

# **Mass Action and Conservation of Charge**

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*January 19, 2015*

*File name: "Mass Action and Conservation of Charge January 19-1 2014 .docx"*

## Abstract

Electronic technology has remade our world in fifty years, increasing capability by factors of billions, unprecedented in human history. Electronics depends on models that precisely represent its devices and circuits. Circuit models are robust and work well over a wide range of conditions without changing parameters.

Circuit models are based on the laws of electricity, conservation of charge, and Kirchoff's current law: current flow is exactly the same everywhere in a series of devices (with two terminals, like diodes or ionic channels). Interruptions anywhere stop current everywhere, even far away.

Chemical and biochemical models have been built on conservation of matter, expressed as the law of mass action, with constant rate constants. Chemical and biochemical technology has made striking progress by making compounds, not so much by making devices.

Device design in the chemical world is difficult because the rate constants of the law of mass action change from one set of conditions to another. The law is not robust in most cases and cannot serve the same role that circuit models do in our electrical technology.

The law of mass action does not conserve charge, as is clear from the math: Consider  $X \rightleftharpoons Y \rightleftharpoons Z$ . It is easy to show that  $I_{XY} - I_{YZ} \neq 0$ , rather  $I_{XY} - I_{YZ} = z_X k_{xy} F[X] - z_Y k_{yx} F[Y] - z_Y k_{yz} F[Y] + z_Z k_{zy} F[Z]$ . The Appendix identifies special symmetrical cases in which charge is conserved. It also evaluates consequences when charge is not conserved.

Variational methods have only recently been developed to ensure that charge is always conserved along with mass in dissipative systems like ions in solution or proteins. The Energy Variational Approach **EnVarA** developed by Chun Liu, more than anyone else, should allow the development of robust models of chemical, biochemical, and biological systems.

I believe robust models and device designs in the chemical world will not be possible until the law of mass action and Kirchoff's current law are embedded together in a consistent variational model of energy and dissipation.

Scientific laws are sometimes vague, sometimes precise. Scientific laws are often residues of revolutions that once gave us new knowledge of the world around and within us. It is easy to continue to use scientific laws uncritically even after they have been overtaken by new knowledge. Scientific laws are usually learned early in our careers before we have refereed grants and papers, before our critical skills are honed.

**Conservation of Charge and Conservation of Mass.** I write to discuss two scientific laws: conservation of charge, and conservation of mass.

Both conservation principles seem precise laws of science and in historical context they certainly once were precise laws, not vague residues of previous revolutions. Both laws are so widely used that they might be called foundations of their fields: chemistry and physics. Ionic solutions must satisfy them both.

Chemistry uses mass conservation almost everywhere, in the form of the law of mass action (derived using conservation of mass in eq. (1)–(4) below). The law of mass action helps design, build, and understand new molecules, the main goal of classical chemistry. It is less useful when the goal is to interact and pass signals to the macroscopic world.

Physics uses conservation of charge everywhere it deals with electricity. Conservation of charge implies Kirchoff's current law, as shown in textbooks [29, 56, 104] for the general case including displacement current. Displacement current is "Maxwell's extension of Ampere's law" (p. 521 of [57]) needed to describe the source of the magnetic field. Maxwell's extension allows light to propagate in a vacuum. Kirchoff's current law says the flow of charge is continuous, without loss in circuits. Current is exactly the same everywhere in a series of two terminal devices. Interruption of current anywhere in a series circuit interrupts current everywhere, even signals far away.

The main interest of electrical engineering is signals. Electrical engineering makes continual use of Kirchoff's laws. Kirchoff's laws allow the robust calculation of electronic devices that behave in one way, with one set of parameters, over a range of conditions. Without Kirchoff's laws, we would not have integrated circuits or digital devices. We would not have computers, smartphones, and the video devices that have remade our world. These devices operate at very high speeds with electrical potentials changing volts in  $10^{-9}$  sec. Devices operating at these speeds could not be described with one set of parameters without Maxwell's extension of the idea of current. Every time we turn on our smartphones or televisions, we depend on the properties of displacement current.

**Biological systems involve both chemical reactions and charge** in their devices. Biological systems are always embedded in ionic solutions, and nearly always involve chemical reactants and enzymes with electrical charge. Substrates of reactions catalyzed by enzymes are usually charged and are always embedded in solutions containing the 'bio-ions'  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  and involving  $\text{Ca}^{2+}$ , often as a variable that turns biological function on or off.

We face a problem when we try to apply both conservation laws and mass action laws together. The laws conflict.

**My goal** is to replicate the success of electronic models in chemistry, biochemistry, and biology. The goal is to produce robust theories (or simulations) of signals in chemical reactions in ionic solutions that successfully use one set of parameters in a range of conditions, and include the global properties of the electric field. My goal is to produce models of signals in electrochemical

devices and technology as robust as those of electronics. I believe that goal can only be reached after the law of mass action is extended to embed Kirchoff's current law.

**The Law of Mass Action** has been a keystone of classical chemistry. It was developed to deal with isolated systems, originally with perfect gases in mind [4, 40, 77, 87, 90], and allowed chemists to deal with molecular and atomic reactions before physicists were convinced that atoms existed. The law of mass action helps chemists build molecules of great use and importance.

But **isolated chemical reactions must make contact** with the outside world to pass signals and interact with it, just as electronic systems make contact with the outside world and pass signals through inputs and outputs. Biological systems make contact with surrounding solutions and cells through ion channels and transporters. **The law of mass action was not designed to contact the outside world.** It was designed to help chemists build and understand individual molecules. Signals and connections with the outside world almost always involve electricity because charge flows through the contacts that connect chemical reactions with the outside world

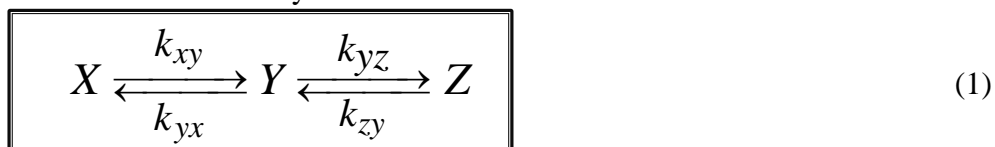
Engineering deals with systems that are not isolated. Its devices contact the world through power supplies. Devices have outputs that follow inputs according to simple rules, for example, the output of an amplifier follows the input according to the gain. The input output rules are derived from Kirchoff's current law and conservation of charge.

Biology deals with systems that are not isolated. They usually have inputs and outputs and are driven by concentration gradients that are power supplies. Biological systems interact with surrounding solutions, cells, and tissues.

I argue that the law of mass action must be extended to deal with inputs and outputs and electrical charge if theories and simulations of nanodevices (technological or biological) are to be useful in more than one set of conditions.

**'The Law of Mass Action does not conserve charge'** seems an unlikely statement and so mathematical proof is desirable before verbal discussion. The essential issues can be shown in a simple case using high school algebra and a little calculus.

Eq. (1) shows the reactions we analyze.



Reactions are written as differential equations in eq. (6) with symbols defined below.

The rate constants are taken as constants and thus of course are independent of each other. If the law were robust, the rate constants found experimentally under one set of conditions would be found under another set of conditions. Such is sometimes the case, but not very often.[21, 22]

Generalizations of rate constants are sometimes made but as we discuss below—in the section **How to extend the law of mass action?**—the generalizations common in the literature do not allow the law of mass action to satisfy Kirchoff's current law in a general global way. The global nature of the electric field (illustrated in Fig. 2 and its discussion) allows remote devices and boundary conditions to change local atomic flows. Indeed, interruption of current in a series

circuit stops current everywhere, even far away. These global realities of the electric field have not been dealt with in the generalizations of the law of mass action in the literature, as far as I can find. Of course, there are special cases in which chemical reactions described by the law of mass action can conserve charge at least approximately and those in fact may be the ones where it has proven most quantitatively useful. A number of those are identified in the Appendix, eq.(10)-(12).

