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Time-dependent Elimination of Substrates Flowing Through the Liver or Kidney

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Established steady-state models of elimination of flowing substrates by Michaelis–Menten kinetics in the intact liver and kidney are extended to time-dependent situations. It is shown how time-dependent distributions of substrate concentration can be calculated using steady-state results and a knowledge of the motion of fluid through the organs. The result is simplest when time-dependence is due to changes in substrate concentrations at the inlet, for example following injection or infusion. The case of the liver is treated in greater detail, and includes an evaluation of the instantaneous overall elimination rate.

1. Introduction and Formulation

A class of models describing elimination of flowing substrates from liver sinusoids (Bass, Keiding, Winkler & Tygstrup, 1976, and references therein) and from renal tubules (Burgen, 1956, and references therein) has been successful theoretically and experimentally in dealing with steady states. In the present paper we give the theory of these models for time-dependent distributions of substrate concentration.

Although the physiological situations described by the hepatic and renal models are different, their mathematical structure is similar enough to permit a substantially common treatment. The physiological assumptions and justifications of the models given in the steady-state papers quoted above will be supplemented to cover situations varying with time at physiological rates of change specified below, with special reference to the elimination of galactose by the liver.

We summarize the common features and then the differences of the models. Consider a number of identical tubes of length L arranged in parallel and perfused with uni-directional flow. We put the axis of x co-ordinates in the direction of flow, with inlets at $x = 0$ and outlets at $x = L$. The sum of all cross-sections being A, the fluid volume in the tubes is AL. Substrate of

concentration c carried by the flow is eliminated at the walls of the tubes by Michaelis–Menten kinetics. Between two infinitesimally neighbouring cross-sections placed at x and $x+\mathrm{d}x$, substrate is therefore eliminated at the local rate of

$$c\,\mathrm{d}v_{\max}/(c+K)$$

where $\mathrm{d}v_{\max}$ and K are the local Michaelis constants ($\mathrm{d}v_{\max}$ is the maximum elimination rate, K the half-saturating substrate concentration). While $\mathrm{d}v_{\max}/\mathrm{d}x$ may vary with x, K will be kept uniform throughout each model. Because of rapid radial diffusion in the narrow tubes, the substrate concentration c near the walls is the same as throughout each cross-section:

$$c = c(x, t).$$

It is this circumstance that permits elimination to be represented in our wall-removal model as a distributed sink rather than in terms of a boundary condition. The flow $F(x)$ across each cross-section is taken to be time-independent. Since diffusion effects are not rate-determining in the models, the longitudinal flux of substrate is Fc, and the local balance of substrate is expressed by

$$-A\mathrm{d}x\,\dot{c} = \mathrm{d}v_{\max}\frac{c}{c+K} + \frac{\partial}{\partial x}(Fc)\,\mathrm{d}x: \tag{1}$$

the rate of change of substrate quantity in the volume element $A\mathrm{d}x$ is due partly to elimination and partly to the difference between the fluxes across the two bounding cross-sections.

In the *liver*, the relevant substrates (e.g. galactose, ethanol) are dissolved in blood which is confined to the tubes (sinusoids), so that the flow F is independent of x. The relevant enzymes are contained in parenchymal cells lining the walls of sinusoids, and the rate-determining step in the elimination is known to obey Michaelis–Menten kinetics. Steady elimination has been treated by Bass *et al.* (1976) for arbitrary enzyme distribution $\mathrm{d}v_{\max}/\mathrm{d}x$. Since elimination depletes the substrate, $c(x)$ falls monotonically with increasing x.

In the *kidney*, the flowing solvent is water which is re-absorbed from the tubules, so that $F(x)$ is reduced with increasing x, remaining positive. The substrate (e.g. glucose) is transported across the tubule surface by a metabolically driven carrier system capable of saturation and also described by Michaelis–Menten kinetics. Steady elimination from the tubules has been treated by Burgen (1956) for the case of uniform carrier density ($\mathrm{d}v_{\max}/\mathrm{d}x$ = const.) and linear dependence of flow on position ($F = F_0(1-x/R)$, R and F_0 are constants, $R > L$). More generally, for the kidney in the steady

state ($\dot{c} = 0$) (1) becomes

$$F\frac{dc}{dx} = -\frac{dv_{max}}{dx}\frac{c}{c+K} - c\frac{dF}{dx}, \qquad \frac{dF}{dx} < 0:$$

thus dc/dx may have either sign throughout the tubule, or it may vanish within the tubule so that the concentration profile may go through a minimum. This is because, depending on the detailed form of $F(x)$, solvent reabsorption may concentrate the substrate faster than the carrier system depletes it, at some or all values of $c(x)$ occurring in the tubule.

