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*Letters to the Editor*

# Concentration-Dependence of Nonelectrolyte Permeability of Toad Bladder

I should like to offer the following comments on Chen and Walser's recent paper [2]. In Appendix A, presented as a mathematical proof of Eq. (12), they derive a relationship between the unidirectional flux of a nonelectrolyte in the absence of net flow, measured under two circumstances ($J_{\leftrightarrows}$, with the mucosal-serosal concentration difference $\Delta c \equiv c_m - c_s$ and hydrostatic pressure difference $\Delta p$ both equal to zero, and $J^{\mathrm{eq}}_{\leftrightarrows}$, with $\Delta p = \Delta p_{\mathrm{eq}}$, the value appropriate to compensate for a given value of $\Delta c \neq 0$). Reasoning in terms of a Taylor's expansion, they write

$$J^{\mathrm{eq}}_{\leftrightarrows}/J_{\leftrightarrows} = 1 + \sum_{k=1}^{j} a_k (c_m - c_s)^k. \qquad \text{(A1)}$$

This formulation ignores the consideration that in principle the unidirectional flux is a function of hydrostatic pressure as well as concentrations, so that a complete Taylor series comprises terms in both $\Delta c$ and $\Delta p$, as well as mixed terms.

Leaving this point aside, for the case of constant $c_s$, Eq. (1) is transformed into

$$J^{\mathrm{eq}}_{\leftrightarrows}/J_{\leftrightarrows} = 1 + \underset{1}{\xi_1}[(c_m - c_s)/c_s] + \underset{2}{\xi_1}[(c_m - c_s)/c_s]^2 + \underset{3}{\xi_1}[(c_m - c_s)/c_s]^3 + \dots \qquad \text{(A3)}$$

where $\underset{k}{\xi_1} = a_k c_s^k$. Stating that the $\underset{k}{\xi_1}$s are binomial coefficients, it is then concluded that

$$J^{\mathrm{eq}}_{\leftrightarrows}/J_{\leftrightarrows} = [1 + (c_m - c_s)/c_s]^{\xi_1} = (c_m/c_s)^{\xi_1} \qquad \text{(A4); (A5)}$$

where $\xi_1 = a_1 c_s$. (The denominator $J_{\leftrightarrows}$ in Eq. (A4) was omitted.)

In analyzing the above, it is unclear why it is considered that the $\underset{k}{\xi_1}$s are binominal coefficients since, even on the basis of Eq. (A1) as written, $\underset{k}{\xi_1}$ is a complicated quantity, being a function of $k$-th order derivatives of the unidirectional fluxes with respect to concentration, which in principle might be expected to depend on concentrations, hydrostatic pressures, and membrane parameters. On the other hand, a binomial coefficient $C_k^{\xi_1} = \xi_1(\xi_1 - 1)\ (\xi_1 - 2) \dots (\xi_1 - k + 1)/k!$, and there is no reason to expect in general that $\underset{k}{\xi_1}$ need equal $C_k^{\xi_1}$.

For these reasons, I do not feel that Appendix A establishes the validity of Eq. (A5) or the relationships deduced from it. In particular, it appears that, as previously, Eq. (12) must be regarded as a postulate [1].

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## References

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2. Chen, J.S., Walser, M. 1979. Concentration-dependence of nonelectrolyte permeability of toad bladder. *J. Membrane Biol.* **48**:21

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# Reply to: Concentration-Dependence of Nonelectrolyte Permeability of Toad Bladder

