Current Flow in Nerve and Mitochondria

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Abstract

Electrodynamics of current provide much of our technology, from telegraphs to the wired infrastructure powering the circuits of our electronic technology. Current flow is analyzed by its own rules. It cannot be analyzed one charge at a time. There are too many charges. Current flow is essential in biology. Currents are carried by electrons in mitochondria in an electron transport chain. Currents are carried by ions in nerve and muscle cells. Currents everywhere follow the rules of current flow: Kirchhoff's current law and its generalizations. The role of electrons in generating ATP was discovered long ago. The flow of protons that generate ATP in ATPsynthase has been determined. The flow of protons and transport of electrons form circuits that should be analyzed by Kirchhoff's law. Circuit analysis is easily applied to short systems like mitochondria that have just one internal electrical potential in the form of the Hodgkin Huxley Katz HHK equation. The HHK equation combined with classical descriptions of chemical reactions forms a computable model of cytochrome c oxidase, part of the electron transport chain. Current laws are now needed to analyze the flow of electrons and protons, as they generate ATP in mitochondria and chloroplasts.

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The figures convincingly document the importance of electron and proton flow as seen in the experimental literature of the respiratory chain, independent of theoretical discussion using current laws.

The figures in this paper are taken from public domain websites. It is not useful to provide individual references to these websites because they change so often. The websites all allow copying, as best I can tell. If I have inadvertently failed to give proper attribution, I will make corrections, and of course apologize.

I repeat: I have made no intellectual contribution to the figures or the work they report beyond ref. [12].

Current flow follows its own rules set by physics—the Maxwell equations of electrodynamics [1-3]. The rules apply to current carried by ions, protons, or electrons. The original Maxwell equations are constitutive equations of materials that depend on a crude dielectric approximation to the polarization properties of matter, e.g., liquids [4]. Polarization describes the compressibility of charged materials when electrical forces are applied. The range of possible motions is enormous, particularly those of ionic solutions and proteins [5-7]. Almost all of life occurs in ionic solutions and depends on protein. The original Maxwell equations, with their over simplified model of polarization, cannot possibly describe ionic solutions and proteins, using just one dielectric constant (a single real positive number). The universal nature of the Maxwell equations is not apparent when the restrictive dielectric approximation is used. The importance (and role) of the Maxwell equations has not always been apparent in biological systems.

The universal nature of the Maxwell equations is seen more clearly once the dielectric approximation is removed [4] and replaced by models of polarization specific for the system of interest [5-9]. The dielectric constant should be taken as a (single positive real) constant only when experimental estimates, or theoretical models are not available, in my view. That is often the case when teaching the Maxwell equations, or when models are constructed of new situations. But one must always remember that using the Maxwell equations with a single dielectric constant obscures their universal nature. Polarization can be analyzed in an energetic analysis by the variational treatment of complex fluids that specifies the free energy of polarization [10]: Section 3.6.

The rules of current flow are known and true in nerve cells and mitochondria. Nerve and muscle fibers, and the syncytia of heart muscle, have long been analyzed as circuits with current flowing in complex biological structures, like a nerve fiber [11]. Electrons transporting in chains and protons flowing in pathways in mitochondria also form circuits that can be analyzed along with coupled chemical reactions, diffusion, even water flow. Quantitative predictions of current voltage relations (for example) and much else can be made in a wide range of conditions for complex 4 of the electron transport chain, cytochrome c oxidase [12].

Current flow generates the signals of nerve cells [11], muscle fibers and the heart, as has been shown by some ninety years of work in biophysics. Currents link and correlate the properties of ion channel proteins to make the signals of nerve cells. Without the correlation of the opening of ion channels, the nerve signal does not exist. The rules of current flow show how the propagation of the action potential depends on the correlations of channel opening at different locations [11], produced by the different potentials at those locations. The longitudinal current down the nerve—carried by whatever ions happen to be present, or even by electrons in a return path [13-15]— produces the different potentials that correlate the openings of various ion channels at different times, making the action potential a propagating wave form.

The chemical approach to ion channels [16] is essential to understand each channel as a protein but it is not enough to determine how channels work together to produce signals. Ion channels in nerve signals are not linked by conformation changes or chemical reactions. The proteins are too far apart and too well shielded by ionic atmospheres and polarization, measured by Debye lengths and Bjerrum lengths respectively [17]. Proteins are linked by potential changes produced by current flow [18] within the nerve cell, down the length of the nerve or muscle fiber. The conformation changes of ion channels are linked by electrodynamics in a natural nerve fiber. The proteins are not linked at all when potential changes and correlations are removed by a voltage clamp apparatus [19]. Indeed, the purpose of the voltage clamp system is to remove such linkages [20].

The forces that link conformation changes are nearly impossible to study atom by atom as is done in classical molecular dynamics. There are just too many charges involved to allow evaluation of forces between atoms from the 'potentials' of molecular dynamics. It should be noted that molecular dynamics is not used to analyze electrical circuits.

Fortunately, the laws of electrodynamics extend beyond the laws of charges and their interactions. Maxwell's version of Ampere's law is labelled equation **A** in his summary paper—see p.465 and 480 of [21] provides extra information [22] that dramatically simplifies the analysis of many systems: only handfuls of currents are needed to analyze many circuits where a multitude of charges would be needed.

Interactions among currents are easy to evaluate using a corollary of the Maxwell Ampere equation. Physicists and engineers have used Kirchhoff's current law and its generalizations [23] for some 150 years [24-27], extending even to microwave frequencies [28-33].

Without using the rules of current flow, analysis of the correlations that create the signals of telegraphs, or our computers, or our nerve cells, would be impossible. Calculations would have to evaluate the interactions of $> 10^{10}$ charges. The number of combinations of 10^{10} charges, two charges at a time is $(10^{10}!)\big((10^{10}-2)!\big)$. An enormous amount of coarse graining would be needed to make such calculations computable, and the result would be inaccurate. As we shall discuss later, coarse graining can be done by using current laws that are exact because they exploit other information beyond the charge interactions. The current laws provide coarse graining inherent to the Maxwell equations. The current laws are mathematical corollaries of the Maxwell Ampere law, derived without approximation and are true independent of models.

Current flow in mitochondria. In this paper, we discuss the rules of current flow in another membrane structure of biological importance: the electron transport chain of mitochondria. The electron transport chain of mitochondria and chloroplasts creates the chemical energy of life that is stored in ATP. Applying the rules of current flow will help analyze these important systems. Ignoring the rules of current flow would require charge by charge analysis. Charge by charge analysis would make quantitative analysis of the currents in mitochondria almost impossible just as it would make quantitative analysis of nerve signals—or most of the circuits of electronic technology—impossible, and for the same reason: there are too many charges.

Coarse Graining by Kirchhoff's Law. Impossibly large calculations of this sort are common in statistical physics. The impossible is often made possible by approximations that reduce the resolution of models. Approximations are necessarily made as coarse graining is used to reduce complexity.

Indeed, analysis of currents—instead of charges—uses Kirchhoff's current law to reduce the complexity of calculations. Far fewer currents are needed in Kirchhoff's current law than

charges are needed in Coulomb's law, or the Poisson equation, or the continuity equation. Kirchhoff's law seems to lower resolution as it replaces charges with currents. But Kirchhoff's current law is an unusual coarse graining because it introduces no errors. It is not an approximation. It is a corollary of the Maxwell equations.

Kirchhoff's law, or rather its generalizations [22, 24, 34, 35], are exact [36]. It is not approximate. Indeed, the movements of all charges (at any time and location) can be calculated from Kirchhoff's law or its generalizations because they are exact. ***Coarse graining by Kirchhoff's law is exact because it invokes additional physics, namely the Maxwell-Ampere current equation.*** Computation of time dependent electrical forces cannot be done using charge by charge analysis, as Feynman discusses at length in Section 15-6 entitled "…statics is false for dynamics" [1]: Coulomb's law, for example, does not apply to time dependent systems. Additional information is needed and that comes from the time dependent properties of charge movement that produce magnetism. Current flow cannot be analyzed without considering magnetism because of the theory of special relativity, well explained by Feynman Section 13-6 of [1].

