1979

A network thermodynamic two-port element to represent the coupled flow of salt and current. Improved alternative for the equivalent circuit

D. C. Mikulecky
Virginia Commonwealth University

Follow this and additional works at: http://scholarscompass.vcu.edu/phis_pubs
Part of the Medicine and Health Sciences Commons


Downloaded from
http://scholarscompass.vcu.edu/phis_pubs/35

This Article is brought to you for free and open access by the Dept. of Physiology and Biophysics at VCU Scholars Compass. It has been accepted for inclusion in Physiology and Biophysics Publications by an authorized administrator of VCU Scholars Compass. For more information, please contact libcompass@vcu.edu.
A NETWORK THERMODYNAMIC TWO-PORT ELEMENT TO REPRESENT THE COUPLED FLOW OF SALT AND CURRENT

IMPROVED ALTERNATIVE FOR THE EQUIVALENT CIRCUIT

D. C. MIKULECKY, Department of Physiology, Medical College of Virginia, Richmond, Virginia 23298 U.S.A.

ABSTRACT A two-port for coupled salt and current flow is created by using the network thermodynamic approach in the same manner as that for coupled solute and volume flow (Mikulecky et al., 1977b; Mikulecky, 1977). This electrochemical two-port has distinct advantages over the equivalent circuit representation and overcomes difficulties pointed out by Finkelstein and Mauro (1963). The electrochemical two-port is used to produce a schematic diagram of the coupled flows through a tissue. The network is superimposable on the tissue morphology and preserves the physical qualities of the flows and forces in each part of an organized structure (e.g., an epithelium). The topological properties are manipulated independently from the constitutive (flow-force) relations. The constitutive relations are chosen from a number of alternatives depending on the detail and rigor desired. With the topology and constitutive parameters specified, the steady-state behavior is simulated with a network simulation program. By using capacitance to represent the filling and depletion of compartments, as well as the traditional electrical capacitances, time-dependent behavior is also simulated. Nonlinear effects arising from the integration of equations describing local behavior (e.g., the Nernst-Planck equations) are dealt with explicitly. The network thermodynamic approach provides a simple, straightforward method for representing a system diagrammatically and then simulating the system's behavior from the diagram with a minimum of mathematical manipulation.

INTRODUCTION

Background

The equivalent circuit representation of electrochemical transport processes through membranes has become an accepted paradigm for biologists. Its earlier applications were the representation of the ionic currents in nerve membrane (e.g., see Cole, 1971; Katz, 1966). Recently, this manner of representation has been applied to organized membranes such as epithelia (e.g., see Helman and Risher, 1977; Schultz et al., 1977), where it is much less useful. Earlier, Finkelstein and Mauro (1963) made an extensive analysis of the equivalent circuit representation of ionic systems and found it to be lacking in some significant ways. The following difficulties were recognized to be inherent in the equivalent circuit paradigm.

LIMITED USEFULNESS OF THE "MIXED" EQUIVALENT CIRCUIT TO DESCRIBE TRANSIENT STATES Two types of equivalent circuit are possible for an ionic system and only one of them (the "pure electrical" equivalent circuit) applies to transient states. The
"mixed equivalent" circuit, which combines information about the ion flows and electrical aspects of the system, happens to be more popular in physiological modeling. The mixed equivalent circuit is applicable only in steady states and is a misleading representation of the actual physical and morphological properties of a given membrane system. These difficulties are manifest in the most modern applications of the mixed equivalent circuit to epithelia and other organized tissues.

**Inability to Give a Physically Meaningful Representation of the Ionic and Electrical Current Flow Through the Various Branches Simultaneously with the Electrical Potential and Concentrations at Each Point in the Circuit**

For example, in the case of multiple ion flows through an epithelial membrane, a problem arises in the representation of the currents carried through the tissue by the cations, Na⁺ and K⁺, and the electrical potential at points inside the tissue (such as in the cell) in each of the ionic current branches. As Schultz et al. (1977) pointed out, the ionic current branches must be kept separate (unconnected) throughout the tissue in order that the ionic currents maintain their chemical identity and do not mix. To achieve this, the circuit had to be drawn so that the electrical potential at a point inside the tissue (e.g., intracellular) would only be the same in the two ionic current branches for one value of the transepithelial electrical potential difference! This problem is inherent in the equivalent circuit paradigm.

**The Use of Batteries to Depict the Electrical Equivalent of the Concentration-Dependent Contribution of an Ion's Electrochemical Potential**

This practice has worked for a limited number of situations, but obscures some of the physical reality of even those cases where it works. The "battery" combines in itself information about the concentration driving force of an ionic species and the contribution of the ionic concentration distribution between two compartments to the electrical potential. This is a typical cross effect in nonequilibrium thermodynamics, and it involves an extra phenomenological coefficient: the transference number (Katchalsky and Curran, 1965). Because the flow involves the amount of ion entering or leaving a compartment, which is proportional to its concentration, whereas the battery depends logarithmically on concentration, the batteries either must be related in a nonlinear manner to the particular ionic current with which they are identified, or the system must be kept at constant ionic concentration. We will show that this battery really is a generalized capacitor, and that the relationship between ionic current and rate of change of potential is characteristic of a nonlinear capacitor.

**Nonlinearity of Various Circuit Elements**

Inherent in any analysis of electrochemical events in a biological system is the problem of nonlinearities, some of which result from concentration dependence. This concentration dependence arises from the well-accepted, fundamental starting point for rigorous analysis—the Nernst-Planck equations. Integration of these equations has been a challenge for many years; often a rigorous application of the global result is difficult, if not impossible, because of the transcendental nature of the concentration-potential-flow relations (Helfferich, 1962, for example). Generally, the equivalent circuit is depicted with nonlinear elements (or, by linear elements when they are indeed nonlinear) but analyzed as if it were linear.

