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Absorption by a moving spherical organelle in a heterogeneous cytoplasm: Implications for the role of trafficking in a symplast

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Abstract

An organelle which absorbs (or secretes) a particular factor will find its mass transfer rate diffusion-limited if it is stationary with respect to its ambient cytoplasm; but organellar motion will raise that limit as a non-decreasing function of the Peclet number **P**. It is shown *analytically* that (i) no Whitehead paradox need be encountered in the creeping flow regime and (ii) the flux of the factor will be an even function of the Peclet number, **P**. By a novel analytic solution method, the flux is shown *numerically* to increase as $\mathbf{P}^2$ for $\mathbf{P} \lesssim 1$. For $\mathbf{P} \gtrsim 10$, a quasi-planar approximating geometry yields analytically a flux which increases as $\mathrm{P}^{1/3}$. These two solutions overlap smoothly in the range $1 \lesssim \mathbf{P} \lesssim 10$. For $\mathbf{P} \approx 1$, convection should increase the mass flux by roughly 100%.

Keywords: Convection–diffusion; Intracellular mass transport; Peclet number; Symplastic transport

1. Introduction

A currently burgeoning field within cell biology is that of *traffic*, a term which broadly denotes all aspects of intracellular transport, including but not limited to: membrane protein and lipid movement, protein translocation, molecular motors, and organelle motion. Its focus is normally upon achieving understanding in depth of the world-line (i.e. trajectory) of a particular intracellular entity. A collateral issue, which has been raised only inconspicuously (Reuzeau et al., 1997; Pickard, 2003), is that of whether organellar motion itself might confer some benefit upon the organelle: in particular, whether an organelle whose operation was impaired by the slow arrival of a diffusion-limited factor might become more productive if it were towed continuously into regions where the factor was relatively less depleted.[1] Since the organelle exists within a cell whose dimensions may be less than a 100-fold greater than those of the organelle[2], this is intrinsically an *interior* (bounded) problem in mass transport; and the solutions of such problems may be qualitatively different from those in which the cellular dimensions are presumed infinite (cf., Batchelor, 1979).

Nevertheless, analogous intrinsically *exterior* (unbounded) problems of mass transport from/to bacteria or phytoplankton are of importance in marine biology, wastewater treatment, chemoreception, etc. (e.g., Berg and Purcell, 1977; Logan and Dettmer, 1990; Karp–Boss et al., 1996; Kiørboe et al., 2001).

Interior and exterior problems alike share the common characteristics: (i) that factor flux across the surface of a target particle diffusively alters factor concentration in the neighboring external medium of the particle; and (ii) that agitation of the fluid surrounding the particle is believed to bring fresh medium into the vicinity of the particle, thereby increasing diffusive flux. This is beautifully summarized by

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[1]The complementary problem of dispersal of a secretion can be treated similarly.

[2]The cytoplasm (contents of a cell) can simplistically be subdivided into organelles, cytoskeletal elements, and putatively fluid ground substance called the cytosol.

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Nomenclature

a radius of a spherical organelle being translated through a macroscopically uniform cytosol

$\mathfrak{a}$ unified atomic mass unit, $1.660\ldots\times10^{-27}$

${}_nA_q$ one of a set of $Q(N+1)$ unknown constants generated by the polynomial expansions of Eq. (41)

$\mathscr{A}_m(\varepsilon)$ a sequence of positive constants defined at (A.5)

$A(\eta), B(\eta), B'(\eta)$ functions related to the Airy functions and defined in Eq. (A.9)

$c(\xi,\zeta)$ in the planar model of Section 5, the dimensionless concentration of a key substance within the cytosol, $c = C/C_0$

$\bar{c}(\xi,s)$ Laplace transform of c with respect to ζ

$\tilde{c}$ $\bar{c} - 1/s$

$\hat{c}(\xi,\omega)$ Fourier cosine transform of c with respect to ζ

C local concentration of a key substance within the cytosol

C_0 nominal background concentration of the a key substance far from any sources or sinks

D effective diffusivity (diffusion constant) of a key substance within a macroscopically uniform cytosol

D_x, D_y, D_z components of a non-tensor diffusivity along the x,y,z Cartesian directions

D_{aq} diffusion constant of a large molecule in a simple aqueous solution

D_{eff} *effective* diffusion constant of a large molecule in an aqueous solution densely packed with macromolecules

$\overleftrightarrow{D}$ tensor diffusivity, a generalization of D

$\mathfrak{d}$ density of a compound

E_{PN} in the parallel plate model, the normalized enhancement of flux to a suitable region of the bottom plate; it is homologous to the $\mathscr{F}_N(\mathbf{P}) - 1$ of the spherical model

$\vec{f}$ vector flux density of a substance suspended in the cytosol

$f(\rho)$ radial variation of the ρ-directed component of the cytosolic velocity

F_E *enhancement* by cytosol motion of the flux density into the bottom plate of a planar geometry; note that the moving cytosol is diffusively anisotropic

F_D flux density into the bottom plate of the planar approximating geometry due solely to normal diffusion

$\mathscr{F}$ total reactant flux integrated over the surface of a moving sphere of radius a

$\mathscr{F}_N$ total steady-state key substance flux $\mathscr{F}$ into a spherical organelle, normalized with respect to the limiting case of zero organellar motion (i.e. diffusion limitation). See Eq. (9)

$\mathfrak{F}$ constant multiplier of the power law asymptotic behavior of $\mathscr{F}_N$ at large Peclet number

$g(\rho)$ azimuthal variation of the θ-directed component of the cytosolic velocity

K_α, K_β constants which appear in solving the parallel plate problem of Section 5

K_{norm} a normalizing constant which sets the peak of $f(\rho)$ to 1

$L_f, L_g, {}_n\mathscr{L}_m$ uncalculated functions of ρ which are bounded over [0,1]

M molecular weight of a compound

$\mathfrak{M}$ a matching constant to conform the predictions of Eq. (A.10) with those of Eq. (36)

N angular degree of a truncated Legendre expansion for $c(\rho,\theta)$

N_A Avogadro number $6.022\ldots\times10^{23}$

$\mathbf{P}$ Peclet number of a spherical organelle of radius a being translated at a constant velocity U through a macroscopically uniform cytosol within which a key reactant had diffusivity D: $\mathbf{P} = Ua/D$

$P_n(\cos\theta)$ Legendre polynomial of the first kind of degree n

Q radial degree of a truncated Taylor expansion of the functions $R_n(\rho)$

$R_n(\rho)$ radial function of the nth term of the Legendre polynomial expansion for the dimensionless concentration $c(\rho,\theta)$. See Eq. (35)

s Laplace transform variable associated with ζ

$\mathfrak{s}^3$ volume of a single molecule (idealized as a cube)

t time

$\vec{u}$ vector velocity of the cytosol about a moving organelle

U constant translational velocity of an infinite cytosol relative to a fixed spherical organelle

$\vec{v}$ normalized velocity defined by $\vec{v} = \vec{u}/U$

x,y,z Cartesian coordinates within the cytosol

$\alpha(\lambda), \beta(\lambda)$ linearly independent solutions of Eq. (A.2) which are defined in (A.4)

$\gamma_n(\rho,\theta)$ functional form of the nth term of the formal perturbation expansion in $\mathbf{P}$ of the normalized concentration $c(\rho,\theta)$ see Eqs. (23)

${}_n\Gamma_m(\rho)$ function describing the radial variation of the mth degree term of the Legendre polynomial expansion of the nth degree term of the perturbation expansion in $\mathbf{P}$ see Eq. (27)

δ $(\mathbf{P}s)^{1/3}$

ζ dimensionless variable z/a

η variable of convenience defined as $\mathbf{P}s$

η_n negative real roots of $B(\eta) = 0$

θ azimuthal angle of a spherical coordinate system

κ constant used to place the peak of the radial component of the cytosolic velocity

λ $(\mathbf{P}s)^{1/3}\xi$

ξ dimensionless variable x/a

ρ normalized radial distance r/a in a spherical coordinate system

ψ_1, ψ_2 functions of ρ defined near Eq. (32)

ω Fourier sine transform variable associated with ζ

Purcell (1978, p. 552)[3] as follows: "It [convection] can [increase the factor flux] by bringing close to the absorber parcels of fluid with the [undisturbed] concentration found further out, thus increasing the concentration gradient around the absorber. Indeed that is the *only* way [convection] can increase the [flux] collected by the absorber. It [convection] cannot convey [a factor]-molecule directly to the surface; the last stage, so to speak, of the molecule's journey must be accomplished by diffusion alone." Biologists seldom ponder the relative contributions of convection and diffusion, especially, as a function of position about a moving particle; with physical scientists and applied mathematicians it seems less rare but is by no means marked. Instead, what many of both categories are apt to do is simply cite a Sherwood number[4].

Qualitatively, it might seem that one could obtain a conceptual grasp of the situation by considering the speciously simple problem of an infinite viscous medium (i) within which the concentration of a diffusible factor is initially uniform, (ii) with respect to which a sphere, that perfectly absorbs the factor, executes a steady rectilinear motion, and (iii) concerning which we desire to know only $\mathscr{F}$ [mol s^{-1}], the *total* steady-state flux of the factor into the surface of the sphere.

Simple qualitative reasoning would suggest that the flux across the surface of the sphere would reflect a balance between the diffusivity D [m^2 s^{-1}] and the speed of the sphere U [m s^{-1}]; moreover, it should depend upon the radius a [m] of the sphere. Historically, these three parameters are combined into a single dimensionless variable, the Peclet number $\mathbf{P} = Ua/D$.[5] By convention, when $\mathbf{P} \gg 1$, convection is said to dominate the flux behavior; and when $\mathbf{P} \ll 1$, diffusion is said to dominate[6].