The Maxwell-Ampere law specifies properties of magnetism. ***Magnetism is not present in Coulomb's law, the Poisson equation, or the continuity equation***. The Maxwell-Ampere equation is what allows light to propagate through a vacuum devoid of charge. Coulomb's law, the Poisson equation, and the continuity equation do not allow that by themselves. The special properties of magnetism $\mathbf{B}$, specifically of $\mathbf{curl\ B}$, determine the properties of currents and circuits, even if magnetic forces and energies are negligible in those circuits and currents. Current laws are derived from the Maxwell-Ampere equation by mathematical, not scientific operations that do not depend on the size of magnetic energy. Current laws do not involve material properties at all. The only parameters involved are (any two of) the electric constant ε_0, the magnetic constant μ_0, and the speed of light c. Coarse graining by Kirchhoff's law is a corollary of the Maxwell equations and is as valid as the Maxwell equations themselves.

The mathematical derivation of the current laws does not depend on approximations or models of material polarization and charge movement. This means that the coarse graining is valid at all times and for all flows, in fact, whenever the Maxwell equations themselves are valid.

Many other coarse graining procedures are more restricted. Some are in fact derived from equilibrium (zero flux) theories like statistical mechanics. Equilibrium theories have debatable validity when applied to systems far from equilibrium such as electrical circuits, nerve signals, or electron transport chains of mitochondria [37, 38]. It is difficult to compute something that has been assumed to be zero. It is difficult to make a meaningful theory of reasonable sized flows that does not include velocity as a variable or friction (i.e., diffusion constant) as a parameter.

Asymptotic analysis of singular perturbation theory shows how small flows can be described more or less uniquely without evident internal contradictions [39], if sufficient care is taken. Singular perturbation theory also shows the ambiguities and contradictions that occur if the explicit analysis of that theory is not done. It also illustrates—Section 2 of [39], particularly Fig. FIGURE 2.3.2)—the difficult ambiguities of systems containing multiple interacting parameters and fields, like the ionic solutions in which biology exists.

What are the rules of current flow? The fundamental rule of conduction current in circuits is a generalization of conservation of charge, called the continuity equation, described in every textbook of electrodynamics, e.g., Zangwill [3], p. 32, and Griffiths [2], p. 222, 356. Conduction current is current produced by the flux of mass with charge. The practical discussion in Ulaby and Ravaioli's 'Applied Electrodynamics', Section 6.1 [40] is particularly relevant to biophysics. Following the practice insisted upon by Maxwell [24, 25], Ulaby and Ravaioli explain that the current in circuits is not just the conduction current. The current in circuits is not just the movement of charges, electrons or ions. **It includes the storage of charge (by displacement current at nodes of a circuit for example) as well as the movement of charge with mass.** It includes the special case of very small currents in very high impedance structures, which are so relevant to the biophysics of single ion channels [41]. Displacement currents play an important role in the study of single channels.

Displacement Current in Circuits. Currents in circuits and systems always include the displacement currents that accumulate to store charge [22, 36]. Displacement is the name for currents that depend on the time rate of change of potential $\partial V/\partial t$. The name 'displacement' emphasizes the importance of time dependence in the process. Charge must move, i.e., be

displaced, to create displacement current. Steady movement of charge (in which the time rate of change of the electric field $\partial E/\partial t$ is zero) does not produce displacement current.

Displacement current has the special property that it is zero when the perturbing potential is zero and steady. Displacement currents are zero when nothing is displaced, when potential does not change with time. Displacement charge returns to its starting place when the perturbation ceases. All the charge that is displaced returns. Displacement current returns to zero when the perturbation ceases. Charge is conserved. No charge or current leaves the system. No steady current flows in such systems, so there is no steady energy loss to friction.

Displacement currents have been extensively studied in biophysics because they are an essential part of the process that produces signaling in nerve cells. The special properties of displacement current—charge displaced at the ON of a rectangular voltage pulse equals charge displaced (actually charge replaced) at the OFF [4]— have allowed measurement of nonlinear voltage dependent gating currents in muscle [42] and nerve [43] that arise in special structures in some channels called voltage sensors [44, 45]. The equality of ON and OFF displacement charge [4] has not been used so far in the construction of energetic functions for polarization [10].

Displacement Current in Biology. Biologists discovered the importance of displacement current in the 1930's. Capacitive displacement current was discovered as biologists studied the signals of the nervous system, and then muscle and the heart. At first, biologists—including the Nobel Laureate Chair of Biophysics A.V. Hill [46]—sought a biochemical explanation of the action potential and its propagation—but the elegant experiments [47, 48] of the Cambridge physiology student A.L. Hodgkin, followed by Tasaki, Huxley, and Stämpfli [13-15] showed that propagation is an electrical phenomenon. Chemical propagation of the action potential does not occur.

Hodgkin [49] and Huxley's [11] later work showed that the electrical analysis gave quantitative understanding of the nerve signal, while the biochemical explanation of propagation—then and now [16, 50, 51]—is qualitative. Biochemical understanding is enormously important of course, but qualitative none-the-less. It cannot compute the shape of

the propagating action potential, or even the conduction velocity, for that matter. Prediction requires numbers to describe potentials because the action potential is a phenomenon, a signal, a waveform distributed in time and space. The action potential is a set of numbers, neither the single number meant by the word 'potential' in physics, nor a phrase without numbers as meant in biochemistry. The biochemical treatment of channels is verbal and qualitative. It does not produce numbers.

Molecular dynamics extends the chemical approach and does produce numbers. But it cannot predict the coupling of sodium and potassium channels in the action potential for a technical reason. Coupling in the action potential is produced by a long-range change in potential that is not included in the simulations of modern molecular dynamics. These simulations keep track of the movement of ions, without considering long range electric fields such as those that spread down the nerve fiber. Long range fields involve long range current flow that cannot occur in the periodic systems studied in molecular dynamics. In periodic systems, potential cannot spread beyond the length of the period. Indeed, the potentials at both ends of the period are the same, so the potential distribution within the period is controlled by an artificial periodic condition not found in the original system before simulation. Artificial boundary conditions produce artifacts.

Classical molecular dynamics also do not deal with capacitive, displacement current. It uses Coulomb's law to evaluate time dependent forces (despite Feynman's emphatic objection that 'Coulomb's law is false in dynamic systems', [1] Section 15.6). Both these issues have been dealt with in plasma physics with particle or even atomic resolution. Particle-in-cloud methods [52] have also been applied to discrete models of current flow in semiconductors for a long time, e.g., see application to **PNP** transistors [53, 54]. These methods seem not to have been applied to molecular dynamics of ionic (i.e., electrolyte) solutions or proteins. 'Plasma' in physics is not the same as 'plasma' in ionic solutions. In physics, plasma refers to a gas of ions, not the dissolved ions of blood without cells. Ions in physical plasmas often have negligible diameters. Ions in electrolytes have finite diameters that are of great importance in determining the selective (non-ideal) properties of ions crowded into channels and enzyme active sites, and in concentrated bulk solutions [55, 56].

Analysis based on the properties of current flow—***not*** the properties of movement of individual charges—forms a quantitative description of nerve signals. Hodgkin and Rushton [57] showed that excitable cells could be analyzed with nearly the same theory that Kelvin used [26, 27] to analyze the Atlantic cable, even though electrons carried the current across the Atlantic and ions carry current down nerve fibers. Hodgkin and Huxley [18, 20] used Kelvin's cable theory to analyze the nerve signals discovered by Volta and Galvani. Tasaki, Huxley, and Stampfli showed how electrons could carry return signals in myelinated nerve fibers [13-15]. Ulaby and Ravaioli have an extended discussion of such cables, transmission lines, and telegrapher's equations in a modern context [40].

