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Catheter Effects in Organ Perfusion Experiments

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In a typical isolated organ perfusion experiment, a substance is injected upstream of an organ and then collected at some distance downstream. To reach the organ from the injection site, and then from the organ to the collector, a solute passes through catheters, usually tubes with circular cross-sections. Catheters cause distortion to the concentration–time profile of the perfusion. In this paper, we analyse catheter distribution kinetics from a mathematical point of view, develop the function most suitable for modeling this distribution and successfully apply this function to experimental data.

1. Introduction

It has been long recognized that catheter effects have to be taken into account in organ perfusion experiments (Silverman & Goresky, 1965). In particular, the importance of catheters has been recognized in liver disposition kinetics (Evans *et al*., 1991), where the inverse Gaussian distribution has been used as a catheter-modeling function. A number of subsequent investigations have also used the inverse Gaussian distribution to model catheter function in this context (Evans *et al*., 1993; Roberts *et al*., 1998; Weiss *et al*., 1998). Parameters in the catheter distribution function have been fitted from experimental data for isolated catheters.

It is noted that catheter effects can also arise in organ-bath pharmacological studies, skin absorption studies, biochemical reaction engineering and other applications, where there is flow of a medium into a receptor, organ or reactor via catheters. In all these cases, catheter effects will become important when the transit time of a catheter is comparable to that of the system under study.

In this paper, we examine how catheter function is best described. We consider first a mathematical description of catheters, more general than previously given, and its effect on an organ concentration–time profile. Let catheters 1 and 2 deliver solute from injection site to organ, and from organ to collector, respectively. Let $f_1(t)$ and $f_2(t)$ be the concentration–time profile which arises at output from catheters 1 and 2, respectively, following unit bolus injection of solute into these catheters in isolation. As the transport of the drug through the catheter is linear, the actual concentration at input to the organ, $C_{in}^r(t)$, is then

$$C_{in}^r(t) = \int_0^t C_{in}(t-\tau) f_1(\tau)\,\mathrm{d}\tau = C_{in}(t) * f_1(t), \quad (1)$$

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where $C_{in}(t)$ is the input concentration at the injection site, "*" denotes convolution, and we assume $C_{in}(t) = 0$ for $t < 0$. Similarly, the concentration measured at the collector will be

$$C^r_{out}(t) = \int_0^t C_{out}(t-\tau) f_2(\tau)\,\mathrm{d}\tau = C_{out}(t)^* f_2(t), \tag{2}$$

where $C_{out}(t)$ is the concentration of solute at output from the organ. Knowing $f_1(t)$, $f_2(t)$ and $C_{in}(t)$, and measuring $C^r_{out}(t)$, it is possible to compute $C^r_{in}(t)$ and $C_{out}(t)$, using eqns (1) and (2).

For bolus experiments [$C_{in}(t) = (Dose/Q)\delta(t)$, where *Dose* is the quantity of solute injected and Q is the flow rate], small values of *Dose* are usually chosen to ensure linear elimination kinetics in the organ. Using eqn (1), in this case, yields for the actual concentration at input to the organ:

$$C^r_{in}(t) = \frac{Dose}{Q} f_1(t). \tag{3}$$

For the linear kinetics in the organ, the output concentration from the organ, $C_{out}(t)$, can be represented as convolution of the input concentration with the concentration which would arise at output from the organ following a hypothetical unit δ-functional (bolus) input to the organ, $C_\delta(t)$. We have therefore,

$$C_{out}(t) = \frac{Dose}{Q} \int_0^t C_\delta(t-\tau)\, f_1(\tau)\,\mathrm{d}\tau$$

$$= \frac{Dose}{Q} f_1(t)^* C_\delta(t). \tag{4}$$

Using eqns (2) and (4), the concentration measured at the collector can be expressed as

$$C^r_{out}(t) = \frac{Dose}{Q} f_1(t)^* C_\delta(t)^* f_2(t). \tag{5}$$

In the Laplace domain, eqn (5) can be written as

$$\hat{C}^r_{out}(s) = \frac{Dose}{Q} \hat{f_1}(s)\hat{C}_\delta(s)\ \hat{f_2}(s) = \frac{Dose}{Q}\ \hat{f}(s)\hat{C}_\delta(s), \tag{6}$$

where the Laplace transform of a function $f(t)$ is designated as $\hat{f}(s)$, $\hat{C}_\delta(s)$ is the Laplace transform of $C_\delta(t)$, and $\hat{f}(s) = \hat{f_1}(s)\ \hat{f_2}(s)$. Using eqn (6), it is easy to take into account catheter effects if the function $\hat{f}(s)$ is known.

One way to determine $f(t) = L^{-1}(\hat{f}(s))$ is by performing an additional experiment for catheters alone. With catheters 1 and 2 joined together, and using a bolus injection, it is possible to recover the concentration–time profile, $f(t)$, by fitting some empirical function with free parameters to the experimental points. This method is widely used (Evans *et al.*, 1991) with the inverse Gaussian distribution $g(t)$ chosen to approximate $f(t)$, where

$$g(t) = \sqrt{\frac{T}{4\pi\sigma t^3}} \exp\left(\frac{(t-T)^2}{4\sigma T t}\right) \tag{7}$$

and T and σ are free parameters which are determined by the fitting.