The above problem is a classic which, for sufficiently large $\mathbf{P} \gg 1$, was long ago was addressed approximately by Levich (1962) and, independently, by Friedlander (1961) and by Acrivos and Goddard (1965) who showed that $\mathscr{F} \propto \mathbf{P}^{1/3}$. A rather more advanced and general derivation of this result was given by Batchelor (1979); and experimental verification has been provided by Kutateladze et al. (1982).

An overview of these and similar studies has been given by Coutelieris et al. (1995), who pointed out that such approximations are "not valid for moderate or low **P**-values"; and an extension to the related case of a "squirming" sphere has been given by Magar et al. (2003). The general problem, including behavior for small **P**, has been studied in depth in a monograph by Leal (1992), in a paper of Romero (1994), and in a review by Polyanin and Vyaz'min (1995). What, however, is striking is that there appear to be no studies which provide simple plots of $\mathscr{F}$ versus **P**, whether experimental or theoretical, over the entire range of **P**-values of relevance to intracellular traffic. Moreover, in the references cited above in this paragraph, there is a notable paucity of *experimental* data which might be used to validate either the formal theoretical models or the approximation techniques used for solving them.

The case of a motionless ideally absorbing sphere of radius of radius a in an infinite cytosol[7] within which the concentration of a diffusible absorbable factor (reactant) was initially C_0 [mol m^{-3}], is known to yield a total flux

$$\mathscr{F} = 4\pi D C_0 a, \tag{1}$$

where D is the diffusivity of the reactant (Carslaw and Jaege, 1959). Initially, when the sphere first begins absorbing factor, the flux will be much, much greater than this; and the steady-state prediction of Eq. (1) will hold only as an equilibrium is reached between absorption at the sphere's surface and diffusion of fresh factor from distant regions of the cytosol. As laminar flow past the sphere increases from zero, regions a few radii from the sphere should be renewed more quickly than by diffusion alone and $\mathscr{F}$ should increase with increasing Peclet number. Only the shape of $\mathscr{F}$ (**P**) should be in question, since it is unclear how the balance between diffusion and convection will play out as the Peclet number becomes progressively larger.

Section 2 will be devoted to mathematical preliminaries in which the question is cast as a problem of anisotropic diffusion in a *infinite* medium that flows past a fixed sphere with a velocity that is specified a priori; however, it will be argued that this velocity is not precisely knowable and that its uncertainty is sufficiently large to admit of a specified form which squelches the Whitehead paradox[8]. In Section 3, a Maclaurin expansion in **P** will be derived for factor

[3]Where appropriate, pointers will be given to page (p.), section (s.), chapter (ch.), equation (eq.), figure (fig.), table (tab.), or experiment (expt.) of the pertinent reference.

[4]The Sherwood number is defined as the ratio (total steady-state flux across absorber surface *with* convective motion in the ambient medium)/(total steady-state flux across absorber surface *in the absence of* convective motion in the ambient medium).

[5]'Peclet' is the anglicized form of the French 'Péclet'. Jean Claude Eugène Péclet (1793–1857), despite a distinguished career in thermal physics, may not have devised the Peclet number. The online edition of the Oxford English Dictionary [http://dictionary.oed.com/cgi/entry/00173688?single=1&query_type=word&queryword=Peclet&edition=2e&first=1&max_to_show=10] attributes the dimensionless group of this name to H. Gröber *Die Grundgesetze der Wärmeleitung und des Wärmeüberganges* (1921) ii. 168. In addition to this memorial, Péclet also has a street in the XVe Arrondissement named after him.

[6]In fact, this convention is really a rough rule of thumb. Although it is unimportant in this paper, the author probably would quantify 'dominate' as follows: consider a stream-surface and a diffusion-limited factor which is being transported inwards across it in the general direction of an absorbing particle; diffusion is said to be 'dominant *sensu stricto*' wherever the convective flux density of the factor parallel to the stream-surface is less than the diffusive flux density perpendicular to that surface.

[7]The cytoplasm (contents of a cell) can simplistically be subdivided into organelles, cytoskeletal elements, and putatively fluid ground-substance called the cytosol.

[8]Actually, there are two related Whitehead paradoxes in fluid mechanics, both of which refer to situations in which higher-order terms of a perturbation expansion over an infinite volume fail to satisfy the prescribed boundary conditions on both a surface near the origin and a surface at infinity (Leal, 1992). The one referred to in this paper is Whitehead's paradox for convective mass (or heat) transfer.

concentration; in this expansion, the coefficients of the powers of **P** are well-behaved as the medium is allowed to become infinite and lead to an $\mathscr{F}(\mathbf{P})$ which increases *quadratically* for adequately small values of **P**. In Section 4, a Legendre function expansion will be introduced which does *not* depend upon perturbation techniques, which permits the numerical calculation of $\mathscr{F}(\mathbf{P})$ for small and intermediate **P**, and which verifies the quadratic prediction of Section 3. In Section 5, behavior for large Peclet number will be examined with a novel approximation technique which validates one's expectations of $\mathscr{F} \propto \mathbf{P}^{1/3}$.

Finally, in the discussion of Section 6, the relevance of the paper's findings to (i) theoretical heat and mass transport (ii) practical plant biology are discussed.

The biologist who is disinterested in the abstruse mathematics of the problem is advised to skip at once to Fig. 3 which shows, relative to the flux expected from pure diffusion and as a function of the Peclet number, the flux *enhancement* due convective flow about the sphere (organelle). The biological significance of this enhancement is examined in the Discussion.

2. Mathematical preliminaries

The equation in moving cytosol of vector velocity $\vec{u}[\mathrm{m\,s^{-1}}]$ for the vector flux $\vec{f}[\mathrm{mol\,m^2\,s^{-1}}]$ of a dissolved factor with tensor diffusivity $\overleftrightarrow{D}[\mathrm{m^2\,s^{-1}}]$ is (Carslaw and Jaeger, 1959)

$$\vec{f} = -\overleftrightarrow{D}\cdot\mathrm{grad}\,C + C\vec{u}, \tag{2}$$

where $C\,[\mathrm{mol\,m^{-3}}]$ is the concentration (number density) of the entity. The equation for the conservation of species number is (Carslaw and Jaeger, 1959)

$$\frac{\partial C}{\partial t} = -\mathrm{div}\vec{f}, \tag{3}$$

where t[s] is the time. For *steady-state* anisotropic diffusion in an incompressible fluid medium (i.e. $\mathrm{div}\,\vec{u} = 0$) of homogeneous orthorhombic diffusivity, Eqs. (2) and (3) combine to yield

$$0 = \vec{u}\cdot\mathrm{grad}\,C - \left[D_x\frac{\partial^2 C}{\partial x^2} + D_y\frac{\partial^2 C}{\partial y^2} + D_z\frac{\partial^2 C}{\partial z^2}\right], \tag{4}$$

where x, y, z [m] are rectangular position variables. In the remainder of this paper Eq. (4) will be solved for C, but only after the velocity $\vec{u}$ has been specified independently.

For the two following Sections (3 and 4), it is convenient to assume: (i) that diffusivity is isotropic so that the tensor $\overleftrightarrow{D}$ collapses into the scalar D and Eq. (4) reduces to

$$0 = \vec{u}\cdot\mathrm{grad}\,C - D\nabla^2 C; \tag{5}$$

(ii) that the organelle is a sphere of radius a fixed at the origin of spherical (r,θ,ϕ) coordinate system; (iii) that $\vec{u} = u_r\hat{r} + u_\theta\hat{\theta}$ (angular symmetry about the polar z-axis); and (iv) that suitable boundary conditions are $C = 0$ at $r = a$ and $C \to C_0$ for $r \gg a$.

Under these assumptions, Eq. (5) reduces to

$$0 = \left[u_r\frac{\partial C}{\partial r} + u_\theta\frac{\partial C}{r\partial\theta}\right] - D\left[\frac{\partial}{r^2\partial r}\left(r^2\frac{\partial C}{\partial r}\right) + \frac{\partial}{r^2\sin\theta\,\partial\theta}\left(\sin\theta\frac{\partial C}{\partial\theta}\right)\right] \tag{6}$$

and the integrated *inward* flux over the surface of the organelle becomes

$$\mathscr{F} = 2\pi a^2 D\int_0^\pi \left.\frac{\partial C}{\partial r}\right|_{r=a}\sin\theta\,\mathrm{d}\theta. \tag{7}$$

If then one makes the transformations $\vec{u} = U\vec{v}$, $\mathbf{P} = Ua/D$, $r = a/\rho$, and $C = C_0 c$,

$$\rho^2\frac{1}{\sin\theta}\frac{\partial}{\partial\theta}\left[\sin\theta\frac{\partial c}{\partial\theta}\right] + \rho^4\frac{\partial^2 c}{\partial\rho^2} = \mathbf{P}\left\{-v_\rho\rho^2\frac{\partial c}{\partial\rho} + v_\theta\rho\frac{\partial c}{\partial\theta}\right\} \tag{8}$$

(where $c = 0$ at $\rho = 1$ and $c \to 1$ as $\rho \to 0$) and

$$\mathscr{F}_N = \frac{\mathscr{F}}{4\pi a D C_0} = -\frac{1}{2}\int_0^\pi \left.\frac{\partial c}{\partial\rho}\right|_{\rho=1}\sin\theta\,\mathrm{d}\theta. \tag{9}$$

$(\mathscr{F}_N - 1)$ is the quantity desired, and Eq. (8) must be solved to provide it.[9]