Even in the case of the constant field approximation, one can observe bifurcation of the global solutions of the same type as demonstrated for the convection-diffusion equation's solution describing global solvent-drag effects (Mikulecky, 1977). In each case, the "bi-
furcation" is of a type that results from the fact that the global solutions depend on the direction of the flow or force which is superimposed on diffusion locally—either volume flow or electrical field/current flow. In the case of wide, charged pore membranes, such as those described by Teorell (1959a and b), the bifurcation may result in interesting oscillations and flip-flop behavior that can now be described in terms of the cusp catastrophe (Mikulecky et al., 1977a; Thedford et al., 1977). The cusp catastrophe is one of the seven elementary catastrophes of Thom (1975). The bifurcation in the "constant field" equation's solution has been recognized (Katz, 1966, p. 60, for example) although not explicitly called by that name. An example of an experimentally demonstrable bifurcation in the behavior of a biological electrochemical system has been discovered by Schwartz and Kado (1976).

The lack of a unique mapping to more detailed models Generally, because of a shortage of experimental data, equivalent circuit models are simplifications (Norton or Thevenin equivalents) or any detailed anatomical compartmentalization of the actual biological system. For example, the frog skin is usually modeled by a two or three barrier system between three compartments, whereas Huf and Howell (1976) have used a more complete compartmentalization suggested by the morphology. Once a simplified model is fit to the experimental data as a Norton or Thevenin equivalent, there is no unique physical significance to the resistances in these circuits relative to the more detailed network which corresponds more closely to the morphology. Thus, an equivalent circuit model may have a limited usefulness as the experimental information available increases. On the other hand, a network model that depicts the anatomy and other complexity from the start is reducible to a simpler model in a unique manner. The relation to the detailed model is easily made explicit.

To the extent that the equivalent circuit affords a useful pictorialization how the various ions traverse a membrane, it has been an aid in the analysis and formulation of some important and difficult physiological problems. It also has been a useful didactic tool. It is now possible to combine these features with a more accurate representation based on rigorous thermodynamic reasoning.

The Advantages of Network Thermodynamics

Network thermodynamics provides a means for overcoming the difficulties inherent in the equivalent circuit. As will be shown in the main part of this paper, the problems listed above are all more easily dealt with using this new approach. The basis for the particular version of network thermodynamics to be used here has been presented elsewhere and compared with other versions (Mikulecky et al., 1977b). Examples of how specific systems are modeled and simulated on the computer are also available. The coupled flow of solute and volume in kidney proximal tubule has been simulated and provides an example of how parameters can be fit once a topology is chosen (Thomas and Mikulecky, 1978b). The compartmental analysis of sodium flow in frog skin is another example (Huf et al., 1978; Mikulecky et al., 1979). Besides explicitly overcoming the difficulties in the equivalent circuit approach, the network models lend themselves to direct simulation using circuit simulation programs (Barocas, 1977; Chua and Lin, 1975; Blattner, 1976; Kaplan, 1975; and Appendix). This allows the computation of the flows through, and concentrations, pressure and electrical potential inside, an organized membrane system by a program that needs

D. C. Mikulecky *Electrochemical Two-Port Network Element* 325
only the schematic diagram of the network and the values of the membrane parameters in the system. In the references cited as examples above, the problems arising in choosing a topology and parameters are discussed in more detail.

Inasmuch as the network thermodynamic approach uses the integrated form of the Nernst-Planck equations or their equivalent, it is possible to incorporate a number of different assumptions and/or approximations into the constitutive relations defining the network elements. In the most complicated cases, the rigorous nonlinear global description may be applied using graphical methods (Mikulecky, 1977) or computer simulation, (Mikulecky et al., 1979; Thomas, 1977; Thomas and Mikulecky, 1978b). The network thermodynamic approach has a diagrammatic representation faithful to the physical nature of the ionic and/or current and salt flows and their driving forces, as well as to the tissue morphology. Even in extreme cases of highly nonlinear, nonreciprocal behavior, the network topology conveys its own information about an organized system independently, so that once a network is anatomically correct and accounts for all the flows to be modeled, its elements' constitutive relations can be manipulated to achieve a best fit with experimental observations (see Thomas and Mikulecky, 1978b). When a qualitative feeling for the system is sought, linearizations, upper and lower limits, and other simplifying approximations can be used initially; then the model can be made progressively more rigorous as required without further modification of the topology. Also, the network models have the property of allowing networks to be "nested" in networks, in complete harmony with the hierarchical nature of living systems (Conrad, 1972; Rosen, 1969; Pattee, 1970).

As a first step in moving from the ionic currents and their conjugate driving forces as used in the equivalent circuit representation, the transformation introduced by Kedem and Katchalsky (Katchalsky and Curran, 1965) for converting to electrical current and salt flow and their conjugate forces can be utilized.

**THE ELECTROCHEMICAL TWO-PORT**

*From Ionic Currents to Electrical Current and Salt Flow in a Discontinuous System*

As an example of the network thermodynamic approach to the description of ionic flows through tissue, a two-port element for a single salt will be developed in detail here. (A port is a set [pair] of input-output pathways through a structure such as a membrane, or an electrical resistor. The familiar electrical resistor and capacitor are one-ports. A transformer is a two-port. In the case of network thermodynamics two-port and multiports are generally energy transducers coupling one form of energy to another. In this case the chemical energy of a salt is coupled to the electrical energy in the electrochemical system. For more detail on these thermodynamic multiports, see Mikulecky et al., 1977).