This experimental method has some disadvantages. The first is the necessity to perform an additional experiment with catheters. The second disadvantage results from the distortion caused by sampling to the approximation of $f(t)$. It is apparent from the experimental data that the function $f(t)$ is sharply peaked. In order to recover $f(t)$ correctly from the experimental points, which represent average concentration during the time of sampling for each point, times between measurements of concentration must be taken relatively short around the peak of the function $f(t)$. This quick sampling is sometimes impossible due to experimental limitations.

In this paper, we want to discuss another, non-experimental approach for determining $f(t)$. Using geometrical parameters of a catheter, like its radius and length, we will try to predict its concentration–time profile by applying the mathematical analysis of dispersion of solute in a tube.

2. Dispersion of Solute Flowing through a Tube

The combined action of molecular diffusion and the variation of velocity over any cross-section, for solute introduced into a cylindrical tube of circular cross-section carrying solvent, were studied theoretically and experimentally by

Taylor (1953). In this section, we will essentially follow his approach and extend it to model catheter function.

We consider a circular pipe of radius r_0 and choose the cylindrical coordinate system with r being the distance from the central line of the tube and x the distance along the tube. If we assume that the concentration C is symmetrical about the axis of the pipe so that it is a function of r, x and t only, the equation for the combined action of molecular diffusion and convection is

$$D\left(\frac{\partial^2 C}{\partial r^2}+\frac{1}{r}\frac{\partial C}{\partial r}+\frac{\partial^2 C}{\partial x^2}\right)=\frac{\partial C}{\partial t}+v(r)\frac{\partial C}{\partial x}, \quad (8)$$

where D is the coefficient of molecular diffusion, assumed independent of concentration here, and $v(r)$ is the velocity of solute, assumed constant in time. For a tube with circular cross-section, Poiseuille flow is realized with distribution of velocity

$$v(r)=v_0\left(1-\frac{r^2}{r_0^2}\right), \quad (9)$$

where v_0 is the maximum velocity, at the axis of the tube. The maximum velocity can be related to the flow rate, as we have

$$Q=\int_0^{r_0} v(r)2\pi r\,\mathrm{d}r \quad (10)$$

and after integration yields for v_0:

$$v_0=\frac{2Q}{\pi r_0^2}. \quad (11)$$

As the coefficient of molecular diffusion is normally less than 10^{-5} cm^2 s^{-1} for most solutes of interest, and the length of a catheter is typically not less than about 10 cm, we can neglect the diffusion in the axial direction here; this cancels the third term in brackets in eqn (8). With the dimensionless variable $z=r/r_0$, and taking into account eqn (9), eqn (8) becomes

$$\frac{\partial^2 C}{\partial z^2}+\frac{1}{z}\frac{\partial C}{\partial z}=\frac{r_0^2}{D}\frac{\partial C}{\partial t}+\frac{r_0^2 v_0}{D}(1-z^2)\frac{\partial C}{\partial x}. \quad (12)$$

The boundary condition which expresses the fact that the wall of the tube is impermeable is

$$\left.\frac{\partial C}{\partial z}\right|_{z=1}=0. \quad (13)$$

Another boundary condition for eqn (12) is that $C(x, z)$ remains finite when $z\to 0$.

It is not possible to solve eqn (12) exactly in general. In this section, we will consider approximate solutions for the following limiting conditions:

(1) The change in concentration due to convective transport along the tube takes place in a time which is so short that the effect of molecular diffusion in the radial direction may be neglected. We will refer to this as the case of a short tube.

(2) The time necessary for convective transport to affect concentration is long compared with the diffusion time during which radial variations of concentration at any given value of x are reduced to a fraction of their initial value through the action of molecular diffusion. We will refer to this as the case of a long tube.

To find the characteristic radial diffusion time, we consider the solutions of eqn (12) for which there is no axial gradient ($\partial C/\partial x=0$). Separating variables z and t in eqn (12) we get for the concentration

$$C(z,t)=\sum_{i=1}^{\infty} b_i\exp(-\alpha_i t)\,J_0(r_0 z\sqrt{\alpha_i/D}), \quad (14)$$

where J_0 is the Bessel function of zero order, b_i are determined by the initial condition, and α_i are such that the boundary condition (13) is satisfied. Since $J_0'(x)=-J_1(x)$, eqn (13) gives

$$J_1(r_0\sqrt{\alpha_i/D})=0. \quad (15)$$

The smallest non-zero root of eqn (15) corresponding to the lowest value of α_i is 3.8, rounded to the nearest tenth. Therefore, the time required for the radial variation of $C(z, t)$ represented by eqn (14) to die down to $1/e$ of its initial value is not more than

$$t_d=\frac{1}{\alpha_1}=\frac{r_0^2}{(3.8)^2 D}. \quad (16)$$

We will refer to this as the characteristic radial diffusion time.