Another specialized case (Section 5) is that of the parallel-plate region. This is quite unrealistic biologically, but nevertheless is very useful for studying the limit $\mathbf{P} \to \infty$. The key to simplifying this case is to assume that the fluid velocity is so great the z-directed diffusion can be neglected in comparison to the z-directed convection: that is, $D_z = 0$ and $D_x = D_y = D$. It is further assumed that the flow is equivalent to that induced by translating the top plate with a speed U in the z-direction, producing a velocity field (Langlois, 1964)

$$u_z = U\left[\frac{x}{a}\right]. \tag{10}$$

With the substitutions $x = \xi a$ and $z = \zeta a$,

Eq. (5) reduces to

$$\frac{\partial^2 c(\xi,\zeta)}{\partial\xi^2} = \mathbf{P}\xi\frac{\partial c}{\partial\zeta} \tag{11}$$

with the boundary conditions $c = 1$ at $\zeta = 0$, $c = 0$ at $\xi = 0$, and $\partial c/\partial\xi = 0$ at $\xi = 1$. In this planar model, the variation of flux with large Peclet number can be studied by evaluating, for arbitrary ζ the *enhanced* flux density F_E $[\mathrm{mol\,m^2\,s^{-1}}]$ into the bottom plate at $x = 0$:

$$F_E(\zeta) = D\left.\frac{\partial C}{\partial x}\right|_{x=0} = \frac{DC_0}{a}\left.\frac{\partial c}{\partial\xi}\right|_{\xi=0}. \tag{12}$$

This enhancement should be compared to $F_D(\zeta)$ $[\mathrm{mol\,m^2\,s^{-1}}]$, the flux density to the bottom plate due to

[9] $\mathscr{F}_N$ and its analogues in this paper are analogous to the Nusselt number of heat transfer and the Sherwood number of chemical reaction engineering. However, as this contribution is intended for physicists and biologists and as the definitions of these numbers are not uniform throughout science and engineering, these terms will not be employed; and symbols defined locally with precise referents will be used instead.

isotropic diffusion in the absence of convection. In particular, the integral of $F_E(\zeta)$ over a suitable interval of length π (corresponding half an equatorial circumference on a sphere), then divided by a similar integral of $F_D(\zeta)$, and finally multiplied by an appropriate matching constant yields a function of $\mathbf{P}$ comparable to $\mathscr{F}_N(\mathbf{P})-1$, the enhancement in the spherical case.

3. Formal Maclaurin expansion for the sphere

3.1. Specification of the normalized velocity $\vec{v}$

Given that diffusion is a physical process which smears out irregularities, it seems reasonable to assume that $c(\mathbf{P};\rho,\theta)$ is well behaved. Therefore, it should admit of a power series expansion in $\mathbf{P}$ within a sufficiently small neighborhood of $\mathbf{P}=0$, where the coefficients of the expansion are well behaved functions of ρ and θ. The radius of convergence of this series is not, however, obvious.

In treating this problem, it is necessary first to settle upon a functional form for the normalized cytosol velocity, $\vec{v}$, relative to the organelle in question. Because such flows seem to occur only with very low Reynolds numbers (Pickard, 2003), the simplifications associated with viscosity-dominant flow will be valid and creeping flow solutions will obtain.

For many years, physiologists modelling the cytoplasm of a cell divided roughly into two camps: one "assumes that cell behavior is quite similar to that expected for a watery bag of enzymes and ligands" and therefore that the cell has a homogeneous cytoplasm; the other "assumes that three-dimensional order and structure constrain and determine metabolite behavior" (Hochachka, 1999) and therefore that the cell has a heterogeneous cytoplasm. If one accepts the first model, then a low-Reynolds-number creeping-flow solution of the Navier–Stokes equations should suffice. If one accepts the second model, then the Navier–Stokes equations are inappropriate because the cytosol is not an homogeneous fluid but more like a saturated porous medium through which fluid percolates and for which Darcy's equation is more appropriate (Bear, 1988). For a sphere moving with respect to an *infinite medium*, the solutions to both flow problems are well known. The Navier–Stokes (homogeneous cytoplasm) case yields (Langlois, 1964; Milne-Thomson, 1950)

$$v_\rho = -\cos\theta[1-(\tfrac{3}{2})\rho+\tfrac{1}{2}\rho^3] = -\cos\theta[(1-\rho)^2(1+\tfrac{1}{2}\rho)], \tag{13}$$

$$v_\theta = \sin\theta[1-\tfrac{3}{4}\rho-\tfrac{1}{4}\rho^3] = \sin\theta[(1-\rho)(1+\tfrac{1}{4}\rho+\rho^2)]. \tag{14}$$

The Darcy (heterogeneous cytoplasm) case yields (Romero, 1994)

$$v_\rho = -\cos\theta[1-\rho^3] = -\cos\theta[(1-\rho)(1+\rho+\rho^2)], \tag{15}$$

$$v_\theta = \sin\theta[1+\tfrac{1}{2}\rho^3]. \tag{16}$$

However, neither case takes account of the biological complications that: (i) the cytoplasm is *finite*, not infinite; (ii) the cytoplasm contains a cytoskeleton which will rapidly damp flow; (iii) cytoskeletal structure metamorphoses with a time-scale of minutes; and (iv) neighboring organelles are moving within the cytoplasm, thereby distorting the flow field in unpredictable fashions. That is, $\vec{v}$ is an unknown which cannot be predicted rigorously but which, possibly, can be usefully approximated.

Eqs. (13)–(16) have the similarity that they are of the forms

$$v_\rho = -\cos\theta[f(\rho)], \tag{17}$$

$$v_\theta = \sin\theta[g(\rho)]. \tag{18}$$

Our first approximation therefore is that, *near the organelle*, $\vec{v}$ will have the form given by Eqs. (17)–(18). This simplicity of variation with polar angle (i.e. latitude) is not surprising since the Reynolds number is orders of magnitude below unity (Pickard, 2003), and the flow is expected to creep around the organelle without complications of pattern. Our second approximation is that, by the continuity equation for incompressible fluids of uniform density (Milne–Thomson, 1950), $\operatorname{div}\vec{v}=0$ and

$$g(\rho) = f(\rho) - \frac{\rho}{2}\frac{\mathrm{d}f(\rho)}{\mathrm{d}\rho}. \tag{19}$$

Since there will be many organelles within a cell, each affecting both the dimensionless concentration c and the dimensionless cytosolic velocity $\vec{v}$ relative to the organelle of interest, neither Eq. (8) nor the choice of $f(\rho)$ will be exact. This conclusion is only strengthened by the observation that as much as 30% of the intracellular volume of a eukaryotic cell can be occupied by macromolecules (Ellis, 2001), a density which would both *increase* the effective viscosity and *decrease* the effective diffusion constant. Our third approximation is then that the cell can be considered to be of infinite extent ($r\to\infty$ & $\rho\to 0$). But these uncertainties mean that any behavior deduced for $c(\mathbf{P};\rho,\theta)$, though qualitatively useful, *should probably not be trusted beyond one significant figure*.

The interior of the cell is more highly organized than most biologists would have thought, even a few years ago (Pickard, 2003), and hence Eqs. (13)–(14) cannot be the whole truth. On the other hand, highly structured and heterogeneous though it may be, the cytosol seems quite unlike the water-saturated granular particulate for which the model of Eqs. (15)–(16) was devised. Moreover, the structure of the cytosol is *not time-invariant*, so that one has to think in terms of time-average or "effective" cytosolic flows; that is, traffic exists (Schroer, 2000), and the ultrastructure of the organelle's heterogeneous ambient is constantly changing. Because (i) the velocity field far from the organelle will be strongly affected by the structure of the cytosol and motions of neighboring organelles and (ii) the concentration $c(\mathbf{P};\rho,\theta)$ will presumably be affected

more by neighboring organelles than by $f(\rho)$, our fourth approximation is that for, $\rho \lesssim 0.1$ ($r \gtrsim 10a$), the choice of $f(\rho)$ is not of great importance as long as it varies slowly and smoothly, is nonnegative, and tends rapidly to zero as $\rho \to 0$. Therefore, since the *effective* cytosolic velocity relative to the organelle is at present so poorly known, there is some justification for picking a *convenient* $f(\rho)$ and constraining it: (i) near $\rho = 1$, to lie between Eqs. (13) and (15); (ii) to peak at 1 several radii out from the organelle's surface; (iii) to decay strongly beyond this peak, reflecting thereby our lack of knowledge concerning the effects of a heterogeneous cytosol containing other organelles; (iv) to vary smoothly and to generate a $g(\rho)$ which also varies smoothly; (v) as $\rho \to 0$, to vanish strongly enough to suppress phenomena akin to the Whitehead paradox (Leal, 1992) and thereby enable perturbation-like solutions. Since the Whitehead paradox appears only at singularities of the governing equations, this constraint could be viewed as an analytically convenient way of compensating for the simplifying assumption of an infinitely large cell.