The models of both organs give rise to the/ following mathematical problem. Abbreviating

$$dv_{max}/dx = \rho, \quad V_{max} = \int_0^L \rho\, dx,$$

and rearranging (1), we wish to find $c(x, t)$ satisfying the equation

$$A\dot{c} + F\frac{\partial c}{\partial x} = -\rho\frac{c}{c+K} - c\frac{dF}{dx} \tag{2}$$

in the spatial interval $0 \leqq x \leqq L$, for given positive functions $\rho(x)$, $F(x)$ of position. A visual representation of the problem is furnished by the *characteristics* of (2), which are the family of curves $x(t)$ given by

$$A\,dx/dt = F(x). \tag{3}$$

The characteristics describe the motion of any fluid element with the velocity F/A, and are sketched in Fig. 1; they are straight in the liver and curved in the kidney. The mean transit time of a fluid element is

$$T = A\int_0^L dx/F(x). \tag{4}$$

For example, T is AL/F for the liver, and $-(AR/F_0)\ln(1-L/R)$ for Burgen's linear $F(x)$ defined above. The substrate concentrations should be envisaged as plotted vertically above Fig. 1. At any one time t_0 the substrate in the model consists of contributions originating from the inflow at earlier times between $t_0 - T$ and t_0, arriving at appropriate spatial positions between $x = 0$ and $x = L$ at time t_0 along characteristics such as those arrowed in Fig. 1(a), and affected on the way by the influences described in the right-hand side of (2).

We shall consider two kinds of boundary conditions.

(a) At the inlet $x = 0$, the concentration $c(0, t)$ is given at all times t. The variable input concentration is the only cause of time-dependence; all characteristics are the same shape [Fig. 1(a)]. This is the case most common in hepatic physiology, with changes in input caused by injection or infusions combined with elimination, by the liver itself, from the volume of distribution of substrate in the body.

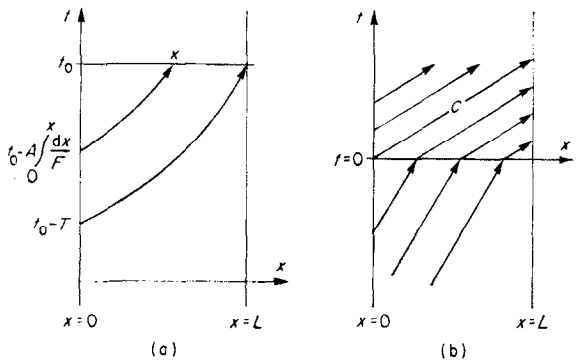

FIG. 1. The domain of elimination, and the characteristics of the elimination equation. Inlet at $x = 0$, outlet at $x = L$, time along the ordinate. (a) The undisturbed kidney. (b) Steady compression of the liver relaxed at $t = 0$.

(b) The more general case is obtained when concentrations at the inlet, $c(0, t)$, are given for $t > 0$, and the spatial distribution $c(x, 0)$ is given at $t = 0$; the problem is to be solved for all positive t. This case includes (a) if $c(x, 0)$ is itself merely the result of variable input concentrations at earlier times. However, (b) includes also the description of results of changes in properties such as $F(x)$ and $\rho(x)$, which become time-independent from $t = 0$ onwards. The effect of a step-change in F in the case of the liver is sketched in Fig. 1(b). In that case $c(x, 0)$ may be obtained by calculation with conditions of the type (a), but it serves as an initial condition of the type (b) for calculating the distribution at $t > 0$.

The representation in terms of characteristics illustrates why it will be easier to obtain the description $c(x, t)$ of substrate concentrations, than to evaluate the overall instantaneous elimination rate $V(t)$

$$V(t) = \int_0^L \rho c \, dx/(c+K), \tag{5}$$

even for boundary conditions of type (a). The whole (x, t) domain (Fig. 1) on which $c(x, t)$ is sought, is covered by characteristics which originate from the inlet $x = 0$ and along each of which the c-values may be found by an observer moving with the fluid. By contrast, the integration (5) at any one time involves simultaneously fluid elements which had passed the inlet at different times, moving along different characteristics.

In the simpler case of the liver we use special methods leading to explicit results, including the evaluation of $V(t)$ by a convenient series; this is done in Section 2, for boundary condition (a), with mathematical details given in Appendix A. A fully worked out example with further discussion is given in

Section 3. A more general treatment of both liver and kidney is given in Appendix B, with results permitting the calculation of time-dependent substrate concentrations from corresponding steady concentration profiles for boundary conditions of both types (a) and (b).

