Interconnected-tubes Model of Hepatic Elimination

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The distributed-tubes model of hepatic elimination is extended to include intermixing between sinusoids, resulting in the formulation of a new, interconnected-tubes model. The new model is analysed for the simple case of two interconnected tubes, where an exact solution is obtained. For the case of many strongly-interconnected tubes, it is shown that a zeroth-order approximation leads to the convection-dispersion model. As a consequence the dispersion number is expressed, for the first time, in terms of its main physiological determinants: heterogeneity of flow and density of interconnections between sinusoids. The analysis of multiple indicator dilution data from a perfused liver preparation using the simplest version of the model yields the estimate 10.3 for the average number of interconnections. The problem of boundary conditions for the dispersion model is considered from the viewpoint that the dispersion-convection equation is a zeroth-order approximation to the equations for the interconnected-tubes model.

1. Introduction

Various models have been used in attempts to describe the enzymatic elimination of substances from blood flowing through the liver (Rowland *et al.*, 1973; Winkler *et al.*, 1974; Bass *et al.*, 1978; Mellick *et al.*, 1997). Although the development of these models has undoubtedly increased our understanding of the physiological, pharmacokinetic and dynamical aspects of these important processes, some aspects of the modelling remain ill-defined. Broadly speaking, the models proposed so far fall into four classes: compartmental (or tank) models, single-tube models, distributed-tube models and dispersion models (Fig. 1).

The simplest model of hepatic elimination treats the liver as a single "well-stirred" compartment or "tank" (Rowland *et al.*, 1973). This model is limited in that it does not correctly describe either the outflow concentration-time profile after a bolus injection or the concentration-distance profile in the liver during steady-state infusion (Roberts & Rowland, 1985).

The single-tube model (Winkler *et al.*, 1974) treats the liver as a single tube (or *n* identical tubes) of constant cross-section through which blood flows and along which elimination occurs, in order to model of the variation of substrate concentrations with distance into the organ.

Distributed tube models (Bass *et al.*, 1978; Goresky *et al.*, 1973) attempt to take account of liver geometry by treating the organ as a large collection of non-identical tubes representing liver sinusoids, or more generally, independent pathways for blood flow, acting in parallel. In the "distributed model" (Bass *et al.*, 1978), each tube accepts a common input concentration of substrate which is depleted as it passes to the downstream, venous end where mixing occurs. In this paper, we modify the discrete version of this model to include micromixing. For the discrete version of the distributed model, with *n* tubes labelled $j = 1, 2, \ldots, n$, the concentration in the *j*-th tube is a function $c_j(x, t)$ of distance *x* along the tube, and time

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t. Governing equations for the *j*-th tube are (Bass *et al*., 1978)

$$a_j(x)\frac{\partial c_j}{\partial t} + f_j\frac{\partial c_j}{\partial x} = -\rho_j(x)g(c_j), \qquad (1)$$

where a_j, f_j and ρ_j are the cross-sectional area at location *x*, the rate of blood flow at time *t* and the density of enzyme elimination activity at location *x*, respectively, for that tube. The function $g(c)$ characterizes the form of liver kinetics responsible for elimination; thus $g(c) = c/(c + K_m)$ for Michaelis–Menten kinetics, where K_m is the half-saturating concentration constant.

We shall be concerned in this paper mainly with modelling of situations appropriate to experiments where a substrate is injected into blood flow at input to the liver, the blood being previously free of that substrate. The corresponding initial and boundary conditions for the distributed model are then

$$c_j(x, 0) = 0, \quad 0 \leqslant x \leqslant l_j$$
$$c_j(0, t) = c_{in}(t), \quad t > 0, \qquad (2)$$

where c_{in} is the common input concentration, and l_j is the length of the *j*-th tube to the output mixing site. The measurable output concentration from the liver is then the "flow-weighted" mean concentration (Bass *et al*., 1983)

$$c_{out}(t) = \frac{1}{F}\sum_j f_j c_j(l_j, t), \qquad (3)$$

where $F = \Sigma_j f_j$ is the rate of total hepatic blood flow, and $c_j(x, t)$ is the solution of (1).

A criticism that has been levelled at the distributed model is its failure to take account of intermixing between sinusoids (Roberts & Rowland, 1985), observed in anatomical studies of the hepatic microcirculation (Koo *et al*., 1975). Despite this, the model has been used successfully to interpret experimental data from steady-state experiments (Bass, 1980). In steady-state situations, the solution of (1) at the output $x = l_j$ involves the total elimination capacity for that tube, but neither l_j nor the form of ρ_j explicitly (Bass *et al*., 1978). Thus, while the distributions of flow rates and total elimination capacities affect steady-state extraction (Bass *et al*., 1978; Roberts *et al*., 1988), the distribution of tube lengths is irrelevant for this purpose.

However, the distributed model is not readily applicable to unsteady situations such as those which apply after bolus injection of substrate (Bass *et al*., 1983; Roberts & Rowland, 1985), because the broad distribution of tube-lengths l_j (and hence of arrival-

times at the downstream mixing site), and the nature of its unknown correlations with the (assumed) narrow distributions of a_j, f_j and ρ_j values, are also needed for the calculation of $c_{out}(t)$ in those cases. Furthermore, it has been argued that parallel tube models do not adequately describe the availability-flow and availability-unbound fraction relationships for highly extracted drugs (Roberts & Rowland, 1986b). Some of these difficulties are circumvented in the "distributed sinusoidal perfusion model" described by Goresky *et al*. (1973), at the expense of making more restrictive, and therefore less realistic, assumptions about sinusoidal structure. Roberts & Rowland (1986a) emphasized the need to use in such a model a distribution of arrival times based on the impulse-response relationship for a vascular reference marker in the liver. Such a model has been applied to time-dependent (Roberts *et al*., 1988; Goresky *et al*., 1992; Luxon & Weisiger, 1993; Schwab *et al*., 1990) and Michaelis–Menten data (Roberts *et al*., 1989).

In order to take into account intermixing within the liver and to adequately describe the transit time distribution of vascular reference markers, the axial-dispersion model was introduced by Roberts & Rowland (1985). Rather than attempt to model the
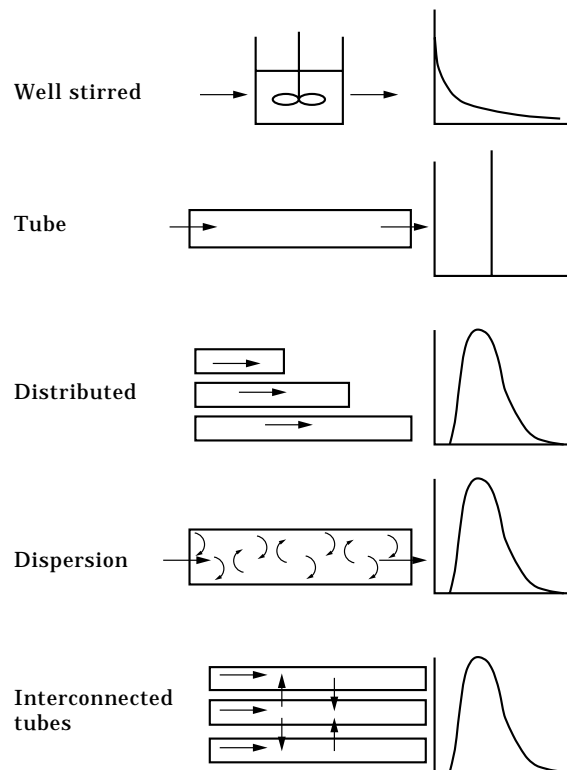

FIG. 1. Models of hepatic elimination: schematic representations and concentration-time profiles after bolus injection of nonelimi-nated substance.

complicated sinusoidal geometry directly, with its many interconnections (Koo *et al.*, 1975), it takes advantage of this complexity by treating the liver as a "fixed-bed chemical reactor" (Levenspiel, 1976), lumping together the mixing effects as a second order space derivative term in the convection-elimination equation. Although the form of the second order term is similar to that in the diffusion equation, it must be emphasized that there is no identity of the terms. Roberts & Rowland (1986a) have stated that dispersion defines the spread in convection flow at a macrolevel as a consequence of the net effect of several events, including: (1) variations in flow velocity and variations in lengths of different sinusoids; (2) mixing of blood at the branch points of sinusoids and at the interconnections between sinusoids; and (3) in principle, molecular diffusion.