The variation selected here is

$$f_C(\rho) = K_{\text{norm}}(1-\rho)^2 \exp\left[\kappa \frac{\rho - 1}{\rho}\right], \tag{20}$$

where κ is a dimensionless constant used to locate the peak of $f(\rho)$ at an appropriate $\rho_{\max}$, and K_{norm} is a dimensionless constant used to normalize the peak to 1; the subscript C denotes cytoplasmic. By Eqs. (19)–(20),

$$g_C(\rho) = K_{\text{norm}}(1-\rho)\left\{1 - \frac{1}{2}\kappa\frac{1-\rho}{\rho}\right\}\exp\left[\kappa\frac{\rho-1}{\rho}\right]. \tag{21}$$

Forms (20)–(21) will be used in this and the following section:

3.2. Existence of a Maclaurin expansion in $\mathbf{P}^2$

With the substitutions described,

$$\rho^2 \frac{1}{\sin\theta}\frac{\partial}{\partial\theta}\left[\sin\theta\frac{\partial c}{\partial\theta}\right] + \rho^4\frac{\partial^2 c}{\partial\rho^2} = \mathbf{P}\left\{\cos\theta f_C(\rho)\rho^2\frac{\partial c}{\partial\rho} + \sin\theta g_C(\rho)\rho\frac{\partial c}{\partial\theta}\right\}. \tag{22}$$

Suppose that, for sufficiently small Peclet number, there is a formal Maclaurin series of the form

$$c = \sum_{n=0}^{\infty}\gamma_n(\rho,\theta)\mathbf{P}^n, \tag{23}$$

where in accordance with the boundary conditions: if $n = 0$, $\gamma_0(1,\theta) = 0$ and $\gamma_0(0,\theta) = 1$; if $n \geqq 1$ $\gamma_n(1,\theta) = 0$ and $\gamma_n(0,\theta) = 0$. If Eq. (23) is substituted into Eq. (22) and terms in $\mathbf{P}^n$ equated, it follows that

$$\rho^2\frac{1}{\sin\theta}\frac{\partial}{\partial\theta}\left[\sin\theta\frac{\partial\gamma_0}{\partial\theta}\right] + \rho^4\frac{\partial^2\gamma_0}{\partial\rho^2} = 0, \quad n = 0, \tag{24}$$

$$\rho^2\frac{1}{\sin\theta}\frac{\partial}{\partial\theta}\left[\sin\theta\frac{\partial\gamma_n}{\partial\theta}\right] + \rho^4\frac{\partial^2\gamma_n}{\partial\rho^2} = \left\{\cos\theta f_C\rho^2\frac{\partial\gamma_{n-1}}{\partial\theta} + \sin\theta g_C\rho\frac{\partial\gamma_{n-1}}{\partial\theta}\right\}, \quad n \geqq 1. \tag{25}$$

Eqs. (24)–(25) define an infinite system of differential equations from which important properties of the γ_n, although *not their exact forms*, must be deduced.

First, as can be verified by direct substitution, the unique solution to (24) subject to the boundary conditions is (Carslaw and Jaeger, 1959)

$$\gamma_0(\rho,\theta) = 1 - \rho. \tag{26}$$

Second, diffusion is a process which flattens peaks, fills valleys, and blurs edges: as a result, the several γ_n should be mathematically well behaved throughout the inverted sphere $0 < \rho < 1$. In particular, for any surface of constant ρ, there should be a valid expansion of $\gamma_n(\rho,\theta)$ in terms of Legendre polynomials (Churchill, 1941). Moreover, since $\gamma_n(\rho,\theta)$ presumably is well behaved, the coefficients of this expansion should vary smoothly so that

$$\gamma_n(\rho,\theta) = \sum_{m=0}^{\infty}{}_n\Gamma_m(\rho)P_m(\cos\theta), \tag{27}$$

where the ${}_n\Gamma_m(\rho)$ are well-behaved functions of ρ. When, for $n \geqq 1$, Eq. (27) is substituted into Eq. (25) and the resulting expression multiplied by $\frac{1}{2}(2p+1)\sin\theta P_p(\cos\theta)$ and integrated over $(0,\pi)$, the left-hand side of Eq. (25) becomes

$$\left\{\rho^4\frac{\mathrm{d}^2{}_n\Gamma_m(\rho)}{\mathrm{d}\rho^2} - m(m+1)\rho^2{}_n\Gamma_m(\rho)\right\}, \tag{28}$$

where use has been made of Legendre's differential equation (Churchill, 1941). Similarly, the right-hand side becomes

$$\left\{[f_C(\rho)\rho^2]\left[\frac{m+1}{2m+3}\frac{d_{n-1}\Gamma_{m+1}(\rho)}{\mathrm{d}\rho} + \frac{m}{2m-1}\frac{d_{n-1}\Gamma_{m-1}(\rho)}{\mathrm{d}\rho}\right] + [g_C(\rho)\rho]\left[-\frac{(m+1)(m+2)}{2m+3}{}_{n-1}\Gamma_{m+1}(\rho) + \frac{m(m-1)}{2m-1}{}_{n-1}\Gamma_{m-1}(\rho)\right]\right\}, \tag{29}$$

where use has been made of the recurrence relations of the Legendre polynomials (Abramowitz and Stegun, 1964).

Third, assuming good behavior of the ${}_n\Gamma_m(\rho)$, the import of Eqs. (28)–(29) is that a Legendre polynomial of degree m in the development of $\gamma_n(\rho,\theta)$ gives rise to Legendre polynomials P_{m+1} and P_{m-1} in $\gamma_{n+1}(\rho,\theta)$. Because $\gamma_n(\rho,\theta)$ involves only P_0 , this leads cascade in which: for even n, $\gamma_n(\rho,\theta)$ involves only Legendre polynomials of even order up to n; and, for odd n, $\gamma_n(\rho,\theta)$ involves only Legendre polynomials of odd order up to n. The higher-order ${}_n\Gamma_m(\rho)$ may, however, be of some complexity.

Fourth, the Whitehead paradox, which leads to solutions poorly behaved as $r \to \infty$, is well known. Therefore, the assumed good behavior of the ${}_n\Gamma_m(\rho)$ as $\rho \to 0$ cannot be

taken for granted, as in the *formal* expansion above: it must be demonstrated! Observe, therefore, that if the formal expansion of order $n-1$ has ${}_{n-1}\Gamma_m(\rho)$ which are well behaved in the sense that *both* ${}_{n-1}\Gamma_m(\rho)$ *and* $d_{n-1}\Gamma_m(\rho)/d\rho$ are bounded over [0,1], then the right-hand side term in $P_m(\cos\theta)$ on the nth-order equation can be expressed as

$$f_C(\rho)L_f(\rho)+g_C(\rho)L_g(\rho), \tag{30}$$

where $L_f(\rho)$ and $L_g(\rho)$ are also bounded over [0,1]. It then follows that the mth degree term of the nth-order equation is of the form

$$\rho^2\frac{d^2{}_n\Gamma_m(\rho)}{d\rho^2}-m(m+1){}_n\Gamma_m(\rho)=e^{-\kappa/\rho}{}_n\mathscr{L}_m(\rho)\rho^{-2}, \tag{31}$$

where ${}_n\mathscr{L}_m(\rho)$ is likewise bounded over [0,1]. The fundamental solutions of the homogeneous reduced Eq. (31) are obviously $\Psi_1(\rho)=\rho^{-m}$ and $\Psi_2(\rho)=\rho^{m+1}$. Following standard methodology (Ince, 1956), the complete solution of Eq. (31) will be

$$\begin{aligned}{}_n\Gamma_m(\rho)=K_2\psi_2(\rho)&-\frac{\psi_1(\rho)}{2m+1}\int_0^\rho\psi_2(\omega)e^{-\kappa/\omega}{}_n\mathscr{L}_m(\omega)\omega^{-2}\,d\omega\\&+\frac{\psi_2(\rho)}{2m+1}\int_0^\rho\psi_1(\omega)e^{-\kappa/\omega}{}_n\mathscr{L}_m(\omega)\omega^{-2}\,d\omega,\end{aligned} \tag{32}$$

if, to meet the boundary conditions on $\gamma_n(\rho,\theta)$, (i) the last two terms on the right-hand side tend to zero as $\rho\to 0$ and (ii) the constant K_2 is chosen to set ${}_n\Gamma_m(1)=0$. To demonstrate (i), note that

$$\begin{aligned}&\left|\int_0^\rho\psi_1(\omega)e^{-\kappa/\omega}{}_n\mathscr{L}_m(\omega)\omega^{-2}\,d\omega\right|\\&<\int_0^\rho e^{-\kappa/\omega}|{}_n\mathscr{L}_m(\omega)|\omega^{-(m+2)}\,d\omega\\&<e^{-\kappa/2\rho}\int_0^\rho e^{-\kappa/2\omega}|{}_n\mathscr{L}_m(\omega)|\omega^{-(m+2)}\,d\omega\\&=\mathscr{O}(e^{-\kappa/2\rho}).\end{aligned}$$

Thus, Arrhenius-type decay of $f_C(\rho)$ is sufficiently powerful to squelch the singularity at $\rho=0$ that generates the Whitehead paradox: using the normalized radial velocity function $f_C(\rho)$, a formal Maclaurin expansion of the form (23) does exist.

Fifth, this means that the normalized flux across the organelle surface will by Eqs. (18), (23) and (27) be

$$\mathscr{F}_N=\frac{1}{2}\sum_{n=0}^{\infty}\mathbf{P}^n\sum_{m=0}^{\infty}\left.\frac{d_n\Gamma_m(\rho)}{d\rho}\right|_{\rho=1}\int_0^\pi P_m(\cos\theta)\sin\theta\,d\theta. \tag{33}$$

With Eq. (26) and the orthogonality relation for the Legendre polynomials (Churchill, 1941), this reduces to

$$\begin{aligned}\mathscr{F}_N=1-\left.\frac{d_2\Gamma_0(\rho)}{d\rho}\right|_{\rho=1}\mathbf{P}^2-\left.\frac{d_4\Gamma_0(\rho)}{d\rho}\right|_{\rho=1}\\\times\mathbf{P}^4-\left.\frac{d_6\Gamma_0(\rho)}{d\rho}\right|_{\rho=1}\mathbf{P}^6-\cdots.\end{aligned} \tag{34}$$

That $\mathscr{F}_N$ should be turn out to be even function of $\mathbf{P}$ is not, after the fact, surprising because $\mathscr{F}_N$ should be insensitive to the sign of U. That is, the total uptake should not depend upon the direction of the flow.

