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FLUX RATIOS FOR BIOLOGICAL MEMBRANES AND RECIPROCITY THEOREMS FOR LINEAR OPERATORS

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Abstract

The constancy in time of the ratio of unidirectional tracer fluxes, passing in opposite directions through a membrane that has transport properties varying arbitrarily with the distance from a boundary face, has been established recently for successively more sophisticated mathematical models of tracer transport within the membrane. Such results are important in that, when constancy is not observed experimentally, inferences can be drawn about the dimensionality of distributions of transport properties of the membrane. The known theoretical results are shown here to follow from much more general theorems, valid for a wide class of models based on linear-operator equations, including elliptic and hyperbolic partial differential equations as well as the essentially parabolic equations of interest in membrane transport problems. These theorems have the general character of "reciprocity theorems" known for a long time in other areas, such as mechanics, acoustics and elasticity. The general results obtained here clarify the conditions on membrane properties under which constancy of a flux ratio can be expected. In addition, flux ratio theorems of a new type are proved to hold under suitable conditions, for the normal components of flux vectors at points on either side of a membrane, as distinct from previously established theorems for total fluxes through membrane faces. Possible new experiments are suggested by the analysis.

1. Introduction

Recent analyses of transport pathways through biological membranes have relied on the use of certain theorems on parabolic partial differential equations–theorems which do not seem to be widely known and which appear counterintuitive in the context of the model adopted for membrane transport. The utility

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of these theorems in this unusual interaction of membrane biology with mathematics has arisen largely from the insight of the biologist H. H. Ussing [15] that, in diffusion-migration processes through media having unknown distributions of transport properties (such as diffusion coefficients and migration velocities of tracers), significant information can be gained from ingenious experiments involving the measurement of transient fluxes, rather than concentrations of tracers. Of particular importance is the measurement of the "flux ratio": tracer passes in one direction through a membrane which is initially tracer free, and the outflux into a medium of zero tracer concentration is measured as a function of elapsed time. The experiment is repeated with the tracer passing in the opposite direction, and the ratio of the two transient outfluxes at corresponding times is then calculated. It is this ratio that is the subject of the theorems mentioned above.

Ussing [15] conjectured that, for suitably simple boundary conditions, this ratio should be constant in time if the membrane is transversely homogeneous, that is to say, if its transport properties depend only on distance from a membrane wall, and not on transverse coordinates. With Sten-Knudsen [14], he gave a proof of the corresponding theorem, using a model of the membrane as an infinite slab between parallel planar walls, and composed of an arbitrary number of laminae, in each of which the transport properties are constant. The transport process was modelled in each lamina by a linear parabolic partial differential equation with constant coefficients. A proof of a more general result, allowing for a wider class of boundary conditions and a continuous variation of transport properties through the slab, was then given by Bass and Bracken [3]. Bass and McAnally [5] extended the result to the case of a membrane modelled as an annular cylinder rather than a slab. Subsequently, Rogers and Bracken [12], in a paper concerned mainly with obtaining ratio theorems for nonlinear equations, showed that the results of [3] for a slab can be obtained as a consequence of a symmetry of the Green's function for the associated parabolic equation, after transformation to a form in which the spatial part of the differential operator is self-adjoint. Such symmetries have been called "reciprocity relations", for example by Sommerfeld [13, pp. 50–51], who remarked that they express "the interchangeability of source point and action point", and they are known to lie at the heart of "reciprocity theorems" for differential equations. Theorems of this type have a long history, dating back at least to Rayleigh and Helmholtz: an 1889 paper of Lamb [11] contains a nice summary of results of this kind in dynamics, optics and acoustics.

In the more recent literature, reciprocity theorems have often been discussed for hyperbolic and elliptic partial differential equations in acoustics [9] and [10] and elastodynamics [1] and [8, p. 368]. Although parabolic equations have been involved in the modelling of tracer transport through membranes, it seems clear that the flux ratio results have the character of reciprocity theorems. On the other hand, they are not tied to a model in terms of partial differential equations: in a more recent development, Bass, Bracken and Hilden [4] have shown that the ratio theorems continue to hold in a more general model, which takes into account the possibility of temporary trapping of tracer in its passage through the membrane. This model is described in terms of an integro-differential equation.

The purpose of the present paper is two-fold: firstly to clarify the relationship of existing flux ratio theorems to reciprocity theorems for partial differential equations and more general operator equations; and secondly to derive new ratio theorems that may be useful in membrane physiology.

We begin by recalling the most general flux ratio theorems proved to date [4]. Let a membrane be represented by a slab occupying the spatial interval $0 \leq x \leq h$, in which a tracer has diffusion coefficient $D(x)$ and drift velocity $v(x)$. We shall suppose that D and v are continuous on $[0, h]$ and that D is positive there; otherwise, D and v are arbitrary. [Note that $v(x)$ may be the drift velocity of a charged tracer in an electric field associated with a fixed or mobile space-charge in the membrane, and can vary in magnitude and sign even in one dimension in an incompressible medium, in contrast to the case of a convective velocity.] At the positive time t, the tracer concentration $c(x,t)$ and flux $j(x,t)$ within the slab are assumed to be related by

$$j(x,t) = -D(x)\partial c(x,t)/\partial x + v(x)c(x,t), \tag{1.1}$$

and the equation of continuity for the tracer is assumed to have the form

$$\partial c(x,t)/\partial t + \partial j(x,t)/\partial x = q(x,t), \tag{1.2}$$

where the source term q is given by

$$q(x,t) = -k(x)c(x,t) + k(x)\int_0^t c(x,t-\tau)g(x,\tau)\,d\tau. \tag{1.3}$$

Here $g(x,t)$ is non-negative and continuous in x on $[0, h]$ for each $t \in [0, \infty)$ and, for each $x \in [0, h]$, is continuous in t on $[0, \infty)$ and satisfies

$$\int_0^\infty g(x,t)\,dt = 1. \tag{1.4}$$

Otherwise g is arbitrary; the function k is also arbitrary except that it is non-negative and continuous on $[0, h]$. The source term q models trapping of tracer and its subsequent release, according to some very general rule. Initially, the membrane is taken to be free of tracer:

$$c(x,t) = 0, \qquad 0 \leq x \leq h,\ t \leq 0. \tag{1.5}$$

We now consider (1.1)–(1.5) under two sets of boundary conditions which, when realised experimentally, bring about the two transient outfluxes whose ratio is measured. Corresponding variables in the resulting two cases are distinguished by subscripts 1 and 2. The first set of boundary conditions is, for $t > 0$,

$$c_1(0,t) = f_1(t) \geq 0, \qquad c_1(h,t) = 0, \tag{1.6}$$

where f_1 is a given bounded, piecewise continuous function on $(0,\infty)$, and the resulting concentration and flux in the slab are $c_1(x,t), j_1(x,t)$. The second set of boundary conditions is, again for $t > 0$,

$$c_2(0,t) = 0, \qquad c_2(h,t) = f_2(t) \geq 0, \tag{1.7}$$

with f_2 given, satisfying the same conditions as f_1, and resulting in $c_2(x,t)$, $j_2(x,t)$. In particular, the unidirectional outfluxes (into well-stirred bathing solutions of zero tracer concentration) are, respectively, $j_1(h,t)$ and $-j_2(0,t)$. We then have [4]:

THEOREM 1.

$$\int_0^t f_2(t-\tau)j_1(h,\tau)\,d\tau = -\exp\left(\int_0^h \frac{v(x)}{D(x)}\,dx\right)\cdot\int_0^t f_1(t-\tau)j_2(0,\tau)\,d\tau \tag{1.8}$$

for all $t > 0$.