For the characteristic convection transport time, we simply take

$$t_c = \frac{l}{v_0}, \tag{17}$$

where l is the length over which solute is spread in a tube, obviously $l \leqslant L$. Using eqn (11), it can be found that

$$\frac{t_d}{t_c} = \frac{2Q}{l(3.8)^2 \pi D} = 0.044 \frac{Q}{Dl} \geqslant 0.044 \frac{Q}{DL}. \tag{18}$$

2.1. SHORT TUBE

We define a short tube as one with $0.044Q/(DL) \gg 1$, so that the radial diffusion time is much greater than the convection transport time, $t_d \gg t_c$. The present analysis for short tubes differs from that of Taylor (1953) in that instead of the initial distribution of concentration, $C(x, t = 0)$, it is the input concentration profile that is given. Furthermore, the concentration in the classical Taylor (1953) approach is determined by shining light through a given cross-section of a tube carrying flowing solute, and measuring its absorption, which is related to the mean solute concentration through this cross-section defined by

$$C_m(x, t) = \frac{1}{\pi r_0^2} \int_0^{r_0} C(x, r, t)\, 2\pi r \, \mathrm{d}r. \tag{19}$$

In organ perfusion experiments, samples are usually collected using a fraction collector and their concentration is then measured. The concentration in the j-th sample which collected flowing solute from time t_j to t_{j+1} is

$$C_j = \frac{1}{Q(t_{j+1} - t_j)} \int_{t_j}^{t_{j+1}} J(L, t)\, \mathrm{d}t, \tag{20}$$

where L is the length of the tube and $J(L, t)$ is the total flux of substrate through the cross-section at $x = L$. If the average concentration in the cross-section of the tube at x is defined as

$$C_a(x, t) = \frac{J(x, t)}{Q}, \tag{21}$$

then the concentration in the j-th sample is simply a time average of C_a at $x = L$:

$$C_j = \frac{1}{(t_{j+1} - t_j)} \int_{t_j}^{t_{j+1}} C_a(L, t)\, \mathrm{d}t. \tag{22}$$

As the total flux of substrate through the cross-section at x of the tube can be found from

$$J(x, t) = \int_0^{r_0} C(x, r, t)\, v(r) 2\pi r \, \mathrm{d}r, \tag{23}$$

the appropriate definition for concentration flowing from the tube, C_o, for the case of measuring concentration using a fraction collector is therefore

$$C_o(t) = C_a(L, t) = \frac{1}{Q} \int_0^{r_0} C(L, r, t)\, v(r) 2\pi r \, \mathrm{d}r. \tag{24}$$

Concentrations defined by eqn (21) are often called flux concentrations (Kreft & Zuber, 1978). Flux concentrations are relevant to perfused organ systems because bolus injections are made into a flowing solute and outflow samples (response) are collected in a fraction collector (Roberts *et al.*, 2000).

For a short tube ($t_d \gg t_c$), both diffusion terms in eqn (8) can be neglected. Thus, for the initial condition $C(0, r, t) = C_{in}(t)$, where $C_{in}(t)$ is the input concentration at the beginning of the tube, we have a simple solution:

$$C(x, r, t) = C_{in}(t - x/v(r)). \tag{25}$$

Using this solution in eqn (24) with $v(r)$ described by eqn (9) for Poiseuille flow yields

$$C_o = \frac{2}{r_0^2} \int_0^{r_0} \left(1 - \frac{r^2}{r_0^2}\right) C_{in}\left(t - \frac{L}{v_0(1 - r^2/r_0^2)}\right) 2r \, \mathrm{d}r, \tag{26}$$

where we have expressed Q using eqn (11). Changing the variable of integration in this equation to

$$\tau = \frac{L}{v_0(1 - r^2/r_0^2)} \tag{27}$$

yields after transformations

$$C_o = 2\tau_m^2 \int_{\tau_m}^{t} C_{in}(t-\tau)\tau^{-3}\,\mathrm{d}\tau, \qquad (28)$$

where $\tau_m = L/v_0$ is the minimal time required for solute to reach the end of the catheter, and we take into account that $C_{in} = 0$ for $t < 0$.

If we define

$$G(\tau) = u(\tau - \tau_m)2\tau^{-3}\tau_m^2, \qquad (29)$$

where $u(t)$ is the unit step function, we can rewrite eqn (28) as

$$C_o(t) = \int_0^t G(\tau)\, C_{in}(t-\tau)\,\mathrm{d}\tau = G(t)^* C_{in}(t), \quad (30)$$

where $*$ denotes the convolution product.

It follows from eqn (30) that for bolus input, we have

$$C_o(t) = \frac{Dose}{Q} u(t-\tau_m)\frac{2\tau_m^2}{t^3}. \qquad (31)$$

The mean transit time (MTT) in this case is

$$MTT = \frac{\int_0^\infty tC_o\,\mathrm{d}t}{\int_0^\infty C_o\,\mathrm{d}t} = 2\tau_m. \qquad (32)$$

Therefore, as expected, $MTT = 2L/v_0 = V/Q$, where $V_t = \tau r_0^2 L$ is the volume of the catheter.

Another important characteristic of concentration–time profiles in organ perfusion experiments is the normalized variance defined as

$$CV^2 = \frac{\int_0^\infty t^2 C_o\,\mathrm{d}t \int_0^\infty C_o\,\mathrm{d}t}{(\int_0^\infty tC_o\,\mathrm{d}t)^2} - 1. \qquad (33)$$

Using this equation, we find that the normalized variance for this case is logarithmically divergent. In reality, eqn (25) for $C(x, r, t)$ is only accurate for $t \ll t_d$, as we neglected diffusion in deriving it. This limitation means that the tail section of the concentration–time profile is not correctly described by eqn (31).

