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MODELS OF HEPATIC DRUG ELIMINATION*

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I. INTRODUCTION

The liver is the primary organ for metabolism of a variety of compounds, including many drugs and xenobiotics. Within the liver, a number of different physiological processes combine to give the observed differences in drug elimination. Net changes in the concentration of these compounds are a consequence of a series of steps:

1. The net flow of blood (perfusing medium) in the vascular network of the organ
2. Uptake of the substrate from the vasculature into the liver cells
3. Enzyme-mediated reactions within the cells
4. Release of metabolic products and unconverted substrate from the cells into the sinusoids
5. Binding to proteins in the blood and liver

An understanding of each of these processes is necessary to fully comprehend the overall process of drug elimination, and these processes must be accounted for, either individually or by grouping and approximation, if a model for drug elimination is to be developed. The major purpose of the model, therefore, is to mathematically describe the dominant physiological processes that are occurring. By focusing on hepatic physiology and physical processes, a model can provide some insight into the nature and function of the liver, and may suggest new types of experiments which can lead to a greater understanding of hepatic elimination. To date, several models for hepatic elimination have been proposed, and to properly evaluate these models, the fundamental assumptions inherent in each model must be examined. Ideally, a model of hepatic elimination should meet the following criteria:

1. The model should accurately represent the physiological processes that regulate hepatic metabolism.
2. The model should be broadly applicable to a variety of drugs and metabolites.

3. The model should contain a minimum number of adjustable parameters, to reduce data requirements and facilitate the use of the model in a predictive fashion.

This review describes the advantages and limitations of existing liver models, and discusses their potential applications. The ability of each model to describe the physiological processes that occur within the liver is examined, and each model is critically assessed according to its mathematical complexity and ease of use, and its breadth of application. To assess the physiological accuracy of each model, some understanding of liver physiology is required, and, therefore, before introducing the various liver models, a brief description of the physiological processes influencing hepatic metabolism is presented.

A. Liver Physiology and Function

The liver is located in the bloodstream between the gastrointestinal tract and spleen and the vena cava leading to the heart. Blood enters the organ through both the portal vein and the hepatic artery, traverses the sinusoids that link the inlet and exit flows, and leaves the liver via the hepatic vein (Fig. 1). The portal vein, hepatic vein, and hepatic artery are all subject to branching; individual branches serve each lobe of the liver [1].

Orally administered substances are absorbed in the gastrointestinal tract, and enter the liver through the portal vein. Drugs administered intravenously circulate through the body, and enter the liver through both the hepatic artery and portal vein. Seventy-five percent of the blood supplied to

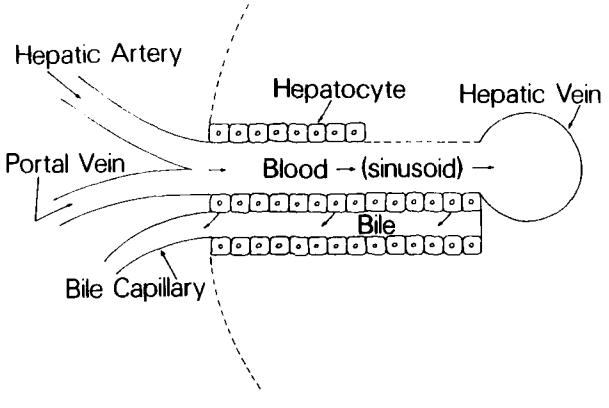


FIG. 1. Schematic diagram of liver structure.

the liver is via the portal vein; 80% of the oxygen is supplied through the hepatic artery [2]. Animals can, however, survive without a blood supply from the hepatic artery, provided the venous blood is oxygenated, and the portal flow exceeds the threshold level of 1.5 mL/(min·g liver) required to prevent collapse of parts of the vascular network [2]. In the normal liver, respiratory action influences total blood flow in the organ. External pressure from the diaphragm affects outflow from the hepatic vein; outflow is stopped during inhalation, and is maximal at the peak of expiration, when the diaphragm is at its highest position. Hence, in live animals, total blood flow is cyclical, subject to periods of full flow and periods when the flow is well below the minimum perfusion rate of 1.5 mL/(min·g liver). This cycle is repeated many times each minute [2].

The vascular network of the organ is comprised of three regions:

1. Inlet vessels, including the portal vein and hepatic artery, which are subject to a high degree of branching
2. The hepatic (or central) vein
3. A bed of sinusoids which serve to link the portal tracts and the hepatic vein

The microvasculature of the liver contains three types of sinusoids: direct, branching, and interconnecting sinusoids. Direct sinusoids form a short circuit between the portal and hepatic veins. Branching sinusoids take a long, circuitous route between the inlet and exit flows, and interconnecting sinusoids link parallel adjacent branching sinusoids like the rungs on a ladder. Koo et al. [3], using electron microscopy, established that direct sinusoids comprised 27% of a typical section of the rat liver; interconnecting and branching sinusoids made up 14% and 59% of the sinusoidal bed, respectively. A diagram of a polymer cast of the vascular bed of the organ (Fig. 2) indicates that the liver is a continuous meshwork of highly interconnected blood spaces. The sinusoidal channels are of varying length, and are oriented in a nearly random fashion. It is very unlikely, therefore, that a volume of blood will pass directly from liver inlet to outlet, or follow a simple, predictable path.

Numerous studies on fluid flow in the sinusoids have been conducted. Brauer [2] emphasized the overall plasticity of the organ, suggesting that each volume of blood may follow any one of several possible alternate pathways; the flow path followed depends only upon the local pressure gradients that prevail at that moment. In addition, reversal of flow within a sinusoid has been observed using *in vivo* microscopy [2]. The concept of flow reversal was supported by Rappaport [4], who suggested that intermittent opening and closing of the arterioles is common, and is not restricted

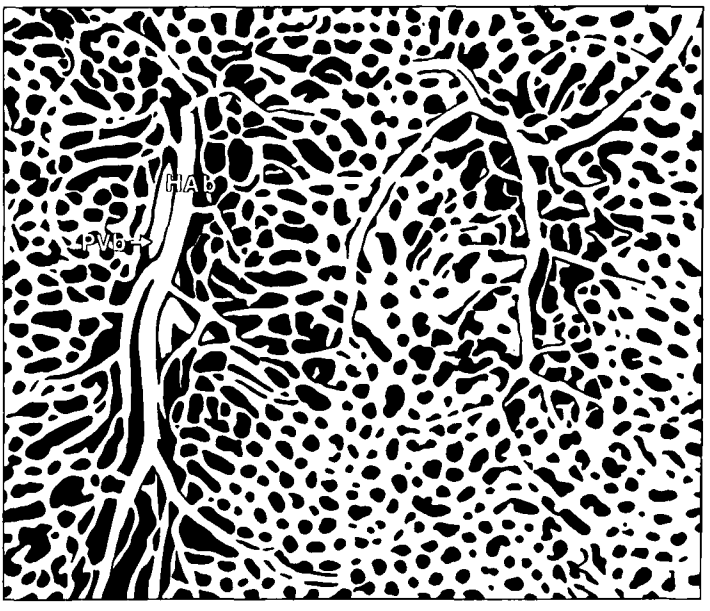


FIG. 2. Representation of the network of blood vessels and sinusoids in the liver (tissue shown in black). PVb is the portal vein; HAb is the hepatic artery. Based upon a micrograph of a polymer cast by Motta et al. [46].

to the short, interconnecting sinusoids. Further evidence was provided by Lubbers [5], who indicated that flow in adjacent sinusoids could be countercurrent. Additional studies with vascular tracers showed transient backflow into adjacent sinusoids [2]. Thus, the characteristic blood flow distribution in the liver changes from moment to moment.

Unquestionably, mixing can occur at various sites within the liver. At each node corresponding to the divergence and convergence of a number of sinusoids, mixing occurs. Furthermore, backmixing within the organ occurs due to flow reversal in the sinusoids. The overall picture of the organ suggests extensive mixing, and the time-dependent distribution of blood flow in the organ suggests that different streams will be mixing at different times. In addition, the time-dependent flow that occurs due to respiration indicates that a true mathematical description of the physiology of hepatic blood flow would be extremely complex. Rather, it is apparent that a time and spatially averaged model may be appropriate to describe blood flow in the vasculature of the liver.

The liver contains four types of cells, including parenchymal cells (or hepatocytes), endothelial cells, Kupffer cells, and fat-storing cells. Kupffer

cells are fixed macrophages located in the sinusoidal lumen at points where sinusoids intersect. The endothelial cells, which line the sinusoids of the liver, contain fenestrae of various sizes. The fenestrae permit dissolved substances to enter the coadjacent endothelial space of Disse, before entering the parenchymal cells of the liver. A monolayer of these hepatocytes is present for each sinusoid (as shown in Fig. 1). A small number of fat-storing cells are situated within the space of Disse. Some vascular materials, such as red blood cells, are so large as to prevent their penetration through the fenestrae into the space of Disse. Certain compounds, including sodium, sucrose, and albumin, are deemed extravascular compounds. These substances have access to the space of Disse, but cannot permeate into the adjoining hepatocytes. Other materials, such as water, potassium, and glucose, have full access to the vascular, extravascular, and cellular regions of the liver. Electron microscopic data indicated that the gaps in the endothelial lining of the sinusoids were rather large, leading Brauer [2] to conclude that the concentration of materials in the space of Disse was very close to the composition of the blood in the sinusoids. Hence, provided a compound is small enough to gain access to the space of Disse, it may be appropriate to approximate the vascular and interstitial space of the liver as a single unit (as shown in Fig. 1).

