

Electrochemistry

or, anyway,

PNP, Well Posed

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The work reported here was stimulated by intensive discussions with Chun Liu and YunKyong Hyon, Pennsylvania State University, and would not have occurred without them. The particular formulation of the Poisson Nernst Planck system I use here is that being used in work in collaboration with Allen Tzyy-Leng Horng, Feng Chia University, Taichung, Taiwan; Tai-Chia Lin 林太家, National Taiwan University, Taipei; Xiaofin Lin and his student Allen Flavel, Illinois Institute of Technology, and Chun. Yoichiro Mori (University of Minnesota) has corrected significant errors. Many thanks. Those that remain are of course only my responsibility!

The title suggest that any formulation of electrochemical cells will have problems of well posedness similar to those analyzed here. I only analyze a differential equation form of PNP. It is entirely possible that other formulations (e.g., variational) will deal with the problems raised here more naturally and more efficiently.

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Biology and chemistry occur in ionic solutions for the most part. Water without ions is lethal for cells and most proteins. Chemistry is often done in ionic solutions. There seems no need here to repeat the extensive documentation in (Eisenberg 2012; Eisenberg 2011a; Eisenberg 2011b; Eisenberg 2011c, 2010) and the historical references to PNP in (Bazant et al. 2004; Coalson and Kurnikova 2005; Damocles 2007; Eisenberg and Chen 1993; Eisenberg 1996b, a; Jerome 1995; Selberherr 1984; Zheng and Wei 2011) .

Ions in water like Na^+ , K^+ and Cl^- move approximately as hard spheres in a frictional dielectric as described by the implicit solvent (so-called) primitive (or implicit solvent) model of electrolyte solutions. A good representation of this primitive model is given by the Poisson Nernst Planck equations once they are modified to deal with ions with different finite sizes (Buyukdagli et al. 2010; Eisenberg et al. 2010; Hyon et al. 2010; Hyon et al. 2011a; Hyon et al. 2011b; Mori et al. 2011; Zheng et al. 2011; Zheng and Wei 2011).

Partial differential equations of this sort couple diffusion, migration, and the electric field and form a system that must be mathematically well defined if they are to be solved. The formulation of a well posed version of these equations, starting at time zero, progressing to time infinity, including multiple species is addressed here. I am unaware of previous treatments of this problem that produce well posed mathematical problems for all mixtures of ions on this complete time scale, although such treatments may well exist beyond the horizon of my knowledge and experience.

The fundamental difficulty is that the equations have usually been viewed as typical flow, conservation of mass, etc. equations, in the tradition of the fluid mechanics of (mostly uncharged) systems. But the ions flowing are charged, the experiments are designed to deal with electrical current and potential first, and the flux of the ions is not dealt with directly in most experiments. The flux of electrical charge (i.e., the electrical current density) is ***not at all*** the same as the flux of ions or the flux of mass.

Plan of Attack

It is my view that the equations of PNP must be written and solved so that ***the electrical properties are dealt with first, and as accurately as possible***, and residual difficulties, if any, appear in the flux and concentration of the least important ions. Because electrical forces and flows are on a different scale from diffusion forces and flows, this can make a very large difference numerically. In particular, the net charge $\rho = \sum_{i=1}^N z_i F c_i$ must never be computed explicitly. The difference in concentrations of positive and negative charge is well within the round-off error of even double precision computer arithmetic because most of the system is nearly electrically neutral with $\rho \rightarrow 0$. Errors in computing ρ can dominate the problem creating dreadful artifacts, numerical instabilities, and inefficiencies.

Shunt Capacitance. Electrical forces and flows are very large, and act on a very fast time scale (sometimes faster than microseconds). That is one of the issues we deal with here. We include the shunt capacitance always present in the real world, so charge can flow in the equations proportional to $\partial V / \partial t$, as it does in the real world, when voltages change rapidly.

The capacitive shunt path (typically 100 pF) allows tiny imbalances in ρ to dissipate very quickly on the capacitive time scale (typically microseconds or faster) without grave effects on the processes that we are interested in, that occur on the time scale of milliseconds. Tiny imbalances in ρ are hard to avoid, no matter how we try, somewhere in the model, modeling, and computational process. They are likely to be present if initial conditions are set only for the concentrations $c_i(t=0)$ ($i=1\dots N$) because $\rho(t=0)$ is so badly determined by $\sum_{i=1}^N z_i F c_i(t=0)$.

