

Modeling Non Equilibrium Potentiometry to Understand and Control Selectivity and Detection Limit

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Abstract

The majority of present theoretical interpretations of ion-sensor response focus on phase boundary potentials. They assume electroneutrality and equilibrium or steady-state, thus ignoring electrochemical migration and time-dependent effects, respectively. These theoretical approaches, owing to their idealizations, make theorizing on ion distributions and electrical potentials in space and time domains impossible. Moreover, they are in conflict with recent experimental reports on ion-sensors, in which both kinetic (time-dependent) discrimination of ions to improve selectivity, and non-equilibrium transmembrane ion-transport for lowering detection limits, are deliberately used.

For the above reasons, the Nernst-Planck-Poisson (NPP) equations are employed here to model the non-equilibrium response in a mathematically congruent manner. In the NPP model, electroneutrality and steady-state/equilibrium assumptions are abandoned. Consequently, directly predicting and visualizing the selectivity and the low detection limit variability over time, as well as the influence of other parameters, *i.e.* ion diffusibility, membrane thickness and permittivity, and primary to interfering ion concentration ratios on ion-sensor responses, are possible. Additionally, the NPP allows for solving the inverse problem *i.e.* searching for optimal sensor properties and measurement conditions via target functions and hierarchical modeling. The conditions under which experimentally measured selectivity coefficients are true (unbiased) and detection limits are optimized are demonstrated, and practical conclusions relevant to clinical measurements and bioassays are derived.

Introduction

Membrane potential formation in ion-selective electrodes (ISEs) depends on the thermodynamic and kinetic properties of the membrane | solution system. This process is strongly time-dependent, as are the constitutive parameters for all ion-selective electrodes: the selectivity and the detection limit.

Results and Discussion

Equilibrium response vs. non-equilibrium models

The conventional (*phase-boundary*) modeling of membrane potential in electrochemistry does not allow to reflect time-dependent potential responses since it is typically characterized by assuming steady-state, which by definition deprives the resulting models of their time dependency. This applies as well to ion the concentration profiles in space for which conventional models predict, at best, linear drops. It applies as well for diffusion potential and migration effects in the membrane, which are typically ignored, *e.g.* (1-3). In other words the conventional models are deeply insufficient for interpreting ISEs, which is especially evident in all cases of non-equilibrium response.

The non-equilibrium response, *i.e.* the propagation of ionic concentrations and electrical potential in space and time in the solution | ion-exchanging membrane system may be accessed by applying Nernst-Planck (NP) and Poisson (P) coupled equations, where the NP equation describes the transport of ions due to diffusion and migration, and the P equation governs the electrical interaction of the species. These two equations and the continuity equation form a system of partial, non-linear differential equations that is solved numerically by a finite difference or finite element methods. This yields what we call the Nernst-Planck-Poisson model (4-9).

Non-equilibrium ISE response by Nernst-Planck-Poisson model (NPP model)

The NPP model applies for a multi-layer system:

Solution 1 (left) | Diffusion Layer | Membrane | Solution 2 (right)

Schematic system for which the NPP is applied is presented in Fig. 1.

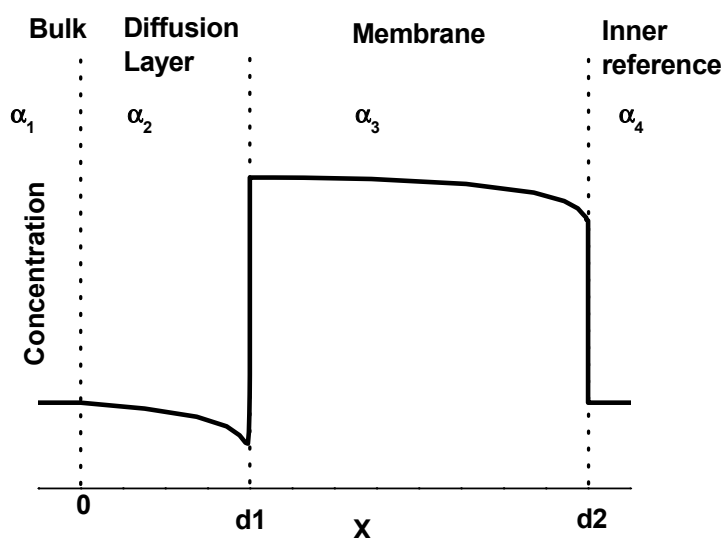


Figure 1. Schematic picture of the multilayer NPP model (9).