As a special case, we have

THEOREM 2.

If $f_1(t) = rf_2(t)$ *for all* $t > 0$, *with* r *a positive constant, then*

$$j_1(h,t) = -r\exp\left(\int_0^h \frac{v(x)}{D(x)}\,dx\right) j_2(0,t) \tag{1.9}$$

for all $t > 0$.

Theorem 2 brings out particularly clearly the surprising nature of these results: the flux ratio $-j_1(h,t)/j_2(0,t)$ is constant in time from the very first appearance of tracer in the bathing solutions kept at zero concentration, no matter what the forms of $v(x), D(x), k(x)$ and $g(x,t)$. To understand this result in the presence of an arbitrary (possibly unidirectional) velocity field $v(x)$, it may help to recall that classical diffusion places no limit on the speed of propagation of the diffusing substance.

2. Extensions to more than one spatial dimension

The usefulness of Theorems 1 and 2 in membrane biology rests on the possibility of their disagreement with experiment. For example, if a time-dependence

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of the flux ratio is observed when the boundary conditions are as in Theorem 2, the failure of the model is attributed to the assumption that transport properties of the membrane depend on x alone: a heterogeneity of transport pathways, transverse to the flux, is inferred and then analysed by methods which do not concern us here (see, for example, Ussing, Eskesen and Lim [16]). It is to be noted that the converse inference is not valid: a constant flux ratio does not exclude transverse heterogeneity. To indicate the presence of such heterogeneity, the flux transients themselves (rather than the flux ratio) must be analysed [2].

In preparing to generalise Theorems 1 and 2, we consider a membrane which is a slab of finite size, occupying a closed 3-dimensional region $\overline{\Omega}$ of the general form shown in Fig. 1, bounded by the surfaces S', S'' and S'''. The planar surface S' lies in the YZ-plane at $x = 0$, and S'' is its translate to $x = h$, so that S''' is generated by lines parallel to the X-axis. We suppose that the surface S''' is impermeable to tracer, and that the transport coefficients D, v, k and g depend only on x (and on t, in the case of g) in $\overline{\Omega}$. We again consider two situations, labelled 1 and 2, for each of which the membrane is initially tracer-free, and for which the boundary conditions are

$$\begin{aligned} c_1 &= f_1 \text{ on } S', \qquad c_1 = 0 \text{ on } S'' \\ c_2 &= 0 \text{ on } S', \qquad c_2 = f_2 \text{ on } S'' \end{aligned} \tag{2.1}$$

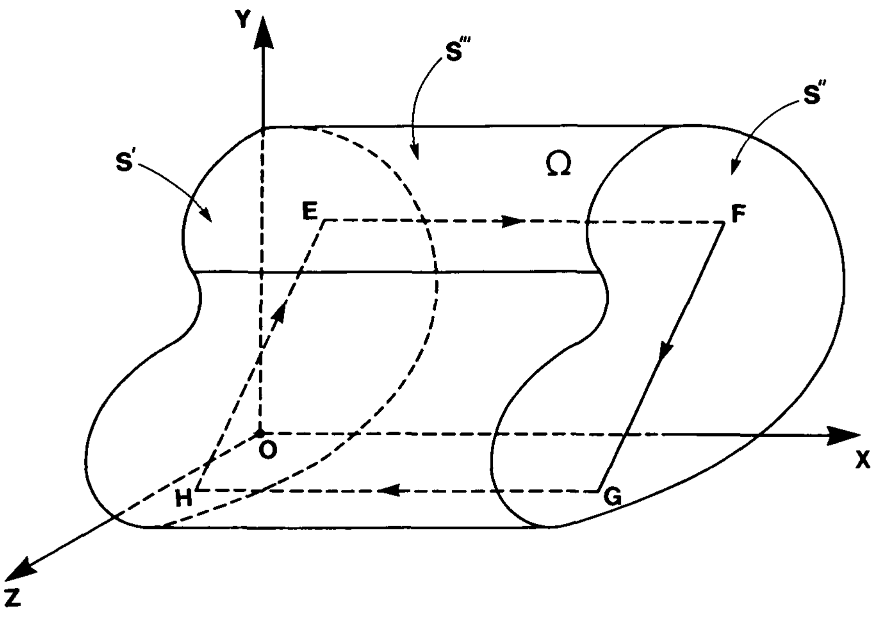

FIGURE 1. Finite membrane slab with parallel planar faces S', S'' bathed by separate well-stirred solutions. Points E, H lie on S' and F, G are corresponding points on S''.

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where f_1 and f_2 are given non-negative functions only of time t for $t > 0$, as in (1.6), (1.7). (In order to realise such boundary conditions, we would have to keep separate the solutions bathing S' and S''; we can, for example, imagine in what follows that the part of the plane $x = \frac{1}{2}h$ located outside $\overline{\Omega}$ is impermeable to tracer.) Then the flux in the membrane for $t > 0$ can in each situation be assumed parallel to the X-axis, and can be described by a scalar function $j(x,t)$. The tracer concentration in the membrane for $t > 0$ will then also depend only on x and t, and we can in fact assume that (1.1) to (1.7) and the associated conditions hold. Theorems 1 and 2 will then apply, just as in the case of the infinite slab.

We now modify this model in two different ways that will enable us to indicate as simply as possible the generalisations we have in mind.

(a) We imagine that the membrane is made up of two parts separated by an impermeable layer occupying the part of the XZ-plane located *inside* $\overline{\Omega}$, and allow the two parts to have different transport properties, leaving unchanged the boundary conditions (2.1)–that is, the specification of the solutions bathing the faces S' and S'' of the membrane.

(b) We leave the membrane and its properties unchanged, but divide the bathing solutions on S' and S'' into two parts separated by an impermeable layer occupying the part of the XZ-plane located *outside* $\overline{\Omega}$, and allowing the non-zero boundary concentrations to be different functions of time for $z > 0$ and $z < 0$.

In the case (a), we allow the functions v, D, k and g to depend on the sign of z as well as on x (and on t, in the case of g), and denote their restrictions to positive or negative z by $v_{\pm}, D_{\pm}$ etc. Let the area of the part of S' (or S'') located above the XZ-plane be A_+, and of the part below be A_-, so that the total area of S' (or S'') is $A = A_+ + A_-$. Each of Theorems 1 and 2 now holds separately for $z < 0$ and $z > 0$, and we ask under what conditions they will hold for the *total* undirectional outfluxes

$$j_{1+}(h,t)A_+ + j_{1-}(h,t)A_- \qquad - (j_{2+}(0,t)A_+ + j_{2-}(0,t)A_-). \tag{2.2}$$

For this it is evidently sufficient to have

$$\int_0^h \frac{v_+(x)}{D_+(x)}\,dx = \int_0^h \frac{v_-(x)}{D_-(x)}\,dx \tag{2.3}$$

or, *a fortiori*, to have

$$\frac{v_+(x)}{D_+(x)} = \frac{v_-(x)}{D_-(x)}, \qquad 0 \le x \le h. \tag{2.4}$$