The governing equation for the dispersion model is

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} - v \frac{\partial c}{\partial x} - \rho(x)g(c), \qquad (4)$$

where D is the "dispersion coefficient" (Roberts & Rowland, 1986a), $c(x, t)$ is an average concentration at distance x into the liver, v is the average velocity of convection throughout the liver, $\rho(x)$ is the average density of enzymatic elimination, per unit area of cross-section, at distance x, and $g(c)$ is as before. The equation for the dispersion model is commonly used in dimensionless form:

$$\frac{\partial}{\partial \tau} c(X, \tau) = -\frac{\partial}{\partial X} c(X, \tau) + D_N \frac{\partial^2}{\partial X^2} c(X, \tau)$$
$$- R_N(c, X)c(X, \tau), \quad (5)$$

where $X = x/L$, $\tau = t/T$, $T = L/v$, $R_N(c, X) = \rho(x)Tg(c)/c$ and $D_N = D/(Lv)$ is the dispersion number (Roberts & Rowland, 1986a).

In a two compartmental form the dispersion model has been used to describe time-dependent data (Roberts *et al.*, 1988; Yano *et al.*, 1989; Chou *et al.*, 1993; Hussein *et al.*, 1994; Evans *et al.*, 1993).

Bass *et al.* (1987) have suggested that "the physiological interpretation of the dispersion coefficient in the liver is problematical. In particular, the model does not predict how the dispersion coefficient changes with the rate of hepatic blood flow. ... A further difficulty is that the dispersion model, necessarily expressed in terms of a second order partial differential equation, requires boundary conditions (additional to those of the sinusoidal perfusion model) that have not yet been formulated unambiguously." One further mathematical difficulty

is that little exact mathematical analysis of (4) is possible in cases. where $\rho(x)$ is non-constant or $g(c)$ is nonlinear, so that one then has to resort to numerical solution on a case-by-case basis. These criticisms have been addressed by Roberts *et al.* (1988) using the dispersion model with mixed boundary conditions and a dimensionless dispersion number. Work by Roberts *et al.* (1990), Chou *et al.* (1993), Hussein *et al.* (1994) and Evans *et al.* (1993) have shown that the dispersion number is independent of flow and protein concentration.

Other limitations of the distributed and the dispersion models have been addressed by Bass *et al.* (1987). There N liver "units" in series with N mixing sites were suggested to describe intermixing between sinusoids. Each liver unit was described in terms of the distributed model, and a value of a dispersion coefficient D for the system as a whole was obtained, enabling a prediction to be made as to how D would behave under variation of total flow rate F. A tanks-in-series model has also been proposed for first-order extraction (Weisiger *et al.*, 1986; Gray & Tam, 1987; Roberts *et al.*, 1988) and Michaelis–Menten (Roberts *et al.*, 1989) elimination.

Overall, the models proposed so far appear to have different domains of applicability, reflecting their different underlying and simplifying assumptions. For example, the dispersion model, which lumps the effects of the sinusoidal network into a diffusion-like term in a second-order partial differential equation, appears to work well in practice in describing time-dependent elimination with first-order reaction kinetics, from a bolus ("delta-function") input of substrate. The distributed model, on the other hand, which models the liver geometry as an ensemble of tubes acting in parallel, leads to uncoupled first-order differential equations, and appears to work well in some steady-state situations involving nonlinear elimination kinetics.

Our purpose here is to approach the modelling of hepatic elimination in a new way. We aim to take into account intermixing between sinusoids, rather than neglect it as in the distributed model, but we aim to do it in a more specific way than in the dispersion model, paying attention to the known vascular architecture of sinusoids. An important outcome of our modelling is that we are able to provide a more direct physiological basis for the applicability of the dispersion model, and to clarify its domains of applicability. We are also able to clarify the meaning of the dispersion number in terms of more fundamental physiological variables.

We propose to call the new model the "interconnected-tubes model".

2. Interconnected-tubes Model

In order to take into account both the sinusoidal structure of the liver, and the high degree of intermixing observed experimentally (Koo *et al*., 1975), we propose to model the elimination process in terms of a large number of tubes acting in parallel, with various flow rates, with elimination within each tube, and with continuous interchange of substrate between tubes along their (common) length L. We suppose that the interchange is the result of convective fluxes from one tube to another which causes a variation of flux f_i along each tube.

The governing equations of the model are, most generally

$$a_i(x) \frac{\partial c_i}{\partial t} + f_i(x) \frac{\partial c}{\partial x} = -\rho_i(x) g(c_i)$$

$$+ \sum_{j=1, j \neq i}^{n} (c_i \hat{k}_{ji}(x) - c_i \hat{k}_{ij}(x)), \quad (6)$$

for $i = 1, 2, \ldots, n$ and $0 \leqslant x \leqslant L$. The symbols have the same meaning as in eqn (1) for the distributed model, the new feature being the final, intermixing term, in which $\hat{k}_{ij}(x)$ is the rate constant for transfer of substrate (and solvent) from the i-th to j-th tube at distance x. From conservation of solvent, we now have an additional equation to be satisfied by the i-th flux,

$$\frac{\mathrm{d}f_i}{\mathrm{d}x} = \sum_{j=1, j \neq i}^{n} (\hat{k}_{ji}(x) - \hat{k}_{ij}(x)), \quad i = 1 \ldots n, \quad (7)$$

and obviously for the model to be valid, $\hat{k}_{ij}(x)$ must be such that $f_i(x) > 0$ for $i = 1 \ldots n$ and $0 \leqslant x \leqslant L$.

We have made the simplifying assumption that all tubes have the same length L, and for the purposes of this paper, we now make the further assumptions that $\hat{k}_{ij}$, a_i, f_i and ρ_i are constants in order to be able to make some progress with the mathematics. Obviously, these approximations are crude in the context of the actual liver physiology, but we believe the resultant modeling still captures the essential features of the transport and elimination processes. In order to have f_i constant we need, according to eqn (7), the restriction

$$\sum_{j=1, j \neq i}^{n} (\hat{k}_{ji} - \hat{k}_{ij}) = 0, \quad i = 1 \ldots n. \quad (8)$$

Furthermore, we suppose that we are dealing with tracer concentrations of substrate, so that $g(c)$ can be assumed linear, i.e. $g(c) = c/K_m$. It is at once clear that there are interesting and important questions, to what extent these simplifying assumptions can be relaxed without making analysis of the model completely intractable; we hope to return to some of these questions elsewhere.

Note that the $\hat{k}_{ij}$ are non-negative, and some may be zero, but it is implicitly assumed that the values of the $\hat{k}_{ij}$ are such that the system of n tubes cannot be regarded as two or more subsystems with no interconnections between them [eqn (34)]. For convenience we will use $k_{ij} = \hat{k}_{ij}/a_i$ for the coefficient of exchange (so that dimension of k_{ij} is T^{-1}).