Investigation of the processes influencing hepatic metabolism usually involves the use of tracers. Vascular and extravascular markers may be infused to estimate residence times in the vascular and interstitial spaces of the liver, and provide information on the relative volumes of each region. Administration of a cellular reference allows estimation of the cellular volume, and permits investigation of the transport processes between the cells and the vasculature. Several researchers [2, 6, 7] have conducted experiments with vascular and extravascular tracers, and have established that the mean residence time of a vascular tracer in the vasculature is approximately 5 to 10 sec, depending upon the size of the organ. An extravascular marker requires an additional 2 to 4 sec to be dispersed through the space of Disse. It has also been determined that the volume of the vascular and interstitial region of the liver is approximately 15% of the total liver volume. The liver cells, which contain the enzymes, occupy about 85% of the liver volume. The bile ducts, which occupy less than 1% or 2% of the liver volume [2], are often lumped with the hepatocytes in heterogeneous models, because the total biliary volume is less than the error in the estimates of the cellular volume of the liver.

Hepatic metabolism is highly dependent upon the physical properties of the substrate relative to the physical characteristics and intrinsic activity of the liver. For example, some compounds are subject to rapid, stereoselective facilitate uptake, yet others may be excluded from specific regions of the liver due to their size or other physical characteristics. Consequently, in

an effort to investigate the vast range of phenomena which affect hepatic metabolism, several classes of compounds have been used as probes of intrahepatic mixing, interphase transport, and elimination. These include:

1. Electrolytes and low molecular weight hydrophilic compounds, such as sodium, potassium, sucrose, and water
2. Hydrophilic compounds subject to facilitated uptake (e.g., galactose, glucose)
3. Lipophilic compounds, which includes many drugs and other xenobiotics of pharmaceutical and toxicological interest

Several models have been developed to account for the hepatic elimination of compounds from these classes. However, many of the models invoke some drug-specific assumptions, and therefore are applicable to only one or two substrates. Nevertheless, by combining the best features of these models, it may be possible to develop a general, "ideal" model that may be used for all classes of compounds. However, it should also be recognized that a model of hepatic metabolism will be used primarily for lipophilic drugs and xenobiotics, and it may be necessary to target the model to this class of compounds.

B. Features of an Ideal Liver Model

It is now possible to consider the implications of liver physiology upon the three features desired in a model of hepatic metabolism. To reiterate:

1. The model should accurately represent the physiological processes that regulate hepatic metabolism. Hence, the ideal model should account for the heterogeneous nature of the organ, with a vascular space for fluid flow, and a stationary cellular space. It should also account for the three different regions of the vascular network, and the three forms of sinusoids in the sinusoidal bed. Furthermore, it should describe the time-dependent flow of blood in the organ, including flow reversals and backmixing, local pressure gradients, and the intermittent operation of some of the sinusoids.
2. The model should be broadly applicable to a variety of substrates and metabolites. Generally, models that incorporate a better description of the physiological processes are applicable to a wider range of compounds.
3. The model should contain a minimum of parameters, to reduce data requirements and facilitate the use of the model in a predictive fashion.

Unfortunately, it is virtually impossible to have all three desirable features in a single model. To have complete physiological accuracy, the model must be mathematically complex with a large number of parameters. Such models are difficult to use in a predictive fashion, and require vast amounts

of data to determine their accuracy. If, in contrast, mathematical simplicity is desired, it is often necessary to make some approximations of the physiology and hepatic blood flow. This usually reduces the amount of data required to verify the model, and makes the model easier to use for predicting drug and metabolite levels. However, such a model may only be applicable for a limited number of drugs and their metabolites. Nevertheless, if justifiable and correct approximations are made, it should be possible to develop a model that is both mathematically simple and broadly applicable.

II. EXISTING MODELS OF HEPATIC ELIMINATION

Existing models of hepatic metabolism may be classified according to the approximations made with respect to liver physiology and the degree of mixing within the organ. The simplest models are nonparametric, having no adjustable parameters to account for intrahepatic mixing and interphase transport. The second class of models are homogenous mixing models. These models attempt to describe the extent of intrahepatic mixing, but do not explicitly account for mass transfer between the cells and the vasculature. The third and fourth categories of models both explicitly account for heterogeneous mass transport, differing only in their description of intrahepatic mixing. The third group includes mixing models that assume little or no mixing on a microscopic level; in contrast, the fourth group of models assume complete mixing on a microscopic level, and therefore use homogeneous compartments to describe intrahepatic mixing.

A. Nonparametric Models

The most commonly used and most extensively investigated models of hepatic elimination are the well-stirred (or venous equilibrium) model and the parallel tube model. Both models ignore the heterogeneous nature of the liver, assuming that compounds are equally and instantaneously distributed between the vascular and cellular regions of the liver. The well-mixed model is based upon the assumption of no concentration gradients within the organ, and therefore, the liver may be treated as a homogeneous continuous stirred tank reactor. The mathematical expression for the well-mixed model and rate of reaction R_j is presented in Eq. (1). The solution of the model in steady state with linear kinetics is presented in terms of the effluent concentration (C) in Eq. (2), and in terms of the extraction ratio (ER) in Eq. (3).

$$\frac{dC}{dt} = \frac{Q \cdot (C_{in} - C)}{V_L} - R_j \tag{1}$$

$$C = \frac{Q \cdot C_{in}}{(Q + f_{ub} \cdot k_R \cdot V_L)} \tag{2}$$

$$ER = \frac{f_{ub} \cdot k_R \cdot V_L}{(Q + f_{ub} \cdot k_R \cdot V_L)} \tag{3}$$

where Q is the volumetric flow rate through the organ, V_L is the total liver volume, k_R is the rate constant for linear reaction, C is the effluent concentration, C_{in} is the concentration at the inlet of the liver, and f_{ub} is the fraction of unbound drug in the blood. The product $k_R \cdot V_L$ is equivalent to the intrinsic clearance, Cl_{int}.

The parallel tube model represents the opposite extreme in mixing behavior, assuming an exponential concentration gradient in a single, unbranched hepatic "tube." It is based upon the assumptions that the liver is homogeneous and that flow is unidirectional. The model equation follows the form for a plug flow reactor [Eq. (4)]. The solution for the steady state effluent concentration with linear kinetics is presented in Eq. (5), and the steady state extraction ratio may be determined from Eq. (6).

$$\frac{dC}{dV_L} = -\frac{R_j}{Q} \tag{4}$$

$$C = C_{in} \cdot \exp(-f_{ub} \cdot k_R \cdot V_L/Q) \tag{5}$$

$$ER = 1 - \exp(-f_{ub} \cdot k_R \cdot V_L/Q) \tag{6}$$

Clearly, the model equations and flow assumptions differ greatly between the well-stirred and parallel tube models. However, the models are functionally equivalent if the extraction ratio is low (<0.5), since both models can be described mathematically by the same Taylor-series expansion [8]. At higher extraction ratios, however, significant differences between the two models can be observed. The effect of perfusion rate (Q) upon effluent concentration is markedly different for the two models: The parallel tube model predicts that the effluent concentration should be exponentially dependent upon Q [Eq. (5)], whereas the well-mixed model predicts that effluent concentrations should be relatively insensitive to Q [Eq. (2)]. Hence, the effect of changes in perfusion rate upon conversion may be used to differentiate between the models. Another technique for discriminating between the two models is to compare the sensitivity of the effluent concentration to changes in the unbound fraction, f_{ub}. As shown in Eq. (5), the parallel tube model

TABLE 1

Applications of Nonparametric Models

Drug or compound	Parameter varied	Best fit model	Ref.
Diazepam	f_{ub}	Parallel tube	[9, 10]
S-Disopyramide	f_{ub}	Inconclusive	[11]
Ethanol	Q	Parallel tube	[12]
Galactose	C_{in}	Parallel tube	[13–15]
Lidocaine	Q	Well-mixed	[16, 17]
Mepiridine	Q	Well-mixed	[17]
Phenytoin	f_{ub}	Inconclusive	[10]
Propranolol	f_{ub}	Well-mixed	[18–20]
Propranolol	Q	Parallel tube	[21]

predicts an exponential relationship between f_{ub} and the effluent concentration. The well-mixed model, however, suggests that the effect of f_{ub} on C should range between a zero-order and first-order relationship, depending upon the relative magnitudes of Q and $f_{ub} \cdot k_R \cdot V_L$ [Eq. (2)]. Therefore, several researchers have used changes in protein binding in an effort to discriminate between the two models.

A summary of the results of several investigations aimed at model discrimination is presented in Table 1. Nonparametric models have also been successfully used for a number of compounds on the basis of their ability to predict steady state extraction ratios at different inlet drug concentrations (C_{in}). The results of several of these studies are also listed in Table 1.

A key advantage of the well-mixed model is that it is mathematically simple and easily applied to the prediction of drug and metabolite levels. However, it cannot describe the metabolism of materials which are limited by transport into the hepatocytes. The parallel tube model is more complex mathematically, requiring the solution of a partial differential equation if unsteady state metabolism is studied. However, the mathematical expressions are much simpler for steady state elimination [e.g., Eq. (5)]. The parallel tube model has been successfully applied to describe the metabolism of galactose, ethanol, diazepam, and propranolol. However, Pang and Rowland [16] demonstrated that the weak dependence of lidocaine metabolism upon flow rate was best described by the well-mixed model (Fig. 3).

