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GENERALIZING THE THEORY OF MICRODIALYSIS

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ABSTRACT

The efficiency of sampling or delivering solutes (analytes) by *in vivo* microdialysis is influenced by the diffusive permeabilities of the probe and the tissue in which the probe is implanted. In tissue, processes removing the analyte from the extracellular space are as important as diffusion in determining permeability. In addition to diffusion, analyte permeation through these media may be augmented or diminished by bulk fluid movement (transmembrane and interstitial convection). Within the perfusate, the dominant process is axial convection. Both diffusive and convective determinants of probe efficiency may be influenced by probe geometry (Figure 1; longitudinal cross-sectional view). The main geometric parameters are the probe membrane length and radii, but inner cannula geometry can also be an appreciable factor.

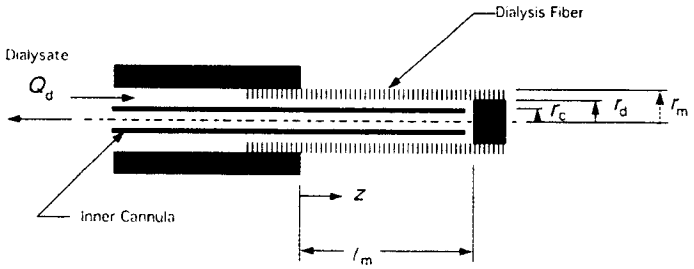

Figure 1. Schematic diagram of longitudinal cross-sectional view of microdialysis probe, indicating symbols for geometric parameters & constant perfusate flow rate, Q_d

The objective of this study is to generalize the mathematical description of microdialysis. The treatment extends in several ways previous mathematical models (Bungay et al. [1]; Morrison et al. [2]; Morrison et al. [3]; Wallgren et al. [4]). In addition to removing some simplifications and approximations and adding convective transport, the revised theory is applicable to low-molecular-weight lipophilic, as well as hydrophilic solutes. This is achieved by incorporating transcellular solute movement as a pathway paralleling interstitial diffusion. This change accompanies employing the combined intracellular and extracellular volumes, rather than the interstitial volume, as the basis for solute mass balances.

METHODOLOGY

For a base line case of no convection in the membrane and tissue, species mass balance is solved in the entire domain in conjunction with dialysate flow in the annulus of the probe.

Dialysate velocity (only axial component is nonzero):

$$u_d[r] = \frac{2Q_d}{\pi r_c^2}\left(\frac{\ln\left[\frac{r}{r_c}\right] - \frac{(r/r_c)^2 - 1}{(\kappa^2 - 1)}\ln[\kappa]}{(\kappa^2+1)\ln[\kappa] + 1 - \kappa^2}\right) \quad \text{at} \quad r_c \le r \le r_d$$

where $\kappa = r_d / r_c$.

Species mass balances:

Dialysate: $\frac{\partial \mathbf{C}}{\partial t} + \vec{u}_d \cdot \nabla \mathbf{C} = D_d \nabla^2 \mathbf{C}$

Membrane: $K_{fm}\frac{\partial \mathbf{C}}{\partial t} = D_m \nabla^2 \mathbf{C}$

Tissue: $K_{et}\frac{\partial \mathbf{C}}{\partial t} = D_t \nabla^2 \mathbf{C} - k_t \mathbf{C}$

Boundary conditions:

Inlet: $\mathbf{C} = 1$ at $r_c \le r \le r_d$, $z = -\ell_x$

Dialysate-membrane interface:

$D_d \nabla \mathbf{C} = D_m \nabla \mathbf{C}$ at $r = r_d$ for $0 \le z \le \ell_m$

Membrane-tissue interface:

$D_m \nabla \mathbf{C} = D_t \nabla \mathbf{C}$ at $r = r_m$ for $0 \le z \le \ell_m$

Solid boundaries: $\nabla \mathbf{C} = 0$

Tissue limit surfaces: $\nabla \mathbf{C} = 0$

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Initial conditions for transient problem is **C** = **0** everywhere except in inflowing perfusate.

Table 1: Nomenclature and parameter values.