In order to assess the range of applicability of the present calculations, we characterize the degree of time-dependence roughly, in orders of magnitude, by the absolute value of the characteristic time $c_i/\dot{c}_i$ (the suffix denotes concentration at the inlet) needed for an appreciable fractional change in input concentration.

(i) If $c_i/\dot{c}_i$ is long as compared with the transit time T given by (4) then a succession of steady states, depending parametrically on time through c_i alone, gives a sufficiently accurate quasi-steady description (Bass *et al.*, 1976). In the liver, T is about 20 seconds, so that the quasi-steady description fails whenever $c_i/\dot{c}_i$ is not longer than a few minutes.

(ii) The present wall-removal model assumes that transport of substrate across the membranes of parenchymal cells is not a rate-determining step in the elimination. This remains true in time-dependence whenever $c_i/\dot{c}_i$ is long as compared with the membrane equilibration time for the substrate. We show in Appendix C that the latter time in the liver is less than one second for galactose at moderate concentrations (below 4 mmol/l).

In the representative example of galactose in the liver, therefore, (i) and (ii) together confine the range of applicability of the present work to inputs with $c_i/\dot{c}_i$ between the orders of seconds and minutes; such inputs occur in physiological and clinical investigations.

Radioactive tracer work (Goresky, Bach & Nadeau, 1973) shows that transit times of fluid elements passing through the liver have an appreciable dispersion from the mean value (4). The present work may be viewed either as an approximate treatment of the entire liver (neglecting this dispersion), or as a more exact treatment of groups of sinusoids which have transit times close to each other. Whenever the distribution of transit times is given empirically, the latter interpretation readily permits the computation of time-dependent relations between observables for the entire liver, by means of a convolution-type integral involving the observed distribution of transit times. (We replace c_i with an *effective* time-dependent input concentration, constructed from the given time-dependent input as a weighted sum of those c_i's which contribute to the c_0 observed at any one time.)

2. Concentration Distributions in Liver Sinusoids

Since the flow F is constant in liver sinusoids, the last term on the right-hand side of (2) vanishes. Dividing the remaining terms through by the factor

$c/(c+K)$, (2) becomes

$$A(1+K/c)\dot{c}+F(1+K/c)\frac{\partial c}{\partial x}=-\rho. \tag{2a}$$

Writing $(1+K/c)\,\mathrm{d}c = \mathrm{d}u$, it becomes apparent that the new dependent variable u,

$$u = c+K\ln c, \tag{6}$$

yields the linear equation

$$A\dot{u}+F\frac{\partial u}{\partial x}=-\rho(x). \tag{7}$$

The general solution of (7) is the sum of the general solution of (7) with the right-hand side set to zero, and of any particular solution of (7). Writing $T = AL/F$ for the transit time, it is easy to check that the general solution of (7) with the right-hand side set to zero is any function f of the argument $t-Tx/L$. For the particular solution we choose the time-independent function

$$-\frac{1}{F}\int_0^x \rho\,\mathrm{d}x$$

which obviously satisfies (7). Thus the general solution of (7) is

$$u(x,t)=f(t-Tx/L)-\frac{1}{F}\int_0^x \rho\,\mathrm{d}x, \tag{8}$$

with an arbitrary (differentiable) function f. We now satisfy the boundary condition (a): let $c(0, t)$ be assigned at all times. Because of our choice of the lower integration limit on the particular solution, we have, from (8), $u(0, t) = f(t)$ which determines the functional form of f. Reverting to the argument $t-Tx/L$ and to the original variable c, we obtain the solution of the liver problem in the form

$$c(x,t)+K\ln c(x,t)=c(0,t-Tx/L)+K\ln c(0,t-Tx/L)-\frac{1}{F}\int_0^x \rho\,\mathrm{d}x. \tag{9}$$