If a disagreement with Theorem 1 or 2 were seen experimentally (for the total outfluxes) under these conditions (a), it is the refutation of (2.3) and hence of (2.4) that would be inferred and interpreted as heterogeneity of the membrane transverse to the flux. Note that agreement with Theorem 1 or 2 does not imply equality of k_+ and k_-, nor of g_+ and g_- (not indeed of v_+ and v_- or D_+ and D_-), and hence, as already observed, does not imply transverse homogeneity. Consider now the closed, oriented, rectangular contour $EFGH$ indicated in Figure 1, where E and F are corresponding points of S', S'', with the same positive z-coordinate, and H and G are corresponding points of S', S'' with the same negative z coordinate. It follows from (2.3) that for this contour

$$\oint \frac{\mathbf{v} \cdot d\mathbf{x}}{D} = 0 \tag{2.5}$$

where $\mathbf{v}$ now denotes the drift velocity vector and $d\mathbf{x}$ the vector line element on the contour. (On FG and HE, $\mathbf{v} \cdot d\mathbf{x} = 0$, because $\mathbf{v}$ is assumed normal to S' and S''.) Furthermore, if (2.4) holds, then (2.5) will hold for any closed contour within $\overline{\Omega}$. These observations provide a clue that ratio theorems for total unidirectional fluxes may hold for $\mathbf{v}, D, k$ and g dependent on x, y and z, and for more general domains, provided in each case a scalar field ϕ exists such that

$$\mathbf{v}/D = \operatorname{grad} \phi \tag{2.6}$$

throughout that domain. It is essentially by assuming (2.6) that we shall make contact with reciprocity theorems for partial differential equations, and more general operator equations, in 3-dimensional space. We obtain in this way new flux ratio theorems which we call *global* because they hold for the total fluxes out of the relevant boundary surfaces.

In the case (b), the transport coefficients of the membrane remain dependent on x alone (in the simplest situation), but the functions f_1 and f_2 in (1.5), (1.6) are now allowed to depend on the sign of z. More precisely, we suppose that diffusion is isotropic at each point of the membrane, with a coefficient dependent only on x; that the drift velocity is parallel or anti-parallel to the X-axis at each point and depends only on x; and that trapping continues to be described by a source term like (1.3), where now c and q will in general depend on y and z as well as x and t, but k and g are dependent only on x. Tracer entering the membrane at $z > 0$ will interdiffuse with tracer entering differently at $z < 0$, before effluxing into the bathing solution at zero concentration, and the flux vector within the membrane or at either of its faces S', S'' will not be everywhere parallel or anti-parallel to the X-axis. We shall see that even in the presence of such interdiffusion and even though the outflux at any point on a face of the membrane may now vary with y and z, Theorem 2 (but not Theorem 1) holds for the normal components of the flux vectors at corresponding points on the two faces of the slab. It therefore holds for the total fluxes through corresponding sections of the two faces. We call such generalisations of Theorem 2, *local* theorems.

3. Generalised global ratio theorems

In this section we shall prove some generalisations of Theorems 1 and 2, along lines suggested by the discussion of case (a) in the previous section. We deal with a time-dependent scalar field c and vector field $\mathbf{j} = (j_1, j_2, j_3)^{\mathsf{T}}$, generalising concentration and flux in the preceding discussions. They are functions of $(\mathbf{x}, t)$, where $t \in \mathbf{R}$ and $\mathbf{x} = (x_1, x_2, x_3)^{\mathsf{T}}$ belongs to an open, connected and bounded set Ω in $\mathbf{R}^3$, with piecewise smooth boundary $\partial\Omega$, and they are assumed to satisfy a system of linear equations, generalizing (1.1) and (1.2), of the form

$$\nabla_k c = L_{kl}(\mathbf{x})[j_l] + a_k(\mathbf{x})c \tag{3.1}$$

$$\nabla_k j_k = L_0(\mathbf{x})[c] + b_k(\mathbf{x}) j_k \tag{3.2}$$

for $\mathbf{x} \in \Omega$, $t > 0$, and

$$c(\mathbf{x}, t) = 0, \quad \mathbf{j}(\mathbf{x}, t) = \mathbf{0} \tag{3.3}$$

for $\mathbf{x} \in \Omega$, $t \leq 0$. Here $\nabla = (\nabla_k) = (\partial/\partial x_k)$, while $L_0(\mathbf{x})$ and $L_{kl}(\mathbf{x})[= L_{lk}(\mathbf{x})]$ are linear operators, acting (for each fixed $\mathbf{x}$) on $c(\mathbf{x}, \cdot)$ and $j_l(\mathbf{x}, \cdot)$ respectively. We use the summation convention for repeated subscripts.

Concerning the form of $L_0(\mathbf{x})$ we make the following assumptions. Suppose that c is in the domain of L_0, satisfies $c(\mathbf{x}, t) = 0$ for $\mathbf{x} \in \Omega$, $t \leq 0$, and has a Laplace transform $C(\mathbf{x}, s)$ for $\mathbf{x} \in \Omega$, $s \in (0, \infty)$, where s is the transform variable conjugate to t. Suppose also that, for such c, $L_0(\mathbf{x})[c(\mathbf{x}, t)] = 0$ for $\mathbf{x} \in \Omega$, $t \leq 0$. Then $L_0(\mathbf{x})[c]$ has a Laplace-transform of the form $A_0(\mathbf{x}, s)C(\mathbf{x}, s)$, for $\mathbf{x} \in \Omega$, $s \in (0, \infty)$. This allows [7] $L_0(\mathbf{x})[c(\mathbf{x}, t)]$ to be a linear combination of $c(\mathbf{x}, t)$, derivatives $\partial c(\mathbf{x}, t)/\partial t$, $\partial^2 c(\mathbf{x}, t)/\partial t^2, \ldots$, delays $c(\mathbf{x}, t - t_1)$ for various positive t_1, convolutions $\int_0^t g(\mathbf{x}, t - \tau) c(\mathbf{x}, \tau)\, d\tau$, etc., with coefficients dependent on $\mathbf{x}$; we suppose that such coefficients are continuous on $\overline{\Omega} = \Omega \cup \partial\Omega$.

Similar assumptions are made concerning the form of $L_{kl}(\mathbf{x})[j_l]$: if j_l is in the domain of $L_{kl}, l = 1, 2, 3$, has Laplace transform J_l, and both j_l and $L_{kl}(\mathbf{x})[j_l]$ vanish for $t \leq 0$, we suppose that $L_{kl}(\mathbf{x})[j_l]$ has Laplace transform of the form $A_{kl}(\mathbf{x}, s) J_l(\mathbf{x}, s)$ where $A_{kl} = A_{lk}$.

We assume also that the initial- and boundary-value problems considered below are meaningful, with sufficiently regular solutions; in particular we assume that the equations involved can be Laplace-transformed. This implies further restrictions on the form of L_0 and L_{kl} which we shall not try to make precise. Suffice it to say that many examples are easily found, where all these conditions are satisfied.