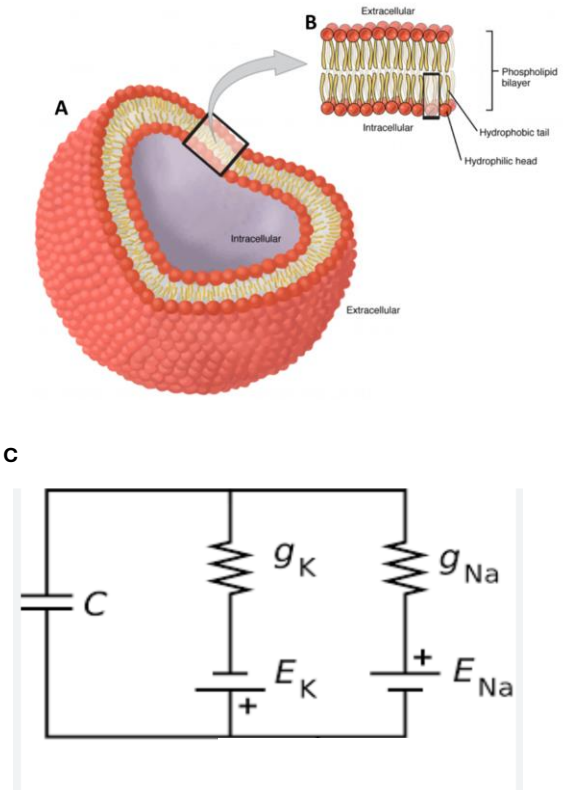


Fig. 1. **A**: a short cell with **B:** lipid bilayer membrane. Ion channels are not shown. **C:**The currents across a short cell. The classical Hodgkin Huxley system is shown of a membrane capacitance C, current pathway for K^+ ions through a potassium conductance g_K driven by the gradient of chemical potential E_K and similarly for sodium Na^+ ions. The sum of the currents through all three pathways is zero. There is no place for the current to go! The HHK equation $\sum I_j = C_m \, \partial V/\partial t$ applies to a short cell or organelle of irregular shape like a mitochondria, as long as all the membranes, channels, and transporters have the same potential across them.

In nerve cells, one set of ions carries a chemical flux of ions through channels across the membrane, carrying charge and creating conduction current as it moves. ***Another set of ions altogether*** carries the current along the nerve cell, creating propagation [11]. It is the current flow—***not the chemical flux*** of one type of ions or other—that produces propagation as shown directly by measurements on axons perfused with different solutions [58, 59]. The longitudinal potential gradient depends only on electrical properties. It depends on the resistance per unit length of ionic solution inside the cell, not on frequency or time even in cells with cytoplasm filled with proteins [60, 61], and not on the composition of the solution. The change in concentration produced by the chemical flux has no role in the Hodgkin Huxley analysis propagation [18, 20]. The current down the axon changes the potential across all molecules in the membrane. ***It is the propagating potential accompanying the longitudinal current that correlates the opening of the channels. The channels are separated***. They are quite distinct, molecularly independent proteins selective for sodium or potassium ions.

(Historical note: the idiosyncratic, if not chauvinistic operator mathematics of Hodgkin and Rushton were replaced by more customary mathematics, in [62] and [63, 64]. Ref [65] uses modern two port theory that allows easy combination of different transmission lines in parallel, series, or almost any other arrangement. Most analysis today is done with software packages which are easily located by searches for "applied electrodynamics software".)

Membrane Capacitance. The capacitive current through the cell membrane played a crucial historical role in validating the voltage clamp analysis of the action potential (personal communications from A.F. Huxley and separately A.L. Hodgkin to the author, in the 1960s). The formula for the displacement current $C_m\, \partial V/\partial t$ in Hodgkin, Huxley and Katz [19] eq. 11 (describing the axial wire setup of Fig. 10) allowed analysis of ionic current when the voltage was changing, for example during an action potential. They needed to study the current during the natural behavior when the voltage was changing during an action potential, when ***the voltage clamp amplifier was not present.*** C_m is the membrane capacitance and $\partial V_m/\partial t$ is the time rate of change of the membrane potential. The axial wire used by Hodgkin, Huxley and Katz [19] removes the current down the axon and prevents propagation but in itself it does not control the time dependence of the voltage. That is a separate function, performed by the

voltage clamp amplifier. The axial wire forces the total current (capacitive plus ionic) across the membrane to be zero [19] eq. 11. In that case, $C_m\,\partial V/\partial t$ equals the total ionic current $\sum I_j$ across the membrane. j identifies the type of ion, typically Na^+ or K^+.

Potentials are uniform in short cells. In fact, the same HHK equation $\sum I_j = C_m\,\partial V/\partial t$ describes ***ANY SYSTEM*** in which all membranes/ion channels/transporters have the same transmembrane potential across them [66, 67]. In any such system the capacitive current equals $C_m\,\partial V/\partial t$ equals the total ionic current $\sum I_i$ The mathematics deriving this result for long and short cells is derived in [67] and explained in textbook detail in [39], pp 218-238. Errors in the approximation (for short cells) are calculated explicitly. Short cable theory is discussed in many texts and other references, e.g., [68, 69].

In words, without mathematics, short cells (and organelles) have (nearly) uniform internal potential. Only cells with long processes like axons and muscle fibers have non-uniform transmembrane potentials. Short cells and organelles have only one transmembrane potential (see Fig. 1) so the total ionic current $\sum I_j$ through the membrane equals the capacitive current $C_m\,\partial V/\partial t$.

HHK equation: $$\text{Sum of All Ionic Currents} = \sum I_j = C_m\,\partial V/\partial t \qquad (1)$$

I_j describes *any* current carried by ions with mass including those carried by electrons, protons, through active transporters or channels. I_j is not restricted to the currents through the Hodgkin Huxley ionic conductances identified in Fig.1.

HHK equation and Kirchhoff Coupling. Eq.(1) is called the HHK equation because it appeared so clearly in [19] in eq. 11 and was so important in their analysis as a check on voltage clamp results [18]. The HHK equation expresses the coupling produced by Kirchhoff's current law in any system characterized by a single transmembrane potential. A version of the equation describes the principle "you must complete the circuit" known to telegraphers for a very long time.

The HHK equation (1) implies a coupling between currents that is driven by electrodynamics, not by chemical interaction. If one current increases, some others must

decrease. A graph of one current vs the other (with everything else fixed) will show a straight line 45-degree dependence. That is an operational definition of coupling that can be applied to any experiment measuring currents or fluxes, whatever their origin. In the setup of eq.(1), the electric field and electrical potentials change fluxes in exactly the amount needed to create coupling.

The Maxwell equations change the potential to create the coupling. It is the NON-constant field [70, 71] that creates the coupling. Insistence on thinking of constant fields makes this coupling hard to understand. The importance of NON-constant fields is not confined to biophysics. It is in fact central to circuit theory in general. Ref. [72], Fig. 2 shows how the microphysics of individual devices accommodates (and enforces) the relations of currents demanded by the Maxwell-Ampere equation. It is fortunate that semiconductor physicists abandoned the idea of constant field (compare [73, 74] and [75, 76]; see [77] for a modern treatment). It is difficult to imagine Shockley's understanding [78-81] of transistors (both bipolar and FET) emerging from a theory based on constant fields.

The coupling of eq.(1) is universal—as universal as the Maxwell equations of electrodynamics [22, 36]—because it arises as a corollary of the Maxwell-Ampere partial differential equation. The coupling occurs between widely separated atoms. It can be remote on the length scale of Kelvin's undersea cable or on the atomic length scale of Angstroms: It occurs in systems screened by ionic atmospheres (measured in Debye lengths) and induced polarization charge (measured by Bejerrum lengths), both a few angstroms in size in most biological situations.