**PROOF.** The **current** flow in the reactions of eq. (1) is easily shown to be

$$I_{XY} = Fz_X \cdot k_{xy} X - Fz_Y \cdot k_{yx} Y \quad (2)$$

$$I_{YZ} = Fz_Y \cdot k_{yz} Y - Fz_Z \cdot k_{zy} Z$$

Units for net current<sup>†</sup>  $I_{XY}$  are (cou/liter)/sec = cou/(liter sec). Units used for unidirectional flux  $J_{xy}$  are (moles/liter)/(sec) = moles/(liter sec), fluxes are used in equations presented later. Units for rate constants units are (moles/(litersec))/(moles/liter) = 1/sec. The valences (i.e., charges) on each reactant are  $z_X$  or  $z_Y$ .  $F$  is Faraday's constant.

It is clear that  $I_{XY} \neq I_{YZ}$ . In general, Kirchoff's current law is violated:

$I_{XY} \neq I_{YZ}$ , for a range of concentrations, rate constants, or charges.	(3)
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**Details of Proof:**

The law of mass action states that the unidirectional flux  $J_{xy}$  can be computed in two ways

$$J_{xy} = \frac{d}{dt} X \quad J_{yx} = 0 \quad (4)$$

$$J_{xy} = k_{xy} X$$

where we use activity in moles/liter  $\llbracket X \rrbracket$  of ions of concentration  $[X]$ .

**Remark.** Unidirectional fluxes  $J_{xy}$  are conventionally measured by tracers—originally radioactive isotopes, now often fluorescent probes—flowing **into** a zero concentration (of tracer; where the concentration of the substance being traced is not zero in most cases). Note that the activity  $\llbracket X \rrbracket$  depends on the concentration of **all the other ions** in a significant way in nonideal solutions [5, 7, 11, 16, 18, 19, 28, 32-36, 52, 59-62, 64, 66-68, 71, 74, 83, 89, 99, 100, 105]. In nonideal solutions, changes in the concentration of one substance  $[Y]$  change the activity of another substance  $\llbracket X \rrbracket$  and its flow  $X$ .

Almost all biological solutions are nonideal. Ionic mixtures or solutions of biology usually involve  $\text{Ca}^{2+}$  and are significantly nonideal often with activity coefficients of the order

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<sup>†</sup> Unidirectional fluxes use lower case subscripts. Net fluxes use upper case subscripts and are marked with an over-bar. Upper case subscripts are used for currents to emphasize the distinction between net currents and unidirectional fluxes. Note that unidirectional currents are not defined or used in this paper.

0.5, implying that half of the thermodynamic driving forces are nonideal and depend on the concentrations of all ions.

**Back to the proof.** The law of mass action eq. (4) yields the definition of rate constant  $k_{xy}$

$$k_{xy} = \frac{J_{xy}}{X} = \frac{J_{xy}}{\frac{d}{dt} X} \quad J_{yx}=0 \quad (5)$$

Rate equations equivalent to chemical reactions involve **net flux** like  $\bar{J}_{XY}$ . The left hand chemical reaction in eq. (1) can be written

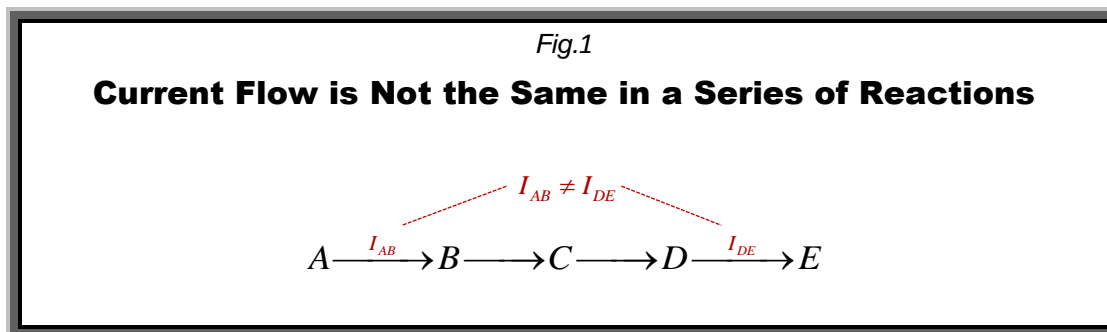
$$\bar{J}_{XY} = k_{xy} X - k_{yx} Y \quad (6)$$

The proof of eq. (2) is completed by writing net fluxes like  $\bar{J}_{XY} = J_{xy} - J_{yx}$  as the difference of unidirectional fluxes and using the proportionality constant  $zF$  between flux and current, to get net current, for example.

$$I_{XY} = zF (J_{xy} - J_{yx}) \quad (7)$$

**This ends the proof.**

Moving on to discuss the results eq. (2) & (3), we see that **continuity of current** (without loss) is violated in most cases with substantial effect (Appendix 1). **The law of mass action conserves charge only under the special circumstances**, shown in Appendix eq. (10)–(12). In these symmetrical circumstances can a series of chemical reactions like those shown in Fig. 1, **have the same current flow in each reaction, if analysis is done by the classical law of mass action eq. (4).**



**Organization of paper.** This paper begins by trying to motivate the treatment of chemical reactions as devices. The properties of charge in between the law of mass action has not been widely discussed, so I use mathematics to show that charge is not conserved by the law of mass action, hoping that this will be more convincing than words. A general discussion follows that is designed to explain verbally why charge cannot be conserved in most cases. The abstract nature of charge is described at considerable length since this crucial idea is not widely known to scientists in my experience. Finally, the Appendix eq. (10)-(12) give symmetrical conditions in

which the law of mass action conserves charge. Asymmetric conditions are shown to produce charge imbalance likely to have noticeable effects.

**Logic of current flow.** Conservation of charge implies that the current is identical in each reaction in the series circuit of Fig. 1, eq. (1), or of Fig. 2: the flow of charge is continuous without loss.

Interruptions anywhere stop current everywhere. If current is forced to be zero in one reaction, it must be zero in every reaction, because Kirchoff's current law says current is the same everywhere in a series.

**'Completing the circuit'** is a necessity familiar to all who have wired up a circuit—the lights on a Christmas tree—even if they do not know the principle 'Kirchoff's current law'. The flow of charge is continuous on all scales because conservation of charge and its movement is true on all scales. Interrupting current on an atomic scale (in a semiconductor diode, or an ionic channel) interrupts current on the macroscopic scale in the inputs and outputs of the diode, or in the solutions and cells connected to the ionic channel.

**Logic of reactions.** In a chemical reaction, rate constants are independent of each other, so interruption of flux in one reaction does *not* stop flux elsewhere in a model of a series of chemical reactions that satisfy *only* the law of mass action. Reactants can accumulate and build up mass in that kind of reaction model. The accumulated mass changes flow in a complex way, different in different systems, that have different constitutive equations.

Accumulated charge is much simpler than accumulated mass. Accumulated charge has universal properties, independent of the nature of the charge. Particle and quasi-particle currents that accumulate at a junction (with sum  $i_{\Sigma}$ ) change the time derivative of electric potential by an invariant equation  $\partial V/\partial t = i_{\Sigma}/C$  (determined by the Maxwell equations). The change in electrical potential carries away a displacement current

$$i_{\text{displacement}} = C(\partial V/\partial t) = i_{\Sigma} \quad (8)$$

This displacement current is *exactly equal to the sum  $i_{\Sigma}$  of the currents flowing into the junction*, and is equal to  $C(\partial V/\partial t)$  without known error, to about one part in  $10^{18}$ . Current cannot accumulate at all if current is re-defined to include  $i_{\text{displacement}} = C(\partial V/\partial t)$ . The redefinition is used in textbooks of electricity and magnetism [29, 56, 104], because the redefined current is the source of the magnetic field.