Although the nonparametric models have been successfully used for a number of compounds, there are no clear reasons why one model or the other fits a particular drug; no *a priori* predictions are possible. In addition, the behavior of some drugs can be described by either model. For example,

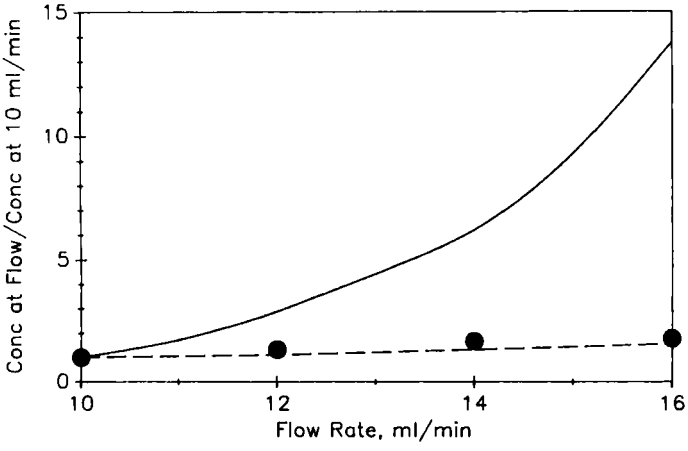


FIG. 3. Effect of volumetric flow rate upon lidocaine elimination. • experimental data; ——— plug flow model; ------ well-mixed model. Data from Pang and Rowland [16]. The vertical axis is the ratio of the effluent concentration at a given flow rate to the effluent concentration obtained with a flow rate of 10 mL/min.

the well-mixed model describes the steady state concentrations of propranolol when protein binding is altered [18–20], yet other researchers concluded that the parallel tube model was best for describing the effect of flow upon propranolol conversion [21]. Studies of *S*-disopyramide did not permit discrimination between the two models, since some data sets were best described by the well-mixed model, yet other data sets were best described by the parallel tube model [11]. Similarly, the effect of protein binding upon the steady-state elimination of phenytoin could be adequately described by either model [10]. Bass et al. [13] proposed the use of the parallel tube model to describe the steady-state metabolism of galactose; however, the well-mixed model with Michaelis–Menten kinetics [Eq. (1)] may also be used to describe their data (Fig. 4), using a Michaelis constant of 0.10 m*M* and a maximum reaction velocity of 0.397 m*M*/min. Clearly, either model is suitable for *correlating* the data, but different values of the kinetic parameters (V_{max} and K_m) may be required for each model.

In reality, V_{max} and K_m should be model independent and if different estimates of V_{max} and K_m are obtained from the two nonparametric models, it suggests that the assumptions inherent in each model are affecting these estimates. Unquestionably, all estimates of V_{max} and K_m should be based upon the local concentration of the compound, i.e. the concentration adjacent to the active site of the enzyme. These local concentrations are influenced by interphase mass transfer, protein binding, and the degree and

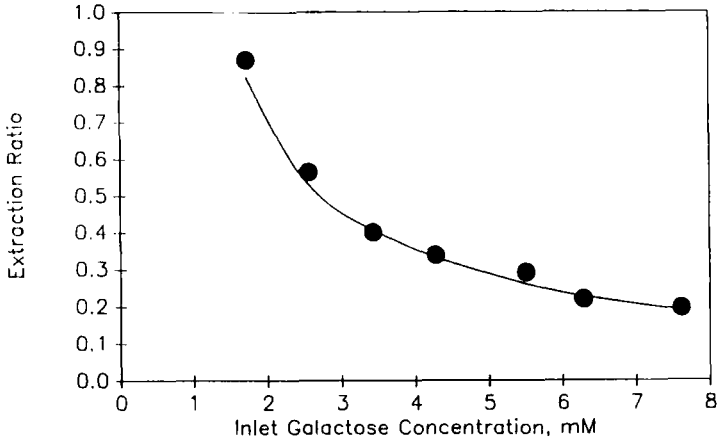


FIG. 4. Fit of the venous-equilibrium model to galactose elimination. Data from Bass et al. [13], originally from Tygstrup and Winkler [47]. The data have been fit using Eq. (1), with R_j as a Michaelis–Menten expression; V_{max} = 0.397 m*M*/min and K_m = 0.10 m*M*.

complexity of intrahepatic mixing. The ability of a model to accurately account for these processes affects the quality of its estimates of V_{max} and K_m. Both the well-mixed and parallel tube models neglect interphase mass transfer, and therefore, the effect of mass transfer on the local concentration is ignored, and mass transfer effects are lumped into the estimates of V_{max} and K_m. Furthermore, the two models predict radically different concentration profiles across the liver, due to their implicit assumptions about mixing within the sinusoids. The different assumptions about intrahepatic mixing, therefore, lead to markedly different predictions of the local concentration, which influence estimates of V_{max} and K_m. Hence, predictions of V_{max} and K_m from the parallel tube and well-mixed models may represent not only the intrinsic kinetics of the elimination process, but may also reflect relative rates of interphase mass transfer, protein binding, and the degree of vascular mixing assumed within the model.

B. Homogeneous Mixing Models

Both the well-stirred and the parallel tube models are extreme descriptions of the mixing phenomena occurring within the liver. The physiology of the liver, however, suggests that the actual extent of mixing in the organ could fall between these extremes. Recognizing this, various researchers

have proposed mixing models in an effort to accurately describe the mixing phenomena that occur within the liver. One such model is the distributed model, presented by Bass et al. [22] to describe galactose elimination. The model describes the liver as an array of parallel sinusoids of varying length, with plug flow in each sinusoid. To account for the physiological characteristics of the liver, the distributed model assumes a Gaussian distribution of the number and lengths of the sinusoids, giving profiles similar to a residence-time distribution (RTD) function. This model, therefore, may be classified as an RTD model, and the form of the model is equivalent to the segregated flow model described in the chemical engineering literature [23, 24]. Within the model, there is no provision for interconnection between the sinusoids; rather, it is assumed that all mixing occurs at the outlet of the liver. This assumption of segregated flow is incompatible with the physiology of the liver (see Fig. 2), which suggests significant mixing on a microscopic level. Nevertheless, the assumption may be used provided that the compound studied does not react or is subject to linear elimination, because zero-order and first-order processes are dependent only upon the length of time that the molecules spend within the organ, and are unaffected by interactions at the microscopic level and the pathway travelled by the molecules through the organ [23–25]. However, for nonlinear, saturable elimination, which is typical of enzyme kinetics, this may be a poor assumption, because the local concentration, which influences the rate of reaction, is dependent upon both the residence time distribution and the pathway followed by each fluid element [25]. Unquestionably, the potential effect of this assumption is greatest when the substrate concentration (S) and K_m are comparable in magnitude. When $K_m << S$ or $K_m >> S$, however, the kinetics are either zero-order or first-order, and the segregated flow assumption is unimportant.

To completely assess the effect of the segregated flow assumption upon estimates of the kinetic parameters, the time scales of the various physical processes must be considered. A few cases may be discussed:

1. Rapid mixing, slow transport: In this case, a compound will be rapidly distributed throughout the vasculature, yet slowly transported into or out of the cells. The changes in the local vascular concentration that occur due to the time-dependent distribution of blood flow within the liver, therefore, will be sufficiently rapid relative to the rate of transport that interphase mass transport will effectively be based upon an average or pseudo-steady-state concentration of the drug within the sinusoids. Consequently, the concentration within the cellular region will be controlled by the rate of mass transfer, and the rate of drug elimination will be essentially unaffected by vascular mixing. Thus, if the time scale for mixing is very short relative

to the time scales for other physiological processes, the effect of the segregated flow assumption is negligible.

2. Transport and elimination are flow limited: When the time scale for vascular mixing is greater than the time scales for interphase mass transfer and elimination, changes in the local vascular concentration that occur due to the time-dependent intrahepatic distribution of blood will influence the rate of reaction. If the rate of transport is slower than the rate of elimination, then cellular uptake will tend to dampen the effect of any mixing phenomena. If, however, the rate of reaction is slower than the rate of mass transfer, then the maximum effect of mixing upon elimination will be observed.

3. Nonlinear facilitated uptake: Facilitated mass transfer is a nonlinear, saturable process, and its time scale is usually less than or comparable to the time scale for vascular mixing. Hence, the rate of uptake may be influenced by any changes in the local vascular concentration that result from time-dependent flow through the vasculature.

It should be noted that, although the pathway or environment experienced by reactant molecules during their passage through the liver may be important, the importance of local mixing processes diminishes for fluids of low viscosity or if interactions with flowing cells and proteins in the medium are negligible. The viscosity of blood is low, and therefore, an assumption of maximum mixing on a microscopic scale is reasonable. Such an assumption permits simplification of mixing processes within the organ, and suggests that the use of compartmental mixing models developed from residence time distribution data may be used. Furthermore, slow mass transfer processes tend to dampen any time-dependent mixing phenomena, and may permit a macroscopic (i.e., compartmental) approach to vascular mixing.