The HHK equation (1) includes displacement current following Maxwell's admonition [24, 25]: **" … that the time-variation of the electric displacement, must be considered in estimating the total movement of electricity."** Quotation and supporting equations are in Vol. 2, Section 610, p. 232. Maxwell could hardly have chosen more emphatic language. He illustrates the general principle with examples and applications calculated in detail, lest his admonition be viewed as a remote abstraction irrelevant to practical applications.

I call the coupling implied by the HHK equation 'Kirchhoff coupling' to emphasize its electrical nature. It might be better called 'Maxwell coupling' [24] when displacement current (like that of the membrane capacitance) is important. The phrase 'Maxwell coupling' emphasizes the dynamic aspect of coupling described vividly in Feynman's admonitions ([1] Section 15.6) not to use Coulomb's law when electric fields vary with time. Coulomb's law might be an adequate approximation for slowly changing systems, but its uncritical use obscures the underlying physics, even when it is an adequate approximation.

'Protons' in biology. Note that the positive charged versions of water—customarily called 'protons' or H_3O^+ in the chemistry literature [82]—all count as one of the types of ions in eq.(1). Proton currents are tricky to deal with, because several forms of hydrated protons exist [82]. Each can participate in a wide variety of protonation reactions with various substrates as they move as a current. Proton currents must be analyzed by electrodiffusion equations in conjunction with the chemical reactions that increase or decrease proton concentration as substrates protonate or deprotonate, as is done in [12].

Proton current needs to be analyzed by the theory of complex fluids because it involves so many different forces and fields. **These fields are not described by the theory of simple fluids**, or by chemical reaction theory that does not deal with electrodynamics, diffusion, or friction. Composite theories tend to be inconsistent if they are not derived using complex fluid theory, particularly in its variational formulation [83-85]. Inconsistent theories produce different results in the hands of different scientists.

We turn now from current flow in nerve and muscle to current flow in mitochondria and chloroplasts.

Mitochondria and chloroplasts. Mitochondria are the powerhouse of animals, closely related to chloroplasts that are the powerhouses of plants as they create oxygen gas, and thus allow animal life. Both generate the ATP that stores chemical energy in both plants and animals. The mechanisms involved have been a central subject in biology for a very long time because they are a keystone in the arch of life. Without ATP production, the arch of life collapses, and both plants and animals die. Life requires the hydrolysis of ATP.

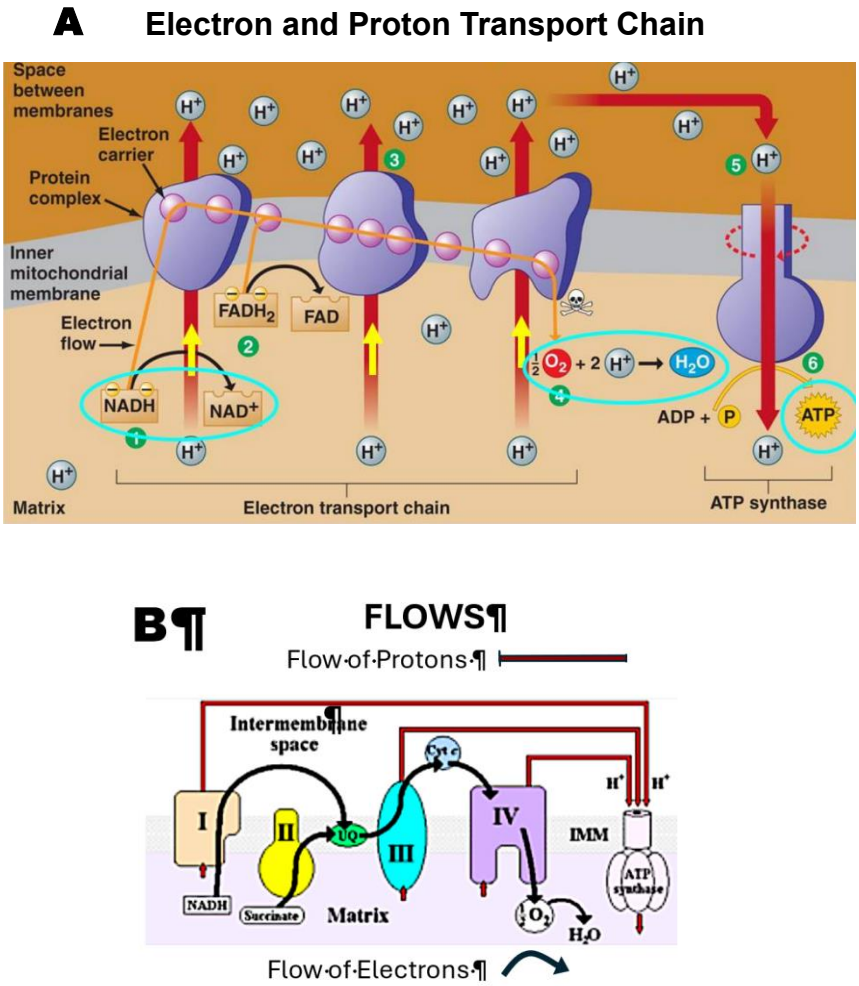


Fig. 2 A: a schematic view of a mitochondrion emphasizing the functionally important roles of the four complexes identified by the Arabic numerals **1**,**2**,**3**, and **4**. The main function of these complexes is to provide proton H^+ current to ATP synthase shown in Fig. 3.

Fig. 2B: shows the functionally important contributions of each complex (here identified by roman numerals I, II, III, and IV. The functionally important contributions are proton H^+ current used by ATP synthase shown in Fig. 3

ATP, crucial to life, is generated in mitochondria shown in Fig. 2 by a set of protein complexes numbered 1 to 4, in Roman numerals **I** to **IV**. The protein complexes are spatially separated in the mitochondrial inner membrane [6, 86, 87]. The outer mitochondrial membrane is not directly involved because it is quite low resistance and does not change current flow very much. From our point of view, the cristae and complex folding of the inner membrane are not important so long as all the membranes have the same transmembrane potential. The function of the complex structure will likely emerge in higher resolution analysis dealing with variation in transmembrane potential, just as the complex structure of skeletal muscle emerged as the function of the transverse tubular T-system was discovered [88-91].

From a chemical perspective, the generation of ATP depends on metabolites like NADH (nicotinamide adenine dinucleotide) that store electrons. The stored electrons produce high energy molecules poised to be electron donors when they participate in the appropriate chemical reactions. Evolution has designed those metabolites and chemical reactions, so they provide functions useful to the survival and reproduction of life.

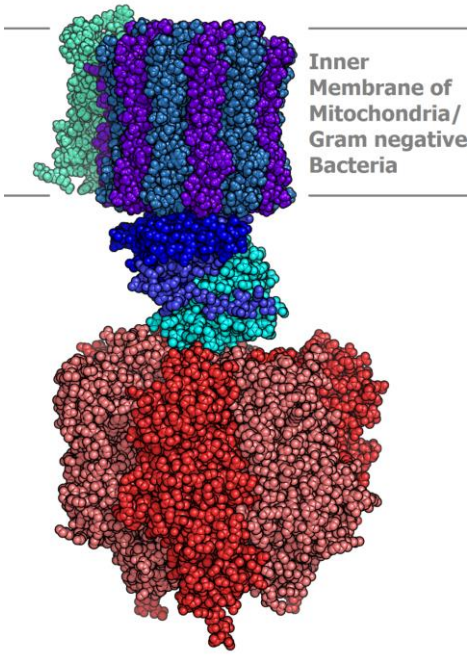
The high energy molecules drive the transfer of electrons from donors to lower energy molecules in a sequence of ***spatially separate*** oxidation reduction reactions moving electron charge from one intermediate to another

Entropic losses are decreased by the use of a sequence of reactions, lessening friction and heat generation in each one of the processes. More energy is then available for other cellular functions. The electrical energy moving in the electron transfer chain is ultimately provided to ATP synthase Fig. 3 in the form of currents of protons.