**Accumulation of charge is special.** The universal and precise linkage between potential change, charge accumulation and displacement current is a special feature of the electric field. No universal precise linkage exists between mass accumulation, rate of change of chemical potential, and flux, for example. The displacement current allows electricity and magnetism to combine into the propagating radiation we call sunlight as it flows through the vacuum between sun and earth.

**Extensions of mass action.** If the law of mass action does not conserve charge it cannot be used to derive robust models that describe charge movement.

In my view, the law of mass action must be extended before it can be included in descriptions of devices that use ions. Ions are always present in biological systems and are often present in chemical systems as well.

Charge movement at power supplies, inputs and outputs are always involved as devices contact the outside world. Charge must be included if a chemical reaction connects to the outside world through electrical inputs and outputs like those used in our engineering technology.

Charge has not been included in chemical reactions in my opinion because the mathematics needed was not available until recently. Mathematics that forces chemical reactions to conserve charge in dissipative systems (like ionic solutions) has been developed only in the last few years as energy variational principles have been developed by Chun Liu, more than anyone else.

**Energy Variational Approach.** The energy variational approach *EnVarA* is defined by the Euler-Lagrange process [27]. generalized by Liu, et al., into an energy/dissipation functional that combines two variations. In this way, *EnVarA* can deal with dissipation (friction) and ionic solutions. *EnVarA* deals with conserved energy using the classical Hamiltonian variational principle of least action described in textbooks of mechanics. *EnVarA* deals with friction using the Rayleigh dissipation principle described in many textbooks of irreversible thermodynamics. When combined, these principles allow energy to be degraded into entropy as flows occur in frictional materials, like electrolyte solutions. Ionic solutions experience friction because an ionic solution is a condensed phase essentially without empty space.

**Skepticism and History:** Most people are skeptical: how has the law of mass action produced such useful chemistry, if it does not conserve charge?

The answer is that chemistry has been interested in making molecules, not signals or charge; and engineering has been interested in signals, and charges, not molecules.

In chemistry the law of mass action has been used build molecules, not to pass signals to or interaction with the outside world. In classical chemistry, the law of mass action has been used as a productive guide to understand and build molecules, but not as an input output relation to understand and design signals and devices.

In classical biochemistry, the law of mass action has been used in a clever and ingenious way to build useful models despite their limitations. A senior biochemist recently told me “The art of biochemistry is to study enzymes in conditions that give insight to biological function, even if the conditions are not just those inside cells. The art is to choose experimental conditions in which biochemical reactions are well behaved and rate constants resemble those in real biological systems, so results are practically useful.”

That is expedient, practical, admirable, and a useful response to human limitations, I think. A scientist should do what she/he can do, even if it is less than what she/he wishes to do.

We turn now to a discussion of charge movement so readers less familiar with electric circuits will know what I am talking about when I discuss current through a vacuum capacitor, for example.

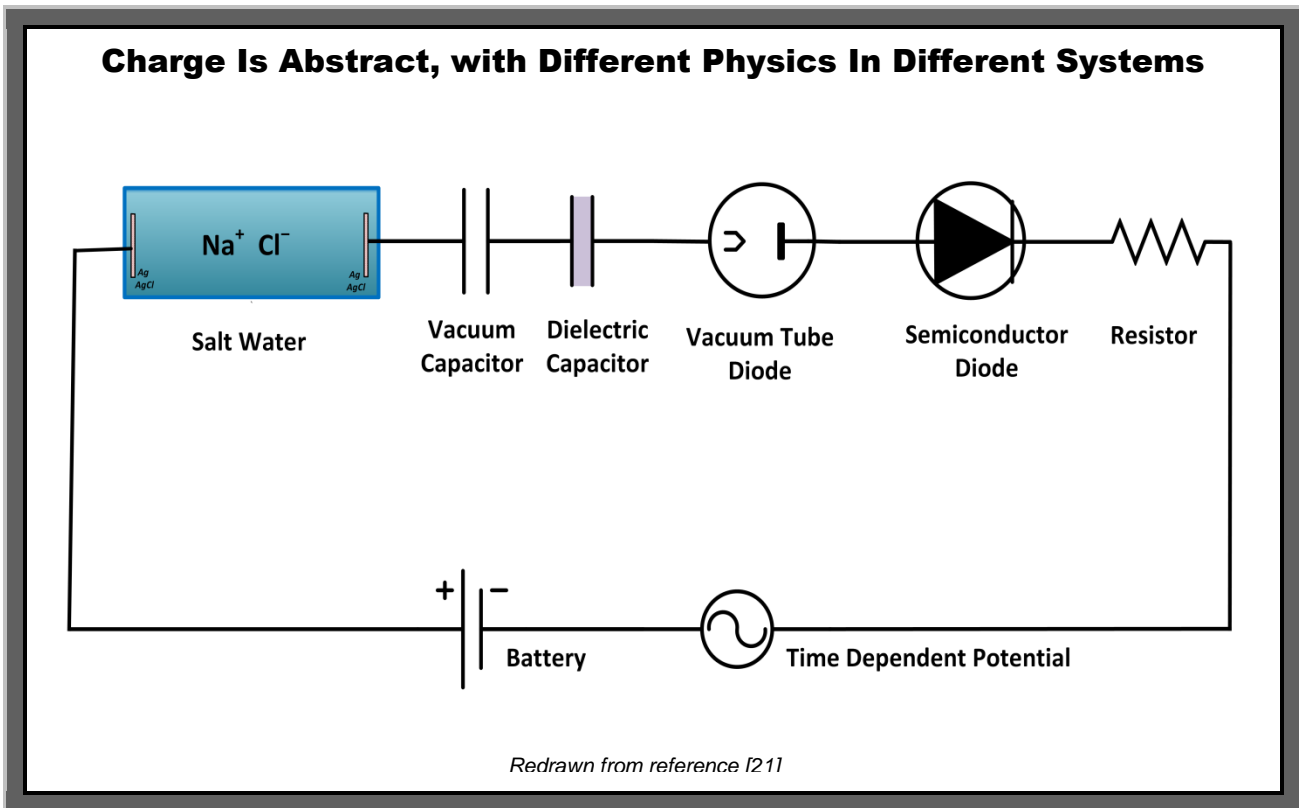
**Charge is an abstraction that is conserved.** Physicists teach that conservation of charge is universally true, exact from very small to very large scales and very small times to very large times.<sup>†</sup> What physicists often do not teach clearly is that charge is an abstract idea.

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<sup>†</sup> Even the Casimir effect of quantum physics [86] is seen as a property of Maxwell's equations by some [53].



Fig. 2



As we examine Fig. 2, we will see that charge in one physical system is quite different from charge in another. Charge flow is **not** simply the physical movement of particles of definite charge (and mass). Charge flow in a vacuum capacitor, in an ionic solution, in a wire are all quite different. Current is not just the movement of ions or electrons or protons.

Many students believe that charge is always carried by particles and so conservation of mass (of charged particles) implies conservation of charge. That is not true. Displacement current is not carried by the movement of particles. [29, 56, 104] Current flow in semiconductors is carried by mathematical fictions called quasi-particles. This is a main result of the study of semiconductors [57, 58] discussed below.