Two single-parameter homogeneous models of hepatic mixing have been proposed: the axial dispersion model [8, 26–29], and the series compartment model [30]. Both are based upon well-established models for chemical reactors. The axial dispersion model assumes that the liver is a packed bed in which different degrees of axial mixing can occur. In theory, a full range of mixing phenomena can be simulated, simply by adjusting the mixing parameter, ϑ_L. The dispersion model, however, suffers from some drawbacks, the greatest of which is its mathematical complexity, which necessitates the solution of a partial differential equation with two boundary conditions [Eq. (7)] for all but the simplest of cases.

$$\vartheta_L \frac{\delta^2 C}{\delta x^2} - u \frac{\delta C}{\delta x} - k_R C = \frac{\delta C}{\delta t} \tag{7}$$

where x is the axial distance (from zero to length L), and u is the flow velocity.

The boundary conditions for the axial dispersion model are based upon the characteristics of the system at the locations where the tracer is injected and collected. In the context of hepatic metabolism, the blood vessels entering and leaving the liver serve as the locations where the tracer is injected and collected, respectively. At these points, the reactor is described as either "closed" or "open," depending upon whether or not plug flow into or out of the test section (i.e., the liver) is assumed. A closed boundary condition is one in which plug flow is assumed within the blood vessels outside of the liver. In contrast, an open boundary condition, by using the same dispersion parameter to describe mixing within the liver and the adjacent blood vessels, assumes that the same degree of mixing will be observed in both the liver and within the blood vessels leading to and from the organ. Since different boundary conditions may be used at the inlet and outlet of the organ, four possible sets of boundary conditions may be defined. These are: completely open, completely closed, open–closed, and closed–open. Different solutions are obtained for each combination of boundary conditions, and differences between the solutions are greatest if significant mixing (or dispersion) is occurring. The initial and boundary conditions following a step increase in tracer concentration in a completely open system are [23]:

$$C(x,0) = 0 \qquad \text{for } x > 0$$

$$C(x,0) = C_{\text{step}} \qquad \text{for } x < 0$$

$$C(x,t) = 0 \qquad \text{for } x = + \text{ infinity}$$

$$C(x,t) = C_{\text{step}} \qquad \text{for } x = - \text{ infinity}$$

The initial and boundary conditions for a completely closed system are:

$$C(x,0) = 0 \qquad \text{for } 0 < x < L$$

$$C(x,\text{infin}) = C_{\text{step}} \qquad \text{for } 0 < x < L$$

$$C(0,t) = 0$$

$$C(L,t) = 0$$

Combinations of the closed–closed and open–open boundary conditions define the boundary conditions for the open–closed and closed–open systems. There has been considerable debate to determine which boundary conditions are correct, and furthermore, the boundary conditions are often

difficult to meet in practice. The completely open boundary conditions give an incorrect prediction of tracer behavior; that is, the tracer can appear upstream of the point of injection. Only by using the open boundary conditions, however, can a simple analytical solution to Eq. (5) be obtained. Roberts and Rowland [8, 26] suggested that the completely closed boundary conditions be used to describe tracer behavior in the liver.

For completely open boundary conditions, analytical solutions to the axial dispersion model are available to describe the time-dependent profiles of noneliminated tracers [Eqs. (8) and (8)]. Equations (10)–(12) describe the time-dependent concentration profile if closed boundary conditions are assumed:

1. Open boundary conditions, no reaction, step increase in inlet concentration [24]:

$$C(t) = C_0 + 0.5\, C_{step} \cdot \left(1 - \text{erf}\left\{0.5(uL/\vartheta_L)^{0.5}\left[\frac{1 - ut/L}{(ut/L)^{0.5}}\right]\right\}\right) \tag{8}$$

where C_0 is the initial concentration, and erf(ξ) is the Gauss error function with argument ξ.

2. Open boundary conditions, no reaction, pulse input of tracer [25]:

$$C(t) = \frac{M_0 \cdot L}{2V_L(\pi\vartheta_L t)^{0.5}} \exp\left[-\frac{(L - ut)^2}{4\vartheta_L\, t}\right] \tag{9}$$

3. Closed boundary conditions, no reaction, pulse input of tracer [25]:

$$C(t) = \frac{M_0 \cdot Q}{V_L 2} \exp(\beta) \cdot \sum_{i=1}^{\infty} \frac{(-1)^{i+1} 8\gamma_i^2}{4\gamma_i^2 + 8\beta + 4\beta^2} \cdot \left[-\frac{ut/L\,(\beta^2 + \gamma_i^2)}{2\beta}\right] \tag{10}$$

where

$$\beta = uL/2\vartheta_L \tag{11}$$

and γ_i the positive roots of:

$$\tan(\gamma_i) = \frac{2\beta\gamma_i}{\gamma_i \cdot \beta^2} \tag{12}$$

Analytical solutions for steady-state concentrations of linearly eliminated compounds are also available. The general form of the equation is pre-

sented in Eq. (13); Eqs. (14) and (15) represent the steady-state concentrations if closed boundary conditions are used [25]:

$$\vartheta_L \frac{\delta^2 C}{\delta x^2} - u\frac{\delta C}{\delta x} - k_R C = 0 \tag{13}$$

$$\frac{C}{C_{in}} = \frac{4\,\alpha\, e^{\beta}}{(1+\alpha)^2\, e^{\alpha\beta} - (1-\alpha)^2\, e^{\alpha\beta}} \tag{14}$$

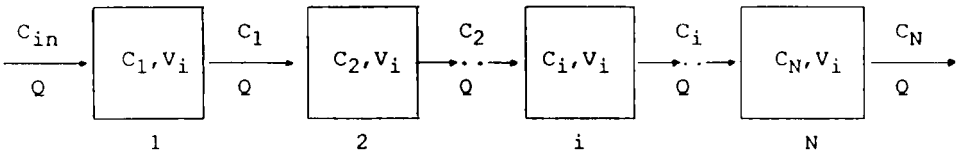
where

$$\alpha = (1 + 2k_R L/\beta u)^{0.5} \tag{15}$$

and β is determined using Eq. (11).

For all other cases, including steady-state concentrations of compounds governed by nonlinear kinetics, time-dependent linear elimination, or metabolite kinetics, analytical solutions of the general partial differential equation [Eq. (7)] are not available. Rather, numerical techniques must be used to solve the equation.

Estimation of the dispersion parameter (ϑ_L/uL) is only theoretically valid for elongated systems, where the ratio of length of the vascular bed to its diameter is significantly greater than 1 [23, 25]. In addition, the model only has a sound theoretical basis if the dispersion parameter is less than 0.15 [23]. Roberts and Rowland [8], however, suggested that a dispersion parameter of 0.2 would accurately describe the mixing of erythrocytes within the liver. Other simulations suggested that, for erythrocytes, a dispersion parameter of approximately 0.12 was appropriate [26]. Since erythrocytes are confined to the vascular space, this value provides a minimum estimate of hepatic mixing. Larger values of the dispersion parameter must be obtained for all other species. Further studies with additional compounds suggested that the dispersion parameter should range between 0.2 and 0.5 [27]. Hence, for the flow and mixing conditions observed in the liver, the model does not have a sound theoretical basis, but rather, provides only an empirical method for analyzing drug elimination by the liver. Nevertheless, as an empirical model, it has been successfully used to describe the steady-state linear elimination of several compounds, including chromium phosphate colloid [27], diazepam [27], phenacetin [28, 29], and acetominophen [28]. The model also proved superior to the well-mixed and parallel tube models for predicting the steady-state concentrations of several highly extracted ($E > 0.9$), linearly eliminated drugs, including pethidine, propranolol, alprenolol, and lidocaine [29]. The model was also successfully used to simulate the time-dependent profiles of erythrocytes from an indicator-



$$V_i = V_L/N$$

FIG. 5. Series compartment model [30].

dilution study [26]. In these simulations, the data could be correlated using either the closed [Eqs. (10–12)] or open boundary conditions [Eq. (9)], provided different dispersion parameters were used.

The series compartment model (Fig. 5), known as the tanks-in-series model in the chemical engineering literature, is a simple empirical model which is capable of describing a continuum of behavior between the extremes in mixing described by the parallel tube and well-mixed models. Its simplicity has made it the preferred model for describing complex flow and reaction [23]. The model considers the liver as a sequence of well-mixed compartments connected in series. The number of compartments, N, is not indicative of liver physiology; rather, it is an arbitrary parameter used to correlate the extent of mixing in the organ. When N is equal to 1, well-mixed behavior is observed, and when N is approximately 30, the plug flow behavior predicted by the parallel tube model is obtained. The model equations are comprised of a series of ordinary differential equations with known initial conditions [Eqs. (16) and (17)]. For compartment i:

$$\frac{dC_i}{dt} = \frac{Q \cdot (C_{i-1} - C_i)}{V_i} - k_R C_i \tag{16}$$

where V_i is the volume of compartment i, equal to V_L/N; and C_i is the concentration in compartment i.

For a first-order reaction at steady state, C_{out}, the effluent concentration from compartment N may be determined using Eq. (17):

$$C_{out} = C_N = C_{in} \cdot (1 + k_R V_i/Q)^{-N} \tag{17}$$

A feature of the model is its ability to empirically describe efflux curves arising from indicator-dilution experiments. Solution of Eq. (16) for a pulse in tracer concentration at the inlet of the liver gives an expression similar to the statistical Γ-distribution:

$$C(t) = \frac{\text{Dose} \cdot N^N \cdot t^{N-1}}{Q \cdot \tau^N \cdot \Gamma(N)} \exp\left[-Nt/\tau - Cl_{int} \cdot t/(Q\tau)\right] \quad (18)$$

where τ is the mean residence time, and Cl_{int} is the intrinsic clearance.