Thus the quantity $c+K\ln c$ at any place and time is obtained from the corresponding quantity at the inlet (reached along the appropriate characteristic by going back by the time-interval Tx/L) by subtracting $1/F$ times the elimination capacity of enzyme placed between the inlet and the position under consideration. In particular, if the enzyme density ρ is constant, we subtract $V_{max}x/FL$. When the quantity $c+K\ln c$ is thus obtained, c is

obtained from it by standard numerical or graphical methods. The solution (9) is to be compared with that of the steady-state equation, obtained from (2a) by setting $\dot{c} = 0$:

$$c(x)+K\ln c(x) = c(0)+K\ln c(0) - \frac{1}{F}\int_0^x \rho\, dx. \tag{9a}$$

Substrate concentrations are observable only at the inlet and the outlet of sinusoids, so that the experimentally useful aspect of (9) is obtained by setting $x = L$. Using also the customary notation $c_i(t) = c(0, t)$ and $c_0(t) = c(L, t)$ (initials of "inlet" and "outlet" as subscripts), we obtain

$$c_0(t)+K\ln c_0(t) = c_i(t-T)+K\ln c_i(t-T)-V_{max}/F, \tag{10}$$

which represents an important result under conditions (a): the relation between instantaneous inflow and outflow concentrations of substrate is the same as if these concentrations were steady, provided that the inflow concentration is taken by the time T earlier than the outflow concentration. (Compare with (9a) at $x = L$, setting $c(0) = c_i$, $c(L) = c_0$.)

In Appendix B we extend this result for any choice of $F(x)$ in equation (2), using the transit time (4). These results are transparent: once a fluid element has passed the inlet, the amount of substrate it carries is changed independently of events in fluid elements that entered earlier or later.

Even simpler is the description of the time-change of $u = c+K\ln c$, since the last term of (9) vanishes on taking a time derivative: $\dot{u}(x, t) = \dot{u}_i(t-Tx/L)$ or, in full,

$$\dot{c}(x, t)(1+K/c(x, t)) = [\dot{c}_i(1+K/c_i)]_{t-Tx/L}, \tag{11}$$

where the suffix on the square bracket denotes the time at which all quantities in the bracket are to be taken. In particular, at the outlet we obtain $\dot{u}_0(t) = \dot{u}_i(t-T)$, which permits a clinical determination *in situ* of the constant K from observations made after a single injection of suitable substrate (Bass *et al.*, 1976).

The results (10) and (11) hold for any distribution of enzyme along the flow; we may therefore include with the liver, blood vessels containing no enzyme. When c_i and c_0 are obtained from blood samples taken some distances upstream and downstream of the liver, the transit time T refers to transit between the sampling instruments, and may be appreciably longer than the mean transit time through the liver.

As the next step we evaluate the instantaneous elimination rate, which is also the rate of creation of the product of the enzymatic conversion of the substrate In order to outline the method without inessential complications,

we now specialize the enzyme distribution along the sinusoids to a uniform one:

$$dv_{max}/dx = \rho = V_{max}/L. \tag{12}$$

Together with the uniformity of F in the liver model, (12) reduces (2) to the form

$$A\dot{c} + F\frac{\partial c}{\partial x} = -\frac{V_{max}}{L}\frac{c}{c+K}. \tag{13}$$

We give a simplified approximate treatment of the instantaneous elimination rate, reserving a fuller treatment for Appendix A We deviate from quasi-steadiness by retaining the $\dot{c}$-term in (13), but we estimate it from the quasi-steady approximation by replacing the argument $t-Tx/L$ with t on the right-hand side of (11):

$$\dot{c} = \frac{c}{c+K}\dot{c}_i(1+K/c_i).$$

Substituting in (13) and rearranging we obtain

$$F\frac{\partial c}{\partial x} = -\frac{1}{L}[V_{max} + AL\dot{c}_i(1+K/c_i)]\frac{c}{c+K}. \tag{14}$$

The square-bracket is x-independent in the present approximation, so that (14) may be viewed as a form of the quasi-steady theory with V_{max} replaced by an apparent (time-varying) V^*_{max},

$$V^*_{max} = V_{max} + FT\dot{c}_i(1+K/c_i), \tag{15}$$

using also $AL = FT$, valid for the liver. When $\dot{c}_i$ is positive (c_i rising), the apparent steady V^*_{max} overestimates V_{max} because a quasi-steady treatment attributes to elimination the lowering of c which is in reality due to c_i having been lower at relevant earlier times (Fig. 1). The discussion of negative $\dot{c}_i$ is similar.

Integration of (14) from inlet to outlet yields, after some rearrangement and the use of definition (5) of $V(t)$, simplified by (12):

$$V = \frac{F(c_i - c_0)}{1+(FT/V_{max})\dot{c}_i(1+K/c_i)-\ldots}, \tag{16}$$

where all quantities refer to time t, and the dots indicate correction terms obtained in Appendix A.