The electrochemical two-port element, and its extension to multiports for the cases of more than one salt and/or other coupled flows, utilizes the transference number as a coupling coefficient in a manner analogous to the reflection coefficient in the convection-diffusion two-port (one definition of the ionic transference number is the fraction of the total current due to the concentration distribution of a given ion. In a reciprocal system it is also the ionic current induced by an overall electromotive force in the system). Because the ionic currents in any ionic system always add to the total current, it is often convenient.
to use neutral salt flow and electrical current flow as independent flows instead of the ionic flows (see Katchalsky and Curran, 1965, for the case of a single salt, and Mikulecky, 1969, for an extension to the case of multiple salts). This is achieved in a simple way when a reversible electrode system (such as Ag-AgCl) is either actually or virtually used to make electrical measurements and to pass current in the system. In a system of a single univalent salt, the ionic currents can be expressed by the equations

\[ I_i = F L_{i1} \Delta \hat{\mu}_i, + F L_{i2} \Delta \hat{\mu}_2, \]  
(1)

\[ I_2 = F L_{21} \Delta \hat{\mu}_1, + F L_{22} \Delta \hat{\mu}_2, \]  
(2)

where \( F \) is the Faraday constant, \( \Delta \hat{\mu}_i \) is the electrochemical potential difference of ion \( i \), and the \( L_{ij} \) are phenomenological coefficients that relate the flows (currents) and forces (potentials).

At the constant pressure, the electrochemical potential of each ion is made up of a concentration-dependent part and an electrical part,

\[ \Delta \hat{\mu}_i = \Delta \hat{\mu}_i + Z_i F \Delta \psi. \]  
(3)

In the case of an electrode reversible to species 2 (for concreteness assumed to be an anion) the electrostatic potential between the electrodes, \( E \) (the electromotive force, which is the potential “seen” by a potentiometer connected between the electrodes), and the membrane potential, \( \Delta \psi \), is related via the concentration-dependent part of the chemical potential of ion 2,

\[ \Delta \psi = E + \Delta \mu_2 / F, \]  
(4)

or

\[ FE = -\Delta \hat{\mu}_2. \]  
(5)

The salt chemical potential is defined by

\[ \Delta \mu_s = \Delta \hat{\mu}_1 + \Delta \hat{\mu}_2. \]  
(6)

Using Eqs. 1–6, the expressions for the ionic currents \( I_1 \) and \( I_2 \) can be transformed into expressions for electrical current and salt flow,

\[ I = \tau E_s + \kappa E, \]  
(7)

\[ I_s = PE_s + \tau E, \]  
(8)

where we have assumed that \( L_{12} = L_{21} \), and the new symbols are defined by \( I_s = I_1 \), \( I = (I_1 - I_2) \), \( \tau = (L_{11} - L_{12}) F^2 \), \( P = L_{11} F^2 \), and \( \kappa = (L_{11} + L_{22} - 2L_{12}) F^2 \), and \( E_s = \Delta \mu_s / F \).

The Network Representation of the Electrochemical Two-Port

Eqs. 7 and 8 are the constitutive relations for an electrochemical two-port element identical in form to that used for coupled salt and volume flow in previous work (Mikulecky et al., 1977b). An example of different representations of this element is shown in Fig. 1. In Fig. 1a, the relation between the diagram and Eqs. 7 and 8 is best seen if the equations are

D. C. MIKULECKY  Electrochemical Two-Port Network Element 327
inverted so that the forces $E$ and $E_s$ are expressed as functions of the flows $I$ and $I_s$. These "resistive form" equations then are readily obtained from the diagram by applying Kirchhoff's voltage law around each loop. In Fig. 1b, the sources should be imagined to be connected so that $E$ is across nodes 1 and 4 and $E_s$ is across nodes 5 and 8. Once again, applying Kirchhoff's voltage law around each loop generates the equations. Thus, it is possible to replace an equivalent circuit representation of a tissue by a network of two-ports (or multiports) which keeps a 1:1 correspondence with the anatomical structure and also preserves the relation between the physical flows and forces at each point in the system. For example, Fig. 2, identical to that used for coupled salt and water flow through an epithelial membrane (Mikulecky and Thomas, 1978), is now equally well interpreted as representing coupled current and salt flow through the epithelium under conditions of zero volume flow. The solid and dotted lines depict the salt and current flow pathways, respectively. Each compartment in the system is represented by one node (connection point) for salt potential (a function of concentration) and another for electrical potential. In the steady state only the dissipative elements (electrochemical two-ports) and sources representing pumps and clamped bath concentrations and potentials (not shown) are necessary to define the system's behavior. For the transient case generalized capacitors will also be necessary as is explained later. (A lucid explanation of the thermodynamic distinction between generalized capacitance [classic thermodynamics] and generalized resistance [steady-state thermodynamics] has been given by Wyatt, 1978.) The two-ports do not allow the identity of salt and electrical current to become lost, i.e., they cannot mix. This isolation of the various flows would be even more important as more chemical species (charged or noncharged), volume flow and pressure effects, or other features were added to the model. The addition of other, distinct flows can be visualized by more branches in the network in Fig. 2 passing through the ports parallel to those already there. These additional branches must be connected at