An essential idea of electricity and magnetism as explained in textbooks [56, 104] is that **charge flow is continuous** (without loss) **no matter what the physical nature of the charge**. Fig. 2 tries to show this idea in a concrete way that anyone can build in their lab. It shows time-varying currents in a series of different devices each with different physics and different constitutive laws.

**Ionic Conductor.** An ionic conductor is shown in Fig. 2 as a cylinder containing  $\text{Na}^+\text{Cl}^-$ . Here, current flow (at a frequency say of 1 Hz) is almost entirely the physical movement of charged

particles, of ions, say sodium and chloride ions and follows simple constitutive laws (when concentrations are  $< 2 \times 10^{-2} M$  and flows are not large enough to change concentrations). These ions are hard spheres. The finite size of these spheres is significant in the ionic mixtures found everywhere in biology and in general at concentrations greater than say  $2 \times 10^{-2} M$ . The finite size makes constitutive equations (valid at all concentrations) much more difficult than the constitutive equations for quasi-particles that are points.

Numerical difficulties in dealing with spheres are substantial. Spheres must be computed in three dimensions because spheres do not exist in one and two dimensions. That is to say, objects with a single radius have very different surface to volume ratios in one, two and three dimensions and so fill space very differently. Phenomena in which spheres fill three dimensional space to saturation are not well approximated by saturation phenomena in one or two dimensions. Computation of the forces that prevent overlap of spheres is difficult because those forces are strong and vary steeply in three dimensions.

**Vacuum Capacitor.** Let's move to a vacuum capacitor, in which the space between the two plates is completely empty of matter (as it would be in outer space, for example). The current flow through this capacitor is just as real as the movement of ions of  $\text{Na}^+\text{Cl}^-$  in the cylinder even though no particles or spheres are present, and no mass moves at all.

The displacement current between the plates of the capacitor is a property of the electric field itself, as explained in textbooks of electricity and magnetism (e.g., [29, 56, 104]) and is described by the exact and simple constitutive equation  $i_{\text{displacement}} = C(\partial V/\partial t)$ , where the displacement current  $i_{\text{displacement}}$  (amps) is strictly proportional to the capacitance  $C$  (farads) and the time rate of change  $\partial V/\partial t$  of the voltage across the capacitor. Unlike other constitutive equations, the constitutive equation for vacuum current is exact, valid to some eighteen significant figures.

This displacement current induces a magnetic field just as current carried by ions produces a magnetic field. Indeed, without displacement current in a vacuum, Maxwell's equations sunlight to propagate through the vacuum of space. With this exact expression for displacement current, light propagation is a solution of the Maxwell equations, and in fact the speed of propagation of light can be computed from measurements of electrical and magnetic constants, entirely independent of measurements on light itself. Light propagates according to Maxwell's equations over astronomical distances, so we know that the constitutive equation that calculates that speed must be accurate to many significant figures.

**Dielectric Capacitor.** In the dielectric capacitor in Fig 2 (filled with real material, for example the plastic = Polytetrafluoroethylene = PTFE = Teflon), current flow is more complex, and involves the effect of an applied electric field on the spatial distribution of the electric charge intrinsic to the atoms, molecules, and substance of the dielectric. ('Intrinsic' here means the distribution of charge present when there is no applied electric field. Note that the electric charge varies significantly on all scales from subatomic to macroscopic in different parts of Fig. 2.)

The properties of dielectrics cannot be described in detail here because they vary so much with material, voltage, and time. But some properties need emphasis. Intrinsic charges do **not** move from plate to plate in a real capacitor. The current that flows from plate to plate and within the dielectric is a dielectric displacement current not carried by the movement of mass (any substantial distance). The current in a real capacitor is an abstraction. It is the sum of the vacuum displacement current and the material displacement current (in the dielectric) produced by the

distortion of intrinsic charges. Calculating this material displacement current involves solving a nonequilibrium time dependent version of the Schrödinger equation, a difficult task.

Scientists have avoided the difficulties of solving the Schrödinger equation by using approximations. They discuss an ideal dielectric with properties independent of field strength and independent of time. The approximation over a wide range of electric field strength is satisfactory in most materials. The approximation is poor over a wide range of times. For example, most solutions of ions in water have effective dielectric coefficients that change—after a step electric field is applied—from about 2 to about 80 as time moves from  $10^{-15}$  sec to say  $10^{-3}$  sec. A factor of 40 is not a small change, but biology is controlled by atomic structures that move significantly in  $10^{-15}$  sec and have dramatic effects on biological functions that take  $10^{-3}$  sec or much longer!

Electric fields during a biological action potential, or those applied to dielectrics in experiments, are strong, typically some 0.1 volts across a  $2 \times 10^{-9}$  meter thick membrane or a  $3 \times 10^{-10}$  meter selectivity filter (EEEE group in a calcium channel),  $5 \times 10^7$  to  $3 \times 10^8$  volts/meter. These electric fields distort the distribution of charge within the dielectric on many scales of time and distance, including electrons inside molecules and atoms, They reorient polar molecules that have an intrinsic asymmetric distribution of charge. Charges only move a small amount in dielectrics in response to the applied electric field—reminiscent of the sloshing of tides in the ocean and on beaches on the earth created by the moon's gravitational field—**and they eventually return to their resting position when the field is turned off** but those small movements of charge produce large effects because the electric field is so strong. Dielectric currents share some of the properties of vacuum displacement currents but they do not have a universal exact constitutive law, not even approximately. It is important not to confuse dielectric and vacuum displacement currents.

Nonlinear components of dielectric current have large effects important in biology (e.g., nerve [1] and muscle [93]) where they control the opening and closing of channels [97] and enzyme function [63], and can be recorded as 'gating' currents because of the Shockley-Ramo theorem [81], which is Kirchoff's current law in another form.

**Any electric field is extraordinarily strong. A one per cent deviation in the density of (net) charge has enormous effects.** As Feynman memorably mentions at the front of his textbook [29], **one per cent of the charge in a person at arm's length produces force enough to lift the earth!** Note that the electric charge in different devices of Fig. 2 varies on very different scales from subatomic (in dielectrics) to atomic (in diodes, ionic conductors, etc.) to macroscopic. Thus, treatments of charge must be multiscale.

**Concentration effects are very small.** A one percent deviation in density of mass has tiny effect on diffusion and chemical reactions, hardly noticeable. Diffusion forces are tiny perturbations on the electric force field and energies involved in diffusion are tiny perturbations in the total energy of charged systems. Electric forces and energies are not small parts of the total energy and it is not wise—to say the least—to treat them as perturbations of uncharged systems.

Charge is indeed an abstraction. In each of the devices in Fig. 2, charge follows different laws, because it has different physical properties, sometimes carried by charged particles, sometimes produced by the rate of change of electric field (displacement current), sometimes the 'movement' of quasi-particles, sometimes the 'movement' of electrons in a macroscopically delocalized quantum state of a wire.

Charge always flows without loss in each device. That abstract property of charge movement is always true, but the ‘laws’ describing current as a function(al) of time and potential (for example) depend on the physical nature of the charge and its movement. Different devices have different relationships between current, voltage, and time. These different ‘constitutive’ equations are described in the engineering literature in great detail.

The different constitutive equations combine with Kirchoff’s current law to describe current flow from one place and one device to another. Together, the equations describe the universal fact that interrupting current flow in one reaction (of a series of reactions) will interrupt current flow in every other reaction (in that series) even if one reaction occurs on the atomic scale (scale = 1 Å) and is meters away from the interruption.