Under the simplifications stated, the defining equation (6) can be written in the form

$$\frac{\partial c_i}{\partial t} = -v_i \frac{\partial c_i}{\partial x} - c_i k_{ei}$$

$$+ \sum_{j=1, j \neq i}^{n} \left(c_j k_{ji} \frac{a_j}{a_i} - c_i k_{ij} \right), \quad i = 1 \ldots n, \quad (9)$$

where, for the i-th tube, v_i ($= f_i/a_i$) is the constant velocity of blood flow, and k_{ei} ($= \rho_i/(a_i K_m)$) is an elimination rate constant.

Initial and boundary conditions for the new model are (2), the same as for the distributed model. Thus we have the simplest form of the interconnected tubes model, defined by eqn (9) and initial and boundary conditions (2).

Consider the coefficient of exchange k_{ij}. Obviously, the larger is k_{ij}, the more changes of velocity a particle of blood containing substrate, and governed by eqn (9), will experience as it passes from inlet at $x = 0$ to outlet at $x = L$. In order to quantify this idea we shall elucidate the connection between the discrete situation for sinusoidal interconnections and the continuous way of modelling these by eqns (6) and (9). Let us do this for the simplest case of two sinusoids (Fig. 2). We emphasize at this stage that the following consideration is not meant to provide a strict physiological basis for the governing equation (6). The intermixing terms in these equations are heuristic, and we can only expect at best to obtain rough estimates for the coefficients k_{ij}. We will simplify the discussion by letting all connecting sinusoids have the same length d, velocity of flux v_3 (either from sinusoid 1 to sinusoid 2 or back) and cross-section area a_3. We further imagine connecting sinusoids distributed uniformly along the length L, so that the number of connecting sinusoids with flux from sinusoid 1 to sinusoid 2 per element of length Δx is $\Delta x K/2$ and is equal to the number of connecting sinusoids with the opposite direction of flux, with $K = N/L$ and N equal to the total number of connecting sinusoids. If we assume that d is small enough in order to have constant concentration along

connecting sinusoids, then considering fluxes of substrate into and out of a small element of length $\Delta x \leqslant d \ll L$ we get

$$\begin{cases} \Delta V_1(c_1(x, t + \Delta t) - c_1(x, t)) = -\Delta V_1 k_{e1} c_1(x, t) \Delta t \\ \quad - a_1 v_1' \Delta t (c_1(x + \Delta x, t) - c_1(x, t)) \\ \quad - v_3 \Delta t \dfrac{\Delta x K}{2} a_3(c_1(x, t) - c_2(x, t)), \\[2mm] \Delta V_2(c_2(x, t + \Delta t) - c_2(x, t)) = -\Delta V_2 k_{e2} c_2(x, t) \Delta t \\ \quad - a_2 v_2' \Delta t (c_2(x + \Delta x, t) - c_2(x, t)) \\ \quad - v_3 \Delta t \dfrac{\Delta x K}{2} a_3(x, t) - c_1(x, t)), \end{cases} \quad (10)$$

where $\Delta V_i = \Delta x a_i + a_3 d \Delta x K / 2$ includes the volume of connecting sinusoids. As Δx and Δt are small, we substitute $c_i(x, t + \Delta t) - c_i(x, t) \approx \Delta t \partial c_i(x, t) / \partial t$ and $c_i(x + \Delta x, t) - c_i(x, t) \approx \Delta x \partial c_i(x, t) / \partial x$ in (10) and divide by $\Delta t \Delta x$ to get the continuous equations

$$\begin{cases} \left(a_1 + \dfrac{dKa_3}{2}\right) \dfrac{\partial}{\partial t} c_1(x, t) = -av_1' \dfrac{\partial}{\partial x} c_1(x, t) - k_{e1} \\ \quad \times \left(a_1 + \dfrac{dKa_3}{2}\right) c_1(x, t) - v_3 \dfrac{Ka_3}{2}(c_1(x, t) - c_2(x, t)) \\[2mm] \left(a_2 + \dfrac{dKa_3}{2}\right) \dfrac{\partial}{\partial t} c_2(x, t) = -a_2 v_2' \dfrac{\partial}{\partial x} c_2(x, t) - k_{e2} \\ \quad \times \left(a_2 + \dfrac{dKa_3}{2}\right) c_2(x, t) - v_3 \dfrac{Ka_3}{2}(c_2(x, t) - c_1(x, t)). \end{cases}$$
$$(11)$$

Dividing eqns (11) by corresponding effective areas $(a_i + dKa_3/2)$ we get eqns (9) for two tubes with effective velocity $v_i = 2v_i' a_i / (2a_i + dKa_3)$ along the i-th sinusoid and coefficients of exchange $k_{12} = a_3 v_3 K / (2a_1 + dKa_3)$, $k_{21} = a_3 v_3 K / (2a_2 + dKa_3)$. We can then write, for example,

$$k_{12} = \frac{a_3}{2a_1 + dKa_3} \frac{v_3}{v_{av}} v_{av} K = \alpha v_{av} \frac{N}{L} = \alpha \frac{N}{T} \quad (12)$$

where

$$\alpha = \frac{a_3}{2a_1 + dKa_3} \frac{v_3}{v_{av}} \quad (13)$$

is dimensionless and independent of small changes of hepatic blood flow, $T = L/v_{av}$ and v_{av} is the average effective velocity of the two tubes [c.f. eqn (15)]. Let us estimate α. Hepatic sinusoids can be classified into
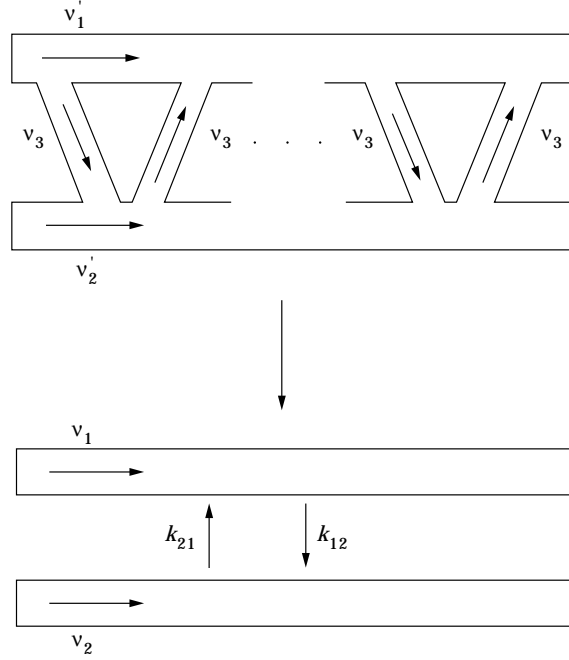

FIG. 2. Transition from the case of two sinusoids interconnected discretely to interconnections modeled as continuous.

three types: branching sinusoids, direct sinusoids and interconnecting sinusoids with average velocities of 0.27 mm s^{-1}, 0.41 mm s^{-1} and 0.37 mm s^{-1}, respectively and average radii of $6.3 \ \mu m$, $6.6 \ \mu m$ and $6.3 \ \mu m$, respectively (Koo et al., 1975). In our example sinusoids 1 and 2 correspond to branching type and a_3, v_3 represent parameters of interconnecting sinusoids, thus using data for the rat liver (Koo et al., 1975) one can get $a_1 = a_3$, $v_{av} = 0.27 \text{ mm s}^{-1}$ and $v_3 = 0.37 \text{ mm s}^{-1}$. If we assume that d is small in order to have $dK \ll 1$, then using (13) we get $\alpha \approx 0.7$. The important point is that $k_{12} T$ is proportional to N, with a coefficient of proportionality α which is of order of magnitude 1. For the more general case of n tubes we therefore argue that each k_{ij} will typically be proportional to the average number of mixing sites N_{mix} along sinusoids. More precisely, we suppose that for each i

$$T \max_{j \neq i} (k_{ij}) \propto N_{mix}, \quad (14)$$

where T is the average time of passage through the liver, and again the coefficient of proportionality is of order 1. For the model as described, this average time is given by $T = L/v_{av}$, where v_{av} is the average velocity defined by

$$v_{av} = \frac{1}{A} \sum_{i=1}^{n} a_i v_i, \quad A = \sum_{i=1}^{n} a_i. \quad (15)$$

Branching sinusoids are characterized by a large number of mixing sites, and it is apparent that they outnumber direct sinusoids (Koo *et al*., 1975). As a result, it is reasonable to argue that $N_{mix} \gg 1$ and so, from (14) that $T \max_{j \neq i} k_{ij} \gg 1$.