Sixth, Eq. (34) neither provides explicit analytic forms for the coefficients *nor predicts a radius of convergence for the series*.

Seventh, the result (34), that the convection-driven increase in reactant flux to the organelle surface is $\mathscr{O}(\mathbf{P}^2)$ at low Peclet numbers, is not a commonplace. To the author's knowledge, such a behavior has been predicted only twice previously (Frisch, 1954; Berg and Purcell, 1977) and is not in harmony with recent expectations (Leal, 1992). Frisch (1954) obtained his result by a perturbation technique and has been sharply criticized for the velocity distribution he used (Acrivos and Taylor, 1962). Berg and Purcell (1977) obtained theirs by a poorly documented numerical technique and have been criticized by Brunn (1981) for allegedly warping an exterior-unbounded problem into an interior-bounded problem, which in turn alters the influence of convection. However, actual experimental measurements by Purcell (1978) show, for Peclet numbers slightly below one, a quadratic variation; but they were obtained using a biaxial straining flow rather than a uniform streaming flow and have been considered by Batchelor (1979) as at risk of being interior-bounded. From the viewpoint of the intracellular mass transfer problem of interest here, one finds encouraging the qualitative expectations voiced by both Batchelor (1979, p. 392) and Brunn (1981, p. 34) that $\mathbf{P}^2$ variation *should* result for an interior-bounded problem.

4. Legendre expansion for arbitrary Peclet number

Because the predictions of the previous section were unexpected when the project was commenced, it was thought advisable to test them by solving Eqs. (8)–(9) using an *unrelated* technique. No size limitations are imposed upon $\mathbf{P}$ in the technique developed below except the current practical limits of computability. Let

$$c=[1-\rho]+\sum_{n=0}^{\infty}R_0(\rho)P_n(\cos\theta). \tag{35}$$

The $[1-\rho]$ term is clearly the solution in the limit $\mathbf{P}\to 0$. By itself, it satisfies the boundary conditions thereby requiring for all n that $R_n(1)=0$ and $R_n(0)=0$. The $R_n(\rho)$ are unknown functions which vary with $\mathbf{P}$ and which will be presumed analytic over [0,1]. When Eq. (35) is combined with Eq. (9), the normalized flux becomes

$$\mathscr{F}_N=1-\left.\frac{dR_0(\rho)}{d\rho}\right|_{\rho=1}=1-R_0'(1). \tag{36}$$

When Eq. (35) is substituted into Eq. (8) and the recurrence relations for the Legendre polynomials employed

$$\begin{aligned}
&\mathrm{P}f_C(\rho)\rho^2 P_1(\cos\theta)\\
&\quad = -\sum_{n=0}^{\infty}\{\rho^4 R_n''(\rho) - n(n-1)\rho^2 R_n(\rho)\}\mathbf{P}_n(\cos\theta)\\
&\qquad + \mathbf{P}\sum_{n=0}^{\infty}\{\rho^2 f_C(\rho)R_n'(\rho)\}\frac{1}{2n+1}\\
&\qquad \times[(n+1)\mathrm{P}_{n+1}(\cos\theta) + n\mathrm{P}_{n-1}(\cos\theta)]\\
&\qquad + \mathbf{P}\sum_{n=0}^{\infty}\{\rho g_C(\rho)R_n(\rho)\}\frac{n(n+1)}{2n+1}\\
&\qquad \times[P_{n+1}(\cos\theta) - \mathrm{P}_{n-1}(\cos\theta)]. \qquad (37)
\end{aligned}$$

Applying the orthogonality properties of the Legendre functions, expands this single equation involving infinite sums into the following infinite set of simple differential equations:

$$n=0:\quad 0 = -\rho^4 R_0'' + \tfrac{1}{3}\mathbf{P}\{\rho^2 f_c R_1' - 2\rho g_c R_1\}, \qquad (38)$$

$$\begin{aligned}
n=1:\quad \mathbf{P}\rho^2 f_c = &-\rho^4 R_1'' + 2\rho^2 R_1 + \mathbf{P}\{\rho^2 f_c[R_0' + \tfrac{2}{5}R_2']\\
&+ \rho g_c[-\tfrac{6}{5}R_2]\}, \qquad (39)
\end{aligned}$$

$$\begin{aligned}
n>1:\quad 0 = &-\rho^4 R_n'' + n(n+1)\rho^2 R_n\\
&+ \mathbf{P}\left\{\rho^2 f_C\left[\frac{n}{2n-1}R_{n-1}' + \frac{n+1}{2n+3}R_{n+1}'\right]\right\}\\
&+ \mathbf{P}\left\{\rho g_C\left[\frac{(n-1)(n)}{2n-1}R_{n-1} - \frac{(n+1)(n+2)}{2n+3}R_{n+1}\right]\right\}. \qquad (40)
\end{aligned}$$

These equations were used to generate numerical values as follows.

First, it was assumed that the expansion of Eq. (35) could be successfully truncated. This forced $R_n(\rho)\equiv 0$ for $n>N$ and yielded $(N+1)$ coupled differential equations for $R_0(\rho), R_1(\rho), \ldots, R_N(\rho)$. Given the known ultrastructural heterogeneity of the cytosol, to choose an N outside the one digit range would be to pretend to a level precision which present day biological knowledge cannot support. For the computations of this paper, the choice was $N=8$, large enough to offer a degree of azimuthal resolution but not blatantly pretentious.

Second, $R_n(\rho)$ was assumed to be adequately approximated by a polynomial of the form

$$R_n(\rho)\sum_{q=1}^{Q} {}_n\mathbf{A}_q\rho^q, \qquad (41)$$

where the ${}_n\mathbf{A}_q$ are a set of $Q(N+1)$ unknown constants. This approximation guarantees the demand that $R_n(0)=0$. The requirement that $R_n(1)=0$ provides $(N+1)$ of the equations needed to find the ${}_n\mathbf{A}_q$.

Third, the remaining $(Q-1)(N+1)$ equations needed were supplied by requiring that the polynomials defined by Eq. (41) satisfy the differential equations (38)–(40) at the points of the grid $\rho = 1/Q, 2/Q, \ldots, (Q-1)/Q$. It should be noted that, in r-space, these points are densely clumped near the organelle's surface, where they can sample the diffusive boundary layer. Obviously, Q must be chosen large enough to resolve $R_0(\rho)$ effectively near the organelle surface. Therefore, a priori, it seemed risky to pick a Q which was not in the two-digit range, even though this necessarily boosted the computational burden significantly.

Fourth, upon beginning computations using MATLAB® Version 6.5.0, it was discovered that, as Q was increased past 10, the linear systems generated became progressively more ill conditioned and resisted solution by normal elimination techniques. This was circumvented in two ways: (i) because, surprisingly, the determinant of a matrix is not usefully related to its condition number (Watkins, 2002), Cramer's rule[10] was used to find *only* the Q coefficients ${}_0\mathbf{A}_q$; (ii) computations were carried out with 48-digit precision using MATLAB's Symbolic Math Toolbox. For technical reasons, the latter strategy made it convenient to substitute for Eqs. (20)–(21) high degree polynomial approximations which contained no zeroth or first degree terms but which well-represented the velocity functions near the organelle (cf. Fig. 1).

Fifth, assuming that $\mathbf{P}=1$ could still be deemed "small", the normalized *incremental* flux $\mathscr{F}_N - 1$ was (for $N=8$) computed over the Q-range 2(1)24 and found, as expected, (a) to jump about erratically for small values of Q and (b) to settle slowly towards an asymptote in the interval 0.55 ± 0.05, for which the $Q=24$ value of $0.579\cdots$ was deemed an adequate approximation. Higher values of Q were prone to encounter limitations in the Toolbox's code. For $Q=24$, $P=1$, and $N=6,7,8$ it was then verified that an azimuthal degree of $N=8$ closely approached a putatively asymptotic limit.

Sixth, for $P=1$, $N=8$, $Q=24$, the ${}_0\mathbf{A}_q$ were found and $R_0(\rho)$ plotted over [0,1]. As illustrated in Fig. 2, the variation is smooth over the entire range and nearly linear near $\rho=1$.

Seventh, $\mathscr{F}_N(\mathbf{P})-1$ was then computed over $\mathbf{P}\in(10^{-3}, 10^{+1.8})$ and plotted as the points ∘ ∘ ∘ ∘ ∘ in Fig. 3; the solid line is a quadratic power law fitted to the point at $\mathbf{P}=0.001$.

Eighth, and finally, $\mathscr{F}_N(\mathbf{P})-1$ was studied for several flow distributions at $\mathbf{P}=1$: (a) the polynomial approximation of Fig. 1 for the velocity about the organelle yielded 0.5791; (b) the Stokes flow approximation of Eqs. (13)–(14) yielded 0.9052; and (c) the Darcy flow approximation of Eqs. (15)–(16) yielded 1.2577. Clearly, *details of the flow about the organelle do matter significantly*. But, since no exact method has ever been found for predicting low Reynolds number flow within a heterogeneous time-varying geometry, one can conclude from these numbers only (a) that convection at Peclet numbers below unity can

[10]Determinants have of course fallen out of favor for solving linear systems. However, when the system matrix is ill conditioned, only a few of the unknowns are needed, and computer time is abundant, they seemed a marked convenience to the author.