The instantaneous rate (16) differs from its quasi-steady approximation implicitly in the numerator and explicitly in the denominator. In the numerator, c_0 is taken simultaneously with c_i, while the $c_0(t)$ curve is shifted, as compared with the quasi-steady approximation, towards later time by the transit time T. The denominator shows the effect of the history of the input,

between $t-T$ and t, upon elimination at t (Fig. 1). When $\dot{c}_i$ is positive (negative), each sinusoid contains fluid elements carrying earlier lower (higher) inputs, whereby the instantaneous rate at t is reduced (increased) by an amount depending also on the degree of saturation. A more complete description of the history of c_i involves higher time derivatives, which appear in the more accurate result (26) in Appendix A. The overall balance of these time-dependent effects will be elucidated in the next section.

3. Specific Example

We illustrate our general results by an example in the liver. For conciseness we introduce the dimensionless quantities

$$\left.\begin{aligned} &z = V/V_{\max}, \quad a = c_i/K, \quad y = c_0/K, \quad \tau = t/T, \\ &\alpha = V_{\max}/FK, \quad w_i = a + \ln a. \end{aligned}\right\} \tag{17}$$

Dots will now denote differentiation with respect to τ. Note that w_i differs from u_i/K only by the constant term $\ln K$. We choose the input a (Fig. 2) such that

$$w_i = 10 - \tau^2/5, \tag{18}$$

so that the highest non-vanishing derivative is $\ddot{w}_i = -2/5$: the series in the denominator of (16), obtained from (26) in Appendix A, breaks off after three terms. We choose also $\alpha = 5$, and we approximate $\bar{x}/L$ by its maximum value $\frac{1}{2}$ (Appendix A). This completes the specification of the example.

The dimensionless counterpart of (10) is

$$a(\tau) - y(\tau+1) + \ln \frac{a(\tau)}{y(\tau+1)} = \alpha \tag{19}$$

which defines y and its quasi-steady counterpart y_s simultaneous with a (solid and broken lines, respectively, in Fig. 2). In practice it is easiest to calculate y_s from $y_s + \ln y_s = w_i - \alpha$, and then obtain y by shifting y_s by one unit towards later time. Solving such transcendental equations is inescapable (but not difficult) both in the time-dependent and steady-state theory. Next, the dimensionless form of (26) of Appendix A is, for the present example,

$$z = \frac{a-y}{\alpha + \dot{w}_i - \frac{1}{2}\ddot{w}_i} = \frac{a-y}{5 - 2\tau/5 + 1/5} \tag{20}$$

with its quasi-steady counterpart $z_s = (a - y_s)/\alpha$ (solid and broken lines, respectively, in Fig. 2).

While a, y_s and z_s share the symmetry of w_i with respect to $\tau = 0$, y is shifted without change of shape by one unit from y_s toward later time. As

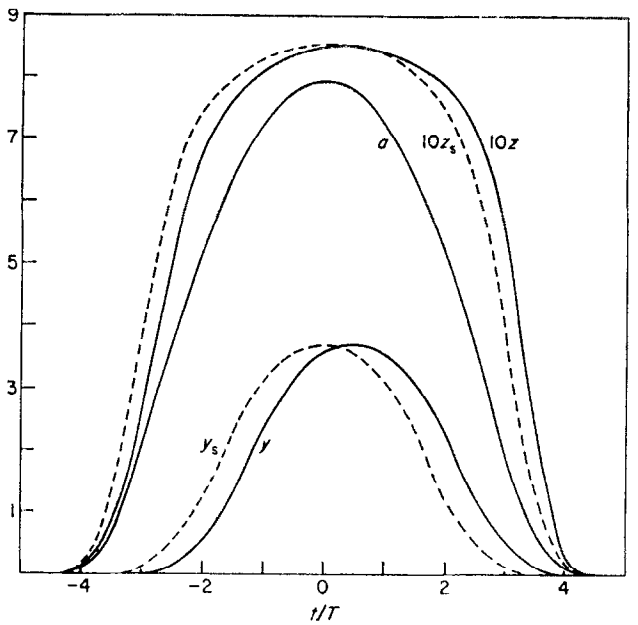

FIG. 2. Example of elimination by the liver with $V_{max}/FK = 5$. Input concentration $a = c_i/K$, output concentration $y = c_0/K$, instantaneous elimination rate $10z = 10V/V_{max}$, all as functions of time t/T. Broken lines give corresponding quasi-steady approximations y_s and $10z_s$. The common scale of the ordinate refers to all five independent variables (all dimensionless and suitably scaled).

a result, $a-y$ is larger than $a-y_s$ for $\tau < 0$, and smaller for $\tau > 1$. Nevertheless, z is smaller than z_s for $\tau < 0$ and larger than z_s for $\tau > 1$ as a result of the deviations from the steady-state theory appearing in the denominator of (20). The overall result is the shift of z towards later times as compared with z_s, but by less than one unit, and not without distortion, of which a salient feature is the lowering of the peak value of z as compared with z_s These features of the present example have wider validity, as we now show by a simplified argument

When the element of fluid containing the peak input is carried along a sinusoid, the fluid elements immediately before and after it carry lower inputs. The instantaneous elimination rate of the whole sinusoid is therefore lower than it would be if the peak input was maintained for at least the full transit time. For this reason the peak elimination rate in a transient is overestimated by the quasi-steady approximation. This consideration depends on second time-derivatives of concentrations, but small first derivatives suffice to elucidate the overall relation of z and z_s, as we show next.