Bearing (2.6) in mind, we now suppose that there exist functions ϕ and ψ, continuous on Ω, such that $\mathbf{a} = \nabla\phi$ and $\mathbf{b} = \nabla\psi$ in Ω. Define

$$\mu = e^{-\phi}, \qquad \nu = e^{-\psi}. \tag{3.4}$$

If (3.1) is multiplied by μ and (3.2) by ν we get, since $\nabla\mu = -\mu\nabla\phi$ and $\nabla\nu = -\nu\nabla\psi$,

$$\nabla_k(\mu c) = \mu L_{kl}(\mathbf{x})[j_l] \tag{3.1$'$}$$

$$\nabla_k(\nu j_k) = \nu L_0(\mathbf{x})[c]. \tag{3.2$'$}$$

Let us Laplace-transform (3.1′) and (3.2′), taking (3.3) into account. According to the basic assumptions described above, we then obtain

$$\nabla_k(\mu C) = \mu A_{kl} J_l \tag{3.5}$$

$$\nabla_k(\nu J_k) = \nu A_0 C. \tag{3.6}$$

Now consider two pairs of solutions $(C_1, \mathbf{J}_1), (C_2, \mathbf{J}_2)$ of (3.5) and (3.6). We find that

$$\begin{aligned}\nabla_k&[(\mu C_1)(\nu J_{2k}) - (\mu C_2)(\nu J_{1k})]\\ &= (\mu A_{kl}J_{1l})(\nu J_{2k}) + (\mu C_1)(\nu A_0 C_2) - (\mu A_{kl} J_{2l})(\nu J_{1k}) - (\mu C_2)(\nu A_0 C_1)\\ &= \mu\nu[(A_{kl}J_{1l})J_{2k} - (A_{kl}J_{2l})J_{1k}]\\ &= 0,\end{aligned} \tag{3.7}$$

because $A_{kl} = A_{lk}$. If (3.7) is integrated over Ω, we get from the Divergence Theorem,

$$\iint_{\partial\Omega} \mu\nu C_1 \mathbf{J}_2 \cdot \hat{\mathbf{n}}\, dS = \iint_{\partial\Omega} \mu\nu C_2 \mathbf{J}_1 \cdot \hat{\mathbf{n}}\, dS, \tag{3.8}$$

where $\hat{\mathbf{n}} = \hat{\mathbf{n}}(\mathbf{x})$ denotes the outward unit normal at the point $\mathbf{x} \in \partial\Omega$.

Equation (3.8) is similar in form to a "reciprocity theorem" in elastodynamics [1, 8]. While its derivation from (3.5) and (3.6) is fairly standard, we shall use (3.8) as a source of ratio theorems which are certainly new in the diffusion-migration context.

Suppose that $\partial\Omega$ consists of three parts S', S'' and S''', and let $(c_1, \mathbf{j}_1), (c_2, \mathbf{j}_2)$ be solutions of (3.1′), (3.2′) and (3.3) satisfying the following boundary conditions for $t > 0$, in generalisation of (1.6), (1.7):

$$\left.\begin{array}{ll} c_1(\mathbf{x},t) = f_1(\mathbf{x},t) \quad \text{on } S', & c_1 = 0 \quad \text{on } S'' \\ c_2 = 0 \quad \text{on } S', & c_2(\mathbf{x},t) = f_2(\mathbf{x},t) \quad \text{on } S'' \\ c_1 = c_2 = 0 \text{ or } \mathbf{j}_1\cdot\hat{\mathbf{n}} = \mathbf{j}_2\cdot\hat{\mathbf{n}} = 0 \quad \text{on } S''' & \end{array}\right\} \tag{3.9}$$

where f_1 and f_2 are given functions. After Laplace-transformation, we get from (3.8)

$$\iint_{S'} \mu\nu F_1 \mathbf{J}_2 \cdot \hat{\mathbf{n}}\, dS = \iint_{S''} \mu\nu F_2 \mathbf{J}_1 \cdot \hat{\mathbf{n}}\, dS, \tag{3.10}$$

where F_1, F_2 are the transforms of f_1, f_2, and so we can conclude that [7]

$$\iint_{S'} \mu(\mathbf{x})\nu(\mathbf{x}) \left[\int_0^t f_1(\mathbf{x},\tau)\mathbf{j}_2(\mathbf{x},t-\tau)\,d\tau\right] \cdot \hat{\mathbf{n}}(\mathbf{x})\,dS = \iint_{S''} \mu(\mathbf{x})\nu(\mathbf{x}) \left[\int_0^t f_2(\mathbf{x},\tau)\mathbf{j}_1(\mathbf{x},t-\tau)\,d\tau\right] \cdot \hat{\mathbf{n}}(\mathbf{x})\,dS. \tag{3.11}$$

If at each time t, f_1 and f_2 are uniform on S' and S'', respectively, and if, for all $t > 0$

$$f_1(t) = r f_2(t) \tag{3.12}$$

with a constant r, then

$$F_1(s) = rF_2(s) \tag{3.13}$$

for all s, and (3.10) gives

$$r \iint_{S'} \mu\nu\mathbf{J}_2 \cdot \hat{\mathbf{n}}\,dS = \iint_{S''} \mu\nu\mathbf{J}_1 \cdot \hat{\mathbf{n}}\,dS. \tag{3.14}$$

Then

$$r \iint_{S'} \mu(\mathbf{x})\nu(\mathbf{x})\mathbf{j}_2(\mathbf{x},t) \cdot \hat{\mathbf{n}}(\mathbf{x})\,dS = \iint_{S''} \mu(\mathbf{x})\nu(\mathbf{x})\mathbf{j}_1(\mathbf{x},t) \cdot \hat{\mathbf{n}}(x)\,dS \tag{3.15}$$

for all $t > 0$.

If we assume also that the vector fields $\mathbf{a}$ and $\mathbf{b}$ in (3.1) and (3.2) are both parallel to $\hat{\mathbf{n}}$ at each point on S' and S'', and if each of S', S'' is a connected surface, then μ and ν are constant on S' and S''. To see this, let $\mathbf{x}_1$ and $\mathbf{x}_2$ belong to S'. Then

$$\phi(\mathbf{x}_2) - \phi(\mathbf{x}_1) = \int_{\mathbf{x}_1}^{\mathbf{x}_2} \mathbf{a}(\mathbf{x}) \cdot d\mathbf{x}, \tag{3.16}$$

where the contour of integration can be a curve in S'. But since $\mathbf{a}(\mathbf{x}) \cdot d\mathbf{x} = 0$ on such a contour, it follows that $\phi(\mathbf{x}_2) - \phi(\mathbf{x}_1) = 0$, so that ϕ, and hence μ, is constant on S'. The other cases are proved similarly. Then (3.11) becomes

$$(\mu\nu)|_{S'} \iint_{S'} \left[\int_0^t f_1(\mathbf{x},\tau)\mathbf{j}_2(\mathbf{x},t-\tau)\,d\tau\right] \cdot \hat{\mathbf{n}}(\mathbf{x})\,dS = (\mu\nu)|_{S''} \iint_{S''} \left[\int_0^t f_2(\mathbf{x},\tau)\mathbf{j}_1(\mathbf{x},t-\tau)\,d\tau\right] \cdot \hat{\mathbf{n}}(\mathbf{x})\,dS, \tag{3.17}$$

and if (3.12) holds, we get from (3.15)

$$(\mu\nu)|_{S''} \iint_{S''} \mathbf{j}_1 \cdot \hat{\mathbf{n}}\,dS = r\ (\mu\nu)|_{S'} \iint_{S'} \mathbf{j}_2 \cdot \hat{\mathbf{n}}\,dS. \tag{3.18}$$

Formulae (3.11), (3.15), (3.17) and (3.18) are different versions of the desired theorems generalising Theorems 1 and 2. We refer to them as generalised global ratio theorems, and write (3.18), for example, in the form

$$\frac{\iint_{S''} \mathbf{j}_1 \cdot \hat{\mathbf{n}}\,dS}{\iint_{S'} \mathbf{j}_2 \cdot \hat{\mathbf{n}}\,dS} = r\frac{(\mu\nu)|_{S'}}{(\mu\nu)|_{S''}}, \tag{3.18$'$}$$

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with the understanding that, when one or both of the denominators vanishes in this equation, the form (3.18) should be used.