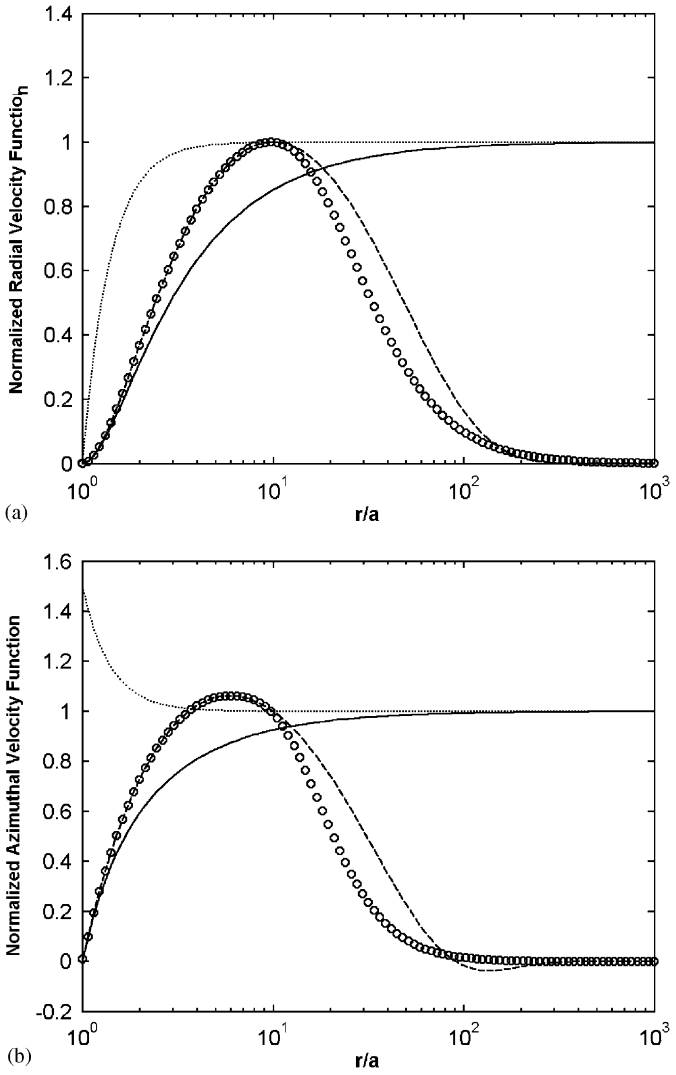

Fig. 1. Normalized fluid velocities in the neighborhood of sphere moving relative to the cytosol. (a) f_S (———) denotes the radial velocity the Stokes flow case (13); f_D (· · · · · · · · · · ·) denotes the Darcy flow case (15); f_C (- - - - - - - - - -) denotes the biologically more realistic exponential paradigm case (20); and the discrete circles (○○○○○○○○○○) represent a technically convenient 23rd degree polynomial which was used to represent f_C for computations. (b) g_S (———) denotes azimuthal velocity in the Stokes flow case (14); g_D (· · · · · · · · · · ·) denotes the Darcy flow case (16); g_C (- - - - - - - - - -) denotes the biologically more realistic exponential paradigm case (21); and the discrete circles (○○○○○○○○○○) represent a technically convenient 23rd degree polynomial which was used to represent g_C for computations.

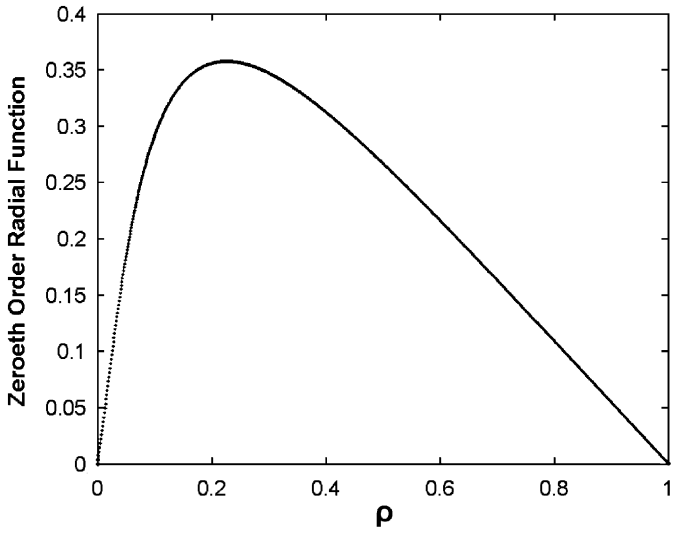

Fig. 2. The radial distribution function $R_0(\rho)$ for the parameter values $\boldsymbol{P} = 1$, $N = 8$, and $Q = 24$.

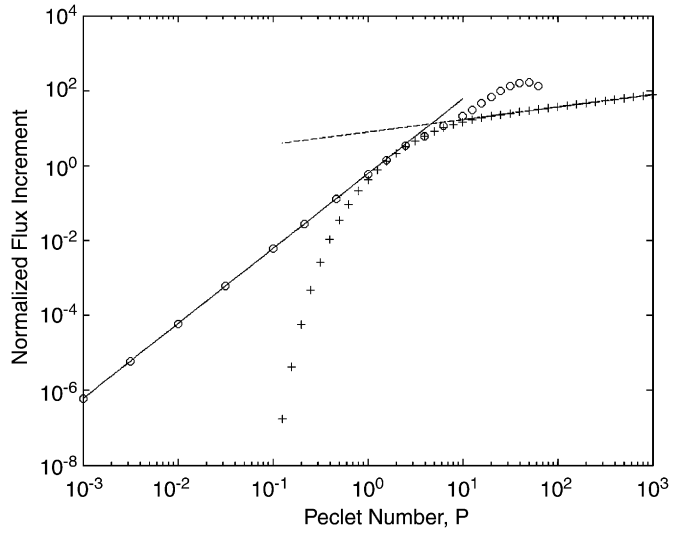

Fig. 3. Predicted variations of the normalized incremental flux $\mathscr{F}_N(\mathbf{P}) - 1$. The points ○○○○○ are from the Legendre expansion; the solid line ———— was fit at the point $\mathbf{P} = 0.001$ and is the quadratic power law $0.6033\mathrm{P}^2$. The points + + + + + are from the anisotropic diffusion approximation and have been scaled as described in the text; the dashed line — — — — — was fit at the point $\mathbf{P} = 1000$ and is the cube-root power law $7.906\mathrm{P}^{1/3}$.

yield a non-trivial increase in the normalized incremental flux and (b) that the velocity distribution used for the low Peclet regime of Fig. 3 probably does not *over*estimate that increase.

5. Large Peclet limit

The behavior for small Reynolds number and large Peclet number has been extensively reviewed by Leal (1992) who emphasized its treatment as a problem in singular perturbation theory. There is considerable agreement on a large Peclet number behavior of the form

$$\mathscr{F}_N(\rho) - 1 = \mathfrak{F}\mathbf{P}^{1/3}, \tag{42}$$

where $\mathscr{F}$ is a constant presumably well within the range $[10^{-1}, 10^{+1}]$. Nevertheless, it seems worthwhile to reexamine the issue. In this paper, the functional form of Eq. (42) will be obtained by a rather different approximation technique, thereby giving additional credence to its validity.

Physically, a large Peclet number means that, except in layers very close to the surface of the sphere, a diffusing

particle on a streamline has virtually zero probability of diffusing to the surface in the normal direction and being absorbed before it has been convected past the sphere. Further, diffusion tangential to the surface should be largely outweighed by tangential convection. Under such circumstances, convective diffusion near the surface of the sphere should behave somewhat like convective diffusion in the parallel plane geometry, only with $r \to x$, $a\theta \to z$, and Eq. (5) collapsing to Eq. (11). The importance of working with Eq. (11) rather than the system (8) is that the former can be solved exactly. The recipe suggested for normalizing involves integration over a "suitable" ζ-interval of length π; in an effort to compensate for stagnation at the upstream pole present in the spherical problem and to avoid complications arising from the singularity at $(0,y,0)$ in the planar problem, this interval will be taken as $(\pi/6, 7\pi/6)$. The problem is then conceptually straightforward but algebraically messy and has been relegated to an Appendix, where it is shown that one procedure for constructing a normalized enhanced flux E_{PN} comparable to $\mathscr{F}_N(\mathbf{P}) - 1$ yields

$$E_{PN} = \mathfrak{M}\frac{\int_{\pi/6}^{7\pi/6} F_E(\zeta)\,\mathrm{d}\zeta}{\int_{\pi/6}^{7\pi/6} F_D(z)\,\mathrm{d}\zeta} = 5.667\mathbf{P}\sum_{n=1}^{\infty}\frac{1}{-\eta_n}\frac{A(\eta_n)}{B'(\eta_n)} \times \left[\exp\left(\frac{\pi}{6}\frac{\eta_n}{\mathbf{P}}\right)\right]\left[1-\exp\left(\pi\frac{\eta_n}{\mathbf{P}}\right)\right], \quad (43)$$

where $\mathfrak{M} = 3.379$ is a matching constant chosen to make E_{PN} and $\mathscr{F}_N(\mathbf{P}) - 1$ comparable at the point $\mathbf{P} = 3.98$, thereby crudely matching both their zeroeth and first derivatives; where the η_n are a sequence of negative constants discussed in the Appendix; and where $A(\eta_n)$ and $B'(\eta_n)$ are higher transcendental functions also discussed in the Appendix.

Direct computation of E_{PN} using Eq. (43) shows that it: (i) increases as $\mathbf{P}^{1/3}$ above $P = 10$; (ii) falls off faster than $\mathbf{P}^2$ below $\mathbf{P} = 1$; and (iii) overlays $\mathscr{F}_N(\mathbf{P}) - 1$ over the intervening decade. This is illustrated in Fig. 3. The $\mathbf{P}^{1/3}$ behavior for large Peclet number is in accord with the asymptotic analysis (Leal, 1992); however, reflecting perhaps the differences in matching strategies, the proportionality constants are different.