---

**Figure 1**

(a) Two-port for coupled current and salt flow after that for coupled solute and volume flow (Mikulecky et al., 1977b). $R_1 = 1/2\alpha$; $R_2 = (\epsilon + \tau)/(2P\alpha - \tau^2)$; $R_{12} = -\tau/(P\alpha - \tau^2)$. Because $R_{12}$ is negative, the controlled source mimics the solvent-drag aspects of the convection-diffusion situation (Mikulecky, 1977). (b) Alternative representation for use in a simulation program. Resistances have the values in (a). The diamond-shaped elements represent current-controlled potential sources which depend on the currents in the other branch of the two-port, so that $E' = R_{12}I_s$, where $I_s$ is the current through $E'_s$, and $E'_s = R_{21}I$ where $I$ is the current through $E'$. The salt flow current branches and the electrical current branches never join in a node so that the currents can, indeed, be separated. The controlled sources provide a means for sensing the currents in the other branch to make it possible to model the coupling between the two processes. An alternative way of accomplishing this coupling would be to make the dependent sources voltage-dependent current sources and to place them in parallel with the resistors rather than in series.
Figure 2  Two-port network for coupled salt and current flow in an epithelium after the case for coupled solute and volume flow (Mikulecky and Thomas, 1978). The two-ports represent the elements described in Fig. 1 at each barrier: 12, brushborder membrane, 34, shunt pathway; 56, basolateral membrane; and 78, basement membrane. The various node voltages are either the electrical potential, $V'$, or the salt potential, $V'_s$, where $i$ stands for the compartment symbols: L, lumen, C, cell, ISS, interstitial space, and B, blood. $I_p$ is the salt pump (a current source).

their own nodes as are the two existing sets of branches. Notice that special features, such as pumps (in this case a salt pump) can be placed in select parts of the system, as in the case of the current source in the basolateral membrane. The internal structure of the multiports would be according to the scheme in Mikulecky et al. (1977b) for algebraic analysis. Alternatively, an extension of the simulation technique depicted in Fig. 1b, utilizing controlled sources to "couple" the various flow-force pairs in the multiport, would be employed for computer simulation. The dependencies of a given flow and/or force on flows and forces in any part of the network can be handled in this way. For coupled systems, the dependent sources generate a flow which arises from a nonconjugate (in the sense of nonequilibrium thermodynamics) force. This is discussed further in the Appendix. The algebraic analysis of Mikulecky and Thomas (1978) for the convection-diffusion two-ports would serve equally well as an algebraic solution to the network in Fig. 2, for the case of linear electrochemical two-ports.

As in the case of coupled salt and volume flow in epithelial membranes (Mikulecky and Thomas, 1978) and more specifically in proximal kidney tubule (Thomas and Mikulecky,
1978b), it is possible to specify the values of only some of the concentrations and potentials (those in the lumen and blood, for example) and to solve algebraically or by simulation for those remaining (those in the cell and interstitial space, for example) as well as for the various salt flows and electrical currents. Each branch of the network has physical significance as a real thermodynamic flow through the system (salt or current). Each node has a concentration or electrical potential that is the true physical value for that compartment in the system. No matter how complicated the anatomic structure, the network can be made to match its complexity. For example, if the basolateral membrane were found to be nonhomogeneous, parallel two-port (or multiport) elements could be inserted to represent this feature.

The example of the epithelial membrane illustrates how the two- or multiport can eliminate the second problem listed earlier in the criticism of the equivalent circuit paradigm. The combination of nodes representing concentrations or electrical potential and the coupling of the salt and electrical parameters through the transference number in the two-ports (or multiports) replace the equivalent circuit "batteries." Sources may be placed at nodes to "clamp" their value (such as in the blood or lumen in Fig. 2), but they are connected between a node (compartment) and "ground" (reference state) and represent only a single compartment's contribution to the battery in the equivalent circuit. This becomes an essential feature in the treatment of nonsteady states or transients, where the sources may be replaced by capacitors if the value is unclamped.

The Use of Generalized Capacitance to Introduce Nonsteady-State Behavior

This technique is described in more detail elsewhere as a means for doing classic compartmental analysis by network thermodynamic methods (Mikulecky et al., 1979). It also has been extensively used along with inductance in the simulation of a number of aspects of the cardiovascular system (Rideout, 1972, 1975, 1976). It is only necessary to realize that the amount of material, \( S \), in a compartment is related to the concentration of that material, \( C \), by the compartment volume \( V \), \( C = S/V \). In the dynamic state, the amount of material entering or leaving the compartment per unit time, \( dS/dt \), is related to the rate of change of concentration, \( dC/dt \), by the volume as well,

\[
V \frac{dC}{dt} = \frac{dS}{dt}. \tag{9}
\]

The flow, \( J \), into or out of the compartment is \( dS/dt \) so that

\[
V \frac{dC}{dt} = J. \tag{10}
\]