Symbol	Values	Description
r_c	0.012 cm	Inner cannula radius
r_{id}	0.020 cm	Membrane inner radius
r_m	0.025 cm	Membrane outer radius
r_e	0.3 cm	Outer radius of tissue
l_m	1.0 cm	Membrane length
l_x	0.3 cm	Axial distance from membrane to tissue edge
D_{id}	7.5×10^{-6} cm^2/s	Analyte diffusion coefficient in free solution at 37°C
Q_{id}	1.667×10^{-5} cm^3/s	Perfusate volumetric flow rate
u_{id}^{in}	0.0207 cm/s	Perfusate inlet mean velocity $[= Q_{id} / \pi(r_{id}^2 - r_c^2)]$
μ	7×10^{-3} g/(cm.s)	Perfusate viscosity
$K_{fm} = \rho\phi_m$	0.5	Partition coefficient for analyte that is retained in the fluid phase of the membrane, C_m / C_f
D_m	2.0×10^{-6} cm^2/s	Effective analyte diffusion coefficient in probe membrane at 37°C
$\bar{\mu}_m$	7×10^{-5} g/(cm.s)	Membrane Brinkman viscosity
κ_m	1.0×10^{-14} cm^2	Membrane Darcy permeability
ϕ_e	0.2 ml ECF/g tiss	Extracellular volume fraction
D_t	6×10^{-7} cm^2/s	Analyte diffusion coefficient in tissue at 37°C
K_{et}	1	Partition coefficient for analyte in tissue, C_t / C_e
$\bar{\mu}_t$	7×10^{-5} g/(cm.s)	Tissue Brinkman viscosity
κ_t	1.0×10^{-12} cm^2	Tissue Darcy permeability
Q_p	1.667×10^{-2} ml/s.g tiss	Effective plasma volumetric flow rate
C_{e0}	0	Initial analyte conc. in ECF (t=0)
C_{id}^{in}	1	Analyte conc. in inflowing perfusate
k_t	2.78×10^{-4} s^{-1}	Rate constant for clearance from extracellular fluid

The equations are formulated in terms of a normalized extracellular concentration, **C** $(= C / C_{id}^{in})$. The accumulation terms on the left-hand-side of the tissue and membrane balance equations have coefficients K_{et} and K_{fm}, that, respectively, represent equilibrium partitioning of species between the extracellular and intracellular compartments of the tissue and the fluid and solid matrix phases of the membrane. The generalized theory incorporates convection in the membrane and tissue by including momentum balances for the three regions (dialysate, membrane and tissue) and adding appropriate convective terms to the solute mass balances for these regions. The three momentum balances are first solved simultaneously to find the steady-state velocity profiles, which are then used in the solution of the mass balances. The solutions are obtained numerically Galerkin Finite Element Method (FEM) [5].

RESULTS

A comparison between analytical and numerical solutions for a base line case of no convection in the membrane and tissue is shown in Figure 2 for parameter values shown in Table 1.

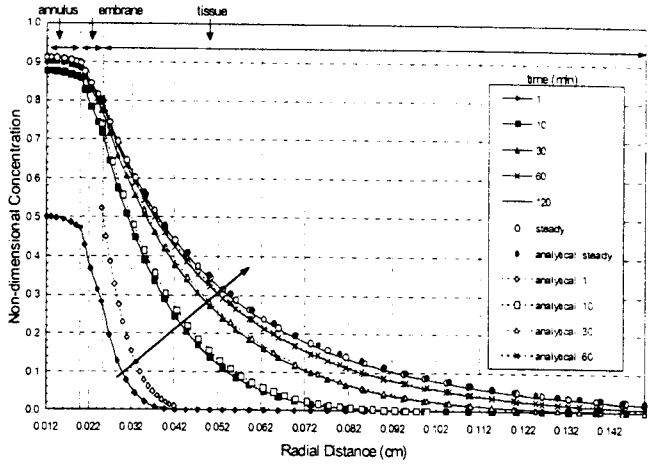

Figure 2: Analytical and numerical comparison of transient and steady state non-dimensional concentration along the radial direction at the mid-axial plane of the membrane

The plots display transient and steady state non-dimens concentration profiles in the radial direction at the midplane of the membrane, $z = l_m/2$. Steady state is approached by about 2 hr time, although more slowly by the numerical solution. A significant difference (more than 50%) between the analytical and numerical solutions is observed at earlier time steps, e.g. at time t = 1 min. The analytical solution predicts that the species penetrates into the tissue faster than the numerical solution. This is due to an assumption in the analytical solution that neglects the accumulation of species mass in the membrane. The discrepancy in concentration between the analytical and numerical solution diminishes as time progresses. At steady state, the analytical and numerical solutions agree within a few percent. The effect of convection in the membrane and tissue will be illustrated for the situation in which 1-atm of back pressure is applied to the dialysate.

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