6. Discussion

A. Implications for theoretical heat and mass transport. Recent overviews of convection–diffusion in the creeping flow regime (Reynolds number negligible) have emphasized (Leal, 1992; Polyanin and Vyaz'min, 1995; Michaelides, 2003), for $\mathbf{P} \lesssim 1$, formulas of the Acrivos and Taylor form (Acrivos and Taylor, 1962) which express the normalized convection-enhanced flux as $k_1\mathbf{P} + k_{2\ell}\mathbf{P}^2 \ln \mathbf{P} + k_2\mathbf{P}^2 + k_{3\ell}\mathbf{P}^3 \ln \mathbf{P} + \mathscr{O}(\mathbf{P}^3)$, where the several constants k depend upon the precise definition of $\mathbf{P}$, and tend (very approximately) to lie (in absolute value) between 0.1 and 1. This does *not* accord with what Eq. (34) predicts because odd powers of $\mathbf{P}$ and logarithms of $\mathbf{P}$ are absent in that equation. One might, therefore, be motivated to reject the low-Peclet theoretical analysis of Section 3 were it not for the fact that the numerical analysis of Section 4 supports the theoretical analysis of Section 3 while in no way depending upon that analysis (beyond the using the same widely accepted convection–diffusion equation). Moreover, the numerical analysis of Section 4 yields the same qualitative behavior for three different velocity profiles and many different values of Q (results not presented): at sufficiently low Peclet numbers, the convection-associated enhanced flux varies as $\mathbf{P}^2$, as the theoretical analysis of Section 3 predicts, as the poorly documented computations of Berg and Purcell (1977) predict, and as the qualitative theoretical arguments of Batchelor (1979) and Brunn (1981) predict.

Recent overviews of convection–diffusion in the large Peclet number regime (Reynolds number negligible) have emphasized (Leal, 1992; Polyanin and Vyaz'min, 1995; Michaelides, 2003), for $\mathbf{P} \gg 1$, formulas of the Acrivos and Goddard form (1965) which express the normalized convection-enhanced flux as $\mathbf{P}^{1/3}[k_{1/3} + \mathscr{O}(\mathbf{P}^{-1/3})]$, where $k_{1/3}$ is a positive constant of order one. At $P \gtrsim 10$, this is in qualitative accord with Eq. (43), although the coefficients of $\mathbf{P}^{1/3}$ differ quantitatively.

An obvious question raised by these results is: "Eq. (34) does not agree with the predictions of the Acrivos group. So who went astray?" The author believes that this is not the proper question to be asking, especially since the problem treated here is not quite the same as that treated by Acrivos and Taylor (1962) and since the assumptions made within the two analyses most definitely are different.[11] A more productive question would be: "Agreement with relevant experimental data being the gold standard by which the predictions of mathematical theories should be judged, which analysis is in better agreement with the published data?" Unfortunately, the author can cite no *experimental* data adequate for the comparison. First, most data on mass (or heat) transfer in fluids are for Reynolds numbers so high that the (often implicit) assumption of laminar flow without vortex shedding is inappropriate; however, what data there are typically suggest (Kramers, 1946; Richardson, 1953; Collis and Williams, 1958) that the normalized flux increment is sublinear in the (large) Peclet number and therefore qualitatively in accord with $\mathbf{P}^{1/3}$ behavior. Second, published experimental data sometimes do not clearly separate the effects of Reynolds number and

[11] Nevertheless, simple computation of the small-$\mathbf{P}$ formula for $\mathscr{F}_N$ given by Acrivos and Taylor (1962) shows that it is convex-upward over its range of validity, whereas the large-$\mathbf{P}$ given formula given by Acrivos and Goddard (1965) is convex-downward over its range of validity. A similar pair of formulas has been provided by Leal (1992). The smooth transition expected from one asymptotic formula of a pair to the other is *not* observed. Moreover, for neither pair of formulas, do the low-P and high-P formulas of the pair intersect.

Peclet number. Third, there seems to be in the field a long-standing tradition of taking data and then attempting to fit them to an empirical equation rather than formulating a theoretical hypothesis and designing an experiment to test it (Garner and Grafton, 1954; Thomas, 1993). Fourth, it seems easier (or at least more popular) to test theory using heat transfer rather than mass transfer; but the thermal properties of the fluids available for testing make it difficult to attain $P \lesssim 10$ using liquids, while a shift to gases exacerbates the confounding effects of both free convection and radiation. Fifth, the need for more experimental data at low Peclet number has been explicitly noted by Batchelor (1979, p. 393) and by Kutateladze et al. (1982, p. 454).

In sum, only a single experimental study by Purcell (1978) even approaches being satisfactory across the important transition region between diffusion-dominated and convection-dominated flow; and this covers just the **P**-region (∼0.4,∼25), makes use of a biaxial straining flow rather than a uniaxial streaming flow, has been criticized by Batchelor (1979, p. 392) for not having its outer boundaries farther from the sphere, and nonetheless shows approximate $\mathbf{P}^2$ behavior at the low end of its range.

Hence, though perhaps possible, a definitive experimental test of theoretical mass transfer predictions for the biologically interesting region $0.1 \lesssim \mathbf{P} \lesssim 10$ seems a challenging endeavor.

6.1. Implications for plant biology

The take home lesson for the plant cell biologist from the very abstruse development of this paper should be that, somewhere near $\mathbf{P} = 1$, the flux enhancement due to convection will equal the basal flux rate due to passive diffusion. As the Peclet number becomes smaller, this enhancement will fall off *quickly* as $\mathbf{P}^2$. As the Peclet number becomes larger, it will rise *slowly* as $\mathbf{P}^{1/3}$. To put this into perspective, consider an organelle 1 μm in radius and a 10 MD macromolecule whose diffusion constant in *water* is $10^{-12}\,\mathrm{m^2\,s^{-1}}$ (Tanford, 1961); then $\mathbf{P} = 1$ at an organelle velocity of $1\,\mu\mathrm{m\,s^{-1}}$. That is, *organellar motion could significantly increase the probability of an organelle receiving in timely fashion important macromolecular messages*.

The take home lesson for a phytoplankton ecologist is quantitatively different. Consider a phytoplankter 100 μm in radius sinking at $100\,\mu\mathrm{m\,s^{-1}}$ (cf. Karp-Boss et al. 1996) through water in which some suspended nutrient has a diffusion constant $10^{-9}\,\mathrm{m^2\,s^{-1}}$ (Reuzeau et al., 1997). Then $\mathbf{P} = 10$; and, by Fig. 3, the uptake across a moving phytoplankter's surface could (in theory) be some 20-fold what it would be for a motionless phytoplankter. Surprisingly, experimental data which bear upon this prediction are hard to come by. It seems a nearly universal belief that increasing **P** increases the potential for nutrient uptake, but data suitable for testing the quantitative predictions of mass flow theory are rare. Indeed, a decade ago Karp-Boss et al. (1996, p. 85) felt constrained to assert that "We know of remarkably few attempts to test these theories even in the engineering context. Empirical data obtained from electrochemical measurements are in good agreement [with theory for large Peclet numbers]. We are not aware of similar experiments for intermediate and low [Peclet] numbers. Experiments with live organisms are even harder to conduct." And a citation search on the experimental studies of Purcell (1978) and of Kutateladze et al. (1982) has provided no reason to modify this judgement today.

6.2. Observations on the nature of mass transport due to trafficking.

Trafficking obviously moves packets of stuff around; and it has been emphasized elsewhere that towing those packets through a viscous cytosol will necessarily cause cytoplasmic streaming (Pickard, 2003). What the preceding section of this Discussion revealed is that only when the *effective* diffusion constant is exceptionally small will the motion of the trafficked organelle itself produce a significant increase in flux to (or from) the surface of an organelle. But what *effective* diffusion constant is to be expected in a heterogeneous cytoplasm for a molecule of arbitrary size?

The mass of one gram-mole of a compound of molecular weight M is

$$M\mathfrak{a}N_A = \mathfrak{s}^3 N_A \mathfrak{d}, \tag{44}$$

where $\mathfrak{a}[= 1.660\cdots\times 10^{-27}\,\mathrm{kg}]$ is the unified atomic mass unit, $N_A[= 6.022\cdots\times 10^{23}\,\mathrm{mol^{-1}}]$ is the Avogadro constant, $\mathfrak{s}^3[\mathrm{m^3}]$ is the volume of a single molecule (idealized as a cube), and $\mathfrak{d}[\mathrm{kg\,m^{-3}}]$ is the density of the compound in question; for a paradigm biological material of $M\sim1000$ and $\mathfrak{d}\sim1000\,\mathrm{kg\,m^{-3}}$, this works out to $\mathfrak{s}\doteq1.2\,\mathrm{nm}$. As Luby-Phelps (Luby-Phelps, 2000) has emphasized, the effects upon diffusion of macromolecular and cytoskeletal crowding should not be underestimated. Indeed, when easily 20% of the cytoplasmic volume can be taken up by macromolecules (Ellis, 2001), the *effective* diffusion constant of a molecule 1 nm wide could be strikingly less in cytoplasm than in simple saline: a random walk through a "dense forest" is a slow business.

Suppose next that the cytosol is so densely packed with macromolecules that the effective diffusion constant of a molecule of a few kilodaltons or above is $D_{\mathrm{eff}}\sim D_{\mathrm{aq}}/10$, where D_{aq} is the diffusion constant of the molecule in a simple aqueous solution. Then the $\mathbf{P}\sim1$ condition would be achieved by a much wider variety of solutes; and the convective enhancement of factor flux to (or from) an organelle would become much more important.