REMARK 3.1. If Ω is simply connected and $\mathbf{a}$ is sufficiently smooth, a function ϕ such that $\mathbf{a} = \nabla\phi$ exists if and only if $\nabla \times \mathbf{a} = \mathbf{0}$ in Ω. The same applies to ψ and $\mathbf{b}$.

REMARK 3.2. The results obtained above also hold, with obvious minor modifications, in two- or one-dimensional regions Ω. The results (1.8) and (1.9) of [4] are recovered in the one-dimensional case for the equations (1.1) and (1.2) with $\Omega = (0, h)$. In this case $a(x) = v(x)/D(x), b(x) = 0$, and consequently $\phi(x) = \int_0^x [v(s)/D(s)]\, ds, \nu = 1$. The cylindrical membrane model considered in [5] is essentially two-dimensional, with (in polar coordinates) $\Omega = \{\mathbf{x}\colon r_0 < r < r_1\}$. The relevant equations are

$$\begin{aligned}\nabla c &= -(1/D)\mathbf{j} + (1/D)\mathbf{v}c \\ \nabla \cdot \mathbf{j} &= -\frac{\partial c}{\partial t}\end{aligned} \tag{3.19}$$

with $D = D(r), \mathbf{v} = v(r)\hat{\mathbf{r}}, c = c(r,t)$ and $\mathbf{j} = j(r,t)\hat{\mathbf{r}}$. In this case our assumptions are satisfied with $\phi(r) = \int_{r_0}^r [v(\rho)/D(\rho)]\, d\rho, \nu = 1$. If $c_1(r_0, t) = f_1(t), c_1(r_1, t) = 0, c_2(r_0, t) = 0, c_2(r_1, t) = f_2(t)$ for $t > 0$, then (3.18′) gives the result of [5], that

$$\frac{r_1 j_1(r_1,t)}{-r_0 j_2(r_0,t)} = p \exp\left[\int_{r_0}^{r_1} \frac{v(r)}{D(r)}\, dr\right] \tag{3.20}$$

if

$$f_1(t)/f_2(t) = p \text{ (const.)}. \tag{3.21}$$

APPLICATION 3.1: Consider a membrane which occupies a closed 3-dimensional region $\overline{\Omega}$ of a general form similar to that shown in Fig. 1, but possibly somewhat distorted. The surfaces S' and S'' need not be exactly the same shape and they need not be planar or parallel; we require only that it be meaningful to talk of two disjoint faces S' and S'' of the membrane, each consisting of a connected surface. The surface S''', now no longer necessarily generated by straight lines, should also be connected and should either be impermeable to tracer, or be maintained at zero tracer concentration. Transport of tracer in the membrane is modelled by the equations

$$\nabla c(\mathbf{x},t) = -\frac{1}{D(\mathbf{x})}\mathbf{j}(\mathbf{x},t) + \frac{c(\mathbf{x},t)}{D(\mathbf{x})}\mathbf{v}(\mathbf{x}) \tag{3.22a}$$

$$\nabla \cdot \mathbf{j}(\mathbf{x},t) = -\frac{\partial c(\mathbf{x},t)}{\partial t} - k(\mathbf{x})c(\mathbf{x},t) + k(\mathbf{x})\int_0^t c(\mathbf{x}, t-\tau)g(\mathbf{x},\tau)\, d\tau \tag{3.22b}$$

which generalise (1.1), (1.2), (1.3). The non-negative functions k and g are continuous in $\mathbf{x}$ on $\overline{\Omega}$ (for each $t \in [0, \infty)$, in the case of g) and g is continuous

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in t and normalised to unity on $[0,\infty)$, for each $\mathbf{x}\in\overline{\Omega}$. We suppose that $D(\mathbf{x})$ is positive on $\overline{\Omega}$; that at each point $\mathbf{x}$ on S' or S'', $\mathbf{v}(\mathbf{x})$ is directed normal to that surface:

$$\mathbf{v}(\mathbf{x}) = v(\mathbf{x})\hat{\mathbf{n}}(\mathbf{x}), \qquad \mathbf{x}\in S' \text{ or } S''; \tag{3.23}$$

and that a function $\phi(\mathbf{x})$ exists, continuous on $\overline{\Omega}$, such that

$$\mathbf{v}(\mathbf{x}) = D(\mathbf{x})\nabla\phi(\mathbf{x}), \qquad \mathbf{x}\in\Omega. \tag{3.24}$$

We set

$$c(\mathbf{x},t) = 0, \qquad t\le 0,\ \mathbf{x}\in\Omega, \tag{3.25}$$

and (3.22) then implies that

$$\mathbf{j}(\mathbf{x},t) = \mathbf{0}, \qquad t\le 0,\ \mathbf{x}\in\Omega. \tag{3.26}$$

Equations (3.22), (3.25) and (3.26) are of the form (3.1), (3.2), (3.3), with

$$\mathbf{a}(\mathbf{x}) = \mathbf{v}(\mathbf{x})/D(\mathbf{x}), \qquad \mathbf{b}(\mathbf{x}) = \mathbf{0}. \tag{3.27}$$

From the second of these equations, we can set $\psi = 0$ and $\nu = 1$ in (3.4); ϕ there is as in (3.24). Adopting boundary conditions in situations 1 and 2 as in (3.9), we arrive at (3.17) in the form

$$\begin{aligned} &\iint_{S'}\left[\int_0^t f_1(\mathbf{x},\tau)\mathbf{j}_2(\mathbf{x},t-\tau)\,d\tau\right]\cdot\hat{\mathbf{n}}(\mathbf{x})\,dS \\ &\qquad = e^{-\Delta\phi}\iint_{S''}\left[\int_0^t f_2(\mathbf{x},\tau)\mathbf{j}_1(\mathbf{x},t-\tau)\,d\tau\right]\cdot\hat{\mathbf{n}}(\mathbf{x})\,dS, \end{aligned} \tag{3.28}$$

$$\Delta\phi = \phi_{S''} - \phi_{S'} \tag{3.29}$$

where $\phi_{S'}, \phi_{S''}$ are the (constant) values of ϕ on S', S'' respectively. In the special case that (3.12) holds, we obtain (3.18′) in the form

$$\frac{\iint_{S''}\mathbf{j}_1\cdot\hat{\mathbf{n}}\,dS}{\iint_{S'}\mathbf{j}_2\cdot\hat{\mathbf{n}}\,dS} = re^{\Delta\phi}. \tag{3.30}$$

Thus the ratio of the total fluxes, through S'' in case 1, and through S' in case 2, is constant.