Even if an initial condition is provided for $\rho(t=0)$, and for only $N - 1$ concentrations, even if $\rho(t=0) = 0$, all sorts of irrelevant charging transients are likely to occur. (Consider what happens between $t=0^-$ and $t=0^+$ when a voltage step is applied at $t=0$. Equivalent problems occur whenever the voltage is stepped, as it is in a typical voltage clamp experiment, or ramped rapidly, as is done in many single channel experiments, or if problems arise because of other physical effects, like series resistance in the bathing solutions.)

These irrelevant charging transients are taken care of in experiments (i.e., forced to a rapid uninteresting time scale) as much as possible, by the combination of the shunt capacitance and the mechanism maintaining the Dirichlet boundary condition on voltage (i.e., the voltage clamp). The equations should deal with the irrelevant charging transients the same way they are dealt with in experiments, both to be realistic, and also so we can recognize and deal with the artifacts using the wisdom of 60 years of experimentation on voltage clamp (since (Hodgkin 1992; Huxley 1992; Huxley 2002; Hodgkin et al. 1952) and on single channels (Sakmann and Neher 1995; Sigworth and Neher 1980; Hamill et al. 1981; Sigworth 1986; Sigworth 1995; Rae et al. 1988; Levis and Rae 1992; Rae and Levis 1992b, a; Levis and Rae 1993; Levis and Rae 1995; Tang et al. 1995; Levis and Rae 1998; Cherny et al. 2003; Rae and Levis 2004)).

My philosophy is that the charge ρ should be treated as much as possible as an independent variable, independent of $\rho_{chemical} = \sum_{i=1}^N z_i F c_i$, as much as possible. ρ should be allowed to take

on any value. This approach seems to me to mimic the effect of capacitance between baths, between the electrodes (i.e., boundaries), and between baths and ground. There is a theoretical inconsistency and overspecification if we specify both ρ and $\rho_{chemical} = \sum_{i=1}^N z_i F c_i$.

However, ρ is so small compared to the c_i or $F \sum_{i=1}^N c_i$, significantly below round off error of even double precision arithmetic that I imagine this inconsistency will not matter. In fact, I suspect the inconsistency will simply produce a rapidly decaying capacitive current that does not interfere with our conclusions at all. Of course, I may be wrong. We will not know until the approach advocated here is actually implemented.

Shunt Conductance. The mathematical system must also be well posed, as it is in experiments, on the long time scale. The problems here come from diffusion forces and flows are very much weaker and act typically on a time scale of minutes or longer. Of course, integrated to time

infinity, the diffusion forces and flows can produce concentration changes of great (even unlimited) importance. That is another of the issues we deal with here. Introducing the shunt conductance (or shunt resistance, typically 10^{11} ohm, i.e., 100 Gohm, or 10^{-11} Siemens, i.e., 10 pS), sometimes called the leakage conductance or the ‘membrane’ conductance (referring to the specific origin of the conductance when a lipid membrane is used to support an ion channel).

Capacitance to ground, a physical low pass filter. Finally, I introduce a new idea, that undoubtedly will have unforeseen consequences and ‘errors’ in application, because I have not had a chance to discuss it with colleagues, unlike the issues just discussed.

I suggest that we also include **explicitly** the capacitance to ground between bathing solutions (and channel, although that is not important) and the grounded metal plate always placed just under the baths in real experiments. This capacitance to ground acts as a ‘low pass filter’; it dampens voltage changes by providing a path for capacitive current (proportional to $\partial V/\partial t$) to leave the system. This damping decreases noise and transients in experiments making recordings much ‘cleaner’. I suspect — but do **not** know for sure — that including this capacitance to ground will make numerical problems easier. We will not know for sure until we implement the idea.

Theoretical Model. The equations we consider are just the PNP equations themselves, with ions treated as points, since as far as I can tell the issues of well posedness are the same in PNP as in more realistic models like the primitive model mentioned above.