3. Two Interconnected Tubes

As a first step towards the treatment of the *n*-tube model, let us consider the simple case of two tubes, which turns out to be exactly solvable. We have the two equations

$$
\begin{cases}
\dfrac{\partial}{\partial t} c_1(x, t) = -v_1 \dfrac{\partial}{\partial x} c_1(x, t) - k_{e1} c_1(x, t) - k c_1(x, t) \\
\qquad + k c_2(x, t) \\
\dfrac{\partial}{\partial t} c_2(x, t) = -v_2 \dfrac{\partial}{\partial x} c_2(x, t) - k_{e2} c_2(x, t) - \gamma k c_2(x, t) \\
\qquad + \gamma k c_1(x, t),
\end{cases}
\tag{16}
$$

where $k = k_{12} = k_{21}/\gamma$, and $\gamma = a_1/a_2$.

Initial and boundary conditions are

$$
c_i(x, 0) = 0, \quad c_i(0, t) = \delta(t), \quad i = 1, 2. \tag{17}
$$

Here and below $\delta(t)$ is Dirac's δ-function. It is assumed without loss of generality that $v_2 > v_1$.

In a more general form the system of eqns (16) has been studied by Hill (1981) and McNabb (1985).

We will use the Laplace transform to solve this system of differential equations. After transformation we have, taking into account the initial condition in (17),

$$
\begin{cases}
v_1 \dfrac{\mathrm{d}}{\mathrm{d}x} \hat{c}_1(x, s) = -(s + k_{e1} + k) \hat{c}_1(x, s) + k \hat{c}_2(x, s) \\
v_2 \dfrac{\mathrm{d}}{\mathrm{d}x} \hat{c}_2(x, s) = -(s + k_{e2} + \gamma k) \hat{c}_2(x, s) + \gamma k \hat{c}_1(x, s),
\end{cases}
\tag{18}
$$

where $\hat{c}_{1,2}(x, s)$ are Laplace images of $c_{1,2}(x, t)$.

The boundary conditions in (17) become

$$
\hat{c}_{1,2}(0, s) = 1. \tag{19}
$$

Equations (18) form a system of two coupled linear first order differential equations, whose solution after tortuous transformations can be written in the form

$$
\hat{c}_1(x, s) = \frac{1}{2} \exp\left(x \frac{k_{e1} - k_{e2} + (1 - \gamma)k}{v_2 - v_1} \right)
$$

$$
\times \left[\exp\left(-s' \frac{x}{v_2} \right)(b v_2 r^{-1} e^{\beta(r - s')} \right.
$$

$$
+ (r - s') r^{-1} e^{\beta(r - s')}) + \exp\left(-s' \frac{x}{v_1} \right)
$$

$$
\left. \times (-b v_2 r^{-1} e^{-\beta(r - s')} + r^{-1}(r + s') e^{-\beta(r - s')}) \right],
$$

$$
\tag{20}
$$

$$
\hat{c}_2(x, s) = \frac{1}{2} \exp\left(x \frac{k_{e1} - k_{e2} + (1 - \gamma)k}{v_2 - v_1} \right)
$$

$$
\times \left[\exp\left(-s' \frac{x}{v_2} \right)(b \gamma v_1 r^{-1} e^{\beta(r - s')} \right.
$$

$$
+ r^{-1}(r + s') e^{\beta(r - s')}) + \exp\left(-s' \frac{x}{v_1} \right)
$$

$$
\left. \times (-b \gamma v_1 r^{-1} e^{-\beta(r - s')} + (r - s') r^{-1} e^{-\beta(r - s')}) \right],
$$

$$
\tag{21}
$$

where

$$
r = \sqrt{(s')^2 + a^2}, \quad a = \frac{2k \sqrt{\gamma v_1 v_2}}{v_2 - v_1},
$$

$$
b = \frac{2k}{v_2 - v_1}, \quad \beta = x \frac{v_2 - v_1}{2 v_1 v_2},
$$

$$
s' = s + \frac{k_{e1} + k_{e2} + k(\gamma + 1)}{2}
$$

$$
+ \frac{k_{e1} - k_{e2} + (1 - \gamma)k}{v_2 - v_1} \frac{v_1 + v_2}{2}.
$$

Now, inverting eqns (20), (21) to the time domain, with the help of known transforms (Erdelyi *et al*., 1954), we get the solution for the system (16) with boundary and initial conditions (17):

$$
c_1(x, t) = \exp\left(-t \frac{k_{e1} + k_{e2} + (1 + \gamma)k}{2} \right.
$$

$$
\left. - \frac{k_{e1} - k_{e2} + (1 - \gamma)k}{v_2 - v_1} \left(t \frac{v_1 + v_2}{2} - x \right) \right)
$$

$$
\times \left[\delta\left(t - \frac{x}{v_1} \right) + \frac{\theta(x, t)k}{v_2 - v_1} \right.
$$

$$
\left. \times \left(v_2 I_0(ky) + v_1 \sqrt{\gamma \frac{t v_2 - x}{x - t v_1}} I_1(ky) \right) \right], \tag{22}
$$

$$c_2(x, t) = \exp\left(-t\frac{k_{e1} + k_{e2} + (1 + \gamma)k}{2}\right.$$

$$\left. -\frac{k_{e1} - k_{e2} + (1 - \gamma)k}{v_2 - v_1}\left(t\frac{v_1 + v_2}{2} - x\right)\right)$$

$$\times\left[\delta\left(t - \frac{x}{v_2}\right) + \frac{\theta(x, t)k}{v_2 - v_1}\right.$$

$$\left.\times\left(\gamma v_1 I_0(ky) + v_2\sqrt{\gamma\frac{x - tv_1}{tv_2 - x}}\,I_1(ky)\right)\right], \quad (23)$$

where I_0, I_1 are modified Bessel's functions,

$$\theta(x, t) = u\left(t - \frac{x}{v_2}\right) - u\left(t - \frac{x}{v_1}\right)$$

$$= \begin{cases} 1 & \text{for } \frac{x}{v_2} < t < \frac{x}{v_1} \\ 0 & \text{otherwise,} \end{cases}$$

and

$$y = \frac{2\sqrt{\gamma(tv_2 - x)(x - tv_1)}}{v_2 - v_1}.$$

From (22), (23) it is clear that $c_{1,2}(x, t) = 0$ if $t \notin [x/v_2, x/v_1]$, so we will consider $t \in [x/v_2, x/v_1]$ or equivalently $x \in [tv_1, tv_2]$.