One is reminded of the power of the electric field when one unplugs a computer. Interruption of a circuit meters away from the diodes of the computer’s power supply stops the flow of quasi-particles—holes and semi-electrons—across atomic scale junctions of semiconductor diodes, often of the **PN** variety. The electric field changes so strongly in response to the interruption (because of the input of the computer power supply stores a great deal of charge) that the electric field increases dramatically, and exceeds the dielectric strength of air. Electrons are stripped off the atoms of the air, a plasma is created, a spark. We see the light of the spark and should be reminded of the frightening strength of the electric field. Sparks start fires, sometimes in nearby upholstery or drapes.

The electric field of charge must be respected on all scales because it has such large effects on all scales. Although charge is an abstraction in each device, it is conserved ‘perfectly’ as charge moves from device to device, according to Kirchoff’s current law.

**Vacuum tubes.** In the next device in Fig. 2, we consider charge movement in a vacuum tube diode. Vacuum tubes control the flow of electron current by changes in their internal electric fields and were called ‘valves’ in the UK for that reason. Vacuum tubes, semiconductors and even some open ion channels follow simple constitutive laws of rectifiers, as described in textbooks of electronic devices or ion channels.

In vacuum tubes, current is indeed carried by a stream of isolated charged particles, electrons with a definite mass and charge, moving through a vacuum, interacting only through their electric fields. At 1 Hz, essentially all the current in a vacuum diode is carried this way. Current through a diode is not proportional to the voltage across the diode because the electric fields within the diode change shape, despite the simple physics of conduction. The fields change shape as the voltage across the diode is changed because of screening and shielding. The electric fields within the tube are different at small and large potentials. The different internal electrical fields change the current flow, creating rectification. The electric field creates a large barrier in one direction so current in that direction is small; the electric field creates a small barrier in the other direction, and current in that other direction is large.

Rectification is of considerable historical interest, because vacuum tubes allowed the early detection of radio waves in American’s homes in the 1920’s, as valves did in the UK. The demand for portable radios led to solid state diodes, then solid state ‘triodes’, field effect transistors, integrated circuits, and our modern digital world.[88]

Vacuum tube diodes had certain difficulties—they were big,  $10^{-2}$  m at their smallest, hot, greedy consumers of power, and electrically unstable. They were quickly replaced with semiconductor diodes, the next device in Fig. 2 that can be as small as  $10^{-8}$  meters nowadays, costing  $<10^{-10}$  dollars each.

**Semiconductor diodes.** Current in semiconductors is carried by quasi-particles [58], called holes and ‘electrons’ (better named quasi-electrons, or semi-electrons in my view) These quasi-electrons and holes are defined because they interact much more simply than the totality of real electrons and lattice of atoms in the semiconductor.[58, 82, 84, 96, 98]. They simplify the quantum mechanical many-body problem into the much simpler motion of imagined quasiparticles. Current is carried in semiconductors by rearrangements of charge in the entire lattice of atoms that make up the semiconductor. Fortunately for our technology and daily life, current in germanium and silicon can be approximated by theories that deal with one quasi-electron or one quasi-hole at a time as they move in mean fields.

As a textbook puts it eloquently (p. 68 of [57]): “Electron is a quasi-particle consisting of a real electron and an exchange correlation hole ... a cloud of effective charge of opposite sign due to exchange and correlation effects arising from interactions with **all** other electrons of the system.” “Hole is a quasi-particle, like the electron, but of opposite charge; it corresponds to the absence of an electron from a single particle state that lies just below the Fermi level.” The motion of these quasi-particles are described by mean field models, evaluated both by simulations [51, 98] and theory [76, 94, 98]. For example, the Poisson drift diffusion equations [54] often called *PNP* (for Poisson Nernst Planck) in biophysics and nanotechnology [6-9, 16, 24, 25, 45, 102] are most important in semiconductor physics.

**Charge carriers in semiconductors can be really quite strange** from a physical point of view. Charge carriers in silicon and germanium do not exist outside the lattice of the semiconductor as distinct entities. They do not exist in the same sense that  $\text{Na}^+$  and  $\text{Cl}^-$  ions exist, but are mathematical representations, with lifetimes sometimes as short as milliseconds. Quasi-particles are the second derivative of a Fermi surface of silicon and germanium semiconductors, under particular conditions. They are defined, as mentioned above, to allow easy analysis compared to the intractable quantum mechanical many-body problem of a macroscopic semiconductor with atomic scale diode (e.g., *PN*) junctions driven by far field boundary conditions. They replace a problem involving the motion of all the atoms of a macroscopic system with those of a swarm of quasiparticles moving in a mean field.

Much of the success of our semiconductor, digital, and video technology is due to the accuracy of the constitutive *PNP* equations describing holes and semi-electrons. They describe the characteristics of semiconductor devices of many different types, as different as an exponentiator and a logarithmic convertor.

*PNP* is so useful because almost all the devices of our digital technology work in a restricted set of conditions in which flows are crucial but are of the special type well described by quasi-particles moving in a mean field. Treatment of distortions of the electric field of all the atoms in the macroscopic device is not needed.

Almost all of the devices of electronics use power supplies to maintain different voltages at different locations far from the *PN* junctions of the device itself (and thus require a global treatment of the electric field). These voltages perturb the distribution of velocities of charged particles so the distribution has net flow [15, 26]. The slight perturbation is enough to imply the *PNP* equations and those provide enough nonlinearity to make amplifiers, switches, and the full set of logical circuits necessary to make a computer.[82, 84, 96, 98]

***PNP* equations describe a wide variety of current voltage relations and devices.** The *PNP* equations are the constitutive laws used to describe semiconductor devices as their current voltage relations change drastically (with voltage, for example) from that of a linear amplifier, to

a switch, to an exponentiator, a multiplier or even a logarithmic converter. [82, 84, 96, 98] Nonlinear input output relations as varied as these enable a rich variety of devices.

Nonlinear input output relations as diverse as these are not described easily—or described at all, for that matter—in most areas of physics and chemistry. All the nonlinear devices in a computer are actually mathematical solutions of the *PNP* equations in a complex silicon structure built to have the particular spatial distribution of permanent charge (‘doping’) that produces the desired properties of the device, i.e., the input output relations.

The predictive power of *PNP* is very important in the design of robust semiconductor devices—that do not fail even when used billions of times a second in computers that contain a trillion transistors. In fact, the intrinsic physical properties of semiconductors (e.g., concentration of fixed charge dopants, geometry, and recently even dielectric coefficients) are adjusted by their designers so *PNP* remains a good description, even as the size of the device has been dramatically decreased by semiconductor engineers in their successive iterations of Moore’s law [73, 78, 79], by factors of a billion or so over 50 years. Evidently, reliable design is more important than raw performance. Evidently, it is more important for the designers (and marketplace) that an equation describes behavior robustly and accurately over a range of conditions than that the device be as fast or small as possible. [10, 12, 13, 91] Evolutionary selection in biology also seems to choose robustness over efficiency in many cases.

Devices of nanotechnology need to be robust, I believe, before they will be used extensively.

**PNP is not enough, however, when ionic solutions are involved.** A great deal of effort has been spent applying *PNP* equations to electrochemical systems [6-9, 16, 24, 25, 45, 102] hoping they might serve as adequate constitutive equations, but that is not the case. The nonideality of ionic solutions, arising in large measure from saturation effects produced by the finite size of ions, demands more powerful mathematics than the partial differential equations of *PNP* used in computational electronics.

**Resistor.** The next device we discuss in Fig. 2 is a resistor, which in some ways is the easiest to describe, because current is proportional to voltage with a single proportionality constant over a wide range of voltages, times, and conditions. A resistor follows Ohm’s constitutive law with a resistance independent of potential over a wide range from  $10^{-5}$  volts to say 100 volts, and from values of resistance from  $10^{-1}$  ohm to  $10^8$  or  $10^9$  ohms.