In order to compare z and z_s by means of (20), we develop

$$y(\tau) = y_s(\tau-1) \approx y_s(\tau) - \dot{y}_s(\tau).$$

Moreover, from $\dot{u}_0(t) = \dot{u}_i(t-T)$ of Section 2 we have, in the quasi-steady approximation, $\dot{y}_s(1+1/y_s) = \dot{w}_i$; using also $\alpha z_s = a - y_s$, we obtain from (20)

$$z - z_s = \frac{\alpha z_s + \dot{w}_i y_s/(1+y_s)}{\alpha + \dot{w}_i} - z_s \approx \frac{\dot{w}_i}{\alpha}\left(\frac{y_s}{1+y_s} - z_s\right), \tag{21}$$

where, in the last expression, we have retained only first powers of the derivatives. Now, the last bracket is never positive because (returning to the original variables)

$$c_0/(c_0+K) \leqq V_s/V_{max},$$

that is: a sinusoid filled throughout with the concentration actually occurring at the outlet would have an elimination rate smaller than (or, at saturation, equal to) the actual quasi-steady rate V_s. Thus $z - z_s$ and $\dot{w}_i$ (and hence $\dot{a}$) have opposite signs, as is illustrated by the example of Fig. 2.

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APPENDIX A

The Instantaneous Elimination Rate

We wish to calculate the instantaneous rate (5), simplified by the uniform enzyme distribution (12),

$$V(t) = \frac{V_{max}}{L}\int_0^L \frac{c}{c+K}\,dx \tag{5a}$$

in which $c(x, t)$ satisfies (13), with $c(0, t) = c_i(t)$ being given at all times. From (11) we obtain

$$\dot{c} = \frac{c}{c+K}\left[\dot{c}_i\left(1+\frac{K}{c_i}\right)\right]_{t-Tx/L} \tag{11a}$$

where the subscript on a bracket indicates the time at which all quantities

in the bracket are to be taken. Substituting (11a) for $\dot{c}$ in (13) and rearranging slightly, we find

$$-F\frac{\partial c}{\partial x}=\frac{c}{c+K}\left\{V_{\max}/L+A\left[\dot{c}_i\left(1+\frac{K}{c_i}\right)\right]_{t-Tx/L}\right\}. \tag{22}$$

As the next step we refer all quantities in (22) to the time t. For this purpose we expand the square bracket in (22) in a series about the time t, reverting to the abbreviation $\dot{u}_i$:

$$\left[\dot{c}_i\left(1+\frac{K}{c_i}\right)\right]_{t-Tx/L}=[\dot{u}_i]_{t-Tx/L}=\dot{u}_i(t)-\ddot{u}_i(t)Tx/L+\tfrac{1}{2}\dddot{u}_i(t)(Tx/L)^2\ldots \tag{23}$$

where the higher derivatives are obtained explicitly by differentiating $\dot{u}_i$ with respect to time, thus:

$$\ddot{u}_i=\ddot{c}_i\left(1+\frac{K}{c_i}\right)-\left(\frac{K}{c_i^2}\right)\dot{c}_i^2, \text{ etc.}$$

Next, in preparation for integrating (22) term by term with respect to position, we define convenient mean values of position on the sinusoids:

$$\overline{x^n}\int_0^L\frac{c}{c+K}\,dx=\int_0^L x^n\frac{c}{c+K}\,dx \tag{24}$$

for $n=1$, $n=2,\ldots$. If needed for accuracy of evaluating $V(t)$, these mean values can be computed numerically from (9). However, for estimates of effects of time-dependence the essential feature of (24) is that $\overline{x^n}$ is less than L^n for all n. More precisely, $\overline{x^n}$ is largest for the rectilinear concentration profiles occurring when $c_0\gg K$, which yield readily $\overline{x^n}=L^n/(n+1)$, so that