Let us estimate the time, t_b, when diffusion becomes important and thus eqn (31) becomes invalid. For bolus input, the contribution to the output concentration at long times is due only to transport of solute molecules in layers with slow velocity which are close to the wall of the tube. This is due to the fact that solute molecules closer to the center of the tube are transported faster [see eqn (9)] and are cleared from the tube at earlier times. For a given time, $t > \tau_m$, all solute molecules which have not been cleared from the tube are therefore confined to a layer of thickness d next to the wall of the tube, where d is defined by

$$\frac{L}{v_0(1-(r_0-d)^2/r_0^2)} = t. \qquad (34)$$

For long times, we have $t \gg \tau_m$, and we expect $d \ll r_0$, therefore eqn (34) gives after some algebra

$$d \approx \frac{Lr_0}{2v_0 t}. \qquad (35)$$

The spread of solute due to diffusion in the radial direction can be approximated as $\sqrt{4Dt}$. When this spread is of the same order of magnitude as d, solute molecules cannot be assumed to be confined to the layer next to the wall, rendering eqn (31) invalid. Therefore, taking $d = \sqrt{4Dt}$ and solving for t, we find the time, t_b, when diffusion becomes important:

$$t_b = \left(\frac{L^2 r_0^2}{16 v_0^2 D}\right)^{1/3} \approx \tau_m \left(\frac{t_d}{\tau_m}\right)^{1/3}. \qquad (36)$$

For a short tube, we assumed that $t_d \gg t_c$ and, if we also require $t_d \gg \tau_m$, then as expected $t_b \gg \tau_m$, and eqn (31) can be used for times $t \leqslant t_b$. Equation (36) can be rewritten as

$$t_b = t_d \left(\frac{\tau_m}{t_d}\right)^{2/3} \qquad (37)$$

so it is clear that $t_b \ll t_d$.

For times t from the interval $t_b \ll t \leqslant t_d$ it is reasonable to expect a decrease quicker than $1/t^3$, possibly exponential, so that after $t = t_d$, C_o must be extremely small. Taking this into consideration, it is possible to estimate upper and lower bounds for CV^2. Exchanging the upper limit in

the integral $\int_0^\infty t^2 C_o \, dt$ in eqn (33) with t_b and then t_d, we get

$$\frac{1}{2}\ln\left(\frac{t_c}{\tau_m}\right) - 1 < CV^2 < \frac{1}{2}\ln\left(\frac{t_d}{\tau_m}\right) - 1 \quad (38)$$

or, using eqn (36),

$$\frac{1}{6}\ln\left(\frac{t_d}{\tau_m}\right) - 1 < CV^2 < \frac{1}{2}\ln\left(\frac{t_d}{\tau_m}\right) - 1. \quad (39)$$

These are, of course, quite rough bounds on CV^2, but at least they give an idea as to what is the dependence of the normalized variance on the catheter parameters. It is clear from eqn (39), for example, that CV^2 need not be small compared with that for a perfused organ, therefore the catheter distortion must be taken into account in organ perfusion experiments with a short catheter.

2.2. LONG TUBE

For the converse situation of a relatively long tube, when $t_d \ll t_c$, we expect only small radial variation in $C(z, x, t)$, because quick diffusion across the tube tends to make concentration uniform in the radial direction. Then, $C(z, x, t)$ can be reasonably approximated by $C^0(x, t) = C(0, x, t)$. Taylor (1953) has shown that in this case $C^0(x, t)$ is approximately described by the convection–dispersion differential equation

$$\frac{\partial C^0}{\partial t} + \frac{v_0}{2}\frac{\partial C^0}{\partial x} = D_{eff}\frac{\partial^2 C^0}{\partial x^2}, \quad (40)$$

where D_{eff} is the effective dispersion coefficient:

$$D_{eff} = \frac{r_0^2 v_0^2}{192\, D}. \quad (41)$$

Taylor (1953) has also demonstrated that experimental data for the mean concentration in the long tube is well described by eqn (40). Due to small radial variation in $C(z, x, t)$, concentration flowing from the tube, C_o as defined in eqn (24), can be approximated by $C^0(L, t)$. (That is, solute and flux concentrations are approximately equal in this case.) The solution of eqn (40) for bolus input, assuming mixed boundary conditions is (Roberts & Anissimov, 1999)

$$C_o = \frac{Dose}{Q}\frac{L}{\sqrt{4\pi D_{eff}\, t^3}}\exp\left(-\frac{(L - tv_0/2)^2}{4D_{eff}\, t}\right) \quad (42)$$

which corresponds to the inverse Gaussian distribution (7). As noted previously, this distribution is commonly used to describe the catheter function in isolated perfused liver disposition studies (Evans *et al.*, 1993; Roberts *et al.*, 1998; Weiss *et al.*, 1998). We now see that this is justified for long catheters, but not for short catheters.