The range of validity of Ohm’s law is an enormous help in circuit design. Circuit models involving resistors, capacitors, inductors and operational amplifiers are transferrable. They behave as real devices behave without changes in parameters. Largely for that reason, designs are inexpensive and robust.

Despite the simplicity of resistors, the actual current carrier in a carbon resistor, is unclear, at least to me. No one cares very much I suspect, because the device works nearly perfectly. The carrier of charge does not matter very much. What matters is the constitutive law that describes the relation of current, voltage and time. The constitutive law satisfies conservation of charge. It can combine conservation of charge and matter with the properties of the physical constituent if written with the energetic form of the variational calculus.

**Current flow in wires.** The current carriers in a wire are delocalized electrons in the simple case of a single solid conductor of metal, and follow the simplest constitutive law of all at long(ish) times, say times longer than  $10^{-5}$  sec.

But most of our electronics occurs at times much shorter than that. Here we confront the importance of the time variable. **The physical nature of current flow depends on the time scale on which the current changes even in wires.** The range of time scales in our technology is enormous from more than one second to less than  $10^{-9}$  sec. At those times, the wires that must be used are often twisted pairs, each made itself of many very fine wires. Without twisting, these pairs of wires do not allow successful connections to the internet because without twisting, rapidly changing signals are not carried reliably by wires. At those short times, currents flow outside wires, guided by the conductor, to be sure, but outside the conductor nonetheless [56]. The twisting of wires is a necessity if they are to carry signals robustly and reliably so we can use them in our video devices and smartphones.

**Physical nature of current depends on time scale.** The physical nature of current in almost any system depends on the time scale, and differs at different times as much as it differs in different devices. Constitutive equations depend on time. Different devices have different constitutive equations with different time dependence.

Again, charge movement is an abstraction, different at different times in one device, as well as different in different devices.

**Charge Movement in Batteries.** Batteries are present in Fig. 2 both as an isolated device and at the  $\text{Ag}||\text{Ag}^+\text{Cl}^-$  interface between wires and  $\text{Na}^+\text{Cl}^-$  solution in the conducting cylinder previously discussed. I hesitate to describe a constitutive equation for the flow of charge in these systems because it is so very complex, different in different devices, and its interaction with surface charges is also subtle and important. It is enough to say here that current flow through electrochemical systems is carried by a wide range of charge carriers. Constitutive equations of different electrochemical systems differ and change nature dramatically with time and frequency. At short times, at  $10^{-6}$  sec—that are still long and slow compared to the times important in computers—current from the  $\text{AgCl}$  wire into the  $\text{Na}^+\text{Cl}^-$  solution is entirely displacement current lagging behind voltage but at the longer times characteristic of biological systems (greater than say 0.1 sec) the current is carried by a complex combination of  $\text{Ag}^+$  and  $\text{Cl}^-$  ions with negligible displacement current.

**We conclude that charge is indeed an abstraction** with different physical meanings in different systems and at different times. No one can visualize and no one knows—at least I do not know anyone who knows—why or even how this abstraction can be so perfectly conserved under all conditions and on all scales, from Angstroms to meters, from femtoseconds to seconds. The reader may have difficulty visualizing the interactions that enforce conservation of the abstraction ‘charge’ in all these devices with all these properties over the entire time scale. I certainly do. However,

**Charge is conserved on and between all scales in all conditions,** even if we cannot visualize how. Experiments demonstrate that fact. Current does flow continuously without loss in a circuit. Interruptions in current flow meters from a chemical reaction does interrupt current flow in that reaction, as can easily be seen when disconnecting a car battery, for example (be careful!). Abstract charge is conserved ‘exactly’ even if we cannot visualize how that happens.

Science often contains mysteries that cannot be visualized—consider Maxwell’s attempts to visualize his equations as properties of an ether—and questions that cannot be answered. For example, why is the charge on an electron  $1.6 \times 10^{-19}$  coulombs? Why are physical laws invariant when locations  $s$  move at constant velocity  $\partial s/\partial t$ —special relativity—or at constant

acceleration  $\partial^2 s / \partial t^2$ —general relativity—but not when other time derivatives of location are constant, like a constant third derivative  $\partial^3 s / \partial t^3$  or linear combinations of  $\partial^n s / \partial t^n$ ? As practical people, scientists cannot afford to just wait while we wonder about such things. Scientists wonder a bit *and* then move on, hoping our successors can do better than we have.

Biologists and engineers in particular cannot afford to linger on the mysteries they do not understand. Think of Thomas Henry Huxley looking at the shortening of the striations of muscle [48] that were not understood until one of his grandsons (Andrew Huxley) studied them many years later.[47] Think of Lee DeForest using vacuum tubes without understanding how they work. Biologists and engineers cannot afford to wait to understand everything. They must isolate the mysteries and move on to study other things. Here, we move on to discuss devices and the theories and simulations used to understand them.

**Biological Implications of Kirchoff’s Current Law.** It is important to note that the Kirchoff’s current law has important biological implications in systems more general than a series of chemical reactions. Kirchoff’s current law implies the cable equations (called the telegrapher’s equation in the mathematics literature). The cable equation is the foundation of the Hodgkin Huxley model of the action potential of nerve and muscle fibers. Kirchoff’s current law links the atomic properties of ions, the molecular properties of ion channels, and the centimeter scale spread of current and potential that creates the propagating action potential in nerve fibers meters in length.

In short or round(ish) cells, Kirchoff’s current law forces coupling between multiple pathways of current crossing membranes, **even if the currents are carried by different ions, or by electrons, through different structures** nanometers apart in the membrane of the finite cells or organelles.

The flux coupling characteristic of active transport systems—including the coupled flows in chemi-osmotic systems that perform oxidative phosphorylation or photosynthesis—might arise in this manner. **Coupling of flows of charges, whether electrons or ions, is an unavoidable consequence of GLOBAL conservation of charge**, of Kirchoff’s current law **GLOBALLY** enforced, and not a consequence of local chemical interactions, just as coupling of membrane currents with axial currents in a nerve fiber is an unavoidable consequence of Kirchoff’s current law, not of local chemical reactions.

It is interesting to compare the incorrect chemical theory of nerve propagation of Nobel Laureate AV Hill [41] with the correct electrical theory of the then undergraduate Alan Hodgkin [42, 43] later Nobel Laureate. Kirchoff’s current law in the form of the cable equation was the key. It links the movement of atoms inside channel proteins to the macroscopic current flow that produces nerve propagation of the macroscopic electrical potential, the nerve signal that spreads meters. Macroscopic potentials modify atomic movements. Atomic movements create the macroscopic electrical potentials.

Equations of the electric field are true on all scales and so allow a unique linkage between models of atomic motion, protein behavior, and macroscopic propagation of electrical signals. I suspect linkage equations of this type—valid on all scales—will be needed to make any multiscale analysis robust and transferrable, if it reaches from atoms to meters, from femtoseconds to minutes as models of nanodevices must.

**Models, Devices, Effective Parameters, and Transferrable Theories.** Parameters of models or devices can often be chosen so an incomplete theory or simulation describes a system in one set



of conditions. Chemistry and biology are filled with examples. Chemical reactions follow rate equations, but the rates are not constant, as conditions change, even though theory assumes they should be.[21, 22] Biology describes enzymes with one set of parameters but finds those are changed when conditions change and attributes that somewhat mysteriously to ‘allosteric effects’ and conformation changes.

Biology and much of chemistry works under a wide range of conditions and so incomplete theories with effective parameters have limited use. Even if sensible, even if valid, theories (and simulations) with effective parameters like these are not accurate enough to design robust devices. By leaving out something important, those theories or simulations leave out an energy term that is almost certain to vary with conditions. The resulting effective parameters change in large and unpredictable ways.