Electrons moving from one location to another form an electron current whether those electrons flow in a mitochondrion or Kelvin's submarine cable or in anything else. Electron currents have been analyzed by Kirchhoff's law from before the discovery of the electron because the law gives a simple successful description of what is seen in experiments.

ATP-synthase. Protons eventually drive the synthesis of ATP in the extraordinary enzyme ATPsynthase shown in Fig. 3. ATP synthase is not mechanically linked with the electron transfer

Structure of ATP-Synthase



Proton H^+ Currents

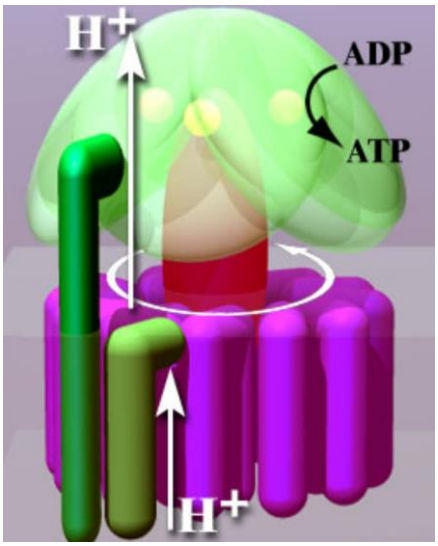


Fig. 3 showing the structure and proton H^+ currents in ATP-Synthase. The proton movements drive the synthesis of ATP from ADP by the rotation of electrostatic turbine. The current flow of protons H^+ can be analyzed—as can any other current— by Kirchhoff's current law and its generalizations because they are corollaries of the Maxwell-Ampere law of electrodynamics. The corollaries are derived without physical models or mathematical approximations. In particular, the current flow of protons H^+ through ATP-Synthase obeys the HHK equation (1) in a short system with a single transmembrane potential. In a short structure like a mitochondrion, the sum of that current and all other currents is zero: everything that flows in, flows out.

complexes. It does not share conformation changes or oxidation reduction (redox) metabolites like NADH for FAD. Rather, ATP synthase is an electrical turbine that uses the flow of protons to perform rotational catalysis. Electrical analysis is needed to analyze the flow of charges like protons from elements of the electron transport chain to ATPsynthase. The flow of charge is the current of Kirchhoff's law.

Rotational catalysis is performed in ATP synthase as the gamma subunit of the synthase spins in a revolving cycle of conformation changes. The rotation allows a different subunit (beta) of the synthase to position the substrates ADP and inorganic phosphate so they can react. The substrates join ('condense' in chemical language), forming ATP. **The mechanical energy of the rotation drives the synthesis of ATP.** The mechanical energy is derived from the flow, i.e., current of protons. The ATP is released when the beta subunits reach their open conformation.

ATP synthase can be viewed as an electrostatic counterpart of the DC electromagnetic motor of our technology. Permanent charges of the synthase play roles rather like the permanent magnetic stators of DC motors. They are structural catalysts that do not directly contribute energy to the process but make it happen nonetheless.

Protein Complexes of the Respiratory Chain. We now turn to a brief discussion of the individual protein complexes [6, 86, 87, 92]. The discussion and figures are meant to show that **electron and proton currents are also the language used in the existing (experimentally oriented) literature of the respiratory chain.** Electron and proton currents are important inside each component of the respiratory chain, as well as in the conjunction of their currents shown in Fig. 1. The conjunction of currents drives the ATP synthase as shown in Fig. 2. It seems appropriate to use the well-established Kirchhoff law of current flow to describe the charge movement that is so well illustrated in the experimental literature.

The charge movements of the respiratory chain arise in different locations. They interact and sum to create the net flow into ATP synthase as shown in Fig 3, Panel B. The flows combine according to specific physical laws, e. g., the HHK eq. (1). Those laws include currents driven by diffusion and electrodynamics as well as electrostatics and chemical reactions.

The role of electrostatics in the respiratory electron transport chain is increasingly recognized. References [93-96] can serve as an introduction to that literature. But the literature seems not to describe the transport of electrons, protons and charge as currents satisfying the Kirchhoff current law. As [96] puts it when dealing with one crucial part of the respiratory chain, "Although the existence of the coupling between the electron transfer and the proton transport (PT) is established experimentally, its mechanism is not yet fully understood at the molecular

level". This paper shows that much useful analysis is possible using the laws of current flow ***without*** full understanding at the molecular level. Circuit analysis can exploit the properties of current flow without understanding the details of the underlying charge movements. Similarly, motion of every atom is not needed to understand many of the properties of the electrical and electronic circuits of our technology. The motion of every atom is not needed to understand the mechanism of action potential propagation. Analysis of the electron transport chain may benefit from this type of approach. Such an approach is feasible [12].

The respiratory chain. Fig. 2 shows the role of current in the entire respiratory chain. The figures in this paper show that each component of the respiratory chain involves current flow. These figures, taken from the existing public domain literature, are chosen to vividly illustrate the importance of current flow. The figures are not my original contribution beyond ref. [12]. They are here to show that the idea of flow already permeates the literature. The contribution of this paper is to say those flows can be analyzed by Kirchhoff's law and its generalizations. Kirchhoff coupling provides an important mechanism correlating the function of the protein complexes of the respiratory chain. That mechanism cannot be analyzed without dealing with current laws because too many charges are involved to allow practical use of Coulomb's law, Gauss law, or the Poisson equation.

On-line videos provide particularly vivid (and beautiful) illustrations of the flows of electrons, protons, and charged groups. See particularly those of the BioVision group at Harvard, http://biovisions.mcb.harvard.edu/ available at https://youtu.be/LQmTKxI4Wn4?si=ykx4ZJrF9Al4ggP- and https://www.youtube.com/watch?v=LQmTKxI4Wn4 when this paper was written.

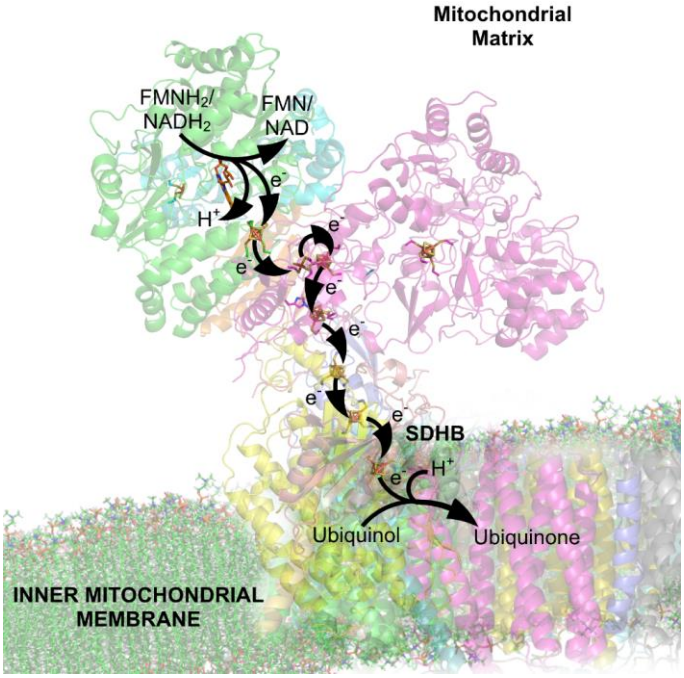


Fig. 4. Complex 1: NADH dehydrogenase. The figure shows the long path for electron currents, >20 Å. FMN and $FMNH_2$ are flavin mononucleotides. NAD and $NADH_2$ are nicotinamides. SDHB is a subunit of succinate dehydrogenase. The intramolecular flow of electrons obeys (quantitatively) the Maxwell Equations, including the generalized Kirchhoff current laws and thus depends on other pathways for current flow. The HHK eq. (1) and Fig. 2B. That dependence is not evident in classical expositions in the chemical tradition.