The central theme is that **electrical variables always take precedence. Equations should always integrate electrical variables explicitly**, dealing with chemical variables secondarily. Net

charge should never be computed from $\rho = \sum_{i=1}^N z_i F c_i$. Indeed, the only use of that equation that

I can imagine is to compute the concentration of a species needed to make the solution electrically neutral, with $\rho = 0$, to chemical precision. Chemical precision here means that in chemical units ρ is much smaller than any c_i . Note that the statement “ $\rho = 0$, to chemical precision” does not mean that the charge term on right hand side of the Poisson equation is zero!

This approach implies a change in the numerical procedure and computer codes as usually written. I believe one should explicitly write and integrate explicitly the flow equation for electrical current.

Historically, the PNP equations are nearly always written to specify the flux of ions, not the flux of electrical charge. The current is computed as the sum of the (weighted) fluxes of the PNP equation, plus the capacity current. The numerical implementation of PNP done this way is always on the edge of disaster. It is very easy somewhere to try to estimate NET charge

$\rho = \sum_{i=1}^N z_i F c_i$, or flux of current, or charge on the boundary etc by summing the concentrations,

flux of ions, or concentrations on the boundary.

Any attempt to estimate electrical variables by summing ‘chemical’ variables is likely to produce disaster.

We shall see that more is involved than simple algebra. There is a tension between the electrical boundary conditions I advocate and the usual formulation for PNP, which specify all of the concentrations c_j corresponding to the fluxes J_i , and not the current J . Specifically, the usual boundary conditions specify the c_j as constants imposed at either $t=0$ or even before that, at $t=-\infty$. They specify a potential applied across the system of V imposed at $t=0$ and switched in a schedule to other potentials at other times. (These are the pulse patterns introduced to such useful effect by (Hodgkin and Huxley 1952c, a) that form the basic paradigm of electrophysiology, ever since then, reviewed in (Bezanilla et al. 1982).

Now, to Equations. Here is a version of PNP in which Maxwell’s version of the continuity equation **for charge** is always used so the resulting flux equation for the flux \mathbf{J} of charge (i.e., flux of total electric current) is always explicitly displayed and integrated.

Everything starts with Poisson

$$-\nabla \cdot (\epsilon \nabla \phi) = P_{Protein} + F \sum_{i=1}^{i=N} (z_i c_i) = F P_{Protein} + \rho \quad (1)$$

$$\rho = \sum_{i=1}^N z_i F c_i \quad (2)$$

It is vital to remember that eq. (2) can NOT be used to compute $\rho = \sum_{i=1}^N z_i F c_i$ because, roughly speaking

$$\frac{\rho = F \sum_{i=1}^N z_i c_i}{F \sum_{i=1}^N c_i} < \sim 10^{-10}, \text{ depending on location and conditions, always very small} \quad (3)$$

The enormous strength of the electric field forces the net charge to be very small. If the net charge is not small, large gradients of potential exist which destroy biological systems. As a rule of thumb, membranes, proteins and ion channels are destroyed if potentials of 200 mV are applied to a system or fields are larger than $200 \text{ mV}/(\text{thickness of a lipid membrane} = 2 \text{ nm}) = 2 \times 10^6 \text{ volts/cm}$. When ρ is this small, it cannot be computed by executing the sum shown in eq. (2). Indeed, eq.(2) can be used to determine a particular concentration c_m from the other concentrations, if for some reason c_m is not known, but it can never be used to determine ρ . Round off and other errors make eq.(2) useless for computation. Rather, the Poisson equation (1) itself must be used to compute ρ .

The flow equation for the total charge in the system without shunt capacitance is

$$\nabla \cdot \mathbf{J} + \frac{\partial \rho}{\partial t} = \nabla \cdot \left(\mathbf{J} + \frac{\partial \mathbf{D}}{\partial t} \right) = 0 \quad (4)$$

or if we suppress Maxwell's dreadful displacement field \mathbf{D} (introduced before the electron was discovered and so before permanent charge was known to exist) and use more modern notation

$$\nabla \cdot \mathbf{J} + \frac{\partial \rho}{\partial t} = \nabla \cdot \left(\mathbf{J} + \frac{\partial (\varepsilon \mathbf{E})}{\partial t} \right) = 0 \quad (5)$$

This is eq. 6.4 of Jackson, p. 238, expanded, see p. 154. I follow Jackson's notation exactly and use ε for the permittivity. Permittivity ε has units. It is not the dielectric 'constant'.