The constitutive relation for an electrical capacitor is

\[
\gamma \frac{dE}{dt} = I, \tag{11}
\]

where \( \gamma \) is the capacity, \( E \) the potential difference across the capacitor, and \( I \) the current through it. Thus, Eqs. 10 and 11 represent special cases of a general concept of capacitance which has this constitutive relation (Oster et al., 1973; Wyatt, 1978), generalized capacity \( \times \) rate of change of "across" variable = through variable. The reader can easily test this notion on the relation between the pressure difference in a U-tube and the volume flow between the two halves.
The picture is not complete. What is missing in Fig. 2 (omitted for flexibility in this discussion) is that in a time-dependent analysis, every node not clamped by a source needs a capacitor to ground. In the salt flow part of the network, these would have values depending on the compartment volumes. In the electrical branch, they would represent a true electrical capacitance. The electrochemical two-ports have been designed so that the parameters pertaining to the salt also have units of electrical forces and flows. They are also linear in the salt "potential," $V_i = \mu_s/F$, so that the constitutive relation for the volume capacitors is,

$$I_s = [VF^2C_s/RT] \cdot \frac{dV_i}{dt}, \quad (12)$$

or

$$I_s = [VF^2\exp(E,F,RT)/RT \cdot (dE_s/dt)]. \quad (13)$$

(In Eq. 13 the exponentional is to be considered as multiplied by unit concentration, corresponding to the state where $\mu_s = 0$ or the "ground" state in the network. This is necessary to notice in order to keep the units consistent.) Thus, if electrical units are used for salt current and potential, there is a priori a nonlinear constitutive relation for the capacitor, i.e., the capacitance (the expression in brackets in Eq. 12) is potential dependent.

The alternative is to reformulate the constitutive relations for the two-port, using Kedem and Katchalsky's "trick" for linearizing in concentration rather than chemical potential, $\Delta \mu_s = RT\Delta C_s/\bar{C_s}$, where $\bar{C_s}$ is the logarithmic average concentration $\bar{C_s} = C_1 - C_2/\ln C_1/C_2$. Eqs. 7 and 8 defining the constitutive relations for the two-port are, in this coordinate system, nonreciprocal,

$$I = xE + (RT/F\bar{C_s}) \Delta C_s, \quad (14)$$

$$J_s = (\tau/F)E + (PRT/F^2\bar{C_s}) \Delta C_s. \quad (15)$$

Because Fig. 1a requires a reciprocal coordinate system, it can no longer be used as a representation (Mikulecky et al., 1977b) in this case, but, inasmuch as the transient problem is best left to simulation, the nonlinear coefficients in this set of equations present no real problem (see Appendix).

The advantages to the network representation are many, as has already been pointed out. The disadvantages are far less severe than those present in the equivalent circuit, but they can be dealt with more readily by following the procedures already established for the convection-diffusion two-ports or by the simulation techniques explained in the Appendix. The main problems, of course, arise as a result of the nonlinear aspects of the system (Mikulecky, 1977). To further examine these nonlinear aspects in the electrochemical case, the integration of the Nernst-Planck equations will be used for an example, with the realization that this leaves out the cross-coupling coefficients in the local ionic flow equations (analogous to $L_{12} = L_{21} = 0$ in the global Eqs. 1 and 2).

**Integration of the Nernst-Planck Equation: Analogy with the Kedem-Katchalsky Linearization of the Convection-Diffusion Equation**

The following discussion follows closely from an analysis of the case of convection and simultaneous diffusion (Mikulecky, 1977). In that analysis it was shown that the Kedem-Katchalsky (e.g., see Katchalsky and Curran, 1965) linear phenomenological equations were
not a rigorous linearization of the nonlinear, global equation, because no linearization other than the one resulting in Fick's law can be obtained from truncating the series expansion of the exponential terms in the nonlinear equations. On the other hand, it was also demonstrated that the Kedem-Katchalsky equations could be obtained by substituting the arithmetic mean concentration into the local convection-diffusion equation and treating this average as a constant during the integration to obtain the global equation. This suggests that the procedure is best viewed as a physically motivated linearization. This is not to say that a rigorous mathematical statement to justify such a physically motivated linearization does not exist. For the arithmetic mean, it is simply an application of the mean value theorem (Bressler et al., 1976) and also has a basis in kinetic theory (Mason et al., 1972). The use of an arbitrary average concentration provides a good approximation to the nonlinear situation as long as the concentration profile in the membrane is sufficiently close to a linear diffusion profile (Thomas and Mikulecky, 1978a), i.e., as long as diffusion significantly outweighs convection in its contribution to the solute flow. With this fact, the Nernst-Planck equation can be integrated as well. We will now show that with additional criteria, the arbitrariness of the average concentration is eliminated.

The local version of the Nernst-Planck equation (MacInnes, 1939) is modified to utilize an average concentration as follows,

\[ J_i = -u_i(R T C_i/dx + z_i F <C_i> d\psi/dx), \]  

where \(<C_i>\) is some average of the local concentration of the \(i\)th ion, \(u_i\) is its mobility, \(C_i\) is its local concentration, and \(Z_i\) is its valence. The variable \(x\) measures distance through the membrane and \(\psi(x)\) is the electrical potential at every point. This equation is readily integrated and multiplied by \(F\), to obtain an expression for the current carried by the \(i\)th ionic species,

\[ I_i = F u_i \frac{RT C_i + Z_i F <C_i> \Delta \psi}{\Delta x}. \]  

Notice that Eq. 17 differs significantly from that obtained by making the constant field assumption and does not require that constraint. It also requires no explicit assumptions about the current. So as long as the concentration profile is nearly linear, the result is valid for any value of the current, sufficiently small to be compatible with that condition. Once more, a nearly linear concentration profile requires that diffusion be dominant over the "convective" effect of current flow. The global result may be obtained by the direct integration used above, or it can also be obtained from applying the continuity equation in order to begin with the concentration profile (see Mikulecky, 1977, where this procedure is followed for convection-diffusion).