This represents a significant generalisation of the previously established result (1.9). In particular, it shows that the constancy of the flux ratio allows a considerable degree of variability in $\mathbf{v}, D, k$ and g, and even in the membrane shape and thickness. What are critical are the conditions (3.23) and (3.24). Of the second of these conditions, we can say that ϕ may have a direct physical interpretation as the potential of an electric field in which a charged tracer migrates (and diffuses). Note that, in regard to our preliminary discussion of this type of situation, as case (a) in Section 2, it is now clear that the assumed presence of the impermeable plane $y = 0$ within the membrane in that case, is unnecessary for the constancy of the ratio of total outfluxes.

4. A local ratio theorem

As indicated in the discussion of case (b) in Section 2, it is possible in special circumstances to obtain a local or "pointwise" ratio theorem. Consider again equations (3.1)–(3.4) for a 3-dimensional region as in Figure 1 and, in the notation of Section 3, suppose that

$$(A_{kl}(\mathbf{x}, s)) = \begin{bmatrix} A_1(x,s) & 0 \\ 0 & \mathbf{A}_2(x,y,z,s) \end{bmatrix}, \tag{4.1}$$

where A_1 is a scalar function, everywhere positive or everywhere negative, and $\mathbf{A}_2$ is a 2×2 matrix of functions, with an inverse of the form

$$\mathbf{A}_2^{-1} = E(x,s)\mathbf{B}(y,z,s), \tag{4.2}$$

$\mathbf{B}$ being a symmetric, positive- or negative-definite 2×2 matrix, and E a positive scalar. Suppose also that $A_0(\mathbf{x}, s)$ has the form $A_0(x,s)$, and that $\mu(\mathbf{x}) = \mu_1(x)\mu_2(y,z), \nu(\mathbf{x}) = \nu_1(x)\nu_2(y,z)$, where μ_1, μ_2, ν_1 and ν_2 are larger than some positive constant for all $\mathbf{x} \in \overline{\Omega}$.

Let

$$\begin{gathered} U(\mathbf{x}, s) = \mu(\mathbf{x})C(\mathbf{x}, s) \\ \kappa_1(x) = \nu_1(x)/\mu_1(x), \qquad \kappa_2(y,z) = \nu_2(y,z)/\mu_2(y,z). \end{gathered} \tag{4.3}$$

Then (3.5) and (3.6) give

$$\nabla_k \left[\frac{\nu}{\mu} (A^{-1})_{kl} \nabla_l U \right] = \frac{\nu}{\mu} A_0 U, \tag{4.4}$$

which reduces to

$$\frac{1}{\kappa_1} \frac{\partial}{\partial x} \left(\frac{\kappa_1}{A_1} \frac{\partial U}{\partial x} \right) + \frac{1}{\kappa_2} \nabla_p [\kappa_2 (A_2^{-1})_{pq} \nabla_q U] = A_0 U \tag{4.5}$$

and hence, from (4.2),

$$\frac{1}{\kappa_1 E} \frac{\partial}{\partial x} \left(\frac{\kappa_1}{A_1} \frac{\partial U}{\partial x} \right) + \frac{1}{\kappa_2} \nabla_p (\kappa_2 B_{pq} \nabla_q U) = \frac{A_0}{E} U. \tag{4.6}$$

The boundary condition on S''' becomes either $U = 0$ or $\hat{n}_k (A^{-1})_{kl} \nabla_l U = 0$. In (4.5) and (4.6) [and in (4.7) below], p and q run over the values 2 and 3 only.

Consider the eigenvalue problem

$$\begin{cases} \nabla_p (\kappa_2 B_{pq} \nabla_q \chi) = \lambda \kappa_2 \chi & \text{in } S \\ \chi = 0 \text{ or } \hat{n}_p B_{pq} \nabla_q \chi = 0 & \text{on } \partial S, \end{cases} \tag{4.7}$$

where S is the 2-dimensional region defined by any cross-section of Ω perpendicular to the X-axis, coordinatised by (y,z), and having boundary ∂S. The corresponding eigenfunctions $\{\chi_n\}_{n=1}^{\infty}$ form a complete orthonormal system in $L_2(S)$, with respect to the weight κ_2 [6, Chapters V, VI]; we denote the corresponding eigenvalues by λ_n. Then we consider solutions of (4.6) in the form

$$U(\mathbf{x},s)=\sum_{n=1}^{\infty}U_n(x,s)\chi_n(y,z,s), \tag{4.8}$$

and obtain from (4.6) that

$$\sum_{n=1}^{\infty}\left[\frac{1}{\kappa_1 E}\frac{\partial}{\partial x}\left(\frac{\kappa_1}{A_1}\frac{\partial U_n}{\partial x}\right)\chi_n+U_n\lambda_n\chi_n\right]=\frac{A_0}{E}\sum_{n=1}^{\infty}U_n\chi_n \tag{4.9}$$

and hence

$$\frac{1}{\kappa_1 E}\frac{\partial}{\partial x}\left(\frac{\kappa_1}{A_1}\frac{\partial U_n}{\partial x}\right)+\lambda_n U_n=\frac{A_0}{E}U_n, \qquad n=1,2,3,\dots. \tag{4.10}$$

Let $W_n=A_1^{-1}\partial U_n/\partial x$, so that we get for each $n=1,2\dots$ the system

$$\begin{cases}\dfrac{\partial(\kappa_1 W_n)}{\partial x}=\kappa_1(A_0-E\lambda_n)U_n\\[2mm] \dfrac{\partial U_n}{\partial x}=A_1W_n.\end{cases} \tag{4.11}$$

We now consider two solutions $U^{(1)}$ and $U^{(2)}$ of (4.6) with boundary conditions

$$\begin{aligned}&U^{(1)}(0,y,z,s)=\mu(0,y,z)F_1(y,z,s)=\sum_{n=1}^{\infty}d_{1n}(s)\chi_n(y,z,s)\\ &U^{(1)}(h,y,z,s)=0\\ &U^{(2)}(0,y,z,s)=0\\ &U^{(2)}(h,y,z,s)=\mu(h,y,z)F_2(y,z,s)=\sum_{n=1}^{\infty}d_{2n}(s)\chi_n(y,z,s)\end{aligned} \tag{4.12}$$

for $(y,z)\in S, s\in(0,\infty)$, corresponding to the first two of (3.9). Then we get two corresponding solutions $(U_n^{(1)},W_n^{(1)}),(U_n^{(2)},W_n^{(2)})$ of (4.11) satisfying

$$\begin{aligned}&U_n^{(1)}(0,s)=d_{1n}(s), \qquad U_n^{(1)}(h,s)=0\\ &U_n^{(2)}(0,s)=0, \qquad U_n^{(2)}(h,s)=d_{2n}(s).\end{aligned} \tag{4.13}$$

Then

$$\frac{\partial}{\partial x}[\kappa_1 W_n^{(2)}U_n^{(1)}-\kappa_1 W_n^{(1)}U_n^{(2)}]=0 \tag{4.14}$$

and hence

$$-\kappa_1(h)W_n^{(1)}(h,s)d_{2n}(s)=\kappa_1(0)W_n^{(2)}(0,s)d_{1n}(s). \tag{4.15}$$