As discussed in Section 2, it is reasonable to expect $kT \gg 1$, where T is the mean transit time. This allows us then to consider times t such that $kt \gg 1$. In formulae (22) and (23), an exponentially small factor occurs, namely

$$\exp\left(-k\left(t\frac{(1 + \gamma)}{2} + \frac{1 - \gamma}{v_2 - v_1}\left(t\frac{v_1 + v_2}{2} - x\right)\right)\right)$$

or, if we put $x = tv$, where $v \in [v_1, v_2]$ (as $x \in [tv_1, tv_2]$)

$$\exp\left(-\frac{kt}{(v_2 - v_1)}(\gamma(v - v_1) + (v_2 - v))\right).$$

Whenever c_1 and c_2 are not exponentially small, this factor must be compensated for, and this is only possible where $ky \gg 1$, because the asymptotic formulae for $I_0(x)$ and $I_1(x)$ for $x \gg 1$ are (Abramovitz & Stegun, 1965)

$$I_0(x) = \frac{e^x}{\sqrt{2\pi x}}\left(1 + \frac{1}{8}x^{-1} + O(x^{-2})\right),$$

$$I_1(x) = \frac{e^x}{\sqrt{2\pi x}}\left(1 - \frac{3}{8}x^{-1} + O(x^{-2})\right).$$

Having substituted these in (22) and (23), we get

$$c_1(x, t) = \exp\left(k\left(y - \frac{t(v_2 - \gamma v_1) - x(1 - \gamma)}{v_2 - v_1}\right)\right.$$

$$\left. + \frac{t(k_{e2}v_1 - k_{e1}v_2) + x(k_{e1} - k_{e2})}{v_2 - v_1}\right)$$

$$\times\frac{1}{\sqrt{2\pi ky}}\frac{k}{v_1 - v_2}\left(v_2\left(1 + \frac{1}{8y}k^{-1}\right)\right.$$

$$\left. + v_1\sqrt{\gamma\frac{tv_2 - x}{x - tv_1}}\left(1 - \frac{3}{8y}k^{-1}\right)\right.$$

$$\left. + O((ky)^{-2})\right), \quad (24)$$

$$c_2(x, t) = \exp\left(k\left(y - \frac{t(v_2 - \gamma v_1) - x(1 - \gamma)}{v_2 - v_1}\right)\right.$$

$$\left. + \frac{t(k_{e2}v_1 - k_{e1}v_2) + x(k_{e1} - k_{e2})}{v_2 - v_1}\right)$$

$$\times\frac{1}{\sqrt{2\pi ky}}\frac{k}{v_1 - v_2}\left(\gamma v_1\left(1 + \frac{1}{8y}k^{-1}\right)\right.$$

$$\left. + v_2\sqrt{\gamma\frac{x - tv_1}{tv_2 - x}}\left(1 - \frac{3}{8y}k^{-1}\right)\right.$$

$$\left. + O((ky)^{-2})\right), \quad (25)$$

where we have neglected in (22), (23) the terms involving δ-functions because they have exponentially small coefficients.

We consider the first term of the exponent in (24) and (25),

$$p(x, t) = k\left(y - \frac{t(v_2 - \gamma v_1) - x(1 - \gamma)}{v_2 - v_1}\right).$$

It can be shown that for $x \in [tv_1, tv_2]$ and t fixed, $p(x, t)$ has its maximal value if $x = tv_{av}$, $v_{av} = (\gamma v_1 + v_2)/(\gamma + 1)$ and that:

$$p(tv_{av}, t) = 0$$

$$p'_x(v_{av}, t) = 0$$

$$p''_{xx}(tv_{av}, t) = -k\frac{(\gamma + 1)^3}{2(v_2 - v_1)^2\gamma t}$$

$$p'''_{xxx}(tv_{av}, t) = k\frac{3(\gamma + 1)^4(\gamma - 1)}{4(v_2 - v_1)^3\gamma^2 t^2}.$$

Then we can write

$$p(x, t) \simeq -k \frac{(\gamma + 1)^3}{4(v_2 - v_1)^2 \gamma t}(x - t v_{av})^2$$

$$+ k \frac{(\gamma + 1)^4(\gamma - 1)}{8(v_2 - v_1)^3 \gamma^2 t^2}(x - t v_{av})^3.$$

In order to have $c_{1,2}(x, t)$ not exponentially small, we need to consider x so that $|p(x, t)| \sim 1$ or $k(x/v_{av} - t)^2 \sim t$. We now introduce the new variable z:

$$z = (x - t v_{av})k^{1/2}, \quad x = t v_{av} + z k^{-1/2},$$

and change x, t to z, t in (24) and (25), keeping only terms of order $k^{-1/2}$:

$$c_1(t, z) \simeq \sqrt{\frac{v_{av}^2(\gamma + 1)^3 k}{4\pi(v_2 - v_1)^2 \gamma t}} \exp\left(-z^2 \frac{(\gamma + 1)^3}{4(v_2 - v_1)^2 \gamma t} - k_{av} t\right)$$

$$\times \left(1 + k^{-1/2} z \left(\frac{k_{e2} - k_{e1}}{v_2 - v_1} - \frac{\gamma v_1(3\gamma + 1) + v_2(\gamma - 1)}{4(v_2 - v_1)v_{av}\gamma t}\right.\right.$$

$$\left.\left. + z^2 \frac{(\gamma + 1)^4(\gamma - 1)}{8(v_2 - v_1)^3 \gamma^2 t^2}\right)\right), \quad (26)$$

$$c_2(t, z) \simeq \sqrt{\frac{v_{av}^2(\gamma + 1)^3 k}{4\pi(v_2 - v_1)^2 \gamma t}} \exp\left(-z^2 \frac{(\gamma + 1)^3}{4(v_2 - v_1)^2 \gamma t} - k_{av} t\right)$$

$$\times \left(1 + k^{-1/2} z \left(\frac{k_{e2} - k_{e1}}{v_2 - v_1} + \frac{\gamma v_1(1 - \gamma) + v_2(3 + \gamma)}{4(v_2 - v_1)v_{av}\gamma t}\right.\right.$$

$$\left.\left. + z^2 \frac{(\gamma + 1)^4(\gamma - 1)}{8(v_2 - v_1)^3 \gamma^2 t^2}\right)\right), \quad (27)$$

where

$$k_{av} = \frac{\gamma k_{e1} + k_{e2}}{\gamma + 1}.$$

If we now change back from z to t and keep just the first term in (26) and (27), we have the physically clear result for large k:

$$c_{1,2}(x, t) \simeq \sqrt{\frac{\omega k}{\pi}} \exp\left(-\omega k\left(t - \frac{x}{v_{av}}\right)^2 - k_{av} t\right), \quad (28)$$

where

$$\omega = \frac{v_{av}^2(\gamma + 1)^3}{4(v_2 - v_1)^2 \gamma t}. \quad (29)$$

Note from (28) that

$$\lim_{k \to \infty} c_{1,2}(x, t) = \exp(-k_{av} t)\delta\left(t - \frac{x}{v_{av}}\right).$$

In this limit, equilibration of concentrations in tubes become instantaneous, so that $c_1(x, t) = c_2(x, t)$, and we have, effectively, one tube with average parameters. Formulae (26) and (27) give an idea of how rapid is this process with respect to the extent of the coefficient of exchange between the two tubes.

4. Strongly Interconnected Tubes

Encouraged by the successful analyses of the two-tube case, and the sensible solutions obtained, we now proceed to the case of n tubes. The two-tube case suggests that the way to approach this mathematical problem, which is not exactly solvable for $n > 2$, is by asymptotic analysis, the important independent variable being z.