Complex 1 is an NADH dehydrogenase [97] that transfers two electrons from NADH to a lipid-soluble carrier, ubiquinone p. 835-837 of [86, 98-100], see Fig. 4. The reduced product flows through the membrane according to the laws of electrodiffusion in a coupled reaction, described in detail in the literature. Complex 1 moves four protons (H^+) across the membrane, producing a proton flow that will be later used to generate ATP, mostly through ATP synthase. Each transfer and flow are an electrical current that can be analyzed by electrodynamics, using Kirchhoff's current law. Currents on this scale have been analyzed this way in ion channels for a long time: the structures in ion channels that control current flow are often only a handful of angstroms long.

Verbal Description of Kirchhoff Coupling. The HHK eq. (1) provides the information needed to understand the interaction of currents by Kirchhoff coupling. A verbal description of the

implications of the equation may also be helpful: The potential in the mitochondrion adjusts itself so all the currents that flow into the mitochondrion also flow out. There is nowhere else for the currents to go. The current through one component of the electron transport chain will thus interact with the current of any other component, because of electrodynamics, independent of chemical interactions.

It is important to remember that this ***Kirchhoff coupling is independent of the nature of the current flow. It only depends on the current itself***. Of course, the Kirchhoff coupling does not conserve the flux of individual ions. All the current that flows in must flow out. It is NOT true that all the flux of a particular chemical species that flows in must flow out. Or more precisely, Kirchhoff's law does not guarantee that. Different time scales and different transport proteins are involved in the processes that eventually balance out the fluxes. Other laws and equations are needed to describe the accumulation of particular chemical species. Kirchhoff coupling occurs on all time scales however fast (when true current is used). At any instant, the total true current that flows in flows out, as long as the word current includes displacement current. The Maxwell generalization of Kirchhoff's current law holds at any instant of time. It is not an average or integral law. It is true on any time scale, no matter how fast, that the Maxwell equations themselves are true.

In contrast to current, flux does accumulate on a range of time scales. Flux accumulation may take a very long time. All the flux flowing in may not equal the flux flowing out on many important time scales. The flux laws are integral laws that are true when integrated over long enough times, in contrast to the current laws which are 'instantaneously' true. The fluxes usually eventually balance out. They are often driven by separate mechanisms not considered here. The mechanisms considered here do not balance out the integrated fluxes. Of course, the mechanisms of the action potential also do not balance out the integrated fluxes. After one action potential, there is more sodium and less potassium concentration inside the nerve than before the action potential. A separate mechanism, the Na-K ATPase, eventually restores the concentrations.

The classical chemiosmotic hypothesis [93-95, 101-105] does not deal with the balance of currents but uses diffusional and chemical interactions. As just explained, the balance of

currents is instantaneous occurring on the fastest time scales; the diffusional and chemical interactions may be slow, in principle, even slower than the time scale of ATP formation by ATP synthase.

Kirchhoff coupling has many names. All are logically equivalent descriptions of the HHK equation (1). I list some here because experience shows that different names are used by different scientists, who may not realize they are all equivalent, i.e., they describe the same HHK equation (1).

1) One current is driven by the sum of the other currents.
2) Currents are correlated.
3) Currents interact.
4) The cause of one current is the sum of the other currents.

Short and Other Structures. The discussion applies to current flows in a short structure like a mitochondrion. If the components of the electron transport chain are not in a short structure, interactions will be different. In particular, if the components are in a lipid bilayer, with a controlled voltage across the bilayer, the currents of the components will not sum to zero. Currents will not interact by electrodynamics and so results will be different from results measured in a mitochondrion.

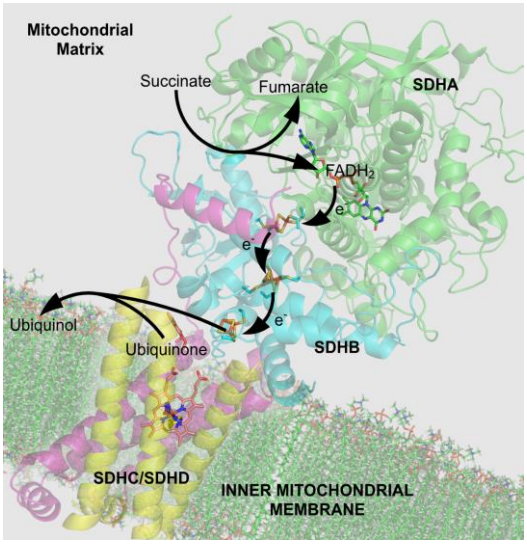


Fig. 5 Complex 2:succinate dehydrogenase complex SDHC, Notice the long pathway for electron transfer and current flow that must be described by the Maxwell equations for current flow including the HHK eq. (1). The current flow will interact with other flows in the system and so be different in measurements from isolated systems compared to mitochondria.

Complex 2 (Fig. 5) includes succinate-coenzyme Q Reductase [106] and participates in both the citric acid cycle of cell metabolism and the electron transport chain. Only electron flow occurs in this complex. Proton flow is not involved. Complex 2 contains a succinate-binding site and ubiquinone-binding chain of oxidation reduction (redox) centers that extend over 40 Å providing an extended path for electron flow often called electron tunneling. The extended path may be partially within the electric field of the membrane. The electrical potentials driving electrons down that path are not clearly stated in the literature that we are aware of. Are those potentials the potential inside the mitochondria or outside the mitochondria, or some combination? What specifies the combination if it exists? Obviously, the amount of electron transport (i.e., current) will depend on the potentials driving the current through chain of redox centers.

It should be clearly understood that the Maxwell equations—and the corollary current laws—apply to all current flow and thus electron transfer, whether by tunneling along an iron sulfur (Fe-S) chain or any other mechanism. See Appendix. The current laws are true independent of the electrical potentials driving them, just as the Kirchhoff law of currents in circuit analysis is true whatever the Kirchhoff voltage law says about the electrical potentials. The current laws of Maxwell remain valid in the quinone transfer chain just as they are in the delocalized electron orbitals of the wires in our computer circuits. They remain valid within the chemical domain described by the Schrödinger equation as shown in the general gauge invariant derivation in [22, 23, 36].

The movement of electrons will interact with other current flows across the mitochondrial membrane according to the HHK eq. eq. (1) as discussed at length previously because that equation is a corollary of the Maxwell equations themselves.

It is important in actual practice that ***current laws do not depend on the description of individual charges.*** It may be much easier to determine currents than charge flow in the various models of super complexes [107]. Interactions thought to depend on exact atomic geometry may well arise simply from the interactions enforced by the HHK equation (1). That is in fact how currents in general interact in circuits, as explained in detail in Ref. [72], Fig. 2. Note again that measurements in isolated systems will give different results from those in mitochondria.

Complex 3 (Fig. 6) has many names coenzyme: Q : cytochrome *c* — oxidoreductase and cytochrome bc_1 complex. It adds electrons to cytochrome c and moves two protons across the membrane while releasing two other protons from ubiquinol as discussed in [108]

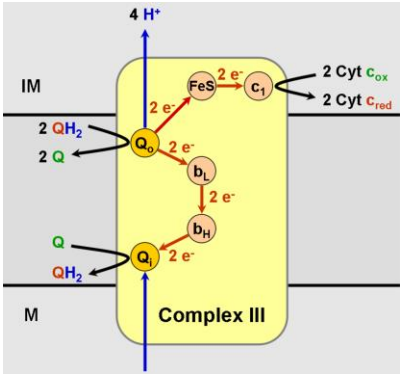


Fig. 6: Complex 3, also known as Coenzyme Q. The coenzyme transfers 4 protons long distances as shown by the vertical blue arrows and so provides an electrical current described by Kirchhoff's current law. The current depends on all the currents across the mitochondrial membrane as shown in HHK eq. (1). Q is the ubiquinone form of CoQ, and QH_2 is the ubiquinol (dihydroxyquinone) form. Substates in circles are identified as parts of the Q cycle. FeS is an iron sulfur protein. Q_0 and Q_i are ubiquinol (QH_2) and ubiquinone (Q), binding sites respectively. b_L and b_h are heme groups and c_1 is the cytochrome binding site.