Now we introduce the Nernst Planck equations for the flux of individual ions (NOT the flux of ionic current \mathbf{J} , rather the flux of the number of ions).

$$\mathbf{J}_i = -D_i \left(\nabla c_i - \frac{F}{RT} z_i c_i \nabla \phi \right); \quad i = 1, \dots, N \quad (6)$$

I use the diffusion coefficient and not mobility to avoid the confusion between the two definitions of mobility (absolute and electrical) in the literature. Obviously if the Einstein approximation fails and enough information is available to distinguish mobility from diffusion coefficient, the mobility should be used explicitly, and the choice of definition should be made explicitly.

It is important to remember that ions of different charge (i.e., valence) z_i are very important in biology (calcium ions Ca^{2+} have charge +2; chloride Cl^- ions have charge -1 ; sodium Na^+ and potassium K^+ ions have charge +1). They all have significantly different diffusion coefficients. It is **NEVER** permissible to treat all ions as having the same diffusion coefficient or the same (magnitude let alone sign) of charge if one wants to deal with biology.

Next, we relate eq. (6) and (5) by explicitly summing over all the ions to get total flux of charge

$$\mathbf{J} = \sum_{i=1}^N \mathbf{J}_i = \sum_{i=1}^N \left(-D_i \nabla c_i - \frac{F}{RT} z_i c_i \nabla \phi \right) \quad (7)$$

Maxwell Continuity eq. (5) gives the equation for continuity of electric charge, i.e., current

$$\nabla \cdot \mathbf{J} = \nabla \cdot \left[\sum_{i=1}^N \left(-D_i \nabla c_i - \frac{F}{RT} z_i c_i \nabla \phi \right) \right] = -\nabla \cdot \left(\frac{\partial (\varepsilon \mathbf{E})}{\partial t} \right) = -\nabla \cdot \left(\frac{\partial (\varepsilon \nabla \phi)}{\partial t} \right) = \frac{\partial (\varepsilon \nabla^2 \phi)}{\partial t} \quad (8)$$

I leave the permittivity inside the brackets so we never forget the assumption that is involved in moving it outside! And then we have the classical continuity equation for the flux of charge \mathbf{J} (remember \mathbf{J} is the flux of charge, not the flux of ions).

$$\nabla \cdot \mathbf{J} = \nabla \cdot \left[\sum_{i=1}^N \left(-D_i \nabla c_i - \frac{F}{RT} z_i c_i \nabla \phi \right) \right] = -\frac{\partial \rho}{\partial t} \quad (9)$$

$$\nabla \cdot \mathbf{J} = \sum_{i=1}^N z_i F \frac{\partial c_i}{\partial t} = \frac{\partial}{\partial t} \sum_{i=1}^N z_i F c_i \quad (10)$$

It is very important that no attempt be made to compute the sum on the right hand sides of eq. (10) from the concentrations c_i . The sum $\sum_{i=1}^N z_i F c_i$ is ill posed, and must be nearly equal to zero, because of the enormous strength of electrical forces, summarized by the (approximate) physical principle of electroneutrality. **One must never compute the sum $\sum_{i=1}^N z_i F c_i$ or its equivalent.** Rather, one must compute ρ the net charge and its time derivative directly, for example, from the Poisson equation (1), without summing concentrations or even their rate of change.