Davenport [31] presented a version of the model for profiles obtained from indicator-dilution experiments with nonreacting tracers, and Gillette [32] proposed the use of a number of sequential compartments for describing steady-state drug elimination. Additional support of the model was provided by Weisiger et al. [33], who used a series of compartments to account for intrahepatic concentration gradients observed during uptake of thyroxine by the perfused rat liver. Gray and Tam [30] found that the series compartment model was superior to the well-mixed and parallel tube models for describing the steady-state elimination of lidocaine, sulfobromophthalein, and chromium phosphate colloid. They also demonstrated that the series compartment model could accurately correlate the time-dependent profiles of red blood cells, sucrose, and galactose obtained from indicator-dilution experiments.

The primary limitation of the series compartment model is that it does not explicitly include physiological phenomena such as variable transit times through sinusoids, substrate binding to liver tissues and proteins, or the effect of transport processes between the vascular and cellular regions of the liver. Rather, the model includes these phenomena in the mixing parameter, N. If these specific processes are to be investigated, a more complex model of the liver is necessary.

C. Heterogeneous Models

A major deficiency of the homogeneous models is their inability to adequately account for transport processes between the vascular and cellular regions of the liver. Although the homogeneous models work well for selected substrates under specific conditions (e.g., lidocaine at steady state), they may be incapable of modelling the concentrations of species when metabolism is limited by interphase mass transport or by binding to proteins, or if physiological and metabolic conditions are significantly altered.

To properly investigate transport processes in the liver, a heterogeneous model of the organ is required. Heterogeneous models are typically more complex than their homogeneous counterparts, and experiments must be carefully designed to obtain accurate estimates of the transport parameters in the model. Several models for heterogeneous metabolism have been developed, with varying degrees of complexity.

1. Tubular and Distributed Models

The classical heterogeneous model of transport in organs is Krogh's cylinder [34]. This model, originally formulated for the transport of oxygen from capillaries into muscle tissue, assumes the organ is a cylindrical capillary (or tube) with a single concentric tissue compartment surrounding the capillary; plug flow was assumed within the capillary. Using this model, diffusive transport of oxygen into the tissue could be simulated based on measurements of the oxygen tension at various distances from the center of the capillary. Bassingthwaighte et al. [35] developed a model which is equivalent to a combination of Krogh's cylinder with the axial dispersion model described by Roberts and Rowland [8]. In this model, described by Eqs. (19) through (24), the liver was assumed to be a single, straight capillary surrounded by a concentric tissue compartment. Within the tissue, both axial and radial diffusion could be accounted for. The original model proposed by Bassingthwaighte et al. [35] allowed for diffusion in plasma. However, Bass et al. [13] indicated that the rate of convective influx was nearly 50 times greater than the rate of diffusive influx. Hence, a simplified model in the form of a partial differential equation is presented, similar to the model of Bassingthwaighte et al., but modified such that plasma diffusion was not included. The general equation to describe the concentration in a capillary is:

$$\frac{\delta C}{\delta t} = -u\frac{\delta C}{\delta x} - 2\pi r_c P\,(C - C_{t,s}) \tag{19}$$

where x is the axial distance, r_c is the radius of the capillary, P is the tissue permeability, C is the concentration in the capillary, and $C_{t,s}$ is the concentration at the interface between the tissue and capillary.

Equation (20), which incorporates coefficients for axial and radial diffusion (D_{TX} and D_{TR}) may be used to estimate C_t, the concentration in the tissue:

$$\frac{\delta C_t}{\delta t} = D_{TX}\frac{\delta^2 C_t}{\delta x^2} + \frac{D_{TR}}{r}\frac{\delta}{\delta r}\left(r\frac{\delta C_t}{\delta r}\right) \tag{20}$$

The following boundary conditions apply:

$$\text{At } r = r_c, \qquad C_t = C_{t,s} \tag{21}$$

$$\text{At } r = R, \qquad \frac{\delta C_t}{\delta r} = 0 \tag{22}$$

$$\left.\frac{\delta C_t}{\delta x}\right|_{x=0} = 0 \tag{23}$$

$$\left.\frac{\delta C_t}{\delta x}\right|_{x=L} = 0 \tag{24}$$

where L is the length of the capillary, and R is the radius of the capillary and tissue compartment.

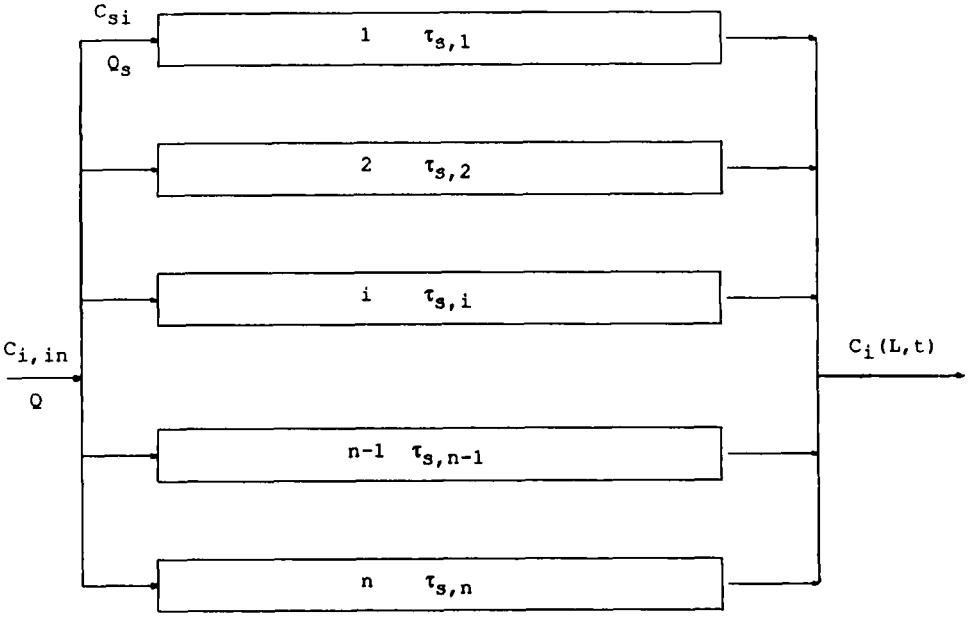
The model allows for axial and radial diffusion of materials in tissue but neglects physiological effects such as bypassing, variable blood flow velocities in an array of sinusoids, and local changes in flow. The model has no provision for chemical reaction, and is based upon net rates of diffusion. To estimate local capillary and tissue concentrations, the equations must be numerically integrated. Unless accurate tissue concentrations are known, estimation of the tissue diffusion coefficients (D_{TR}, D_{TX}) may be difficult. The model may be useful for estimating precise tissue levels of noneliminated tracers if diffusion coefficients are already known. For general application, the model must be modified to account for reaction and different rates of transport into and out of the tissue.

Goresky and co-workers [6, 36–39] developed a heterogeneous model (Fig. 6) for multiple indicator dilution studies, and applied it to various compounds. The model combined a residence time distribution for the vascular space with transport between the vascular space, the space of Disse, and the hepatocytes. Goresky determined the mixing characteristics within the organ from a pulse injection of a tracer confined to the vascular space; concomitant injection of extravascular and cellular markers permitted estimation of the volume of the space of Disse and the cellular volume. A discussion of the model equations is presented next.

Applying the principle of conservation of mass to single sinusoid gives the following expression:

$$\frac{\delta C_{si}}{\delta t} + W_s \frac{\delta C_{si}}{\delta x} + \gamma \frac{\delta C_{vi}}{\delta t} + \theta \frac{\delta C_{ci}}{\delta t} + \frac{k_3}{K_{cr}} \cdot \theta \cdot C_{ci} = 0 \tag{25}$$

where x is the axial distance along the sinusoid, C_{si} is the concentration in sinusoid i, C_{vi} is the concentration in the interstitial space surrounding sinusoid i, C_{ci} is the concentration in the cellular space surrounding sinusoid i, W_s is the flow velocity in the sinusoid, γ is the ratio of the interstitial volume to the vascular volume, θ is the ratio of the cellular volume to the vascular volume, k_3 is the rate of intercellular reaction, and K_{cr} is the partition coefficient between the cellular and vascular space.



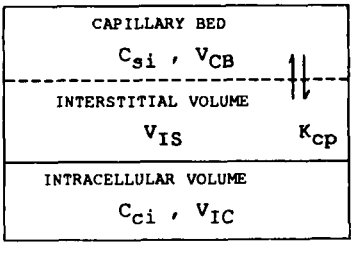


FIG. 6. Heterogeneous transit-time-distribution model [6, 36–39]. (a) Representation of the liver as a parallel set of tubular reactors. The number of tubes and length (or volume) of each tube are determined based on the residence-time-distribution of a vascular tracer. Note that the model assumes *all* mixing occurs at the outlet. (b) Diagram of the heterogeneous form of a tube. Each tube is comprised of a vascular space, interstitial space, and an intracellular region.