$$\overline{x^n}/L^n\leqq 1/(n+1). \tag{25}$$

We now substitute expansion (23) in (22), integrate through from 0 to L and make use of (24) and of the definition (5a) of $V(t)$:

$$F(c_i-c_0)=V\left\{1+\frac{AL}{V_{\max}}\left[\dot{u}_i-\ddot{u}_iT(\bar{x}/L)+\tfrac{1}{2}\dddot{u}_iT^2(\overline{x^2}/L^2)-\ldots\right]\right\}, \tag{26}$$

with all variable terms now referring to time t. Dividing through by the curly bracket and returning to the original variable c, we obtain the final expression for $V(t)$. In Section 2 we write $AL=FT$ and discuss the result (26) in the form (16), in which higher derivatives of u_i are indicated by dots following the leading term. The magnitude of these correction terms may be readily estimated from any given $c_i(t)$, using the inequalities (25).

APPENDIX B

Joint Treatment of Liver and Kidney Models

We return to the problem of distributions of substrate concentrations in the general class of liver and kidney models with any prescribed $F(x)$ and $\rho(x)$ in (2). Supposing that steady-state concentration distributions are known, we deduce effects of time-dependence for boundary conditions of both types (a) and (b).

We note in passing that the more general transformation corresponding to (6), with a conveniently chosen lower integration limit b,

$$u = \int_b^c \frac{\mathrm{d}c}{\rho c/(c+K) - c\,\mathrm{d}F/\mathrm{d}x} \tag{6a}$$

linearizes the full equation (2) when the integrand in (6a) does not depend explicitly on x, that is, when F is linear in x and ρ is independent of x (Burgen's original kidney model, 1956). In view of the general results obtained below, we shall not pursue this special approach.

Recalling the discussion of fluid elements moving along the characteristics (end of Introduction), we replace time by a new independent variable which is a constant along each characteristic: the independent variables are transformed† to ξ, η,

$$\xi = x, \quad \eta = t - A\int_0^x \mathrm{d}x/F. \tag{27}$$

Transforming (2) (most easily by equating the total differentials of $c(x, t)$ and $c(\xi, \eta)$, using the differentiated form of (27) and comparing coefficients of $\mathrm{d}t$ and $\mathrm{d}x$) we find

$$F(\xi)\frac{\partial c}{\partial \xi} = -\rho(\xi)\frac{c}{c+K} - c\frac{\mathrm{d}F}{\mathrm{d}\xi}, \tag{28}$$

which is the equation for the steady-state concentration distribution. Let the solution of (28) be written in the form

$$E(c, \xi) = G, \tag{29}$$

with G independent of ξ. For example, in the case of the liver we have (Section 2)

$$E(c, \xi) = c + K\ln c + \frac{1}{F}\int_0^\xi \rho\,\mathrm{d}\xi = G,$$

where G may be determined at the inlet. Now, (28) is a partial differential equation, the general solution of which involves an arbitrary function:

† If A is inserted under the integral sign in (27), results similar to those described in this paper can be derived in the case when both F and A in (2) depend on x. We are indebted to Mr C. J. Burden for this observation.

G in (29) is independent of ξ but it is an arbitrary function of η. In the original variables (29) becomes

$$E(c, x) = G\left(t - A\int_0^x \mathrm{d}x/F\right). \tag{30}$$

Next, we choose G so as to satisfy the initial condition (a), that is, $c(0, t) = c_i(t)$:

$$E[c_i(t), 0] = G(t)$$

determining the functional form of G. Altogether,

$$E(c, x) = E\left[c_i\left(t - A\int_0^x \mathrm{d}x/F\right), 0\right] \tag{31}$$

is the implicit solution of the problem including the initial condition (a). In particular, at the outlet $x = L$, $c = c_0(t)$,

$$E[c_0(t), L] = E[c_i(t-T), 0]. \tag{32}$$

In the steady state, G in (29) is constant in space and time, so that $E(c_0, L) = E(c_i, 0)$. The meaning of (32) is, therefore, that c_0 is related to c_i at any time as if they were both steady, provided that c_i is taken by the transit time T earlier than c_0. This generalization of the result given for the liver at the end of Section 2 permits the determination of outflow concentrations from steady-state theory and from the history of the inflow concentrations. The method of proof based on transformation (27) was chosen for readers unacquainted with relevant theorems on quasi-linear equations of the first order (Sneddon, 1957), which may be used instead.