The definition of current for a solution containing only a univalent salt is

\[ I = (I_+ - I_-). \]  

Substituting from Eq. 17 for \(I_+\) and \(I_-\),

\[ I = (F/\Delta x)(RT(u_1 - u_2) \Delta C + F(u_1 + u_2) <C_i> \Delta \psi). \]  

Up to this point, the nature of the average concentration has been arbitrary, although a
number of criteria favor the choice of the arithmetic mean for convection-diffusion (Mikulecky, 1977). If the average concentration, \(<C_i>\), is chosen as Kedem and Katchalsky's logarithmic average,

\[
\bar{C}_i = \frac{\Delta C}{\ln C_L/C_R},
\]

then at zero current the result is the classic diffusion potential equation (MacInnes, 1939),

\[
\Delta \psi = \frac{RT}{F} \frac{u_1 - u_2}{u_1 + u_2} \ln \frac{C_L}{C_R}.
\]

Thus, the criteria for the choice of the average concentration are provided in both cases considered. The logarithmic average is compatible with the electrochemical contributions to the phenomenological equations, whereas the arithmetic average is most compatible with the convection-diffusion situation (Mikulecky, 1977; Mason et al., 1972). In the context of the Kedem-Katchalsky format the current flow equation can be rewritten as

\[
I = \tau E_s + \kappa E,
\]

where \(\tau = u_1 F^2 <C_i>/\Delta x\) and \(\kappa = F^2 (u_1 + u_2) <C_i>\). Likewise, the salt flow current is

\[
I_s = PE_s + \tau E,
\]

where \(P = RTF u_1 /\Delta x\). Comparing this result with the previous one (Eqs. 22 and 23 with Eqs. 7 and 8), the following identifications can be made, remembering that in the Nernst-Planck equations \(L_{12} = L_{21} = 0\),

\[
L_{11} = u_1 <C>/\Delta x,
\]

\[
L_{22} = u_2 <C>/\Delta x.
\]

Thus, the explicit nature of the concentration dependence of \(L_{11}\) and \(L_{22}\) at the local level would appear to be a linear dependence. The reasoning used thus far justifies the Kedem-Katchalsky format for the constitutive description of the two-port as long as the concentration-profile in the membrane does not deviate too severely from the linear diffusion profile.

**The Constant Field Approximation**

Situations involving significant deviations in the local concentration from the average concentration are better handled by using the constant field assumption and noticing the similarity of the resultant form of the Nernst-Planck equation with the convection-diffusion equation. Now the local form of the Nernst-Planck equation for the cation is

\[
J_s = u (RT dC_i/dx + FC_i \Delta \psi /\Delta x).
\]

The integrated form of this equation (Mikulecky, 1977) is

\[
J_s = P^b C_L - P^b C_R,
\]

where \(P^b\) is:
\[ P^f = P \cdot \lambda (\Delta \psi / \Delta x) / [1 - \exp(\lambda \Delta \psi / \Delta x)] \]  
(28)

and

\[ P^b = P \cdot \lambda (\Delta \psi / \Delta x) / [\exp(-\lambda \Delta \psi / \Delta x) - 1] \]  
(29)

where \( \lambda = z_i F / P \) and \( P = RTu \). As \( |\lambda \Delta \psi / \Delta x| \) gets large (>4.5), the value of \( J_1 \) approaches the limiting values

\[ J_1^{+*} \rightarrow C_l F \Delta \psi / \Delta x, \]  
(30)

and

\[ J_1^{-*} \rightarrow C_R F \Delta \psi / \Delta x. \]  
(31)

These results have the same form as those obtained for the convection-diffusion two-port which have been discussed extensively elsewhere (Mikulecky, 1977). The nonlinearity is easily handled by graphic techniques, circuit simulators (see Appendix), or a piecewise linearization based on Eqs. 30 and 31 as well as the Kedem-Katchalsky current flow equation (Thomas and Mikulecky, 1978a). The three linear expressions fit together at \( |\lambda (\Delta \psi / \Delta x)| = 2 \) with Eq. 30 being used if \( \lambda (\Delta \psi / \Delta x) > 2 \) and Eq. 24 being used if \( \lambda (\Delta \psi / \Delta x) < -2 \).

**SUMMARY AND CONCLUSIONS**

The equivalent circuit representation of ionic flows and electrical potentials and currents in organized tissues is not able to match both the anatomy and the physical nature of the flows (Finkelstein and Mauro, 1963). To overcome this difficulty, as well as to provide a computational and simulation capability tying into the remaining body of network thermodynamics, an electrochemical two-port is introduced. The constitutive relations of this two-port are arrived at from the Kedem-Katchalsky paradigm and independently from the local Nernst-Planck equations using either of two assumptions—that the concentration profile does not deviate significantly from the linear diffusion profile or that the electric field is constant. For more precise descriptions, one can employ the results of the Teorell-Meyer-Sievers or Schlögl calculations (Helfferich, 1962), which can only be used graphically or in a circuit simulator which allows some general statement of constitutive relations to be written in FORTRAN as ASTEC2 does (Barocas, 1977). By combining these two-port elements in networks and using capacitors to represent the charging and depletion of compartments, the relation between ionic flow and current flow in an organized tissue such as frog skin can readily be obtained and used to model experimental results with relative ease. (Mikulecky et al., 1977c; Gary-Bobo et al., 1978). The compartmental analysis model of Huf and Howell (1976) for sodium distribution and flow in the frog skin has been simulated on ASTEC2 in a simple straightforward manner by representing the compartmental system as resistance-capacitance network (Mikulecky et al., 1979; Huf et al., 1978). The Huf and Howell model has been made to reproduce a variety of experimental results (Huf and Howell, 1976). The information from that simulation has been used to further refine the two-port network for the frog skin and, eventually, other ionic species and volume flow effects will be included by replacing the two-ports by appropriate multiports. Various models for the pump behavior were tested as well.
The ability to nest networks within networks in a hierarchical organization provides a means by which some of the most complex levels of biological organization are readily being approached (Conrad, 1972; Rosen, 1969; Pattee, 1970). Other applications of these network thermodynamic techniques have reached the simulation stage of development, including models of hydraulic aspects of glomerular filtration (Thomas et al., 1978), pharmacokinetic studies of the fate of anticancer drugs at the cellular level (a reaction-diffusion problem), \(^1\) \(n\)th-order reaction kinetics in a reaction-diffusion situation, and a pump-leak model of calcium transport in sarcoplasmic reticulum. We have also carried out an analysis of coupled solute and volume flow in kidney proximal tubule (Thomas and Mikulecky, 1978b).