Let us rewrite eqn (9) in a matrix form:

$$\frac{\partial}{\partial t}\mathbf{c} = -\mathbf{V}\frac{\partial}{\partial x}\mathbf{c} - \mathbf{K}_e\mathbf{c} + \mathbf{Mc}, \quad (30)$$

where $\mathbf{c}^T = (c_1, c_2, \ldots, c_n)$, n is the number of tubes, $\mathbf{V} = \text{diag}(v_i)$, $\mathbf{K}_e = \text{diag}(k_{ei})$, v_i and k_{ei} represent distributions of velocities and elimination rate constants, $\mathbf{M} = \{m_{ij}\}$ is the matrix of coefficients of exchange between tubes, so that

$$m_{ij} = -\delta_{ij}\sum_{l=1}^{n} k_{il} + k_{ji}\frac{a_j}{a_i}, \quad i, j = 1 \ldots n. \quad (31)$$

The initial and boundary conditions are

$$\mathbf{c}(x, 0) = 0, \quad \mathbf{c}(0, t) = \mathbf{e}\delta(t) \quad (32)$$

where $\mathbf{e}^T = (1, 1, \ldots, 1)$.

The form of $\mathbf{M}$ automatically provides conservation of substance for eqn (30) if $\mathbf{K}_e = 0$, since

$$\sum_{i=1}^{n} a_i\left(\frac{\partial}{\partial t}c_i + v_i\frac{\partial}{\partial x}c_i\right) = \sum_{i=1}^{n} a_i\frac{d}{dt}c_i = \sum_{i=1}^{n}\sum_{j=1}^{n} a_i m_{ij}c_j = 0,$$

as

$$\sum_{i=1}^{n} a_i m_{ij} = -a_j\sum_{l=1}^{n} k_{jl} + a_j\sum_{i=1}^{n} k_{ji} = 0.$$

With $\mathbf{a}^T = (a_1, a_2, \ldots, a_n)$ we can write for $\mathbf{M}$

$$\mathbf{a}^T\mathbf{M} = 0. \quad (33)$$

It is physically reasonable to expect that the only uniform steady-state concentrations, possible in a system of inter-connected tubes (if there is no elimination) are $c_i = c_0$, $i = 1 \ldots n$, or $\mathbf{c} = c_0\mathbf{e}$, where c_0 is some constant. That is if $\mathbf{Mg} = 0$, $\mathbf{g}$ some vector,

then there exists a real f so that $\mathbf{g} = f\mathbf{e}$. Then we have more properties for $\mathbf{M}$:

$$\mathbf{Me} = 0, \quad \text{rank}\,(\mathbf{M}) = n - 1. \qquad (34)$$

Let us now consider the case $\max_{i \neq j}(m_{ij}) \gg v_{av}/L$, where L is the length of tubes and v_{av} is the average velocity $v_{av} = 1/A \sum_{i=1}^n a_i v_i$, $A = \sum_{i=1}^n a_i$. More precisely, suppose:

$$m_{ij} = k r_{ij}$$

where $k \gg 1$ and $\max_{i \neq j}(r_{ij}) \sim v_{av}/L$. Obviously $\mathbf{R} = \{r_{ij}\}$ must possess properties (33) and (34).

When $k \to \infty$, n tubes behave virtually as one with the average velocity, so that if $\mathbf{K}_e = 0$ we expect that

$$\mathbf{c} \to \mathbf{e}\delta\left(t - \frac{x}{v_{av}}\right), \quad k \to \infty.$$

Given that, and the analysis of two tubes for $k \to \infty$ [formulae (26) and (27)], it is reasonable to suggest for $\mathbf{c}$ the asymptotic series expansion

$$\mathbf{c}(x, t) = \mathbf{e}k^{1/2}c_0(z, t) + \mathbf{c}^{(1)}(z, t) + k^{-1/2}\mathbf{c}^{(2)}(z, t) + \cdots \qquad (35)$$

where $c_j^{(i)}(z, t) = O(1)$ for $z = L/v_{av}\,O(1)$ and $c_j^{(i)}(z, t) \to 0$ for $|z| \gg L/v_{av}$ as $k \to \infty$, with $z = k^{1/2}(t - x/v_{av})$. The coefficient $k^{1/2}$ in the first term in (35) provides that

$$\int_0^\infty \mathbf{c}(x, t)\,\mathrm{d}t \to \mathbf{e}, \quad k \to \infty.$$

We will represent $\mathbf{c}^{(i)}$ by two components, one parallel to and one orthogonal to $\mathbf{e}$

$$\mathbf{c}^{(i)}(z, t) = \mathbf{e}c_0^{(i)}(z, t) + \mathbf{d}^{(i)}(z, t), \qquad (36)$$

so that $\mathbf{e}^T \cdot \mathbf{d}^{(i)}(z, t) = 0$, and using (34) we can write

$$\mathbf{Rc}^{(i)}(z, t) = \mathbf{Rd}^{(i)}(z, t). \qquad (37)$$

Let us change variables in (30) to z and t, to get

$$k^{1/2}\left(\mathbf{I} - \frac{1}{v_{av}}\mathbf{V}\right)\frac{\partial}{\partial z}\mathbf{c}(z, t) + \frac{\partial}{\partial t}\mathbf{c}(z, t$$
$$= -\mathbf{K}_e\mathbf{c}(z, t) + k\mathbf{Rc}(z, t), \qquad (38)$$

where $\mathbf{I}$ is a unit matrix.

Now we substitute $\mathbf{c}$ in the form (35), (36) into (38) and group terms with the same power of k:

$$k : \mathbf{b}\frac{\partial}{\partial z}c_0(z, t) = \mathbf{Rd}^{(1)}(z, t), \qquad (39)$$

$$k^{1/2} : \mathbf{b}\frac{\partial}{\partial z}c_0^{(1)}(z, t) + \left(\mathbf{I} - \frac{1}{v_{av}}\mathbf{V}\right)\frac{\partial}{\partial z}\mathbf{d}^{(1)}(z, t)$$
$$+ \mathbf{e}\frac{\partial}{\partial t}c_0(z, t) = -\mathbf{K}_e\mathbf{e}c_0(z, t) + \mathbf{Rd}^{(2)}(z, t), \quad (40)$$

$$k^{\frac{2-i}{2}} : \mathbf{b}\frac{\partial}{\partial z}c_0^{(i)}(z, t) + + \left(\mathbf{I} - \frac{1}{v_{av}}\mathbf{V}\right)\frac{\partial}{\partial z}\mathbf{d}^{(1)}(z, t)$$
$$+ \mathbf{e}\frac{\partial}{\partial t}c_0^{(i-1)}(z, t) + \frac{\partial}{\partial t}\mathbf{d}^{(i-1)}(z, t)$$
$$= -\mathbf{K}_e\mathbf{e}c_0^{(i-1)}(z, t) - \mathbf{K}_e\mathbf{d}^{(i-1)}(z, t)$$
$$+ \mathbf{Rd}^{(i+1)}(z, t), \quad i \geqslant 2, \qquad (41)$$

where $\mathbf{b} = (\mathbf{I} - (1/v_{av})\mathbf{V})\mathbf{e}$ is orthogonal to $\mathbf{a}$:

$$\mathbf{a}^T \cdot \mathbf{b} = \mathbf{a}^T\mathbf{Ie} - \frac{1}{v_{av}}\mathbf{a}^T\mathbf{Ve} = A - \frac{1}{v_{av}}\sum_{i=1}^n a_i v_i = 0.$$

Equation (39) can be solved for $\mathbf{d}^{(1)}$ if $c_0(z, t)$ is a known function:

$$\mathbf{d}^{(1)}(z, t) = \mathbf{w}^{(1)}\frac{\partial}{\partial x}c_0(z, t), \qquad (42)$$

where $\mathbf{w}^{(1)}$ is the solution of the linear algebraic equations

$$\mathbf{Rw}^{(1)} = \mathbf{b}, \quad \mathbf{e}^T \cdot \mathbf{w}^{(1)} = 0. \qquad (43)$$

As we have $\mathbf{a}^T \cdot \mathbf{b} = 0$, $\mathbf{a}^T\mathbf{R} = 0$, $\text{rank}(\mathbf{R}) = n - 1$ and $\mathbf{Re} = 0$, it follows that $\mathbf{w}^{(1)}$ exists and is unique.