Complex 4 (Fig. 7) also known as cytochrome c oxidase is a protein complex containing many subunits. The complex contains two hemes, a cytochrome a and cytochrome a3, and two copper centers, the CuA and CuB centers. It is a cathedral of atomic design of great biological importance and so has been studied extensively [109, 110] for a long time [111]. It has been modeled with powerful techniques in the chemical tradition using master equations [99, 100] and with variational methods of the theory of complex fluids [12] (pioneered by Chun Liu [83, 112]) applied to complex biological structures [113]. The approach advocated here and attempted in [12], buttresses the master equations of [99, 100] with the universal laws of current flow.

Cytochrome c oxidase is the last enzyme complex in the electron transport chain which delivers protons to ATP Synthase, see Fig. 2. Cytochrome c oxidase is where the electron transport chain delivers electrons to oxygen (from cytochrome c), yielding two molecules of water (H_2O). The complex transfers four protons across the membrane. Both electron and proton flows are currents that follow Maxwell equations and current law, e.g., the HHK eq. (1).

Fig. 7 is drawn without conformation changes because "cytochrome c oxidase … seems to work almost purely by Coulombic principles without the need for significant protein conformational changes" [110].

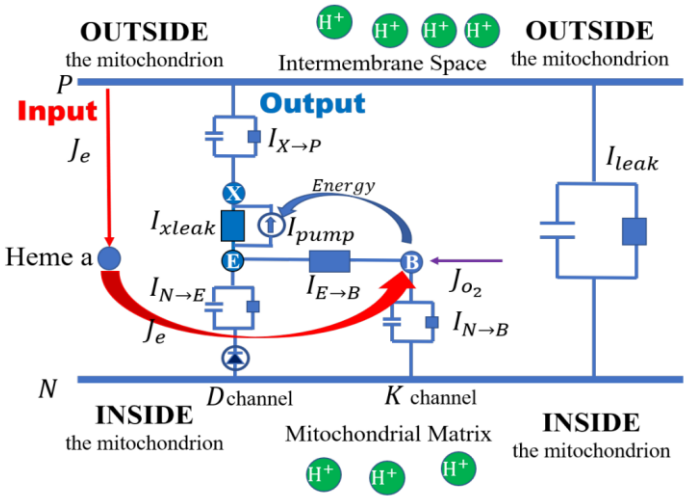


Fig 7: Complex 4. An oversimplified but possible model of cytochrome c oxidase and associated current flows: symbols defined and explained in text and reference [12].

The circuit in Fig. 7 is drawn to show the minimal circuit complexities needed to deal with the main function of cytochrome c oxidase, namely generation of proton flow. Important chemical details are found elsewhere in the literature [110, 114, 115] . The experimental literature provides experimental details that exceed what is needed to describe electrical properties and current flows. Of course, one of the advantages of the circuit approach adopted in this paper is that it rarely needs atomic detail. Atomic detail is not often needed in descriptions of electronic circuits of our computers. Atomic detail was not used by Hodgkin and Huxley [11, 49] to compute the propagating action potential of nerve fibers. However, some atomic detail is needed on occasion. Fig. 7 will surely need additional detail to deal with the wealth of experimental data available.

A circuit analysis of Fig. 7 has been completed [12] which includes description of all chemical reactions shown in the figure. The constraints of the HKK equation (1) are built into the model itself and include the role of the membrane capacitance in the circuit shown. ***The analysis allows prediction of any current for any input conditions of interest.*** More than forty graphs are shown in [12] to show the utility of this approach.

A serious limitation of this kind of model is its lack of detail in describing the switch that prevents backflow [93, 94]. This issue is central to all models of active transport [93, 94, 100, 114-116], including our own: conformation change does not, in my view, explain the mechanism because it is not based on ***physical*** properties of the protein and its structure. The description 'conformation change' does not permit quantitative predictions in a range of experimental conditions, in contrast to the predictions in a wide range of conditions made by the rest of the electro-osmotic model [12]. in my view, theories of protein structure need to be extended to deal with protein conformation in a physically consistent manner: molecular dynamics must be extended to deal with the electric field more realistically to solve this problem. Molecular dynamics today uses periodic boundary conditions and these seriously distort long range electric fields and flows. Work has started in that direction [117-119] although it has not included Maxwell current laws, as far as I know. Maxwell current laws have been used to analyze the near switching ('gating') behavior of the voltage sensor of sodium channels [120-123]. Gates that activate and inactivate can provide the switching needed in transporters [124-126].

It is important to realize that the switch involved in all these transporters is in essence an extreme form of rectification. Rectification occurs in any fixed charge system when the charge changes sign. This is the mechanism of **PN** diodes that underly the behavior of transistors. The

shape of the electric field changes when the diode is forward biased or reverse biased. The rectification allows current flow or not because it includes a large potential barrier or not. These barriers and this rectification do not depend on any significant change in the spatial distribution of mass, i.e., they do not depend on conformation change in the normal sense of the word as used in protein chemistry. Rather it depends on the change in the spatial distribution of the electric field, i.e., it depends on the conformation (i.e., the shape) of the electric field, without violating the dictionary meaning of the word 'conformation'. This issue is discussed at length in [12] which includes an historical perspective as well. Switching of this sort has been seen in ionic systems. using a biological protein as a template [127] and is now found in nanotechnology [128] and even in practical technological applications [128-130] .

DISCUSSION

Electron transport is electrical current, as is proton transport and the transport of metabolites like NADH and FAD. In particular, electron transport in a quinone chain remains a current, rather like electron transport in the delocalized electron orbitals of wires of our technology.

Electric current has properties of its own that make analysis of charge transport quantitative and at the same time much easier than in classical chemiosmotic theory. The paths for electrons form circuits for currents and can be analyzed that way, just as paths for electrons in wires are analyzed by classical methods of circuit theory.

The chemiosmotic theory brought electricity into view as an essential part of respiratory metabolism [93-95, 101-105]. In that theory, proton **motive** force and the electron **transport** chain emerged as central players in ATP synthesis. Together they provide the proton **flow** that powers ATP synthase as it generates ATP (Fig. 2). The bold-faced words of the last sentences show the importance of movement in respiratory metabolism and the chemiosmotic hypothesis itself. The figures of this paper were chosen from the existing experimental literature to show flow inside each component of the respiratory chain in detail. The flows culminate in the proton flows (shown in Fig. 2B) that sum to drive ATP production by ATPsynthase. The figures are taken from public domain sources to emphasize the widespread acknowledgement of the importance of flow. The cited videos are even more eloquent in that regard.

History. Movement seems, however, to have been overlooked in the ***analysis*** of the respiratory chain in contrast to its role in visualizations of models. Movement is shown vividly in widely available figures, as reproduced here, and videos emphasize it. But the movement seems not to have been analyzed. A chemiosmotic theory that does not include current has been used when an electro-osmotic theory including current was needed to analyze the models with their visualizations of transport.

Electro-osmotic theory is needed because moving charge creates an electrical current subject to its own rules beyond that of conservation of matter. The total current across the total mitochondrial membrane must sum to zero at any time, however short, according to the HHK

equation (1) and the Maxwell equations. Integrated over long time scales, the fluxes of chemical species also add to zero. But ***the fluxes of chemical species do NOT have to sum to zero on a short time scale***, e.g., that of ATPsynthase, as we have discussed.

Electrons were recognized as the current carriers of classical electrodynamics, in wires, for example, ever since electrons were discovered [131, 132]. Electrons in the electron transport chain play the same role. (The role of true (total) current was well understood by Maxwell, long before the discovery of the electron, interestingly enough [24, 25]) The special properties of current are described in equation **A** of the Maxwell equations [21], p. 465. The Kirchhoff laws of current flow were known before that [23]. They were used extensively, for example in the design and use of telegraphs almost two hundred years ago. The current laws, however, receive little emphasis in many texts of electrodynamics today. The Kirchhoff current law is not included in the index of the broadly cited advanced text [133] or the widely used introduction [2]. Zangwill's modern advanced text [3] presents Kirchhoff's current law on p. 524 in a form that contradicts the continuity equation presented on p. 32 as discussed in [134].