Mean transit time and normalized variance can be obtained for C_o defined in eqn (42):

$$MTT = \frac{\int_0^\infty tC_o \, dt}{\int_0^\infty C_o \, dt} = \frac{2L}{v_0} = \frac{V_t}{Q}, \quad (43)$$

$$CV^2 = \frac{\int_0^\infty t^2 C_o \, dt \int_0^\infty C_o \, dt}{(\int_0^\infty tC_o \, dt)^2} - 1 = \frac{4D_{eff}}{Lv_0}. \quad (44)$$

Using eqn (41) or D_{eff}, CV^2 can be rewritten as

$$CV^2 = \frac{r_0^2 v_0}{48DL} = \frac{3.8^2\, l}{48L}\frac{r_0^2}{3.8^2\, D}\frac{v_0}{l}. \quad (45)$$

For the case of a long catheter, the spread of solute in the catheter is less than its length, that is $l < L$, so that

$$CV^2 < 0.3\frac{t_d}{t_c}. \quad (46)$$

Using the condition for a long tube, $t_d \ll t_c$, yields $CV^2 \ll 1$. A small value of normalized variance is an indication that the dispersion in a long catheter is not important. Indeed, if we also have $CV^2_{cath} \ll CV^2_{organ}$, where CV^2_{cath} and CV^2_{organ} are normalized variances for the catheter and the organ, respectively, it follows that the distortion caused by the catheter can be neglected.

3. Applicability of Poiseuille Flow for Catheters

In the previous sections, we used Poiseuille flow to describe dispersion of solute in catheters. Poiseuille flows are realized in very long tubes

with Reynolds numbers, R less than $R_c \approx 2000$, where

$$R = \frac{r_0 v_0}{\nu} \tag{47}$$

with ν being the kinematic viscosity of the solvent (Landau & Lifshits, 1989). For the catheters used in rat liver perfusion experiments, $r_0 \approx 0.1$ cm, with flow rate Q lying between 0.5 and 1 $cm^3 s^{-1}$ (or $ml s^{-1}$) and kinematic viscosity $\nu = 0.01\ cm^2 s^{-1}$ for water. The corresponding values for Reynolds number are $318 \leqslant R \leqslant 636$. Therefore, we can safely assume that the flow in these catheters is laminar. The question remaining is whether the catheters are long enough to justify the assumption of Poiseuille flow. More exactly, we want to know at what distance from the beginning of the pipe the distribution of velocity becomes close enough to the distribution of velocity in Poiseuille flow. If this distance, say L_p, is much less than the length of the catheter ($L_p \ll L$), then the use of Poiseuille flow for the catheter is justifiable.

The problem of flow near the inlet of a circular pipe for large Reynolds numbers ($R \gg 1$) has been analysed (Goldstein, 1938). The experimental data (Goldstein, 1938) show that at distance $x = 0.07 r_0 R$ from the inlet of the pipe the maximal deviation of velocity from that described by the Poiseuille flow assumption (9) is less than 4% and the Poiseuille flow can be assumed to be fully developed at this distance. The appropriate formula for L_p is therefore

$$L_p = 0.07 r_0 R. \tag{48}$$

For catheters with radius $r_0 = 0.1$ cm and rate of flow Q between 0.5 and 1 $cm^3 s^{-1}$, this yields $2.2 \leqslant L_p \leqslant 4.4$ cm. Thus, if the catheter is longer than about 15 cm, the use of Poiseuille flow is quite justifiable.

4. Evaluation of Model with Experimental Data

In catheter experiments two tubes, one delivering solute from the injection site to the organ and another from the organ to the collector (catheters 1 and 2), are joined together. Those tubes are usually of different diameters and the junction between them obviously produces perturbations to the Poiseuille flow, especially downstream of the junction. As was discussed in Section 3, this perturbation reduces quite quickly, but the important result of it is mixing of solute leaving catheter 1. This mixing makes it impossible to treat two joined tubes as one and use eqn (31) directly.

In order to avoid the problem of accounting for the mixing at the junction between two catheters and directly checking eqn (31), experiments with simple tubes were first performed.

4.1. EXPERIMENTS WITH SIMPLE TUBES

Two different tubes were used: tube I with length $L = 27.6$ cm and internal radius $r_0 = 0.08$ cm and tube II with $L = 28$ cm and $r_0 = 0.157$ cm.

Tubes II and I were perfused with distilled water at flow rates $Q = 15$ and 30 $ml min^{-1}$, respectively. An injection of 25 µl of tritiated water was made as a bolus and samples collected at intervals of 0.5 s at first and 2.5 s later. All outflow samples and injectate were analysed for total ^3H activity on a TriCarb 2700TR Liquid Scintillation Analyzer (Packard) and the concentration was presented as a fraction of the injection dose per ml of the sample (outflow fraction per ml).

Experimental results and theoretical predictions using eqn (31) are shown in Fig. 1. The theoretical prediction of experimental points (asterisks) takes into account the fact that the concentration of the sample is the time average [see eqn (22)] of the output concentration over the time of sampling (often referred to as pooling effect). It is clear from Fig. 1 that this pooling effect is important for the first non-zero prediction only. That is, the time average of the theoretical prediction of the output concentration for $t > \tau_m$ is very close to the output concentration at the mid-sampling time $((t_j + t_{j+1})/2)$. We note that the theoretical prediction of the first experimental point is zero and therefore, cannot be presented on the logarithmic plot.

The values of τ_m, t_d and t_b were calculated to be (in s) $\tau_m = 1.11$, $t_d = 22.2$, $t_b = 3.01$ and $\tau_m = 2.13$, $t_d = 85.4$, $t_b = 7.29$ for tubes I and II, respectively.