If we now assume that in (3.9)

$$f_1(y,z,t) = rf_2(y,z,t), \qquad (y,z) \in S,\ t > 0 \tag{4.16}$$

with r constant, so that, in (4.12),

$$F_1(y,z,s) = rF_2(y,z,s), \qquad (y,z) \in S,\ s > 0, \tag{4.17}$$

then

$$d_{1n}(s) = r\frac{\mu_1(0)}{\mu_1(h)}d_{2n}(s) \tag{4.18}$$

and (4.15) gives

$$W_n^{(1)}(h,s) = -r\frac{\nu_1(0)}{\nu_1(h)}W_n^{(2)}(0,s), \tag{4.19}$$

provided $d_{2n}(s)$ (and hence $d_{1n}(s)$) does not vanish. However, if (4.10), (4.13) have unique solutions $U_n^{(1)}(x,s), U_n^{(2)}(x,s)$, then evidently $d_{1n}(s) = d_{2n}(s) = 0$ implies $U_n^{(1)}(x,s) = U_n^{(2)}(x,s) = 0$. Then (4.11) implies that $W_n^{(1)}(x,s) = W_n^{(2)}(x,s) = 0$, and (4.19) holds in this case also. Uniqueness of the solutions of (4.10), (4.13) can be guaranteed by requiring, for example, that A_0 and A_1 are both negative and $\mathbf{B}$ is negative-definite; such conditions hold in Application 4.1 below. The x-component of $\mathbf{J}(\mathbf{x},s)$ is

$$J_1 = \frac{1}{\mu}A_1^{-1}\frac{\partial U}{\partial x} = \frac{1}{\mu}\sum_{n=1}^{\infty} W_n\chi_n. \tag{4.20}$$

From this and (4.19) we obtain

$$\begin{aligned} J_1^{(1)}(h,y,z,s) &= \frac{1}{\mu(h,y,z)}\sum_{n=1}^{\infty} W_n^{(1)}(h,s)\chi_n(y,z,s) \\ &= -\frac{1}{\mu(h,y,z)}r\frac{\nu_1(0)}{\nu_1(h)}\sum_{n=1}^{\infty} W_n^{(2)}(0,s)\chi_n(y,z,s) \\ &= -r\frac{\mu_1(0)}{\mu_1(h)}\frac{\nu_1(0)}{\nu_1(h)}J_1^{(2)}(0,y,z,s). \end{aligned} \tag{4.21}$$

Taking inverse Laplace transforms, we get

$$\frac{j_1^{(1)}(h,y,z,t)}{j_1^{(2)}(0,y,z,t)} = -r\frac{\mu_1(0)\nu_1(0)}{\mu_1(h)\nu_1(h)} \tag{4.22}$$

which is the desired "local" ratio theorem in this case. We can of course obtain directly from (4.22) a ratio theorem for total fluxes through S' and S'':

$$\iint_{S''} \mathbf{j}^{(1)} \cdot \hat{\mathbf{n}}\,dS = r\frac{\mu_1(0)\nu_1(0)}{\mu_1(h)\nu_1(h)}\iint_{S'} \mathbf{j}^{(2)} \cdot \hat{\mathbf{n}}\,dS. \tag{4.23}$$

We emphasise that this global result does not follow as a special case of (3.18), because of the more general form (4.16) for f_1, f_2 in (3.9), allowed by the boundary conditions (4.12).

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APPLICATION 4.1: Consider a membrane as in Application 3.1, but now occupying a region of the general form shown in Figure 1 (without distortion).

Equation (3.22b) is retained, with k and g dependent only on x in $\overline{\Omega}$ (and on t, in the case of g), but (3.22a) is replaced by

$$j_k(\mathbf{x},t) = -D_{kl}(\mathbf{x})\nabla_l c(\mathbf{x},t) + c(\mathbf{x},t)v_k(\mathbf{x}) \tag{4.24}$$

where (D_{kl}) is a symmetric "diffusion tensor" matrix, with the special form

$$(D_{kl}) = \begin{bmatrix} D_1(x) & 0 \\ 0 & d(x)\mathbf{D}_2(y,z) \end{bmatrix}. \tag{4.25}$$

Here $D_1(x)$ and $d(x)$ are positive functions on $[0,h]$ and $\mathbf{D}_2$ is a positive-definite symmetric 2×2 matrix of functions on $\overline{S} = S \cup \partial S$. Equations (3.23) and (3.24) are retained [with D in (3.24) replaced by the matrix (D_{kl})] but it is now necessary to assume that ϕ can be found in the form

$$\phi(\mathbf{x}) = \phi_1(x) + \phi_2(y,z). \tag{4.26}$$

This requires in particular of the components of the convective velocity $\mathbf{v}$, that v_1 depends only on x and each of v_2, v_3 depends only on y and z. For example, we might suppose that $\phi_2 = v_2 = v_3 = 0$ in $\overline{\Omega}$, and could then satisfy (3.24) by setting

$$\phi_1(x) = \int_0^x \frac{v_1(x')}{D_1(x')}\,dx'. \tag{4.27}$$

The analysis of this section now applies, and we deduce that, with boundary conditions defined by (3.9) and (4.16), the result (4.22) and hence (4.23) holds, with

$$\frac{\mu_1(0)\nu_1(0)}{\mu_1(h)\nu_1(h)} = e^{\Delta\phi_1} \tag{4.28}$$

$$\Delta\phi_1 = \phi_1(h) - \phi_1(0). \tag{4.29}$$

The case (b) discussed in Section 2 is seen to be a special case, with $v(\mathbf{x}) = (v_1(x), 0, 0)^{\mathsf{T}}$, and with the matrix (D_{kl}) in (4.25) being a multiple of the 3×3 unit matrix by a positive function $D_1(x)$. This result again represents a significant generalisation of the previously established result, throwing further light on the possible structure of transport coefficients consistent with the observation of a constant (total) flux ratio, perhaps under more general boundary conditions as in (3.9) and (4.16).

5. Limitations of local theorems

The condition (4.26) in the general discussion above appears rather special and restrictive, even though we might well expect transport properties in a membrane to differ markedly between longitudinal and transverse directions. In order to clarify the necessity of such a condition if a local theorem is to hold, we consider a special, simplified case of the equations considered in Application 4.1, with $k = 0$ in (3.22b), and (D_{kl}) in (4.25) equal to a positive, constant multiple D_0 of the 3×3 unit matrix, so that we have

$$\nabla(\mu c) = -(\mu/D_0)\mathbf{j} \tag{5.1}$$

$$\nabla \cdot \mathbf{j} = -\partial c/\partial t, \tag{5.2}$$

where $\mu = e^{-\phi}$ as before, and $\mathbf{v} = D_0 \nabla\phi$. After taking Laplace transforms we get

$$D_0 \nabla \cdot \left[\frac{1}{\mu}\nabla(\mu C)\right] = sC. \tag{5.3}$$

In order to simplify the analysis further, we take $\Omega = \{(x, y, z): 0 < x < 1, 0 < y < 1, 0 < z < 1\}$, we set $D_0 = 1$, and we suppose that there is no z-dependence in any of the dependent variables or boundary conditions. Letting $U(x, y, s) = \mu(x, y)C(x, y, s)$ we get from (5.3)

$$U_{xx} + U_{yy} + \phi_x U_x + \phi_y U_y = sU \tag{5.4}$$

where

$$U_x(x, y, s) = \partial U(x, y, s)/\partial x \tag{5.5}$$

etc.

