, and all chemical species, but not including displacement current), 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 [2, 24, 29, 30]). C_m 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. I_i and C_m are usually referred to the area of membrane, i.e., units are per cm^2 of membrane area, not the area of the channel protein or its pore.

The dielectric currents are mostly in the lipids but also have important components in proteins, as measurements of gating current in muscle [31] and nerve [1, 5, 27] reveal so clearly, exploiting continuity of current that links atomic motions of the voltage sensor [3, 4] with macroscopic current flows in bath electrodes (centimeters away from the membrane) measured by voltage clamp amplifiers. The dielectric currents are as important in determining the propagation of the action potential as the channels themselves [13] as the disease of multiple sclerosis demonstrates all too clearly.

In the steady state, Kirchoff's law (1) becomes

$$\sum I_i = 0 \tag{2}$$

In a long thin axon, without the applied constraints of space or voltage clamp, Kirchoff's current law becomes [2, 24, 30] the cable equation (called the telegrapher's equation in the mathematical literature) that couples the atomic properties of individual channels with the macroscopic electric field. The cable equation couples 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

$$\overbrace{\frac{1}{r_i}\frac{\partial^2 V}{\partial x^2}}^{\substack{\text{Axoplasmic}\\ \textit{Axial Current}}} = \overbrace{c_m \frac{\partial V}{\partial t} + i_i}^{\substack{\text{Membrane}\\ \textit{Radial Current}}} \tag{3}$$

Note that the flow of current in the real physical world is orthogonal, axial for the longitudinal current flowing down an axon, and radial for the membrane current flowing across the membrane, even though in this (accurate) one dimensional approximation, only the longitudinal (axial) variable x appears explicitly. The mathematical analysis in Kevorkian and Cole's textbook [24] shows how this comes about. Physical explanation is in [2] and [28]. In this equation r_i is the longitudinal resistance of the axoplasm per unit length, i_i is the radial current carried by particles (including ions, protons and electrons) across the membrane, per unit length, c_m is the capacitance of the membrane per unit length. The original reference in the biological literature [15] (compare with the original engineering/physics references [22, 23]) uses operator methods unknown to present day students to solve the differential equations so it is wise to consult a modern textbook [8].

Coupling of fluxes in independent channels of nerve. There are strong couplings indeed of current flow in the action potential mechanism described by eq. (1) & (3). In the voltage clamp experiments of [10, 17], for example, the flow of sodium and potassium ions are closely related, because they must sum to the applied current. But the relationship 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 [25, 32] when in a voltage clamp set up, thus satisfying Hodgkin's 'independence principle' for ionic currents across membranes (which only true for highly selective channels that open and close independently). In a propagating action potential the relation of sodium and potassium currents are different because the setup is different. That is what makes propagation possible!

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 axon membrane in different proteins would be mysterious, since no chemical source of coupling could have been 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 [11, 12], evidently to the surprise of Nobelist AV Hill [9]).

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 were always imposed as an additional constraint (in appropriate form, usually steady state).

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 purely local chemical explanation of couplings seems unlikely to be more successful than it was in studying the action potential.

Coupling arising from a physical law is too global, general (and intangible) to grasp as a specific chemical interaction.

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