The modeling of a physiological system using network thermodynamics has two basic aspects: the determination of the network topology and the determination of the constitutive relations for resistive and capacitive elements. Because simulation of networks by a program such as SPICE2 is so quick and efficient, much of the fitting of a model to data can be done by trial and error. If values for parameters are not known, high and low limiting estimates often cause the behavior of the global model to bracket experimental results. The convenience and speed of SPICE2 also make variations in the topology relatively simple, so that it is generally adequate to try and fit the model to the most complex topology suggested by morphology. The model can then be simplified by lumping compartments or neglecting high resistance pathways or both, to obtain simpler but almost equally accurate models. The time-dependent behavior can also be systematically simplified by time-domain analysis, a method for lumping kinetic steps with similar time constants. The details of modeling procedure is a broad topic, and mainly beyond the scope of this paper. (For a good discussion of time-domain analysis and its use in modeling reaction networks, as well as a good discussion of modeling dynamic systems, see Heinrich et al., 1977.) Parameter estimation for linear systems is the topic of textbooks in electrical engineering and is still a relatively unexplored area for nonlinear systems. (One should not be surprised at this. The motivation for creating programs such as SPICE2 arises from this situation.) With the first generation of network models, the advent of fast, efficient network simulation programs such as SPICE2 has opened the doorway to an unbelievably fast means for testing ideas about dynamic, coupled physiological systems.

Using the bond-graph representation, which lends itself to simulation on a program called ENPORT, other biological applications of network thermodynamics have been accomplished (Schnakenburg, 1977; Horowitz and Plant, 1978; Plant and Horowitz, 1978; Wyatt, 1978). There is also a bibliography of applications of bond-graphs to a variety of systems including biological systems (Gebben, 1978).

I wish to thank C. M. Gary-Bobo for presenting the problem of modeling short circuit current in frog skin which caused me to attack the question of electrochemical events in tissue after having focused on convection-diffusion for some time. It was exciting to see that an electrochemical two-port has its own unique attributes as well as many in common with the convection-diffusion two-port. Also, discussions with S. Schultz and M. Civan were very helpful in encouraging me to compare the network thermodynamic approach with the equivalent circuits. By demanding

---


D. C. MIKULECKY Electrochemical Two-Port Network Element
to be shown, they helped me to reformulate my ideas between the first and second draft of this paper. J. Rich has been a good teacher, provided much stimulating discussion, and introduced me to V. Rideout's simulation work.

Received for publication 19 March 1978 and in revised form 20 October 1978.

APPENDIX

The Simulation of the Networks Using Circuit Simulation Programs

One of the most powerful aspects of the network thermodynamic approach is that once the system is represented by an appropriate network, it can be readily simulated on a digital computer. Simulation programs such as SPICE2 or PCAP are available for a variety of computer systems and can be obtained for a nominal cost, if they are not already in the system library. These programs seem to be updated fairly regularly and, thus, the simulation power can be anticipated to increase.

As an example of how simulation works, the electrochemical 2-port (Fig. 1b) will be used. The nodes and branches in the diagram in Fig. 1b have been numbered. In the program the number zero is reserved for the reference node or ground. For this illustration the linear 2-port described by Eqs. 7 and 8 will be used. The salt concentrations in the baths on either side of the membrane will be "clamped" at 115 and 10 mM, respectively. The electrical potential on the side with the lower concentration will be clamped at zero and the other allowed to float. Writing the simulation program is simply a matter of prescribing the network topology by numbering the nodes (and branches in PCAP) and describing the elements connected between them. For example, in SPICE2,

\[
\text{RELEC1} \quad 1 \quad 2 \quad \text{(Resistance value)}
\]

would indicate that a resistor, named RELEC1, is between nodes 1 and 2 and of the value (a number) specified in the entry following the node designation. Furthermore, because node 1 precedes node 2 in the designation, the direction of positive current is from 1 to 2. In PCAP the element would also have a branch number, and the node designation is somewhat different.

\[
\text{B2} \quad \text{N}(1, 2), \quad \text{R} = \text{(Resistance value)}.
\]

Capacitors would be treated similarly, but in this case a transient analysis would be automatically needed and initial (time zero) values would also be specified.