From Application 4.1, we know that if

$$\phi(x, y) = \phi_1(x) + \phi_2(y) \tag{5.6}$$

and if the functions f_1 and f_2 appearing in the boundary conditions (3.9) satisfy $f_1(y,t)/f_2(y,t) = r$ (constant), then $j_1^{(1)}(1, y, t)/j_1^{(2)}(0, y, t)$ is constant. We shall now show by a counterexample that when (5.6) does not hold, the constancy of this flux-ratio is not guaranteed.

Suppose that U satisfies the boundary conditions

$$U(x, 0, s) = U(x, 1, s) = 0 \tag{5.7}$$

and choose

$$\phi(x, y) = \varepsilon x \cos \pi y \tag{5.8}$$

where ε is a small parameter $(0 < \varepsilon \ll 1)$. Then (5.4) becomes

$$U_{xx} + U_{yy} + \varepsilon \cos \pi y U_x - \varepsilon \pi x \sin \pi y U_y = sU \tag{5.9}$$

and we consider the solutions $U^{(1)}, U^{(2)}$ of this equation satisfying the boundary conditions (5.4) and

$$\begin{aligned} U^{(1)}(0, y, s) &= F_1(y, s), \qquad U^{(1)}(1, y, s) = 0 \\ U^{(2)}(0, y, s) &= 0, \qquad U^{(2)}(1, y, s) = F_2(y, s). \end{aligned} \tag{5.10}$$

We choose $f_1(y,t) = f_2(y,t) = \sin \pi y$ so that

$$F_1(y,s) = F_2(y,s) = (1/s)\sin(\pi y). \tag{5.11}$$

Consider $U^{(1)}$. For $\varepsilon = 0$ we have

$$U^{(1)}(x,y,s) = A(s)\sinh[\beta(s)(1-x)]\sin(\pi y) \tag{5.12}$$

where

$$\beta(s) = [s+\pi^2]^{1/2}, \qquad A(s) = [s\sinh\beta(s)]^{-1}. \tag{5.13}$$

For $\varepsilon \neq 0$, we try to find the solution in the form (suppressing the s-dependence)

$$U^{(1)}(x,y) = A\sinh[\beta(1-x)]\sin(\pi y) + \varepsilon V(x,y) + O(\varepsilon^2). \tag{5.14}$$

By identifying coefficients of ε we find that V must satisfy

$$\begin{aligned} V_{xx} + V_{yy} - sV &= \frac{1}{2}A(\beta\cosh[\beta(1-x)] + \pi^2 x\sinh[\beta(1-x)])\sin(2\pi y) \\ &= p(x)\sin(2\pi y), \text{ say,} \end{aligned} \tag{5.15}$$

and

$$V(0,y) = V(1,y) = V(x,0) = V(x,1) = 0. \tag{5.16}$$

The solution of (5.15), (5.16) has the form $V(x,y) = q(x)\sin(2\pi y)$, where q satisfies

$$\begin{cases} q''(x) - (s+4\pi^2)q(x) = p(x) \\ q(0) = q(1) = 0. \end{cases} \tag{5.17}$$

After some elementary calculations we find

$$\begin{aligned} q(x) = {} & \frac{\beta A}{18\pi^2}\left(\cosh[\gamma(1-x)] - \frac{\cosh\gamma - \cosh\beta}{\sinh\gamma}\sinh[\gamma(1-x)]\right) \\ & - \frac{\beta A}{18\pi^2}\cosh[\beta(1-x)] - \frac{1}{6}Ax\sinh[\beta(1-x)], \end{aligned} \tag{5.18}$$

where

$$\gamma = [s+4\pi^2]^{1/2}. \tag{5.19}$$

Then we get

$$\begin{aligned} J_1^{(1)}(1,y) &= -e^{\phi(1,y)}U_x^{(1)}(1,y) \\ &= -e^{\varepsilon\cos(\pi y)}[-\beta A\sin(\pi y) + \varepsilon q'(1)\sin(2\pi y) + O(\varepsilon^2)] \\ &= \beta A\sin\pi y + \varepsilon\beta A\left[\frac{1}{3} - \frac{1}{18\pi^2}\frac{\gamma}{\sinh\gamma}(\cosh\gamma - \cosh\beta)\right]\sin(2\pi y) + O(\varepsilon^2). \end{aligned} \tag{5.20}$$

For $U^{(2)}$ we find in the same way that

$$\begin{aligned} U^{(2)}(x,y) = {} & A\sinh(\beta x)\sin\pi y \\ & + \varepsilon\sin(2\pi y)\left\{\frac{1}{\sinh\gamma}\left[\frac{1}{6}A\sinh\beta + \frac{\beta A}{18\pi^2}(\cosh\gamma - \cosh\beta)\right]\sinh(\gamma x)\right. \\ & \left. + \frac{\beta A}{18\pi^2}\cosh(\gamma x) + \frac{\beta A}{18\pi^2}\cosh(\beta x) - \frac{1}{6}Ax\sinh(\beta x)\right\} + O(\varepsilon^2), \end{aligned} \tag{5.21}$$

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and

$$J_1^{(2)}(0,y) = -\beta A \sin \pi y - \varepsilon \frac{\gamma A}{\sinh \gamma}\left[\frac{1}{6}\sinh\beta + \frac{\beta}{18\pi^2}(\cosh\gamma - \cosh\beta)\right]\sin(2\pi y) + O(\varepsilon^2). \tag{5.22}$$

Since the coefficients of ε in the expressions for $J_1^{(1)}(1,y)$ and $J_1^{(2)}(0,y)$ differ in their s-dependence, the ratio of these two functions cannot be independent of s for all ε sufficiently small. It follows that the ratio of $j_1^{(1)}(1,y,t)$ to $j_1^{(2)}(0,y,t)$ is not independent of t, and there is no local ratio theorem in this case.

6. Concluding remarks

Flux ratio theorems in their various forms are seen from our analysis to belong to a wide class of "reciprocity theorems". In this connection, we emphasise that our results in Section 3, based on (3.1)–(3.4), are not limited to equations of the form (3.22), which are essentially parabolic in character, but include elliptic and hyperbolic systems as well. For such systems the interpretation of boundary conditions, and of the ratio theorems themselves, will of course differ in character from the cases of primary interest to membrane physiology. We have made no effort to explore the applications to such other systems, for which results are already known of this general type, if not exact form [1], [8], [9] and [10].

Our results clarify the conditions on transport properties under which one can expect to observe experimentally a constant (total) flux ratio for a real membrane, in the kind of experiments that have been conducted to date [16]. Application 3.1 in particular shows that the result is more robust than might have been expected from earlier analysis: for example, the shape of the membrane sample is not as critical as one might have imagined. The key role played in the analysis by the functions ϕ puts the whole subject in a new perspective, leading us to focus attention on the physical meaning of this "potential", rather than the diffusion coefficients and drift velocity separately.

Our analysis also suggests new experiments that could further illuminate the structure of the transport properties of a membrane. For example, it should be possible to construct an experiment reflecting the theoretical discussion of case (b) in Section 2. Although it may not be possible to test experimentally the validity of a local ratio theorem in such a case, the constancy of a total flux ratio could again be measured. The interdiffusion in the domain Ω would make this prediction highly nontrivial even in the steady state.

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