Moreover, it is now suggested (Heidemann and Wirtz, 2004) that the cytoplasm should perhaps be thought of as composed of contiguous "microdomains". In such a scenario the role of trafficking and its associated convective enhancement of diffusive flux would be larger still.

6.3. Conclusions

To summarize, the important findings of this paper are:

(i) Under the biophysical conditions expected within a cell, Whitehead-type paradoxes will not occur: solutions will be regular everywhere within the domain of interest. Hence, in the abstract, it will be possible to evaluate mass transfer to an organelle using perturbation techniques; however, it is an open question whether convenient closed form expressions can be obtained for the coefficients of the Maclaurin series (34).

(ii) Whether the matched asymptotic expansions obtained by the Acrivos and co-workers (Acrivos and Goddard, 1965; Acrivos and Taylor, 1962) accord better with biophysical reality than the predictions of Sections 4 and 5 is an open question. Obtaining relevant experimental data is predicted to be challenging.

(iii) Both sets of predictions do however agree that, starting somewhere in the vicinity of $\mathbf{P} \approx 1$, a moving organelle will have improved its mass transport (both as a receiver and a transmitter) by more than 100%. *This could be important to organelles, especially with respect to massive macromolecular messages diffusing through a densely packed heterogeneous cytosol.*

Appendix

Let the Laplace transform of $c(\xi,\zeta)$ with respect to ζ be $\bar{c}(\xi,s)$. Eq. (11) becomes (Oberhettinger and Badii, 1973) $\bar{c}|_{\xi=0} = 0$, $[\mathrm{d}\bar{c}/\mathrm{d}\xi]_{\xi=1} = 0$, and

$$\frac{\mathrm{d}^2\bar{c}}{\mathrm{d}\xi^2} - \mathbf{P}\xi s\bar{c} = -\mathbf{P}\xi. \tag{A.1}$$

With $\bar{c} = \tilde{c} + 1/s$ and $\lambda = (\mathbf{P}s)^{1/3}\xi$, (A.1) becomes

$$\frac{\mathrm{d}^2\tilde{c}}{\mathrm{d}\lambda^2} - \lambda\tilde{c} = 0. \tag{A.2}$$

The solution of this differential equation is known in terms of Airy functions (Abramowitz and Stegun, 1964):

$$\tilde{c}(\lambda) = K_\alpha\alpha(\lambda) + K_\beta\beta(\lambda), \tag{A.3}$$

$$\alpha(\lambda) = \sum_{m=0}^{\infty} \mathscr{A}_m(0)\frac{\lambda^{3m}}{(3m)!} \quad \text{and}$$
$$\beta(\lambda) = \sum_{m=0}^{\infty} \mathscr{A}_m(1/3)\frac{\lambda^{3m+1}}{(3m+1)!}, \tag{A.4}$$

where $\mathscr{A}_m(0) = 1$ and $\mathscr{A}_m(\varepsilon) = (3\varepsilon+1)(3\varepsilon+4)\cdots(3\varepsilon+3m-2)$. Thus,

$$\bar{c} = K_\alpha\alpha(\delta\xi) + K_\beta\beta(\delta\xi) + 1/s, \tag{A.5}$$

where $\delta = (Ps)^{1/3}$. From (A.5) and the boundary conditions, it follows that

$$K_\alpha = -\frac{1}{s} \quad \text{and} \quad K_\beta = \frac{1}{s}\frac{\alpha'(\delta)}{\beta'(\delta)}. \tag{A.6}$$

Eqs. (12) and (A.5) then imply

$$\frac{a}{DC_0}F_E = \mathfrak{L}^{-1}\left\{\left.\frac{\mathrm{d}\bar{c}}{\mathrm{d}\xi}\right|_{\xi=0}\right\} = \mathfrak{L}^{-1}\left\{\frac{\delta}{s}\frac{\alpha'(\delta)}{\beta'(\delta)}\right\}. \tag{A.7}$$

This inverse is not tabulated in standard transform tables (Oberhettinger and Badii, 1973), so the obvious path to inversion is by contour integration (Churchill, 1972). However, before proceeding, some comments are in order.

(i) By (A.4), $\delta\alpha'(\delta)$ is positive non-decreasing on the positive real s-axis and possesses a Taylor expansion in s for sufficiently small s. Moreover, $\delta\alpha'(\delta)/s$ is $\mathscr{O}(1)$ as $s\to 0$ and introduces neither a branch cut nor a pole at the origin.

(ii) By (A.4), $\beta'(\delta)$ is positive non-decreasing on the positive real s-axis and possesses a Taylor expansion in s for sufficiently small s. Moreover, $\beta'(\delta)$ is $\mathscr{O}(1)$ as $s\to 0$ and introduces neither a branch cut nor a pole at the origin.

(iii) Physically, one would not expect diffusive processes to introduce oscillatory behavior. Hence, the contour to evaluate (A.8) should have no complex poles within it.

(iv) Therefore, the contour integration should be influenced only by poles on the negative real s-axis and be expressible as a sum-over-residues (Churchill, 1972).

Therefore, with some algebraic manipulation, the application of standard inversion techniques (Churchill, 1972) and the substitution $\boldsymbol{P}s = \eta$, Eq. (A.7) becomes

$$\frac{a}{DC_0}F_E = \mathfrak{L}^{-1}\left\{\frac{\delta}{s}\frac{\alpha\prime(\delta)}{\beta\prime(\delta)}\right\} = \mathbf{P}\frac{1}{2\pi}\oint \mathrm{e}^{s\zeta}\frac{A(\mathbf{P}s)}{B(\mathbf{P}s)}\,\mathrm{d}s$$
$$= \sum_{n=1}^{\infty}\exp\left(\zeta\frac{\eta_n}{\mathbf{P}}\right)\frac{A(\eta_n)}{B'(\eta_n)}, \tag{A.8}$$

where the η_n are the negative real roots of $B(\eta_n) = 0$ and

$$A(\eta) = \sum_{m=1}^{\infty}\mathscr{A}_m(0)\frac{1}{(3m-1)!}\eta^{m-1} \quad \text{and}$$
$$B(\eta) = \sum_{m=0}^{\infty}\mathscr{A}_m\left(\frac{1}{3}\right)\frac{1}{(3m)!}\eta^m, \tag{A.9}$$

where $B\prime(\eta) = d\{B(\eta)\}\,\mathrm{d}\eta$. The negative real roots of $B(\eta)$ were found by tabulating this function at selected points along the negative η-axis, looking for changes of sign, and performing a Newton–Raphson iteration to the exact root whenever the presence of a zero was inferred. In this fashion, 22 roots were found over (0,−10 200). Plots of the data suggest that, for large n, the $-\eta_n$ increase following a power law of exponent slightly greater than 2. The $A(\eta_n)/B'(\eta_n)$ are always positive but, with increasing n,

decrease slowly towards a presumed asymptote slightly below 0.4.

There is of course no foolproof way of matching the behavior of Eq. (A.8), which relates to convection–diffusion in a planar geometry, to the spherical geometry of interest. However, since by Eq. (A.9) $F_E(\mathbf{P})$ tends smoothly to zero as $\mathbf{P}\to 0$, it is one measure of the convection-associated enhancement of flux to the bottom plate; and suitably normalized it should overlap $\mathscr{F}_N(\mathbf{P})-1$ in a meaningful way. Therefore, using Eq. (A.9), the numerator of the middle term of Eq. (43) becomes

$$\int_{\pi/6}^{7\pi/6} F_E(\zeta)\,\mathrm{d}\zeta = \frac{DC_0}{a}\,\mathbf{P}\sum_{n=1}^{\infty}\frac{1}{-\eta_n}\,\frac{A(\eta_n)}{B'(\eta_n)} \times\left[\exp\left(\frac{\pi}{6}\,\frac{\eta_n}{\mathbf{P}}\right)\right]\left[1-\exp\left(\pi\,\frac{\eta_n}{\mathbf{P}}\right)\right]. \quad (A.10)$$

Moreover, since $\eta_{22}=-10\,185$, it is apparent that a truncated sum over these 22 roots will suffice to evaluate this integral for $0\lesssim P\lesssim 1000$.

Finding $F_D(\zeta)$ requires first a solution of the purely diffusive system

$$\frac{\partial^2 c(\xi,\zeta)}{\partial\xi^2}+\frac{\partial^2 c(\xi,\zeta)}{\partial\zeta^2}=0, \quad (A.11)$$

with $c=1$ at $\zeta=0$, $c=0$ at $\xi=0$, and $\partial c/\partial\xi=0$ at $\xi=1$. Taking the Fourier sine transform of $c(\xi,\zeta)$ to be $\hat{c}(\xi,\omega)$, it then follows that (Sneddon, 1972)

$$\frac{\mathrm{d}^2\hat{c}}{\mathrm{d}\xi^2}-\omega^2\hat{c}=-\omega\sqrt{\frac{2}{\pi}}, \quad (A.12)$$

with boundary conditions $\hat{c}=0$ at $\xi=0$, and $\mathrm{d}\hat{c}/\mathrm{d}\xi=0$ at $\xi=1$. From this it follows that

$$\frac{\mathrm{d}\hat{c}}{\mathrm{d}\xi}=\sqrt{\frac{2}{\pi}}\sinh\omega(1-\xi)/\cosh\,\omega, \quad (A.13)$$

$$F_D(\zeta)=\frac{DC_0}{a}\,\mathrm{csch}\,\tfrac{1}{2}\pi\zeta \quad \text{and}$$

$$\int_{\pi/6}^{7\pi/6} F_D(\zeta)\,\mathrm{d}\zeta=\frac{DC_0}{a}0.596\cdots. \quad (A.14)$$

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