The distribution in the extravascular space was considered flow limited. Hence, the concentrations in the interstitial space and the vascular space can be related via a partition coefficient, K_{cp} [Eq. (26)]:

$$\frac{\delta C_{vi}}{\delta t} = K_{cp} \frac{\delta C_{si}}{\delta t} \tag{26}$$

The intracellular concentration is described by:

$$\frac{\delta C_{ci}}{\delta t} = k_1 \cdot C_{si} - k_2 \frac{C_{ci}}{K_{cr}} - k_3 \frac{C_{ci}}{K_{cr}} \tag{27}$$

k_1 and k_2 are the rate constants for cellular uptake and release, respectively, and k_3 represents the rate of intracellular reaction.

The boundary conditions, based on a pulse experiment, are:

$$C_{si}(0,t) = \frac{M_0}{Q_s} \delta\ (t - \epsilon) \tag{28}$$

where M_0 is the initial quantity of tracer in the pulse Q_s is the volumetric flow rate through a single sinusoid, and $\delta\ (t - \epsilon)$ is a Dirac delta function; ϵ is a time infinitesimally greater than zero. The initial conditions are:

$$C_{si}(x,0) = 0 \quad ; \quad C_{ci}(x,0) = 0 \quad ; \quad \frac{\delta C_{si}}{\delta t}(x,0) = 0$$

The general solution for the effluent concentration from a *single* sinusoid is given by Eq. (29):

$$\begin{aligned} C_{si}(L,t) = {} & \frac{M_0}{Q_s} \exp\ (-k_1\theta t/\Phi)\cdot\delta\ (t - \Phi \cdot \tau_s) \\ & + \frac{M_0}{Q_s} \exp\ [-(k_2 + k_3)/K_{cr}\cdot(t - \Phi\cdot\tau_s)] \\ & \times \exp\ (-[k_1\theta\tau_s]\cdot[k_1k_2\theta/K_{cr}(t - \Phi\cdot\tau_s)]^{0.5}) \\ & \times I_1[(4k_1k_2\theta\tau_s/K_{cr}\cdot\{t - \Phi\cdot\tau_s\})^{0.5}] \cdot S\ [t - \Phi\cdot\tau_s] \end{aligned} \tag{29}$$

where $\Phi = (1 + \gamma\cdot K_{cp})$, $S(t - \Phi\cdot\tau_s)$ is a step function at $t = \Phi\cdot\tau_s$, $I_1\ (\xi)$ is a first-order modified Bessel function of argument ξ, and τ_s is the residence time in the sinusoid.

Equation (29) may be simplified for various limiting rates of transport and reaction. For example, if the volumetric flow rate is limiting ($k_1 \cong$ infinity; $k_2 \cong$ infinity; k_1/k_2 = constant), the effluent concentration from a single sinusoid is described by:

$$C_{si}(L,t) = \frac{M_0}{Q_s} \exp\left[\frac{-k_1 k_3 \theta \tau_s}{k_2}\right] \delta\left(t - \left[1 + K_{cp}\gamma + \frac{k_1 \theta K_{cr}}{k_2}\right] \tau_s\right) \qquad (30)$$

For the whole liver, the general equation for the overall effluent concentration at any time, t, is:

$$C_l(t) = Q^{-1} \int_{\tau_{s,min}}^{\tau_s} \frac{MQ_s^2}{M_0 Q} C_{si}(L,t-t_0) \cdot n(\tau_s) d(\tau_s) \qquad (31)$$

The term $n(\tau_s)d(\tau_s)$ is a discrete function describing the proportion of the sinusoids with transit times between τ_s and $\tau_s + d\tau_s$, and is obtained from the residence time distribution of a vascular tracer. $\tau_{s,min}$ is the minimum transit time through the sinusoid, Q is the volumetric flow rate through the organ, and M is the quantity of material remaining from the initial pulse at time t.

Integration of Eq. (31) with substitution for $n(\tau_s)d(\tau_s)$ and $C_{si}(L,t-t_0)$ from either Eq. (29) or Eq. (30) is required to obtain effluent concentration–time curves for the entire organ. For vascular and extravascular tracers, the resulting expressions are very straightforward. However, the expression for the effluent concentration of a species undergoing linear intracellular reaction and subject to uptake and release from the cells is an integral equation. Because $n(\tau_s)d(\tau_s)$ is a discrete function that can only be obtained experimentally, Eq. (31) must be integrated numerically. Similarly, to estimate intracellular concentrations, an expression for the time-dependent cell concentration in a single sinusoid [Eq. (32)] must be combined with discrete residence-time-distribution data and numerically integrated. The appearance and distribution of metabolites in the cells and vasculature was not accounted for, and extension of the model to include these phenomena would be complicated.

$$C_{ci}(L,t) = k_1 \frac{M_0}{Q_s} \exp\left[-(k_2 + k_3)/K_{cr} \cdot (t - \Phi \cdot \tau_s)\right] \cdot \exp\left[-k_1 \theta \tau_s\right]$$
$$\times I_0[(4k_1 k_2 \theta \tau_s / K_{cr} \cdot \{t - \Phi \cdot \tau_s\})^{0.5}] \cdot S\left[t - \Phi \cdot \tau_s\right] \qquad (32)$$

where $I_0(\xi)$ is a zero-order modified Bessel function of argument ξ.

Profiles from the injection of the compound of interest permitted the estimation of four species-dependent parameters; the effective cellular volume, a rate constant for cellular uptake (k_1), a rate constant for cellular release (k_2), and a linear rate of reaction (k_3). Effluent tracer profiles of a specific drug could then be used to analyze simple changes in steady-state elimination with subsequent changes in blood flow. Nevertheless, the transit-time-distribution model has limitations. From a practical perspective, it requires a measured, discrete residence time distribution before the model can be applied. Hence, the data requirements of the model are significant. Furthermore, like the distributed model of Bass et al. [14], the transit-time-distribution model is an RTD model, and assumes that all mixing occurs at the outlet of the liver. As discussed earlier, this assumption is unimportant only if transport and elimination are linear or zero-order processes, or if the time scale for mixing is much less than the time scales for transport and reaction.

Forker and Luxon [40] used a similar heterogeneous model to describe the elimination of galactose. The model is comparable to the transit-time-distribution model proposed by Goresky, except that the mass flux was related to the mass of material, rather than the concentration. Unlike Goresky and co-workers, who used a measured residence time distribution to describe vascular mixing, Forker and Luxon assumed that mixing within the liver could be represented using a Gaussian distribution of sinusoid transit times (similar to the distributed model of Bass et al. [22]). Furthermore, only the special case of linear transport and metabolism was considered.

The primary advantage of these microscale models is that they explicitly account for interphase transport. However, they do not accurately represent intrahepatic mixing and time-dependent flow within the organ, and the inherent assumptions about the nature of mixing and flow within the vasculature are only valid if transport and reaction are linear, or if the time required for fluid distribution within the vasculature is very short relative to the time required for mass transfer and reaction. A model which can accurately describe microscopic mixing within the vasculature may be needed if rates of transport and reaction are faster than the rate of fluid distribution throughout the vasculature.

The mathematical complexity of the transit-time-distribution model limits its use as a predictive model. Furthermore, estimation of parameters for metabolite transport and elimination is difficult. The version of the model proposed by Goresky and co-workers has significant data requirements—an experimentally measured residence-time-distribution must be obtained. This forces numerical integration to be used since the model equations must be matched with discrete data, and further limits the generality of the model and its ability to be used in a predictive fashion. The version proposed by

Forker and Luxon does not have the data requirements of the Goresky version, because they assume a Gaussian transit-time-distribution for blood flow and mixing in the sinusoids. This, however, is not an improvement, since intrahepatic mixing and blood flow are best described by a Γ distribution, rather than a Gaussian distribution [31].

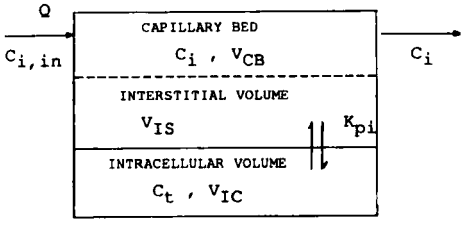
Despite their limitations, these microscale models have been used for correlating effluent concentrations of compounds subject to rapid uptake into the cells or carrier-mediated transport (e.g., galactose). In general, these models are most effective if transport and reaction are linear, and if the time scale for the net interphase transport is greater than the time scale for mixing in the vasculature.

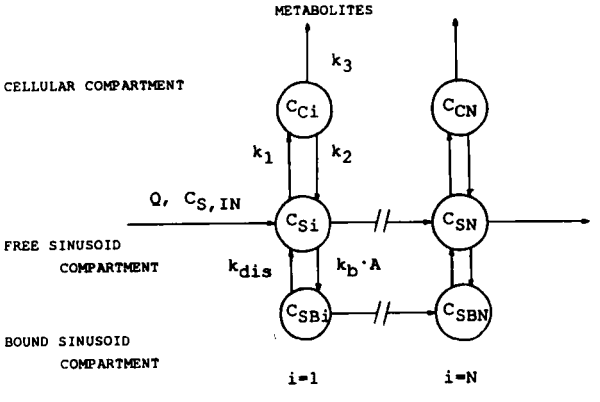
2. Compartmental Models of Hepatic Transport and Reaction

If the time scale for transport is significantly greater than the time scale for vascular mixing, it may be possible to use compartments and a macroscopic approach to liver modeling. The compartmental approach was first used by Kety [41], and applied to compounds that undergo diffusive, reversible transport between the cells and the vasculature. The slower net rate of transport for these compounds permitted successful application of a compartmental model.