It is unclear why the rules of current flow have been neglected in texts of electrodynamics. That neglect makes it easier to understand why the rules of current flow have also been neglected in the study of the electron transport chain of mitochondria

Maxwell Equations are Difficult Constitutive Equations. The classic form of the Maxwell equations involving the $\mathbf{D}$ field are hard to understand [4]. Experimental data shows that the use of a single dielectric constant in the classical Maxwell equations cannot deal with the movements of charge in the ionic solutions of life in references cited previously [135, 136]. See Appendix for further discussion and documentation.

The relevance of the classical Maxwell equations to biological systems is obscure, because they involve an over-approximated dielectric approximation. The classic Maxwell equations are then easy to ignore. This seems to have been the case in the chemiosmotic theory. The dielectric approximation used in the definition of $\mathbf{D}$ is obviously unable to deal with the various forms of charge movement in proteins. The hierarchies of structures that make proteins involve an enormous range of motions from angstroms to microns. The resulting

charge movements cover a vast range of times, from femtoseconds to seconds, to minutes. A single dielectric constant obviously cannot describe such the variations of charge density when proteins respond to the electric field and polarize [135, 136]. In fact, the idea of polarization itself has been severely criticized as ill posed in a text by a Nobel Laureate, see the Appendix.

The classical form of the Maxwell equations cannot deal with this range of phenomena (with a single dielectric constant) because the classical Maxwell equations are in fact constitutive equations that depend on constituents [137]. Constituents vary, so the classical form of the Maxwell equations vary. They are not universal.

The dielectric approximation is nonetheless an important teaching tool and a necessary approximation for models investigating new phenomena or seeking a low-resolution understanding. It is widely and appropriately used for that reason. But the dielectric approximation must be used with care, and treated as the over approximation that it actually is.

Electrodynamics as a universal theory of everything electric emerges when the dielectric approximation is replaced by core Maxwell equations [4] and an explicit model of polarization [4, 10]. When core Maxwell equations are written, they do not include material constants and are universal in that sense. What is not apparent, or at least was not to me for a long time, is that core Maxwell equations could be useful as well as universal.

Why should equations that do not specify specific properties of polarization and dielectrics be of any general use, when everything that the equations describe have specific (and often diverse) dielectric properties? The answer to this question lies in the current laws implied by the core Maxwell equations.

The current equations are both universal and useful because they are corollaries of the Maxwell equations that do not depend on the properties of matter. They only depend on the electrical and magnetic constants, or speed of light. Because they are universal and as exact as any known physics, the currents laws serve as the basis of our electrical and electronic technology.

The current laws are derived by applying the divergence operator to both sides, the Maxwell-Ampere law. Then, a universal current law appears [4] that is useful everywhere and

does not depend on dielectric properties or polarization in any way. The key property then depends only on mathematics: the divergence of the curl on the left-hand side of the Maxwell-Ampere law is always zero. The divergence of the right-hand side (which defines total current) is also zero. The total current does not accumulate because it has zero divergence. Maxwell clearly understood that his total 'true' current does not accumulate, ever, anywhere, at any time, according to his field equations [21, 22, 24].

Current laws derived from the Maxwell equations are helpful [138] as well as universal [4]. The Kirchhoff current law (and its generalizations) has been used innumerable times to design the electrical and electronic technologies of human technology, since more or less 1850, and of course, in the digital technology we rely on today. In a very practical sense, Kirchhoff's current laws are the most used application of electricity, because billions of people use computers every day and each computer contains billions of circuits designed with those laws. All the more surprising that the word Kirchhoff does not appear in the beautifully sculpted introductory electrodynamics text by Griffiths [2] the widely used treatise of Jackson [133].

It is clear that all theories of ion movement must satisfy the core Maxwell equations and the current laws that are corollaries of the core Maxwell equations. Modern science does not allow vitalist exceptions, even when complex biological structures perform vital functions, like generating ATP in mitochondria and chloroplasts. In fact, this paper shows that universal current laws simplify the analysis of such complex biological structures, much as they simplify the analysis of complex engineering structures in our digital technology [36].

Current laws do not fully describe systems like the electron transport chain of mitochondria until they are combined with the rate constant laws showing how substrates and chemical reactions combine with each other. No doubt, the classical laws of chemical reactions oversimplify the dependence of their rate constants on electrical potentials [70]. That issue remains to be dealt with in future work [139].

Current laws have been combined with classical descriptions of chemical reactions to compute the properties of cytochrome c oxidase [12]. Diffusion, convection and electrical migration were combined using the theory of complex solutions and its variational approach.

One can hope that similar methods will be useful in understanding the respiratory complex in general, as it uses electron transport to create proton flows in the protein complexes of mitochondria, as the proton flows create ATP in the exquisite machine of ATP synthase.

Acknowledgement

I am most grateful to the anonymous authors and artists who made the figures reproduced here. I have made no contribution to the figures and the work summarized, except ref [12].

The figures document the importance of electron and proton flow in the thought of experimentalists working on the chemiosmotic hypothesis, over many decades. The figures in this paper are taken from public domain websites with changing URL (universal resource locator) where authorship is rarely given. The websites allow copying as best I can tell. If I have inadvertently failed to give proper attribution, I will make corrections, and of course apologize.

The paper was significantly improved by many suggestions of Ardyth Eisenberg, who has contributed so much to my life beyond these words.

Appendix

Polarization in the Maxwell Equations

The Maxwell equations as ordinarily presented are constitutive equations that depend on the properties of materials in a particular approximation. They represent the polarization response of material to a change of electric field in a dielectric approximation that is severely criticized by a Nobel Laureate [140], who says on p.507, "This example teaches us that in the real atomic world the distinction between bound charge and free charge is more or less arbitrary, and so, therefore, is the concept of polarization density $\mathbf{P}$."

The difficulty with polarization can be seen by purely mathematical arguments as discussed at length in [4]. An extract (lightly edited) is included here so this paper is complete in itself: "The ambiguity in $\mathbf{P}$ in the Maxwell differential equations means that any model $\mathbf{P}_{\boldsymbol{model}}(x, y, z|t)$ of polarization can have $\mathbf{curl}\ \tilde{\mathbb{C}}(x, y, z|t)$ added to it, without making any change in the $\mathbf{div}\ \mathbf{P}(x, y, z|t)$ in the Maxwell version of Gauss' law. In other words, the polarization $\mathbf{div}\ \mathbf{P}(x, y, z|t)$ does not provide a unique structural model of polarization $\mathbf{P}_{\boldsymbol{model}}(x, y, z|t)$. In particular a model drawn from an atomic detail structure can be modified by adding a polarization $\widetilde{\mathbb{P}}(x, y, z|t) \triangleq \mathbf{curl}\ \tilde{\mathbb{C}}(x, y, z|t)$ to its representation (i.e., 'drawing') of polarization without changing electrical properties at all: $\mathbf{div}\ \mathbf{P} \equiv \mathbf{div}\left(\mathbf{P} + \widetilde{\mathbb{P}}\right)$.

Models of the polarization $\mathbf{P}^{\mathbf{1}}_{\boldsymbol{model}}$ and $\mathbf{P}^{\mathbf{2}}_{\boldsymbol{model}}$ of the same structure written by different authors may be strikingly different but they can give the same electrical forces and fields. Misunderstanding and unproductive argument result: "what is the true description of a dielectric object (e.g., protein)?" is a question likely to arise and be unanswerable if the polarization field $\mathbf{P}$ is itself not unique. If the field cannot be defined mathematically, polarization is unlikely to be productively definable by words.

Obviously if polarization $\mathbf{P}$ is an arbitrary idea [4], so are equations like the classical Maxwell equations that embody $\mathbf{P}$.

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