To find t_d and t_b the diffusion coefficient for water was taken to be $D = 2.0 \times 10^{-5}\ cm^2 s^{-1}$,

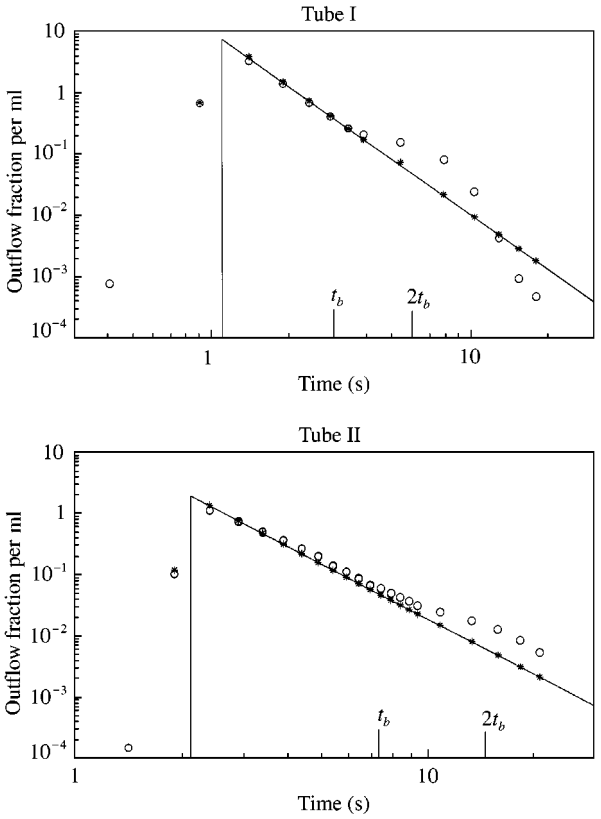

FIG. 1. Experimental data (○○○), theoretical prediction of concentration (——) and theoretical prediction of experimental points (∗∗∗).

which corresponds to the diffusion coefficient of the deuterium water ($H^1H^2O^{16}$) at temperature 20°C (Gray, 1972).

The agreement between the experimental data and theoretical prediction of concentration is good for both tubes for times $t \leqslant t_b$ (note that the prediction does not involve fitting the data). During this time, 86 and 91% of solute is already recovered for tubes I and II, respectively. For times $t_b < t < 2t_b$ when, as predicted, diffusion in the radial direction becomes important, the decrease of concentration is slower than $1/t^3$. For times somewhat greater than $2t_b$, the decrease of concentration is quicker than $1/t^3$. Starting from about $t = 4t_b$, experimental points are below the curve predicted by eqn (31), as seen from Fig. 1 for tube I.

4.2. CATHETER EXPERIMENTS

Experiments were performed with the catheter normally used in liver perfusion experiments. The

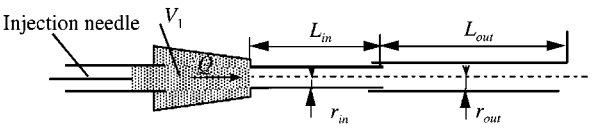

FIG. 2. Sketch of the catheter (not to scale) used to perform catheter perfusion experiments. V_1 is the volume between the end of the injection needle and the beginning of the input tube (shaded area), L_{in} and L_{out} are the lengths of the input and output tubes and r_{in} and r_{out} are their radii, respectively: ($V_1 = 0.08$ ml, $L_{in} = 32$ mm, $L_{out} = 93$ mm, $r_{in} = 0.65$ mm, $r_{out} = 0.78$ mm.)

sketch of the catheter (not to scale) is shown in Fig. 2. In liver perfusion experiments, the input tube of the catheter is inserted into the portal vein and the output tube is connected to the hepatic vein. For catheter perfusion experiments, the input and output sections of the catheter are connected together. The dimensions of the catheter are shown in Fig. 2.

The catheter was perfused with a standard buffer used in liver perfusion experiments (see e.g. Mellick & Roberts, 1996) at flow rate $Q = 30\,\text{ml}\,\text{min}^{-1}$. Bolus injection of 25 µl of the buffer with radioactively labeled red blood cells (^{99}Tc) was used and outflow samples were collected with fraction collector at intervals of 0.5 s at first and 2.5 s later. To measure the output concentration all outflow samples and injectate were analysed for total gamma-activity on a Packard Cobra II Auto Gamma counter. The concentration was presented as a fraction of the injected dose per ml of the sample (outflow fraction per ml).

Due to the assumed extensive mixing in volume V_1, it was decided that concentration in V_1 is best described by the well-stirred model. Equation (31) was used for the input and output tubes. As the extent of the mixing of solute at the junction between the input and output tubes is not known, two alternative theoretical assumptions were considered:

(I) The concentration profile at the outlet from tube I is well mixed before entering tube II.

(II) The mixing at the outlet from tube I is negligible, so that the concentration entering tube II is $C(L_{in}, t, r)$ and the two tubes effectively behave like one tube with the total volume $V = V_{in} + V_{out}$.