Having multiplied eqn (40) by $\mathbf{a}^T$ at the left, we get

$$\mathbf{h} \cdot \mathbf{w}^{(1)}\frac{\partial}{\partial z^2}c_0(z, t) + A\frac{\partial}{\partial t}c_0(z, t) = -Ak_{av}c_0(z, t), \quad (44)$$

where $\mathbf{h} = \mathbf{a}^T(\mathbf{I} - (1/v_{av})\mathbf{V})$ and we have used (42), $\mathbf{a}^T \cdot \mathbf{e} = A$, $\mathbf{a}^T\mathbf{R} = 0$ and $\mathbf{a}^T\mathbf{K}_e\mathbf{e} = Ak_{av}$, with $k_{av} = 1/A \sum_{i=1}^n a_i k_{ei}$.

Now we have an equation for $c_0(z, t)$:

$$\frac{\partial}{\partial t}c_0(z, t) = \frac{-\mathbf{h} \cdot \mathbf{w}^{(1)}}{A}\frac{\partial^2}{\partial z^2}c_0(z, t) - k_{av}c_0(z, t). \quad (45)$$

For the variables x, t that equation has the form

$$\frac{\partial}{\partial t}c_0(x, t) = -v_{av}\frac{\partial}{\partial x}c_0(x, t) + D\frac{\partial^2}{\partial x^2}c_0(x, t)$$
$$- k_{av}c_0(x, t), \quad (46)$$

where

$$D = -\frac{\mathbf{h} \cdot \mathbf{w}^{(1)}}{A}v_{av}^2 k^{-1}. \qquad (47)$$

Equation (46) is the same as eqn (4) for the dispersion model, with first order elimination kinetics and with $\rho = const$. Thus the assumption $k \gg 1$ for the inter-connected tubes model leads in zeroth-order of

approximation to the convection-dispersion model. In (47) we have an explicit expression for the dispersion coefficient in terms of the parameters of the coupled tubes.

Equations for $\mathbf{d}^{(i+1)}(z, t)$ and $c_0^{(i)}(z, t)$ can be obtained by considering components of eqn (41) for $i+1$ and i respectively, orthogonal to and parallel to $\mathbf{a}$:

$$\frac{1}{A}\,\mathbf{h}\cdot\frac{\partial}{\partial z}\,\mathbf{d}^{(i+1)}(z, t) + \frac{\partial}{\partial t}\,c_0^{(i)}(z, t) = \mathbf{a}^T\cdot\frac{\partial}{\partial t}\,\mathbf{d}^{(i-1)}(z, t)$$

$$-k_{av}c_0^{(i)}(z, t) - \frac{1}{A}\,\mathbf{a}^T\mathbf{K}_e\mathbf{d}^{(i)}(z, t), \qquad (48)$$

$$\mathbf{R}\mathbf{d}^{(i+1)}(z, t) = \mathbf{b}\,\frac{\partial}{\partial z}\,c_0^{(i)}(z, t) + \left(\mathbf{I} - \frac{\mathbf{a} \otimes \mathbf{a}^T}{\mathbf{a}^T\cdot\mathbf{a}}\right)$$

$$\times\left[\frac{\partial}{\partial t}\,\mathbf{d}^{(i-1)}(z, t) + \left(\mathbf{I} - \frac{1}{v_{av}}\,\mathbf{V}\right)\frac{\partial}{\partial z}\,\mathbf{d}^{(i)}(z, t)\right.$$

$$\left. + \mathbf{K}_e(\mathbf{e}c_0^{(i-1)}(z, t) + \mathbf{d}^{(i-1)}(z, t))\right]. \qquad (49)$$

We need to solve first eqn (49) for $\mathbf{d}^{(i+1)}(z, t)$, which is similar in structure to eqn (39) and can be treated analogously, then substitute $\mathbf{d}^{(i+1)}(z, t)$ into (48). As a result we will have a generalized convection-dispersion differential equation for $c_0^{(i)}(z, t)$.

5. Boundary Conditions

Equations (9) are first order partial differential equations. In order to solve them we need only one initial condition and one boundary condition per equation. The result of the zeroth-order approximation to eqn (9) is the second order partial differential eqn (46) and this equation requires two boundary conditions. There are three types of boundary conditions now in use for the dispersion model (Roberts & Rowland, 1986a), namely Danckwerts (or closed), mixed and open boundary conditions. They all have been derived supposing eqn (46) to be exact for the liver kinetics. Now we have the opportunity to consider the problem of boundary conditions from the view point that eqn (46) is only the zeroth-order approximation to the liver kinetics described by eqns (9).

Consider again the zeroth-order approximation solution (28) for two tubes, given by

$$c_{1,2}(x, t) = c_0(x, t) = \sqrt{\frac{v_{av}^2(\gamma + 1)^3 k}{4\pi(v_2 - v_1)^2\gamma t}}$$

$$\times \exp\left(-\frac{(x - tv_{av})^2 k(\gamma + 1)^3}{4(v_2 - v_1)^2\gamma t} - k_{av}t\right). \quad (50)$$

This is the solution of the partial differential equation

$$\frac{\partial}{\partial t}\,c_0(x, t) = -v_{av}\frac{\partial}{\partial x}\,c_0(x, t) + D\,\frac{\partial^2}{\partial x^2}\,c_0(x, t)$$

$$-k_{av}c_0(x, t) + v_{av}\delta(t)\delta(x), \quad (51)$$

for $-\infty < x < \infty$ and $t > 0$, with the boundary condition

$$c_0(x, t) \to 0, \quad x \to \pm\infty, \qquad (52)$$

initial condition

$$c_0(x, 0) = 0, \quad x \neq 0, \qquad (53)$$

and with

$$D = \frac{(v_2 - v_1)^2\gamma}{(\gamma + 1)^3 k}. \qquad (54)$$

This expression for D is in agreement with eqn (47).

Roberts et al. (1988) have recognized that the usual boundary condition eqn (52) is not appropriate for steady states arising from the steady infusion of a non-eliminated substance. They have suggested the boundary condition $c'(x) \to 0$, $x \to \infty$ for such cases, and hence a weaker condition then (52), namely

$$\frac{\partial}{\partial x}\,c_0(x, t) \to 0, \quad x \to \infty \qquad (55)$$

in the time-dependent case.

Note that (51) reduces to (46) for $x > 0$, and that (50) is only valid anyway for

$$\frac{kx}{v_{av}} \gg 1. \qquad (56)$$

These features of the two-tube case strongly suggest that for bolus input we should adopt the boundary conditions (52) and initial condition (53) with eqn (51) in the n-tube case also, and keep in mind that the solution obtained will only be valid far downstream from the boundary at $x = 0$, or more precisely, where (56) is valid.

In the case of a continuous infusion of substance at $x = 0$, at a rate $M(t)$ for $t > 0$, linearity of the modelling implies that eqn (51) should be replaced by

$$\frac{\partial}{\partial t}\,c_0(x, t) = -v_{av}\frac{\partial}{\partial x}\,c_0(x, t) + D\,\frac{\partial^2}{\partial x^2}\,c_0(x, t)$$

$$-k_{av}c_0(x, t) + M(t)\delta(x), \quad (57)$$

again with the boundary conditions (52) or (55) and initial condition (53).