In fact, the numerical properties of ρ are so different, depending on how it is computed, that it would be wise to use separate symbols in computer programs for the ρ of eq. (9) and the ρ of eq. (1), on the right hand side of the Poisson equation. That way they will not be inadvertently interchanged

Note the form of the continuity of mass for each species

$$\nabla \cdot \mathbf{J}_i + \frac{\partial c_i}{\partial t} = 0 \quad (11)$$

and the form for the continuity equation of total 'mass'.

$$\sum_{i=1}^N (\nabla \cdot \mathbf{J}_i) = -\sum_{i=1}^N \frac{\partial c_i}{\partial t} = -\frac{\partial}{\partial t} \sum_{i=1}^N c_i \quad (12)$$

The mass continuity equations are **not** equivalent to the Maxwell continuity equation. They do not involve the charge $z_i F$, at all. For example, the sum $\frac{\partial}{\partial t} \sum_{i=1}^N c_i$ is well posed and easy to compute because all its terms are positive while the corresponding terms in the sum for net charge ρ in eq. (10) can be positive or negative. In order to avoid confusion we do not even have a symbol for the flux of total mass $\sum_{i=1}^N \mathbf{J}_i$.

Boundary Conditions. We need to set boundary conditions on the electrical potential and charge, and write equations defining how we measure current \mathbf{J} to correspond with experiment. Here is where we will introduce the shunt conductance and the shunt capacitance discussed in the beginning of this paper. The basic plan is to **relax our boundary conditions on concentration and charge ρ . We must allow one of the concentrations c_m (for example) to**

'float', i.e., to be determined by the rest of the problem. We also must allow the charge ρ to float, to be determined by the rest of the system. We do this by including additional pathways for flux and current. These additional pathways always exist in experiments. The pathway for shunt electrical current is the shunt capacitance $\mathbf{J}_{capacitance}$. The pathway for individual ionic flux current is the leak or shunt conductance \mathbf{J}_{shunt} .

The shunt capacitance drives a current $\mathbf{J}_{capacitance} = C_{shunt} (\partial V / \partial t)$ that adds to the current \mathbf{J} of eq. (7) once units are sorted out. The units of $\mathbf{J}_{capacitance}$ are amps. The units of C_{shunt} are farads, i.e., Coulombs volt⁻¹. The units of \mathbf{J} in eq. (7) are not the same as the units of $\mathbf{J}_{capacitance}$. The current \mathbf{J} in eq. (7) must be scaled to be a new variable to deal with the geometry of the system. The units of the new (unnamed) scaled variable is amps, so it can be added to $\mathbf{J}_{capacitance}$ in amps. The exact formulas depend on the geometry and so have to be worked out separately for each application, easily enough.

Shunt Conductance. The usual formulation of PNP sets boundary conditions on all N of the ionic species and ignores the experimental reality that \mathbf{J} is measured, not \mathbf{J}_i . It is obviously impossible to specify N concentrations and deal with their fluxes as if they are independent, and also place conditions on the total current \mathbf{J} .

This apparent paradoxical situation is resolved when we realize that to make the system well posed (i.e., to reach steady state when concentrations and potentials on the boundaries are constants independent of time), we must introduce a shunt path that allows one of the concentrations to 'float', i.e., to take on any value as a function of time. The floating concentration is specified at $t = 0$ but not at later times.

In experiments, the leak flux \mathbf{J}_{shunt} arises in many places. It can be flux through the lipid membrane, or through the seal between membrane and the plastic of the bath. Or it can be leakage through inadvertent unspecified pathways (i.e., dirt) that can easily arise in systems where resistances are of the order of 10¹¹ ohms. (The resistance of most insulators is much less than 10¹¹ ohms and so very special methods are necessary to record single channel currents (Sakmann and Neher 1995; Sigworth and Neher 1980; Hamill et al. 1981; Sigworth 1986; Sigworth 1995; Rae et al. 1988; Levis and Rae 1992; Rae and Levis 1992b, a; Levis and Rae 1993; Levis and Rae 1995; Tang et al. 1995; Levis and Rae 1998; Cherny et al. 2003; Rae and Levis 2004). So we do not have a unique way to describe \mathbf{J}_{shunt} .

I suggest that we describe it in the same 'space' of physics that we have been using., which, by the way, is the approach Hodgkin and Huxley used in their treatment of their leakage conductance (Hodgkin and Huxley 1952e, b; Hodgkin and Huxley 1952d, c, a; Hodgkin et al. 1952).