The predicted output concentration after the bolus input for Assumption (I) is

$$C_0^{(I)}(t) = \frac{Dose}{Q}\int_0^t \left[\frac{\exp(-(t-\tau)/t_1)}{t_1} \times \int_0^\tau u(\tau'-\tau_{m_1})\frac{2\tau_{m_1}^2}{\tau'^3}\,u(\tau'-\tau-\tau_{m_2}) \times \frac{2\tau_{m_2}^2}{(\tau'-\tau)^3}\,d\tau'\,d\tau, \quad (49)$$

where $t_1 = V_1/Q$, $\tau_{m_1} = V_{in}/(2Q)$ and $\tau_{m_2} = V_{out}/(2Q)$. Integration with respect to τ' in eqn (49) yields

$$C_0^{(I)}(t) = \frac{Dose}{Q}\frac{\exp(-t/t_1)}{t_1}\,u(t-\tau_{m_1}-\tau_{m_2}) \int_{\tau_{m_1}+\tau_{m_2}}^t \exp(-\tau/t_1)\varphi(\tau)\,d\tau, \quad (50)$$

where

$$\varphi(t) = \frac{(2\tau_{m_1}\tau_{m_2})^2}{t^3}\left[\frac{6}{t^2}\log\frac{(t-\tau_{m_1})(t-\tau_{m_2})}{\tau_{m_1}\tau_{m_2}} + \frac{1}{2\tau_{m_1}^2} + \frac{1}{2\tau_{m_2}^2} - \frac{1}{2(t-\tau_{m_1})^2} - \frac{1}{2(t-\tau_{m_2})^2} + \frac{3}{t}\left(\frac{1}{\tau_{m_1}} + \frac{1}{\tau_{m_2}} - \frac{1}{t-\tau_{m_1}} - \frac{1}{t-\tau_{m_2}}\right)\right]. \quad (51)$$

The integral in eqn (50) can easily be evaluated numerically.

For Assumption (II), the output concentration is

$$C_0^{(II)}(t) = \frac{Dose}{Q}\int_0^t \frac{\exp(-(t-\tau)/t_1)}{t_1}\,u(\tau-\tau_m)\,\frac{2\tau_m^2}{\tau^3}\,d\tau, \quad (52)$$

where $\tau_m = \tau_{m_1} + \tau_{m_2}$. Integration with respect to τ in eqn (52) yields

$$C_0^{(II)}(t) = \frac{Dose}{Q}\frac{\tau_m^2}{t_1^2}\left[\frac{\exp(-t/t_1)}{t_1}(\mathrm{Ei}(t/t_1) - \mathrm{Ei}(\tau_m/t_1)) + \exp((\tau_m - t)/t_1)\frac{t_1+\tau_m}{\tau_m^2} - \frac{t_1+t}{t^2}\right], \quad (53)$$

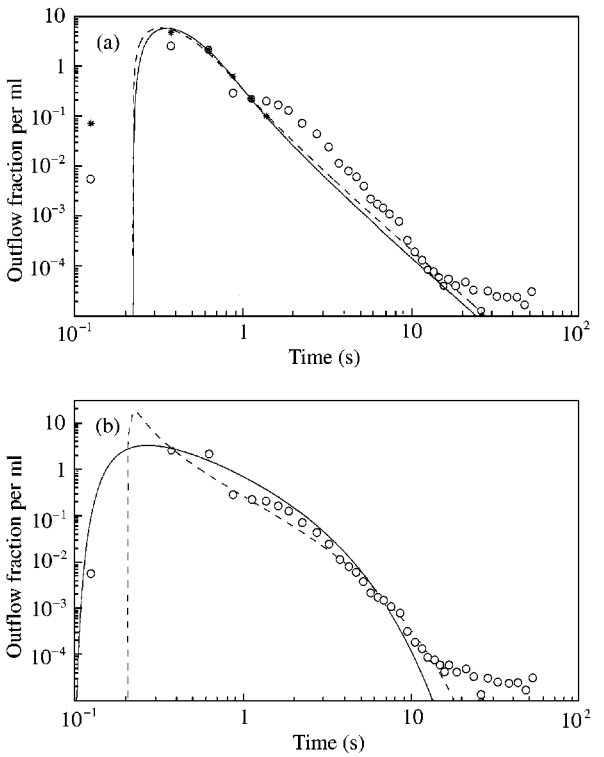

FIG. 3. (A) Experimental data for catheter (○○○), theoretical prediction of concentration [solid line for Assumption (I) and dashed line for Assumption (II)] and theoretical prediction of experimental points (∗∗∗). (B) The same data and their best fit (—— = unweighted and – – – = weighted) by the inverse Gaussian.

where $\mathrm{Ei}(x)$ is the exponential integral function defined as a Cauchy principal value integral:

$$\mathrm{Ei}(x) = \int_{-\infty}^x \frac{\exp(\xi)}{\xi}\,d\xi. \quad (54)$$

Theoretical predictions of the output concentration for Assumptions (I) and (II) for a catheter with dimensions as in Fig. 2 are presented in Fig. 3(a) together with the experimental points. For Assumption (I), the theoretical prediction of experimental points taking into account the effect of pooling was also presented. As the theoretical predictions for Assumptions (I) and (II) are very close to each other, the pooling effect is not presented for Assumption (II). In Fig. 3(b), the same data as in Fig. 3 (a) are presented together with the best fit of these data by the inverse Gaussian, equation (7).

It is apparent that there is no significant difference in the predicted concentration for

Assumptions (I) and (II). In fact, eqn (53) gives a slightly better agreement with experimental points for times $t > 3$ s. As eqn (53) is also simpler than the corresponding eqn (50), its use might be preferred.