6. Discussion

The major outcome of this work is the extension of a distributed-tube model to include intermixing between sinusoids. In the simplest case of identical transit times through tubes [all v_i equal in (9)], intermixing has no effect. As heterogeneity of transit times increases, the importance of intermixing becomes more evident. In physiological situations, the heterogeneity of transit times is significant and is characterized by a normalized variance of about 0.5 (Roberts *et al.*, 1988).

A second outcome is the identification of the dispersion number used in the dispersion model (Roberts *et al.*, 1988), in terms of the rate of transfer between interconnected tubes and distribution of velocities. This identification throws new light on the meaning of the "diffusion-like" coefficient used to create the dispersion model.

An important characteristic of liver models is their ability to describe the concentration-time profile after bolus injection of a non-eliminated substance (such as erythrocytes for example). The exact solution for the interconnected-tubes model in the simplest case of two tubes gives us an opportunity to compare predictions of this model with experimental data. In Fig. 3, we present the best fit of c_{av},

$$c_{av} = \frac{c_1 v_1 \gamma + c_2 v_2}{v_1 \gamma + v_2},$$

with c_1, c_2 defined in eqns (22) and (23), to experimental data (unweighted, and not corrected for catheter effects) for bolus injection of sucrose into *in*
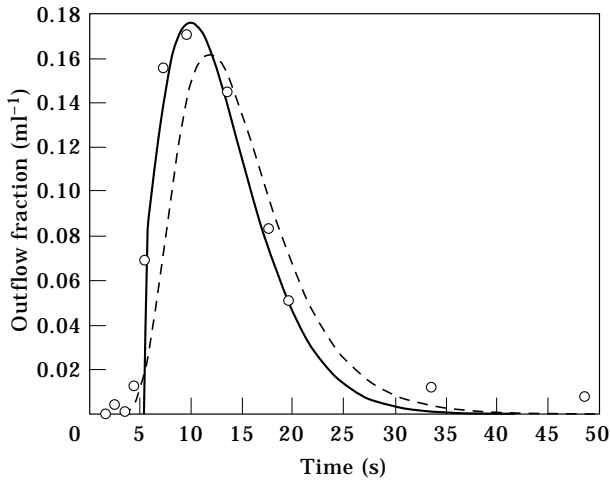

FIG. 3. The best fit of experimental data using an exact solution for two tubes (solid line) and its corresponding zeroth-order approximation (dashed line).

situ perfused rat liver (Mellick & Roberts, 1997), for various v_1, v_2, γ and k (solid line). The dashed line represents the zeroth-order approximation to c_{av}, as given by (28). It is clear that, even in its simplest non-trivial form, the interconnected-tubes model gives sensible results. We point out that the estimate of kT obtained from fitting this experimental data is 7.2. As we discussed in Section 2, $kT = \alpha N_{mix}$, so with $\alpha \approx 0.7$ we have the estimate $N_{mix} \approx 10.3$ for the average number of mixing sites along sinusoids. This result for N_{mix} does not seriously contradict the estimate of average number of mixing sites along sinusoids calculated by Bass *et al.* (1987), $N_{mix} \approx 5.8$, when we bear in mind the approximate nature of the estimation of the coefficient α in Section 2. When known values of D_N (corrected for catheter effects and appropriate weighting of data) of $0.15 - 0.4$ (Chou *et al.*, 1993; Hussein *et al.*, 1994) are used, a value for N_{mix} of $2 - 5.4$ is estimated from eqns (54) and (60). This calculation assumes $v_2 \gg v_1$ and $\gamma = 1.35$, obtained from fitting experimental data as above. This difference in predictions is not surprising as we are using here only the simplest two-tube form of the interconnected-tubes model.

A particularly interesting result of the interconnected-tubes model is its ability to predict the change of dispersion coefficient with change of hepatic blood flow. Suppose that a change of hepatic blood flow F is small enough not to change the distribution of velocities v_i in sinusoids, more exactly $v_i \propto F$ for all i. Then, for the average velocity (15) we also have $v_{av} \propto F$. From the definitions of vectors $\mathbf{h}$ and $\mathbf{b}$ in Section 4,

$$\mathbf{h} = \mathbf{a}^T \left(\mathbf{I} - \frac{1}{v_{av}} \mathbf{V} \right), \quad \mathbf{b} = \left(\mathbf{I} - \frac{1}{v_{av}} \mathbf{V} \right) \mathbf{e}, \quad (58)$$

it is clear that they are independent of flow rate, as $\mathbf{V}/v_{av} = \text{diag}(v_i/v_{av})$ does not change with F. It was shown in Section 2 that $T \max_{j \neq i} k_{ij} \propto N_{mix}$, and with N_{mix} unchanged and $T = L/v_{av} \propto 1/F$, we have for the coefficient of exchange $k_{ij} \propto F$, and thus $r_{ij} \propto F$, as we expect k to be flow-independent. Using eqn (43) we now obtain $\mathbf{w}^{(1)} \propto 1/F$, and for the dispersion coefficient, defined in eqn (47), we have $D \propto F$. Equation (46) for the dispersion model is usually used in dimensionless form:

$$\frac{\partial}{\partial \tau} c_0(X, \tau) = -\frac{\partial}{\partial X} c_0(X, \tau) + D_N \frac{\partial^2}{\partial X^2} c_0(X, \tau)$$

$$- R_N c_0(x, t), \quad (59)$$

where $X = x/L$, $\tau = t/T$, $R_N = k_{av}T$ and the dimensionless dispersion number (Roberts *et al*., 1988) is given by

$$D_N = \frac{D}{Lv_{av}}. \tag{60}$$

As we have $D \propto F$ and $v_{av} \propto F$, the dispersion number D_N is flow-independent. This result is in agreement with experimental data (Roberts *et al*., 1990; Chou *et al*., 1993; Hussein *et al*., 1994; Evans *et al*., 1993) and the theoretical result of Bass *et al*. (1987), based on a comparison of the distributed and the dispersion models. The outcome of this analysis is an explicit definition of the dispersion number in terms of micromixing through interconnections between tubes. From eqns (47), (60)

$$D_N = -\frac{\mathbf{h} \cdot \mathbf{w}^{(1)} v_{av}}{ALk}. \tag{61}$$

Hence, D_N is a function of a number of parameters including: (i) distributions of tube cross-sectional areas and velocities in $\mathbf{h}$, as in (58); (ii) distributions of velocities and interconnections in $\mathbf{w}^{(1)}$ as in (43); (iii) the average velocity in the organ v_{av}; (iv) the parameter k characterizing strength of interconnections between tubes; (v) the total cross-sectional area A of all tubes; and (vi) the length of tubes L. Accordingly, we have now expressed in explicit form the determinants for D_N which have previously been ill-defined mathematically.

The reader may note that there are some similarities in structure of our model and Taylor dispersion processes in axial flow (Taylor, 1953). Indeed, if a flow in a tube of circular cross-section is considered as flow in n concentric annular shells, then diffusion in the radial direction will produce exchange of solute between neighbouring shells. Equations for concentration in each shell will be similar to eqn (9) with $k_{ei} = 0$. However, it is important to note that in this case each shell will be connected to just two neighbouring shells with closely similar values of velocities, whereas in our model any one tube may be connected to any number of other tubes with arbitrary values of velocities.

It is hoped to test the model against experimental data more fully in the future, in particular by obtaining estimates of N_{mix} from experimental data such as that of Koo *et al*. (1975), and comparing predicted and measured dispersion numbers. It is also planned to investigate the predictions of the interconnected-tubes model for steady-state experiments.

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