Tsuji et al. [42] developed a three-compartment heterogeneous model for nonreactive species [Fig. 7(a)]. The first compartment represented a well-mixed capillary bed; the second and third compartments were parallel to the first and represented the space of Disse and the intracellular space, respectively. Flow of material was restricted to the capillary bed; materials gained access to the peripheral compartments by mass transfer. It was assumed that transport processes were much faster than other processes, leading to rapid equilibration between species in the capillary bed and the tissue. Hence, transport parameters were not specifically evaluated. Instead, differences in drug levels between the capillary bed and the tissue were encompassed within a coefficient for partitioning between the compartments. The model was extended to account for drug elimination, but the reactions were assumed to occur in the capillary bed. Nevertheless, by using a partition coefficient, K_{pi}, the model was capable of predicting drug concentrations in the tissue. The governing equation for the model is:

$$(V_{is}+V_{si})\frac{dC_i}{dt} = Q\cdot(C_{i,in} - C_i) - \frac{V_m C_i}{(K_m + C_i)} \tag{33}$$





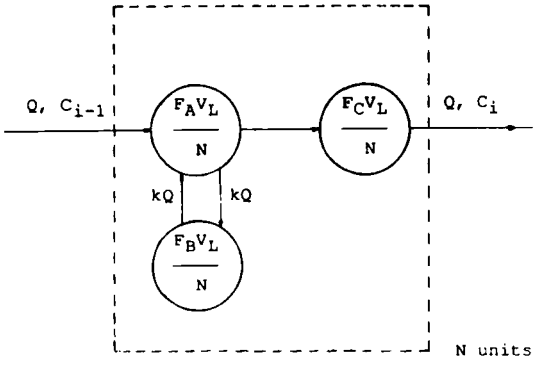


FIG. 7. Compartmental heterogeneous models for drug elimination in the liver. (a) Model of Tsuji et al. [42]. (b) Model for binding and transport proposed by Weisiger [43]. (c) Finite-stage transport model [45].

where V_{is} and V_{si} are the interstitial volume and sinusoid volume, respectively.

To estimate the tissue concentrations (C_t) of the compounds, Eq. (34) was used:

$$C_t = K_{pi}C_i \tag{34}$$

The model was successful in predicting the time-dependent tissue and plasma concentrations of several β-lactam antibiotics. The primary advantage of the model is its mathematical simplicity—the equations are easy to manipulate and integrate. However, some of the assumptions in the model limit its generality. For example, the physiological processes influencing mixing within the vasculature were described using a single well-mixed compartment; deviations from complete mixing cannot be accounted for. Similarly, it was arbitrarily assumed that metabolism is limited solely by the rate of reaction. Hence, the model must be modified to account for the elimination and distribution of drugs when metabolism is limited by the rate of cellular uptake or release. Furthermore, the existing model cannot account for metabolite formation and elimination; however, extension of the model to describe metabolite levels is straightforward.

Weisiger [43] developed a compartmental model to describe dynamic exchange between bound and free fractions of species in plasma [Fig. 7(b)]. Separate sets of compartments were used to represent the vasculature and the tissue; the vasculature was divided to account for the free and bound fractions of the drug. Complete mixing was assumed within each compartment. The model is an extension of the series compartment model, using separate peripheral compartments to describe tissue concentrations and another set of compartments to account for protein binding. The model incorporated separate rates for uptake and release of species between the plasma and in the cells, and included parameters to describe the intracellular reaction of the unbound species. Separate rate constants were used to account for nonequilibrium binding to and dissociation from proteins in the plasma. The model equations are as follows:

For unbound species in vascular compartment i:

$$V_{si}\frac{dC_{si}}{dt} = Q\cdot(C_{s,i-1} - C_{si}) - (k_1 + k_b\cdot A)\cdot V_{si}\cdot C_{si} + k_2\cdot V_{ci}\cdot C_{ci} + k_{dis}\cdot V_{si}\cdot C_{sbi} \tag{35}$$

For bound species in vascular compartment i:

$$V_{si}\frac{dC_{sbi}}{dt} = Q\cdot(C_{sb,i-1} - C_{sbi}) - k_{dis}\cdot V_{si}\cdot C_{sbi} + k_b\cdot A\cdot V_{si}\cdot C_{si} \tag{36}$$

For species in cellular compartment i:

$$V_{ci}\frac{dC_{ci}}{dt} = k_1 \cdot V_{si} \cdot C_{si} - (k_2 + k_3) \cdot V_{ci} \cdot C_{ci} \quad (37)$$

where A is the albumin concentration, C_{ci} is the concentration in cell compartment i, C_{si} is the concentration of unbound species in vascular compartment i, C_{sbi} is the concentration of the bound species in vascular compartment i, k_1 is the rate constant for cellular uptake, k_2 is the rate constant for release from the cells, k_3 is the rate constant for intracellular reaction, k_b is the rate constant for binding to plasma proteins, and k_{dis} is the rate constant for dissociation of the bound complex. V_{si} and V_{ci} represent the volumes of the individual vascular compartments and cellular compartments, respectively, and are equal to the total volume of the region (e.g., V_s or V_c) divided by the total number of compartmental units, N.

Weisiger did not attempt to fit experimental data using the model, but simulations of a variety of limiting cases and predicted trends were presented and discussed. Depending upon conditions, single-pass drug extraction could be limited by flow, influx, elimination, and dissociation of the compound from a bound complex. Under flow-limited conditions, 100% extraction was predicted, whereas if influx or elimination were limiting, the drug could pass through the organ virtually unchanged. A broad spectrum of conditions could be handled by the model, suggesting that the model would be applicable to a variety of substrates and physiological conditions.

A revised form of Weisiger's model was developed by Saville et al. [7] to follow the formation and elimination of metabolites. Experiments were conducted with a vascular tracer to investigate the extent of mixing within the vasculature and to determine the number of vascular compartments required to account for intrahepatic mixing. The model was then successfully applied to describe the time-dependent profiles of lidocaine and two of its primary metabolites obtained during continuous single-pass perfusion of the isolated rat liver. It was observed that, for these lipophilic compounds, which are probably not subject to active or facilitated transport, vascular mixing was complete within approximately 20 sec, whereas 3 to 5 min was required for the drug to distribute throughout the tissues of the organ. Hence, the time scale for mixing was very short relative to the time scale for distribution into the liver tissue. Consequently, the effect of intrahepatic mixing upon effluent concentrations was minimal, and a detailed mathematical description of the complex physiological phenomena that influence vascular mixing and hepatic blood flow was not necessary.

There are several advantages of this model. It accounts for the heterogeneous nature of the organ, combining cellular uptake and release with

intracellular reaction and protein binding. The model is relatively simple mathematically, consisting of sets of ordinary differential equations which may be easily integrated to predict intracellular and vascular levels of a drug and its metabolites. Furthermore, the model is not data intensive, and Weisinger demonstrated the generality of the model, showing that the model could account for the influence of a variety of physical processes upon drug levels. The primary limitation of the model is that it does not explicitly account for the processes that control intrahepatic mixing. However, Saville et al. concluded that for compounds distributed by passive diffusion, the short time scale for intrahepatic mixing (relative to the time for distribution into the tissue) warranted the use of a time and spatially averaged model of vascular mixing and hepatic blood flow.

Additional models for chemical reaction and flow in multiphase systems have been presented in the chemical engineering literature, and these may be adapted to describe hepatic elimination. Buffham and Gibilaro [44] discussed a model for noneliminated species in porous media. This model (known as the Deans–Levich model in the chemical engineering literature) contains a series of well-mixed vessels (analogous to the vasculature) with exchange between each vessel and a peripheral vessel representing the stationary phase (i.e., the tissue or cells). Exchange between the flowing and stationary phases was assumed to be in equilibrium; an equivalent fraction of the material enters and leaves the stationary phase at any given time. Essentially, then, the model is similar to that of Tsuji et al. [42], except that Buffham and Gibilaro used a series of compartments to represent the sinusoids, and the space of Disse was not explicitly accounted for. For practical use, the model as described must be modified to allow for substrate elimination and different rates of transport between the flowing and stationary compartments.

Rogers and Gardner [45] used a six-parameter finite-stage transport concept to describe residence-time distribution functions of continuous processes. The model used units of three compartments [Fig. 7(c)] to describe tracer behavior. In each unit, a primary well-mixed compartment and a plug flow compartment were arranged in series (representing flow and mixing in the vasculature); the well-mixed compartment undergoes equilibrium exchange with a peripheral well-mixed compartment. The peripheral compartment represented a dead volume or stationary phase within the reactor, analogous to the cells, and the plug flow compartment represented a simple time delay. The model equations are as follows:

For the primary well-mixed compartment (compartment A):

$$\frac{F_A V_L}{N}\frac{dC_{Ai}}{dt} = Q\cdot(C_{i-1} - C_{Ai}) + kQ\cdot(C_{Bi} - C_{Ai}) \tag{38}$$

For the peripheral well-mixed compartment (compartment B):

$$\frac{F_B V_L}{N}\frac{dC_{Bi}}{dt} = kQ\cdot(C_{Ai} - C_{Bi}) \tag{39}$$

where k is the fraction of fluid exchanged between the primary and peripheral compartments; N is the number of units; and F_A, F_B, and F_C are the fraction of the total volume occupied by regions A, B, and C, respectively.