There is some essential deviation of the theoretical prediction from experimental points for times between 1 and 10 s. This could be due to the very simplified modeling of volume V_1 of the catheter as a well-stirred compartment. Obviously, some sections of this volume could be poorly mixed with others, leading to the necessity to introduce an additional compartment or compartments in the modeling. This complication of the model will require the introduction of additional coefficients which are not determined from the geometry of the catheter, and therefore will require fitting of the experimental data. Overall, considering times from 0.1 to 20 s, the theoretical prediction of the experimental points is better than the corresponding fit of experimental points by the inverse Gaussian (weighted or unweighted, see Fig. 3), which is currently used to account for the catheter effect. Therefore, we conclude that the modeling of the catheter outflow profile presented in this paper is sufficient to describe the catheter distortion of the output concentration in liver perfusion experiments. We stress again that while the standard approach used hitherto requires fitting experimental data for the catheter, the approach we suggest in this paper allows the theoretical prediction of the catheter output concentration and does not involve fitting.

5. Conclusion

The main outcome of the work presented in this paper is the formulation and analysis of equations for the output concentration from the tube at $x = L$ when input concentration at $x = 0$ is known. A similar problem of the dispersion of solute in tubes when initial concentration at $t = 0$ is known and concentration for $t > 0$ and $x > 0$ is to be found was formulated and solved by Taylor (1953). In this paper, we used his approach to derive our equations.

The assumption of Poiseuille flow in a tube is critical for deriving the equations in this paper, especially for the short tube. Our analysis of the applicability of Poiseuille flow for tubes typically used in catheters shows that such a flow assumption is relevant, though some measurable distortion from Poiseuille flow is evident for the inlet section of the tube. The characteristic length of this distortion is given by eqn (48).

Equation (31) for the short tube is valid if diffusion is not important. It was shown that for times $t > t_b$, where t_b is defined in eqn (36), diffusion becomes important and therefore the output concentration must deviate from the curve predicted by eqn (31). It has been demonstrated that this analysis is in good agreement with experimental results for simple tubes.

The catheter used in liver perfusion experiments is not a simple tube, therefore some additional modeling is required. Two equations for the output concentration from the catheter were derived, based on simple assumptions. Comparison with the experimental data confirms as satisfactory the predictions of these equations.

Apart from its importance in the analysis of the dispersion of solute in catheters, the work presented in this paper might be used to examine the dispersion of drugs in blood vessels, where the assumption of Poiseuille flow in a blood vessel is justifiable. In this case, it has to be borne in mind that complications such as these arising from flexibility of the vessels will of course also have to be taken into account.

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REFERENCES

EVANS, A. M., HUSSEIN, Z. & ROWLAND, M. (1991). A two-compartment dispersion model describes the hepatic outflow profile of diclofenac in the presence of its binding protein. *J. Pharm. Pharmacol.* **43,** 709–714.

EVANS, A. M., HUSSEIN, Z. & ROWLAND, M. (1993). Influence of albumin on the distribution and elimination kinetics of diclofenac in the isolated perfused rat liver: analysis by the impulse–response technique and the dispersion model. *J. Pharm. Sci.* **82,** 421–428.

GOLDSTEIN, S. (1938). *Modern Developments in Fluids Dynamics: an Account of Theory and Experiment Relating to Boundary Layers, Turbulent Motion and Wakes.* Oxford: Clarendon Press.

GRAY, D. E. (1972).*American Institute of Physics Handbook.* New York: McGraw-Hill.

KREFT, A. & ZUBER, A. (1978). On the physical meaning of the dispersion equation and its solutions for different initial and boundary conditions. *Chem. Eng. Sci.* **33,** 1471–1480.

LANDAU, L. D. & LIFSHITS, E. M. (1989). *Fluid Mechanics*. Oxford: Pergamon Press.

MELLICK, G. D. & ROBERTS, M. S. (1996). The disposition of aspirin and salicylic acid in the isolated perfused rat liver: the effect of normal and retrograde flow on availability and mean transit time. *J. Pharm. Pharmacol.* **48,** 738–743.

ROBERTS, M. S. & ANISSIMOV, Y. G. (1999). Modelling of hepatic elimination and organ distribution kinetics with the extended convection–dispersion model. *J. Pharmacokinet. Biopharm.* **27,** 343–382.

ROBERTS, M. S., ANISSIMOV, Y. G. & WEISS, M. (2000). Commentary: using the convection–dispersion model and transit time density functions in the analysis of organ distribution kinetics. *J. Pharm. Sci.* **89,** 1579–1586.

ROBERTS, M. S., BALLINGER, L. N. & WEISS, M. (1988). Relative dispersions of intra-albumin transit times across rat and elasmobranch perfused livers, and implications for intra- and inter-species scaling of hepatic clearance using microsomal data. *J. Pharm. Pharmacol.* **50,** 865–870.

SILVERMAN, M. & GORESKY, C. A. (1965). A unified kinetic hypothesis of carrier mediated transport: its applications. *Biophys. J.* **5,** 487–509.

TAYLOR, G. I. (1953). Dispersion of soluble matter in solvent flowing slowly through a tube. *Proc. R. Soc. London A* **219,** 186–203.

WEISS, M., BALLINGER, L. N. & ROBERTS, M. S. (1998). Kinetic analysis of vascular marker distribution in perfused rat livers after regeneration following partial hepatectomy. *J. Hepatol.* **29,** 476–481.