I suggest we **define** the \mathbf{J}_{shunt} by the conductance of the ion m of least interest, that changes the concentration in the bath most slowly. We add an additional shunt path **for just this ion** giving us now $N + 1$ fluxes \mathbf{J}_i where we only had N before. (I do not count the capacitive flux because its equation is so different in form and behavior.)

$$\mathbf{J}_{shunt} = -D_m \left(\nabla c_m - \frac{F}{RT} z_m c_m \nabla \phi \right); \quad i = 1, \dots, N+1 \quad (13)$$

We choose values of D_m so the flux \mathbf{J}_{shunt} has no significant effect on the properties of interest. \mathbf{J}_{shunt} exists so that the concentration c_m can float (after it starts at an initial specified value). That way, we have N total flux equations. $N - 1$ of these are equations for individual ion fluxes, with Dirichlet boundary conditions at all times. One of these equations is the equation for total current \mathbf{J} , see eq. (7). The system is well posed.

We now have two flux equations for the same ionic specie c_m , one the real one and the other the leak. This does not cause trouble in the cases of interest because we can choose parameters for the leak path so the system is not perturbed in the time domain we study. The leak ensures that at infinite time the system will be stable.

There is quite legitimate concern that not every system can be handled this way. For example, this approach will work if the flux of species c_m through \mathbf{J}_{shunt} is not of interest, is small compared to the fluxes through the membrane, perhaps including \mathbf{J}_m , etc. It will work best if the baths are so large that the flux of c_m through \mathbf{J}_{shunt} does not change concentrations we care about in the times of interest. A looser way to choose the properties of the leak is to choose parameters so the leak flux is 0.001 times the flux of the rest of the system. Typical values in experiments would be 10^{11} ohms (converting to strictly electrical units, for the entire system).

In general, this approach will fail when experiments cannot be done. Such cases exist mathematically, and in thought experiments, but obviously they have not been studied very much in the lab!!

Shunt Capacitance. Now, we introduce the shunt capacitance. We also must allow the charge ρ to float, to be determined by the rest of the system. We do this by including additional pathways for shunt electrical current, the shunt capacitance. The additional pathway always exist in experiments. It physically has many components: (1) the capacitance across the insulating lipid membrane in a typical single channel lipid bilayer setup (2) the capacitance between wires (3) other stray capacitances in the system. A typical number would be 100 pF 10^{-10} farads (coul volt⁻¹).

The shunt capacitance drives a current $\mathbf{J}_{capacitance} = C_{shunt} \frac{\partial V}{\partial t}$ that adds to the current \mathbf{J} of eq. (7), once units are sorted out. The units of $\mathbf{J}_{capacitance}$ are amps. The units of C_{shunt} are farads, i.e., Coulombs volt⁻¹. The units of \mathbf{J} in eq. (7) are not the same as the units of $\mathbf{J}_{capacitance}$. The current \mathbf{J} in eq. (7) must be scaled to be a new variable to deal with the geometry of the system. The units of the new (unnamed) scaled variable is amps, so it can be added to $\mathbf{J}_{capacitance}$ in amps. The exact formulas depend on the geometry and so have to be worked out separately for each application, easily enough.

Capacitance to ground. In a real experiment a grounded metal plate is close to the baths in an electrochemical cell creating a total capacitance of hundreds of pF, i.e., some 3×10^{-10} farads (coul volt⁻¹). This capacitance decreases noise, acting as a low pass filter, because, I imagine it damps rapid voltage excursions, siphoning away the displacement current $C(\partial\phi/\partial t)$ that produces those voltage changes.

If the system has little depth, so the potential in the baths is not a function of the distance from ground plate, I suggest we simply add a flux through this capacitance to ground (in suitable) units to the flux of charge, the current \mathbf{J} in eq. (7) I suggest we use the modified flux equation for charge

$$\mathbf{J} = -C_g \frac{\partial\phi}{\partial t} + \sum_{i=1}^N \mathbf{J}_i = -C_g \frac{\partial\phi}{\partial t} + \sum_{i=1}^N \left(-D_i \nabla c_i - \frac{F}{RT} z_i c_i \nabla \phi \right) \quad (14)$$

I hope the sign on the capacitance term is correct. The units of C_g are chosen to be commensurate with those of \mathbf{J} . The total capacitance over both baths to ground should be around 200 pF, i.e., 2×10^{-10} farads (coul volt⁻¹).

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