In reply to Dr. Essig, we agree that in the case of nonelectrolyte transport at constant temperature, the unidirectional solute flux is a function of gradients of hydrostatic pressure ($\Delta p$) and solute concentration ($\Delta C$). However, it must be kept in mind that we are dealing only with passive transport systems at equilibrium. Under this condition, $\overset{\Delta}{J}=0$ in which $\overset{\Delta}{J}$ represents the net solute flux transported, and as described by Eq. (7) of our paper [1],

$$\Delta p=(RT/\bar{v})\ln(C_m/C_s). \tag{7}$$

Hence, even if $J^{eq}_{\leftrightarrows}$ is a function of both $\Delta p$ and $\Delta C$, since $\Delta p$ is a function of $C_m$, according to Eq. (7), it is clear that $J^{eq}_{\leftrightarrows}$ is a function of the one independent variable, $C_m$ [2]. To see this, we consider the unidirectional solute flux as a function of $\Delta p$ and $\Delta C$. Note that this statement is also valid when the transport system is at equilibrium. Thus,

$$J^{eq}_{\leftrightarrows}=J^{eq}_{\leftrightarrows}(\Delta p, \Delta C). \tag{B1}$$

By the use of chain rules [2], we obtain from Eq. (B1)

$$dJ^{eq}_{\leftrightarrows}=(\partial J^{eq}_{\leftrightarrows}/\partial \Delta p)_{\Delta C}d\Delta p+(\partial J^{eq}_{\leftrightarrows}/\partial \Delta C)_{\Delta p}d\Delta C. \tag{B2}$$

From Eq. (7), for fixed $C_s$ and constant $T$,

$$d\Delta p=(RT/\bar{v}C_m)d\Delta C. \tag{B3}$$

Introducing Eq. (B3) into Eq. (B2), we obtain, by rearranging,

$$dJ^{eq}_{\leftrightarrows}=\{(RT/\bar{v}C_m)(\partial J^{eq}_{\leftrightarrows}/\partial \Delta p)_{\Delta C}+(\partial J^{eq}_{\leftrightarrows}/\partial \Delta C)_{\Delta p}\}d\Delta C$$
$$=f(\Delta C)d\Delta C, \tag{B4}$$

which by integration over the thickness of the membrane gives the expression for $J^{eq}_{\leftrightarrows}$ in terms of $C_m-C_s$.

Dr. Essig also questions that in Eq. (A3)

$$J^{eq}_{\leftrightarrows}/J_{\leftrightarrows}=1+\underset{1}{\zeta_1}\{(C_m-C_s)/C_s\}+\underset{2}{\zeta_1}\{(C_m-C_s)/C_s\}^2+\dots$$
$$+\underset{k}{\zeta_1}\{(C_m-C_s)/C_s\}^k+\dots \tag{A3}$$

there is no reason to claim that the coefficient $\underset{k}{\zeta_1}$ as defined by $\underset{k}{\zeta_1}=a_k C_s^k$ need equal the binomial coefficient, $C_k\zeta_1$, because the parameter $\underset{k}{\zeta_1}$ might be expected to depend on $\Delta C$, $\Delta p$ and membrane parameters. It should be remarked here that in writing Eq. (A1), which has been justified above to be a valid statement for transport systems at equilibrium, the coefficient $a_k$, in the Taylor's series must be evaluated by differentiating both sides of Eq. (A1) $k$ times and setting $C_m=C_s$, i.e.,

$$a_k=J^{eq(k)}_{\leftrightarrows}(C_s)/k!J_{\leftrightarrows} \tag{B5}$$

where $J^{eq(k)}_{\leftrightarrows}(C_s)$ is the $k^{th}$ derivative of $J^{eq}_{\leftrightarrows}$ evaluated at $C_m=C_s$. From Eq. (B5), clearly, $a_k$ and thus $\underset{k}{\zeta_1}$ are independent of $\Delta p$ and $C_m$ but depend on the constant parameter $C_s$ and the membrane. Moreover, according to Eqs. (A1) and (B5), if all derivatives of $J^{eq}_{\leftrightarrows}$ exist at $C_m=C_s$, it is apparent that $J^{eq}_{\leftrightarrows}$ can be expressed by a binomial series as represented by Eq. (A3), since the coefficients ($a_1$, $a_2 \dots a_k$) are not necessarily independent of each other [2].

Based on the above theoretical analysis, we conclude that the method used for the derivation of Eq. (12) as shown in Appendix A of our paper [1] is mathematically and physically justifiable and the validity of Eq. (A5) is thus warranted.

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