The constitutive equations for the NPP model are:

a) Ion fluxes in space (x) and time (t) are described by the Nernst-Planck equation:

$$f_i(x, t) = -D_i \left[\frac{\partial c_i(x, t)}{\partial x} - z_i c_i(x, t) \left(\frac{F}{R \cdot T} \right) E(x, t) \right] \quad [1]$$

where $f_i(x, t)$ is the flux of the I^{th} ion, $c_i(x, t)$ is the concentration of the I^{th} ion, D_i is the diffusion coefficient of the I^{th} ion, z_i is the charge of the I^{th} ion, and $E(x, t)$ is the electrical field.

b) The continuity equation (law of mass conservation):

$$\frac{\partial c_i(x, t)}{\partial t} = - \frac{\partial f_i(x, t)}{\partial x} \quad [2]$$

c) The total current (I) density equation:

$$I = F \cdot \sum_i z_i \cdot f_i(x, t) + \varepsilon \cdot \frac{\partial E(x, t)}{\partial t} \quad [3]$$

where ε is the dielectric permittivity.

d) The Chang-Jaffe boundary conditions (7,9):

$$f_i^{\alpha_n / \alpha_{n+1}} = \bar{k}_i^{\alpha_n / \alpha_{n+1}} \cdot c_{i,L}^{\alpha_n} - \bar{k}_i^{\alpha_n / \alpha_{n+1}} \cdot c_{i,F}^{\alpha_{n+1}} \quad [4]$$

where $f_i^{\alpha_n / \alpha_{n+1}}$ is the flux between two adjoining layers, $\bar{k}_i^{\alpha_n / \alpha_{n+1}}$, $\bar{k}_i^{\alpha_n / \alpha_{n+1}}$ are the forward and backward rate constants between two adjoining layers, $c_{i,L}^{\alpha_n}$, $c_{i,F}^{\alpha_{n+1}}$ are the concentrations of ions at the first and last discretization point in a given layer.

It is demonstrated that both the boundary and diffusion potentials contribute to the overall membrane potential, which contradicts interpretations assuming that only the boundary potential dictates the potential of ISEs, and that modeling at steady-state is insufficient to obtain adequate knowledge about ISEs. There are several manifestations of the power of our approach.

The power of NPP

One striking illustration, calculated by the NPP, is in space and time dependent concentration of sites $R(x)$, which, in phase boundary models, is time and space independent (Fig. 2).

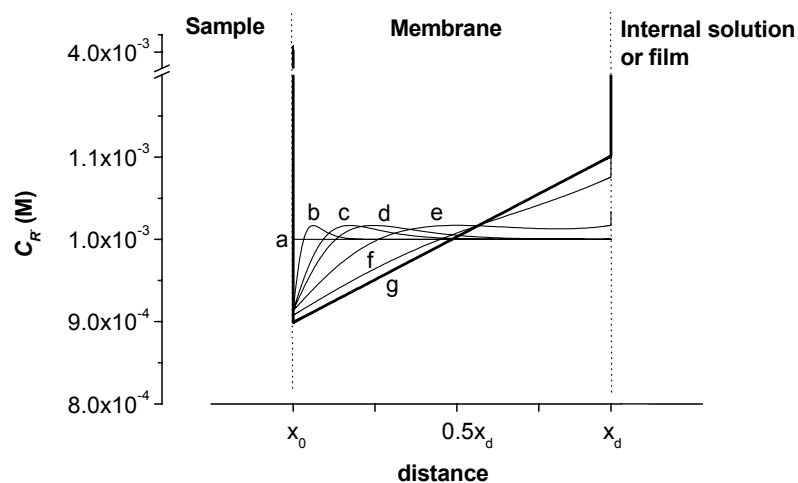


Figure 2. Time-dependent concentration profiles for site R^- modeled by the NPP (5). ($c_i = 10^{-4}$, $c_j = 10^{-3}$, $\frac{\bar{D}_i}{\bar{D}_j} = 0.5$, $K_{i,j} = 0.1$ and $\bar{R}_{TOTAL}^- = 10^{-3}$). Curves a-g show profiles after: a) $4 \cdot 10^{-4}$, b) 1.64, c) 13.1, d) 26.2, e) 104.8, f) 420, and g) 13440 seconds (steady-state).

Another example of the NPP power is in disclosing migrational effect to the potential of ion-selective membrane electrodes, which paradoxically is ignored by phase boundary interpretations even if plastic membranes and the transmembrane fluxes of ions of different charges are considered (Fig. 3).

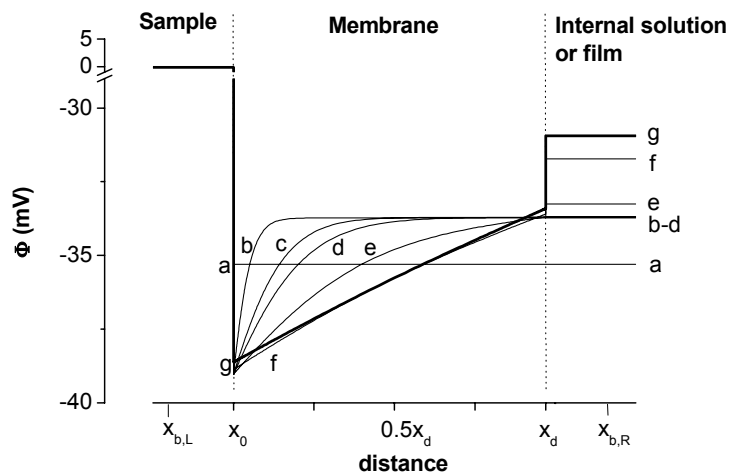


Figure 3. Time-dependent and distance-dependent potential profiles, calculated as $\varphi(x,t) = \int E(x,t)dx$ by using the NPP equations (1-4). Total membrane potential is:

$$E_M(x,t) = \int_{x_{b,L}}^{x_{b,R}} E(x,t)dx$$
, where $x_{b,L}$ and $x_{b,R}$ are the points in the bulk of bathing sample solution (on the left side of the membrane, L) and internal solution / film (on the right side of the membrane, R); x_0 and x_d denotes the left and right membrane-solution interface. Curves a-g show profiles after: a) $4 \cdot 10^{-4}$, b) 1.64, c) 13.1, d) 26.2, e) 104.8, f) 420, and g) 13440 seconds (steady-state) (5).

The simplified conventional models are not as powerful as the NPP model. This fact as can be seen from the Table I.

TABLE I. Assumptions of the NPP and conventional models.	
NPP model	Simplified models
Migration allowed	Migration ignored
Electroneutrality not assumed	Electroneutrality assumed
Any number of ions of any charge	Only two ions of the same charge
Any number of ions of any charge	No ions of opposite charge
Any diffusion coefficients allowed in the membrane	Equal diffusion coefficients in the membrane are assumed

Simpler models are obviously special cases of the NPP. If in the NPP model we used the same assumptions as those used in the simplified models, the NPP would give the same results. In other words, the NPP model and the so-called simpler models are not equivalent. It is possible to reduce a more general model to a simpler one, but not to deduce a more complicated model from a simpler one.

Non equilibrium modeling - practical applications and new frontiers

As a logical consequence of the NPP, challenges related to application of the ISEs could be answered. Time-dependent selectivity is the one (8). It can be shown (6) that the validity of so-called unbiased selectivity method (2) is restricted by measurement time, and can be unproductive when too long measurement time is used. Additionally, for short measurement time one can exploit the effect of *kinetic ion discrimination (apparent selectivity)* (6, 11) which is of great analytical advantage if an ISE is interfered by a strong interfering ion (*e.g.*, Cl-ISE by salicylates) or when the ISE is purposely used for measurement of strongly interfering ions by exploring so-called *Hulanicki effect* (*e.g.*, Cl-ISE for heparin). This is because the selectivity coefficients in both above cases are dictated by ion transport and tend to be equal to one.

Very recently, by using the NPP, we showed (10) that the detection limit for plastic membrane ISEs could also be dependent on time. However, the value of the NPP in this case is not only in direct predictions, but also in a possibility of its use in inverse simulation (*inverse problem*). The NPP as closed and mathematically rigorous model, in contrast to arbitrary and open conventional models, can be used to serve a defined analytical demand (*target function*), *e.g.*, demand of lowering detection limit. We show that by inverse numerical simulation the NPP allows to find optimal values for measurement time and internal solution concentration, while keeping in power the demand of reproducible measurements in ultralow concentrations (Fig. 4).

The same strategy can be applied in the case of electrochemical impedance spectra (EIS). This shows that the NPP is a platform (*umbrella*), which allows finding interdependence between the EIS and potentiometric characteristics. This never explored possibility opens new frontiers both in ISEs theory and the application of ion-sensors.

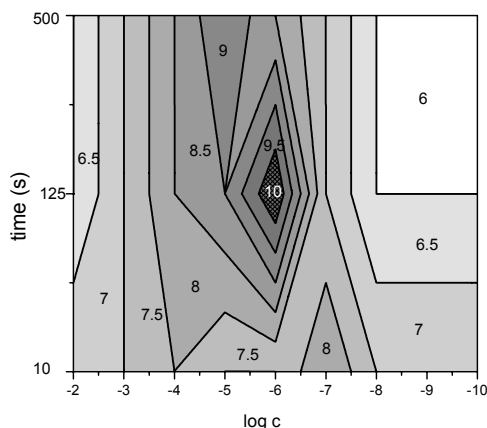


Figure 4. Dependence of the detection limit on the inner filling solution concentration and the measurement time. The darker the shade of gray, the lower the detection limit (represented also by the numbers on the plot) (10).

Conclusions

The NPP model is more rigorous, complete and more general than previous models. The NPP allows to directly predict the ISE response over space and time, propagation of selectivity and detection limit over time or to solve inverse problems with a given target. The target can be potentiometric response curve or electrochemical impedance spectra or their interdependence.

In particular, the NPP is an appropriate platform for dealing with the theory of ion-selective membrane electrodes for analytical applications, in particular when the advantages of time dependent selectivity and/or detection limit are to be exploited or disadvantages of poor response diagnosed and avoided.

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