Theories and parameters of incomplete theories cannot be transferred successfully from one set of experiments and conditions to another. Incomplete theories are not likely to be transferable in the language of the chemistry literature. Devices designed from incomplete theories or simulations are unlikely to be robust or work well under a range of conditions.

Biological systems analyzed with non-transferable theories (or simulations) are unlikely to be realistic in general because biological systems almost always work in a range of ionic concentrations different from those used in the laboratory. Biological systems usually work in mixtures with a range of  $\text{Ca}^{2+}$  concentrations, in which  $\text{Ca}^{2+}$  concentration has important practical effects, often turning systems on or off or controlling their rate monotonically. Simulations and theories in biology have limited use until they are calibrated so we can be sure they actually are correct in the range of conditions and  $\text{Ca}^{2+}$  concentrations the biological system uses. Simulating  $\text{Ca}^{2+}$  activity in pure solutions is a challenging problem. [92] Simulating  $\text{Ca}^{2+}$  activity in biological mixtures in the  $10^{-8}$  to  $2 \times 10^1$  molar concentrations that are physiological, has not been attempted as far as I know.

Biological and chemical science will benefit enormously if theories and simulations can be made transferable, using one set of parameters to describe systems in a range of conditions, as many physical and most engineering theories and simulations do. I believe the law of mass action must be extended to conserve charge before theories and simulations can be made transferable from condition to condition, from physics, to chemistry to biology, using only mathematics.

**How to extend the law of mass action?** An obvious way to extend the law of mass action is to include an electrical potential in the rate constant to ‘right the rates’ by making them exponential functions of potential. This in fact has been done for a very long time in the study of reactions at the electrodes of electrochemical cells. The Butler-Volmer and Tafel equations [3] include electrical potential in rate constants in an empirical way with limited [37, 38] but real success.

The difficulties of just embedding an electrical potential in a rate constant are formidable. **We must ‘fix the fields’ so they are global and depend on current flow everywhere.** The only way to ‘right the rates’ is to fix the fields, **everywhere**. Otherwise, they cannot conserve charge and support continuity of current as required by Kirchoff’s current law.

- (1) A thermodynamic treatment is clearly impossible since the goal is to calculate large fluxes and currents that do not occur in a thermodynamic system at equilibrium by definition without flows. Clearly a frictional treatment of flux over a large potential barrier as in the classical drunken man problem of Kramers [30, 39] is a necessary step forward, even if it is inconsistent because it does not compute the potential

barrier from the charges in the system. A simple generalization of Kramers for any shape barrier is available [15] and needed [2] because so few barriers are both symmetrical and large as required in classical high barrier approximations.

- (2) A general theory of all nonequilibrium processes is not likely to be useful: a general theory has to describe too much. A general theory must include hydrodynamic behavior of considerable complexity, since aqueous solutions are fluids satisfying the Navier Stokes equations of fluid mechanics. A general theory should also include explosions since they occur with regrettable frequency at electrodes of electrochemical cells, when H<sub>2</sub> gas is generated (inadvertently) by an overvoltage.
- (3) The rate constants in one reaction must depend on the electrical potential in far locations. Otherwise, interrupting current flow in a far location is not likely to interrupt current locally. This requirement implies that the electrical potential must be determined by a global equation like Poisson's equation, including boundary conditions far from the individual chemical reactions.
- (4) The rate constants in one reaction must depend on concentrations throughout the system because the solutions containing the reactants are not ideal. A general characteristic of nonideal solutions is that 'everything depends on everything else'. More specifically, the activity of one reactant (the free energy per mole) depends on the concentrations of other species in practice, as well as in principle.

**Variational methods can extend the law of mass action.** If the goal is to build transferable systems, so we can build robust devices, as in electronic technology, we must use a mathematics that allows interactions of charges and fields, extending from atomic to macroscopic scales.

Variational methods are designed to deal with systems with multiple forces and flows, in which interactions are unavoidable and complex. In these systems interactions must be included in all analysis. Otherwise, theories have more adjustable parameters than can be determined experimentally and still cannot deal with a range of conditions, because interactions change with conditions in ways too complex for ordinary theories.

Sadly, theories of ionic solutions—even the assignment of properties to single ions in infinitely dilute solutions [46]—seem to have these difficulties. Theories of ionic solutions need a large number of adjustable parameters and still cannot describe biological solutions (for example). References [17, 20, 32, 34, 59-61, 64, 83, 95, 105] draw particular attention to the difficulties.

The sad limitations of our understanding of ionic mixtures, like those in which all of biology occurs, is not widely known, and so vexing that many do not want to know of it. It is necessary then to document the frustration by quotations from leading workers in that field. The classical text of Robinson and Stokes [89] is still in print and widely used. It is a book not noted for emotional content that still gives a glimpse of its authors' frustration when it says (p. 302) "In regard to concentrated solutions, many workers adopt a counsel of despair, confining their interest to concentrations below about 0.02 M, ..." (Almost all biology occurs in solutions much more concentrated than that.) In a recent comprehensive treatment [61] of nonideal properties of solutions, the editor Werner Kunz uses his introductory overview [62] to say (p.11) "It is still a fact that over the last decades, it was easier to fly to the moon than to describe the free energy of even the simplest salt solutions beyond a concentration of 0.1M or so."

New mathematical tools are needed in my view to remedy this situation which has been stalemated since the 1920's. The more powerful tools of variational calculus are needed, in my

view, so the mathematics used automatically deals with interactions that vary dramatically with conditions. If the mathematics does not deal with interactions, those interactions will not be computed correctly and will wreck theories, based (for example) on algebraic descriptions of interactions or theories based on the law of mass action with constant rate constants.

Energetic variational methods are particularly useful because they allow multiscale derivation of partial differential equations (and far field boundary conditions) from physical principles when multiple fields are involved, like convection, diffusion, and migration in an electric field. Energetic variational principles have recently become available for systems involving friction [31, 49, 103], that is to say, for systems involving ionic solutions [23, 45, 80, 101]. They combine the full power of the Navier Stokes equations (1) with either a Lennard Jones representation of finite size ions or (2) with a density functional theory of ionic solutions built from Rosenfeld's DFT of liquids [23, 50]. These formulations must be computed in three dimensions because spheres do not exist in one and two dimensions. These theories and their simplifications [44, 65, 69] are difficult to compute in three dimensions because of the steeply singular forces used to ensure that atoms do not overlap. Overlap must not be permitted because spheres cannot overfill space: space can be saturated with spheres. Saturation effects are a main cause of nonideality, particularly in the extremely crowded conditions in and near enzyme active sites, ionic channels, nucleic acids, and the working electrodes of electrochemical cells where twenty molar solutions are not uncommon [55]. (As a rule of thumb, ions are crowded where they are most important in technology and biology.)

If saturation is described by a Fermi-like distribution—as recently derived for spheres of unequal sizes [70, 71]—some of these difficulties can be attacked. A fourth order partial differential equation can be derived [72] which is easily integrated in three dimensions, after it is reduced to a pair of second order partial differential equations (with carefully defined boundary conditions) and computed with appropriate numerical methods.

But it is still not clear how best to apply any of these methods to chemical reactions (Fig. 1) described by the law of mass action with rate constants extended to be functions or functionals and not constants.

**And that is not a bad place to move this essay towards its coda.** We now have the tools, and we now have the goal—a global treatment combining conservation of mass in chemical reactions described by the law of mass action with conservation of charge described by Kirchoff's current law everywhere. Now we have to do the work.