The cross terms (\(E'\) and \(E'_i\) in the diagram) are a bit more complicated. The real power in the simulation programs for network thermodynamics is in the controlled sources (represented by the diamond-shaped elements in Fig. 1b). This is also where simulation has tremendous advantages over analog computers and breadboarding. The actual devices represented by the controlled sources may be very complicated if they were to be constructed from electronic hardware (Chua, 1969). In the simulation program, they are very simple to "create" and serve a number of important purposes, including the specification of the accomplishment of thermodynamic coupling. There are four types, either voltage or current sources controlled by current or voltage in some part of the network. In SPICE2, nonlinear \(I-V\) characteristics must be specified by a polynomial (multivariable if needed), whereas in PCAP a larger variety of nonlinear characteristics is possible, including Michaelis-Menten (saturation). The French program ASTEC allows the "design" of a nonlinear characteristic in FORTRAN so nonlinear elements can be made to order. One of our long-term goals is to synthesize a "physiological" simulation program from the best features of all these. In SPICE the cross-coupling between current flow and the salt potential, \(E_{s1}\), would be achieved by the use of a current-controlled voltage source:

\[
\text{HES} \quad 6 \quad 7 \quad \text{HE \ (Value of } -R_{12})
\]

which is a current-controlled voltage source called "HES" connected between nodes 6 (positive) and 7 (negative) controlled by the current in the voltage source called "HE" (\(E'\) in the diagram), and giving a voltage of value \(-R_{12} \cdot (\text{current in HE}) = -R_{12} \cdot I\).
Nonlinear resistors and capacitors can be made from these devices in a simple way. Both programs have user's manuals describing the "menu" of elements and techniques at one's disposal. Finally, the entire program in SPICE2 and PCAP for the two-port under the experimental conditions specified above is:

\[
\begin{align*}
\text{RELEC1} & : 1 2 \quad \text{(Value of } 1/2x) \\
\text{RELEC2} & : 3 4 \quad \text{(Value of } 1/2x) \\
\text{R PERM1} & : 5 6 \quad \text{[Value of } (k + \tau)/2(Px - \tau^2)] \\
\text{R PERM2} & : 7 8 \quad \text{[Value of } (k + \tau)/2(Px - \tau^2)] \\
\text{HE} & : 2 3 \quad \text{HES} \quad \text{[Value of } \tau/(Px - \tau^2)] \\
\text{HES} & : 6 7 \quad \text{HE} \quad \text{[Value of } \tau/(Px - \tau^2)] \\
\text{VSBATH1} & : 1 0 0 \\
\text{VSBATH1} & : 5 0 \quad -276.3 \\
\text{VSBATH2} & : 8 0 \quad -129.8 \\
\text{CELEC2} & : 4 0 \quad \text{(Value)}.
\end{align*}
\]

The \( V \) elements are sources clamping the baths and CELEC is a capacitor with a value of the actual membrane capacitance. To allow one or more of the salt concentrations to vary in time, nonlinear capacitors would be needed to replace VSBATH1 and/or VSBATH2. These would be constructed from a current-controlled current source so that a linear capacitor having the value \( C/FV \) and the characteristic (Eq. 13 in the text),

\[
dC/J/dt = (1/FV)I_s,
\]

is used as an auxiliary computational device, where \( C_s = \exp(E/FRT) \). Using a controlled source, the current in the auxiliary subcircuit would be set at the value of \( I_s \). Also, a controlled source will keep the bath at the potential \( E_s \).

The same program written in PCAP would look like this:

\[
\begin{align*}
\text{B1} & \quad \text{N}(1,0), \text{R} = 1E-6, \text{E} = 0 \\
\text{B2} & \quad \text{N}(1,2), \text{R} = \text{(value of } 1/2x) \\
\text{B3} & \quad \text{N}(2,3), \text{R} = 1E-6 \\
\text{B4} & \quad \text{N}(3,4), \text{R} = \text{(value of } 1/2x) \\
\text{B5} & \quad \text{N}(4,0), \text{C} = \text{(value of membrane electrical capacitance)}, \text{EO} = 0 \\
\text{B6} & \quad \text{N}(5,0), \text{R} = 1E-6, \text{E} = -276.3 \\
\text{B7} & \quad \text{N}(5,6), \text{R} = \text{(value of } (k + \tau)/2(Px - \tau^2)] \\
\text{B8} & \quad \text{N}(6,7), \text{R} = 1E-6 \\
\text{B9} & \quad \text{N}(7,8), \text{R} = \text{(value of } (k + \tau)/2(Px - \tau^2)] \\
\text{B10} & \quad \text{N}(8,0), \text{R} = 1E-6, \text{E} = -129.8 \\
\text{B11} & \quad \text{N}(2,3), \text{R} = 1E + 15 \\
\text{A1} & \quad \text{B}(12,3), \text{RM} = \text{(value of } -\tau/(Px - \tau^2)] \\
\text{A2} & \quad \text{B}(11,8), \text{RM} = \text{(value of } -\tau/(Px - \tau^2)]
\end{align*}
\]

To simulate an entire system, such as an epithelial membrane, the two-ports must be connected as in Fig. 2. Additional information in the program for time control and specification of output complete it. For instance, the statement

\[
\text{TAB, NV(1,5,4,8), I(2,5)}
\]

in PCAP would provide a table of node voltages at nodes 1, 5, 4, and 8 and currents through branches 2 and 5. Alternatively, the command PLOT would generate both a table and a graph for each parameter specified. SPICE superimposes the graphs if desired. The programs are extremely flexible in their output format. Notice that no equations are needed. All the mathematics, including and
especially the differential equations, is done from the network topology and element constitutive relations (capacitors generate the differential equations). No program is foolproof, but these come very close. With practice, it is child's play to build and simulate the networks. For some examples of programs created to model complete systems and how they are used to fit or at least give bracketing estimates of unknown parameters, the reader is referred to the models of the compartmental analysis of frog skin (Huf et al., 1978; Mikulecky et al., 1979) and the two-port model of coupled volume and solute flow in proximal kidney tubule (Thomas and Mikulecky, 1978b).

REFERENCES


D. C. Mikulecky

Electrochemical Two-Port Network Element