The time lag is accounted for by including a plug flow compartment, C. The appropriate equations are:

$$C_i(t) = C_n(t - F_c\tau)\cdot H(t - F_c\tau) \tag{40}$$

where $H(t - F_c\tau)$ is a step function described by: $H(t - F_c\tau) = 0$ if $t < F_c\tau$; $H(t - F_c\tau) = 1$ if $t > F_c\tau$; and $\tau = V_L/Q$. Similar expressions can be written for each of N units.

The model as stated [Eqs. (38) to (40)] does not have any provision for chemical reaction, nor does it allow for different rates of transfer between the primary and peripheral well-mixed compartments. To be effective as a model of hepatic metabolism, the model must be extended to include these features. Like most compartment models, this model is mathematically simple but cannot explicitly account for the detailed physiological processes that control hepatic mixing and blood flow. When the model was used to analyze time-dependent tracer profiles, it was deemed more versatile and accurate than the series compartment model. However, it has not been tested as a model of hepatic elimination.

III. CONCLUSIONS AND RECOMMENDATIONS

It is apparent that none of the existing models of hepatic metabolism meet all of the criteria of the ideal model. Some models, such as the well-mixed and parallel tube models, require so many approximations as to limit their use to a very select number of substrates, or a limited range of conditions (e.g., steady state). Other homogeneous models incorporate a range of mixing phenomena, but are restricted in other ways. The dispersion model is mathematically complex, and the range of dispersion parameters proposed by Roberts and Rowland [8, 26, 27] indicate that as a model of hepatic elimination, the model does not have a sound theoretical foundation. Nevertheless, as an empirical model of hepatic metabolism, the

dispersion model has been useful. The series compartment model [30] is very general for species without transport limitations, and is mathematically simple. However, it is completely empirical in nature, and, like all of the other homogeneous models, there is no direct means of accounting for physiological phenomena such as interphase mass transport and variable flow through the liver. The distributed model [22] is sufficiently complex mathematically that its use is limited. None of the homogeneous models are useful for investigating transport processes; for this, a heterogeneous model is required.

The heterogeneous models are more accurate physiologically, because they explicitly account for transport processes between species in the cells and the vasculature. The distributed-transit-time heterogeneous models that have been tested are complex (e.g., Goresky [6, 36–39]; Forker and Luxon [40]) and are very difficult to use as predictive models or if metabolites are to be studied. However, they may serve as a basis for simpler models. The heterogeneous model proposed by Tsuji et al. [42] was effective for a variety of antibiotics but invoked some drug-specific assumptions, and it is, therefore, not general. Further refinement of the model to include metabolites and nonequilibrium rates of transport could, however, lead to a useful hepatic model. Similarly, the Deans–Levich model [44] and the finite-stage transport model [45] are promising, but require modification to include reaction and different rates of transport between adjacent compartments before they can be used to describe liver metabolism. The compartmental model proposed by Weisiger [43] meets at least two of the criteria: It requires a minimum of data, is mathematically simple, and is easy to use as a predictive model for both drugs and metabolites. Furthermore, it can account for several physiological processes, including protein binding, cellular uptake and release, intracellular reaction, and incomplete hepatic mixing. It cannot, however, explicitly account for time-dependent blood flow, local pressure gradients, and other physical phenomena that affect mixing within the vasculature, simply because the model uses a macroscopic approach to describe intrahepatic mixing. Nevertheless, use of such a time and spatially averaged model of hepatic metabolism is likely appropriate, especially for lipophilic compounds where the time scale for mixing is much shorter than the time scale for mass transfer and distribution into the tissue.

Of the three criteria for an ideal model, probably the most desirable feature is that the model be useful for correlating and predicting the time-dependent profiles of a wide variety of compounds. Although none of the existing models completely meet all three of the criteria, and none are completely general, some models come close. Selecting which model to use is often a matter of personal choice, guided by one's knowledge of the limi-

tations of the model and the desired applications of the model. Nevertheless, a few recommendations can be made:

1. If explicit knowledge of rates of mass transfer is not needed, then use of a homogeneous model is appropriate. Of the homogeneous models presented herein, the best model is the series compartment model. This model covers the full range of mixing conditions, is mathematically simple, requires a minimum of data, and is easy to use as a predictive model for both the parent drug and its metabolites.
2. If a detailed knowledge of mass transfer rates is required, then a heterogeneous model must be used. Although none of the existing models are completely general, the compartmental model proposed by Weisiger [43] and modified by Saville et al. [7] comes closest to the ideal model. The model accounts for a variety of physiological phenomena, is mathematically simple, and is easy to use, both for correlating data and as a predictive model. Although the model has not been widely used, numerical simulations suggest that the model should be capable of describing the time-dependent profiles of a variety of compounds. Experimental evidence indicates that the model is particularly effective for species subject to passive transport.
3. If metabolite levels are unimportant, as they might be for some species subject to irreversible uptake, then the transit-time-distribution model [6, 36–39] may be appropriate. Use of this model, however, significantly increases data requirements, and is restricted either to compounds subject to linear transport and reaction, or to cases where metabolism is not flow limited. Furthermore, the model is best suited for data correlation only; it is difficult to use for the prediction of drug profiles.

IV. SUMMARY

The liver is, by nature, heterogeneous. It contains a complex vascular network for blood flow and a stationary phase consisting of enzymes within parenchymal cells. Several physiological processes, therefore, may combine to give observed ranges in drug elimination. Net changes in concentration are a consequence of a series of steps: uptake of substrate into liver cells, enzymatic reactions within the cells, release of metabolites and unconverted substrate from the cells into the sinusoids, and the net flow of the perfusing medium in the vasculature. In addition, substrate binding to proteins in the blood and in the liver can influence hepatic elimination. An

understanding of each of these processes is necessary to fully comprehend the overall process of drug elimination, and these processes must be accounted for, either individually or by grouping and approximation, if a model for drug elimination is to be developed.

Existing models of hepatic elimination may be classified according to their treatment of mixing within the vasculature and whether or not the model explicitly accounts for mass transfer between the heterogeneous phases of the liver. Four major classes may be defined:

1. Nonparametric homogeneous models, which assume that either complete mixing or no mixing occurs within the vasculature of the organ.
2. Homogeneous mixing models, which allow for a range of mixing phenomena.
3. Heterogeneous micromixing models, which allow for mass transport between the cells and vasculature and describe mixing within the vasculature on a microscopic level.
4. Heterogeneous compartmental models, which also describe interphase mass transfer but assume complete mixing on a microscopic level, and therefore use a time and spatially averaged approach to model mixing.

The utility of these models of hepatic elimination will be critically assessed based upon (1) their ability to account for the influence of the aforementioned physiological processes upon elimination; (2) the data requirements of the model, in addition to its mathematical complexity and ease of use; and (3) the range of compounds and metabolites which may be described using the model.

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NOMENCLATURE

A	concentration of albumin for binding process
C_i	concentration of species i
C_{in}	inlet concentration
$C_{i,in}$	inlet concentration of species i
C_{Ai}	concentration in the primary compartment of composite unit i

C_{Bi}	concentration in the peripheral compartment of composite unit i
C_{ci}	concentration of free species in cellular compartment i
C_{ij}	concentration in segment i,j
Cl_{int}	intrinsic clearance
C_{si}	concentration of free species in sinusoid compartment i
C_{sbi}	concentration of bound species in sinusoid compartment i
C_{step}	step increase in the inlet concentration of a tracer or drug
C_t	concentration of species i in tissue
$C_{t,s}$	concentration at the tissue–sinusoid interface
C_{vi}	concentration of material in the interstitial space
D_{TX}	coefficient for axial diffusion in tissue
D_{TR}	coefficient for radial diffusion in tissue
ER	extraction ratio
F_A	fraction of total system volume in the primary compartments
F_B	fraction of total system volume in the peripheral compartments
F_C	fraction of total system volume in the plug flow compartments
f_{ub}	fraction of unbound drug
i	index for species identification
k	fraction of the volumetric flow exchanged with the peripheral compartment
k_1	rate of cellular uptake
k_2	rate of cellular release
k_3	rate of intracellular reaction
k_b	rate constant for protein binding
k_{dis}	rate of dissociation of bound complex
k_R	rate of linear reaction
K_{cr}	partition coefficient between the cellular and the vascular space
K_{cp}	partition coefficient between the interstitial and the vascular space
K_m	Michaelis constant for Michaelis–Menten kinetics
K_{pi}	pattern coefficient between the tissue and vasculature
L	length of cylinder or reactor
M	quantity from pulse remaining at any time
M_0	initial quantity in the pulse
N	number of composite compartmental units
P	permeability
Q	volumetric flow rate through the organ
Q_s	volumetric flow rate through a single sinusoid
r	radius
r_c	radius of capillary
R_j	rate of reaction j
t	time

u	flow velocity in reactor
V_c	total volume of the cells (or tissue)
V_{ci}	volume of cellular compartment i
V_{is}	volume of interstitial space
V_L	total volume of the liver
V_m	maximal reaction velocity
V_s	total vascular volume (includes the sinusoids and interstitial space)
V_{si}	volume of sinusoid compartment i
W_s	flow velocity in the sinusoid
x	distance along the sinusoid
δ	Dirac delta function; also designates a partial differential operator
γ	ratio of the interstitial volume to the vascular volume
ϑ_L	dispersion parameter
θ	ratio of the cellular volume to the vascular volume
τ	average residence time of the system
τ_s	residence time in the sinusoid = L/W_s

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