**Coda: our grasp must be sure, but our reach should exceed our grasp,** as we do the work. We must grasp both charge conservation and mass action before we can produce robust theories (or simulations) of chemical reactions in ionic solutions that successfully use one set of parameters in a range of conditions, and include the global properties of the electric field.

There is no engineering without numbers and computations. All calculations from theories and simulations—of electronic or ionic or biologically inspired devices—must be checked and calibrated against known results. Otherwise devices built from those calculations will not work.[14, 75, 85] There is little engineering without robust theories because devices have much less tolerance for error than abstractions. If theories and simulations of electrical devices were not robust, if parameters had to be changed as conditions changed, our electronic technology would be severely limited, to say the least.

Chemical reactions involving charge must be within our theoretical grasp before we can develop transferable theories, in my view. Only then can we build devices that perform as

expected, as electronic devices usually do. Only then can we expect exponential growth in molecular engineering whether biological or technological. It seems no coincidence that exponential growth in electronic technology came after scientists had a secure grasp of global electrostatics and the *PNP* equations of electrodiffusion in semiconductors. Let us hope that energetic variational methods can grasp ions and chemical reactions as well and as successfully as *PNP* has grasped the useful properties of holes and (semi)-electrons in silicon and germanium.

## **Acknowledgement**

It is a pleasure to thank John Prausnitz for suggesting the theme ‘There are laws, and there are laws’. Fred Cohen and Eduardo Rios provided most useful criticisms and suggestions. Many thanks! Ardyth Eisenberg edited the manuscript with vigor and love, for which I am most grateful, as it motivates me every day.

## Appendix

### When does mass action conserve charge? What does unconserved charge do?

**Size of discontinuity of current flow.** The reader may hope that the amount of charge involved in the discontinuity of current flow is too small to matter, but small charges have large effects because of the strength of the electric field.

The difference in current shown in eq. (9) is the discontinuity of current, the violation of Kirchoff's law of continuity of current flow.

$$\frac{I_{XY} - I_{YZ}}{F} = z_X \cdot k_{xy} [X] - z_Y \cdot k_{yx} [Y] - z_Y \cdot k_{yz} [Y] + z_Z \cdot k_{zy} [Z] \quad (9)$$

**Special Cases when both conservation laws are satisfied.** When the discontinuity  $I_{XY} - I_{YZ} = 0$  in eq.(9) - (12), the law of mass action is consistent with Kirchoff's current law and conservation of mass and conservation of charge are both satisfied.

**Significance of the error** is seen by considering reduced cases, remembering that the units of current  $I_{XY} - I_{YZ}$  here are (cou/sec)/liter.

**Special Case A:** If all concentrations are set equal to one, the currents (in the special case with a tilde)

$$\frac{\tilde{I}_{XY} - \tilde{I}_{YZ}}{F \cdot 1 \frac{\text{mole}}{\text{liter}}} = z_X \cdot k_{xy} - z_Y \cdot k_{yx} - z_Y \cdot k_{yz} + z_Z \cdot k_{zy}; \quad \text{concentrations} = 1 \frac{\text{mole}}{\text{liter}} \quad (10)$$

**Special Case A\*:** If we also set all charges equal to one, along with concentrations equal to one,

$$\frac{\hat{I}_{XY} - \hat{I}_{YZ}}{F \cdot 1 \frac{\text{mole}}{\text{liter}}} = k_{xy} - k_{yx} - k_{yz} + k_{zy}; \text{concentrations} = 1 \frac{\text{mole}}{\text{liter}}; z_X = z_Y = z_Z = 1 \quad (11)$$

In this special case of eq.(11), labelled A\*, asymmetry (net difference) in rate constants determines the discontinuity of current, the violation of Kirchoff's current law.

**Special Case B:** Alternatively, we can set all rate constants and all concentrations equal to one,

$$\frac{\hat{I}_{XY} - \hat{I}_{YZ}}{F \cdot 1 \frac{\text{mole}}{\text{liter}} \cdot 1 \frac{1}{\text{sec}}} = z_X - z_Y - z_Y + z_Z; \text{concentrations} = 1 \frac{\text{mole}}{\text{liter}}; \text{rate constants} = 1 \frac{1}{\text{sec}} \quad (12)$$

In this special case of eq.(12), labelled **B**, asymmetry (net difference) of charges (valences) determines the discontinuity of current, the violation of Kirchoff's current law.

**Asymmetry of parameters violates conservation of charge** and produces discontinuity of current, it seems safe to say.

**Size of effects.** To estimate the effect on electrical potential  $V$ , we need to know the size of the system. Imagine a spherical capacitor of radius  $R$ . Its capacitance to ground—or coefficient of the self-energy, if one prefers the phrase in the chemical literature—is  $C = Q/V = 4\pi\epsilon_r\epsilon_0R$  or numerically  $4\pi \times 8.85 \times 10^{-12}$  [farad/meter]  $\epsilon_r R = 1.11 \times 10^{-10} \epsilon_r R$  [farad] where  $\epsilon_r$  is the relative dielectric coefficient, about 80 in water solutions at longish times (say  $> 10^{-5}$  sec). Then, a 1 nm radius capacitor with dielectric coefficient 80 has capacitance of  $8.9 \times 10^{-18}$  farads. Small charges produce large voltages in such a tiny capacitor. Even the charge on just one ion ( $1.6 \times 10^{-19}$  cou) would produce 18 mV, large enough (compared to the thermal potential of 25 mV) to have a noticeable (~50%) effect in theories and simulations, because  $\exp(-18/25) = 0.49$ . (Rates often vary exponentially according to  $\exp(-V/k_B T)$ .) The discontinuity in current lasting for a second would produce a voltage of  $V = Q/C = 1/(8.9 \times 10^{-18}) = 1.1 \times 10^{17}$  volts.

Of course, 1 second is a long time for current to flow. If current flowed on a biological time scale, for 1 msec in a structure 1 nm in radius, with dielectric coefficient 80, the electrical potential would be much less, 'only'  $10^{14}/\epsilon_r$  volts. Current flow of even a picosecond, would produce some thousands of volts.

**Rate of change of potential.** We can also look at the effect on the rate of change of potential. The discontinuity of current is connected to the rate of change of potential by a version of Coulomb's law

$$\frac{\partial V}{\partial t} = \frac{1}{C} I \quad (13)$$

If we apply this formula to the discontinuity of current in the special case of eq. (11), labelled **A\***, we can estimate how quickly that discontinuity of current would change the potential

$$\frac{\partial V}{\partial t} = \frac{\hat{I}_{XY} - \hat{I}_{YZ}}{F \cdot 1(\text{mole/liter})} \frac{1}{C} = \frac{\hat{I}_{XY} - \hat{I}_{YZ}}{F \cdot 1(\text{mole/liter})} \frac{1}{4\pi\epsilon_r\epsilon_0R} = \frac{k_{xy} - k_{yx} - k_{yz} + k_{zy}}{4\pi\epsilon_r\epsilon_0R} \quad (14)$$

For a capacitor  $R = 1$  nm with  $\epsilon_r = 80$  and capacitance of  $8.9 \times 10^{-18}$  farads (see above)

$$\frac{\partial V}{\partial t} = 1.1 \times 10^{17} \text{ farads} \times (k_{xy} - k_{yx} - k_{yz} + k_{zy}) \quad \text{in volts/sec} \quad (15)$$

In other words, the breakdown voltage (~0.2 volts) of membranes and proteins would be reached in  $1.82 \times 10^{-18} / (k_{xy} - k_{yx} - k_{yz} + k_{zy})$  sec, not a very long time. The breakdown voltage for matter (say  $10^6$  volts) would be reached in picoseconds in all likelihood.

We conclude that

**failure of the law of mass action to conserve charge is likely to have noticeable effects.**

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