For boundary conditions (b), we are given $c(0, t)$ for $t > 0$, and $c(x, 0) = f(x)$ for $0 \leq x \leq L$; the solution is sought for positive time only. We note first that the domain (x, t) of interest is divided into two parts by the characteristic C starting from the point $x = 0$, $t = 0$ [Fig. 1(b)], viz. the regions

$$t \gtrless A\int_0^x \mathrm{d}x/F. \tag{33}$$

The solution in the upper part (upper inequality sign) is given by (31), since the initial distribution $f(x)$ cannot influence the domain beyond the characteristic C ($f(x)$ is swept out by the flow). It remains to determine the solution in the lower part (lower inequality sign) of the domain. This is done by inserting the conditions (b) in the general solution (30),

$$E(f(x), x) = G\left(-A\int_0^x \mathrm{d}x/F\right) \tag{34}$$

which determines the functional form of G for any given $F(x)$.

We clarify the rather abstract result (34) on a useful example concerning the liver with $\rho = V_{max}/L$. Suppose that at $t = 0$ the flow F through the liver has attained a new constant value (for example, by the relaxation of a steady compression of the liver). As shown in Fig. 1(b), the characteristics break at $t = 0$, with $c(x, 0) = f(x)$ calculable by (31) using the flow value before $t = 0$. Because of the lower inequality (33), it is convenient to replace the arbitrary function G in (30) by the closely related arbitrary function H, inserting at the same time the special features of the liver:

$$c + K\ln c + V_{max}x/(FL) = H(x - Ft/A) \tag{35}$$

which is to hold in the domain $x > Ft/A > 0$. Inserting the condition at $t = 0$ in (35) we obtain

$$f(x) + K\ln f(x) + V_{max}x/(FL) = H(x)$$

determining the form of H. Returning to the general argument $x - Ft/A$ we thus obtain the desired solution (after some cancellations):

$$c + K\ln c = f(x - Ft/A) + K\ln f(x - Ft/A) - V_{max}t/(LA) \tag{36}$$

which joins on to (31) along the characteristic C. In particular, at the outlet we insert $x = L$ in (36), remembering that the result is relevant only in the time-interval $0 \leq t \leq AL/F$. The solution does not contain c_i explicitly because of the event at $t = 0$ (earlier c_i's are implicit in $f(x)$).

APPENDIX C

Hepatocyte Equilibration Time

In order to estimate the characteristic time of galactose equilibration between sinusoidal blood and adjoining cells containing enzyme, we assume facilitated equilibrative membrane transport with overall Michaelis constants V^*_{max}, K^* for the liver as a whole. Assuming that carriers are distributed uniformly along the sinusoids, and considering only the rapid effects of membrane transport for a region bounded by cross-sections at x, $x + dx$ (Section 1), we have

$$A\frac{dc}{dt} = \frac{V^*_{max}}{L}\left(\frac{c'}{c' + K^*} - \frac{c}{c + K^*}\right) = -A'\frac{dc'}{dt}, \tag{37}$$

where c' and c are local substrate concentrations in the cells and in the blood, respectively; A' is the sum of cross-sections of all relevant cells while A is, as previously, the sum of cross-sections of all sinusoids.

Rearranging (37) and forming the difference of the concentrations we obtain

$$T^* \frac{\mathrm{d}}{\mathrm{d}t}(c'-c) = -(c'-c),$$

where T^* is a time given by

$$T^* = \frac{AA'}{A+A'}(c+K^*)(c'+K^*)\frac{L}{K^*V^*_{\max}}. \tag{38}$$

Using results of Goresky *et al.* (1973) we estimate, for a typical liver, $K^* \sim 4$ mmol/l, $V^*_{\max} \sim 80$ mmol/min, both having some 40 times the values of K and of $V_{\max}$ of the galactose phosphorylation system in the liver (0·1 mmol/l and 2 mmol/min, respectively). For c and c' below K^*, the time T^* varies slowly with concentration and at lower concentrations tends to the constant equilibration time ($1/T^*$ tends to the exponential constant of equilibration):

$$T^* = ALK^*/V^*_{\max}(1+A/A'). \tag{39}$$

The approximation (39) gives an estimate of the equilibration time for concentrations up to 4 mmol/l (from zero to about 40 K), within which all elimination regimes of galactose are represented (Bass *et al.*, 1976).

Assuming further $A \sim A'$ suggested by liver anatomy, and taking $AL \sim 0{\cdot}2$ l for the blood volume of the liver, we obtain

$$T^* \approx ALK^*/2V^*_{\max} \approx 0{\cdot}3 \text{ sec}. \tag{40}$$

With a safety margin for somewhat higher values of c, c' sometimes used in practice, and for the roughness of the anatomical estimate, we arrive at T^* of less than 1 sec.