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Development of appropriate equations for physiologically based pharmacokinetic modeling of permeability-limited and flow-limited transport

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Abstract

Although the implementation of a flow-limited, well-stirred tank (WST) single-compartment tissue model in pharmacokinetics and toxicokinetics is widespread, its use is not always justified biophysically or physiologically. The WST model introduces a loss of biophysical detail, specifically the vascular space, which is present in the standard permeability-limited two-subcompartment (PLT) tissue model. To address this loss of detail when evaluating the *in vivo* kinetics of drugs, toxins, nutrients, and endogenous metabolites, a novel set of physiologically based pharmacokinetic tissue compartment equations is developed through application of an asymptotic approximation to a two-region vascular–extravascular system to arrive at a permeability-limited two-region asymptotically reduced (P-TAR) model and a flow-limited (F-TAR) model. Development of the TAR modeling approach illustrates the importance of relative timescales in PBPK tissue compartment model selection and the conditions under which improved biophysical realism is advantageous. In the permeability-limited regime, the TAR model formulations enable drug or toxicant concentration to be modeled in the vascular and extravascular spaces equivalent to the PLT tissue model while invoking only one state variable to represent the vascular and extravascular spaces. In the flow-limited regime, the F-TAR model is more biophysically realistic than the WST model because it maintains the anatomical distinction between the vascular and extravascular spaces, and hence offers greater pharmacological and physiological insight than the WST model, without introducing additional computational complexity.

Keywords

Physiologically based pharmacokinetics; Flow-limited; Permeability-limited; Well-stirred tank; Compartmental modeling; Singular perturbation

Introduction

Physiologically based pharmacokinetic modeling has found widespread use in the pharmaceutical sciences and toxicology because it is a detailed, mechanism-based approach leading to a greater understanding of pharmacodynamic and/or toxic effects by quantifying tissue exposure [1]. To achieve this, whole-body PBPK models define anatomic spaces, e.g.

tissue and organ compartments, as fixed volumes with mass transport between compartments based on vascular connectivity and physiologic blood flows. Each compartment may be further defined by drug-specific terms for tissue clearance, which are dependent on absorption, distribution, metabolism, and excretion processes. The development of PBPK models allows the translation of findings between preclinical and clinical studies [2], across species [3], from adult to pediatric populations [4], and between normal and altered physiologic and pathophysiologic states [5].

PBPK tissue compartment models used in pharmacokinetic and toxicokinetic studies are generally described as being one of two types: flow/perfusion-limited or permeability/diffusion-limited. The flow-limited tissue compartment model (Fig. 1c) is described by the mass balance differential equation

$$\frac{dc}{dt} = \frac{F}{V} \left(c_{in} - \frac{c}{\lambda} \right), \quad (1)$$

where c is the concentration of drug in the well-stirred compartment, c_{in} is the arterial or inflow concentration of drug, F is flow, V is the total volume of the organ or tissue, and λ is the partition coefficient of the drug. Widespread and indiscriminant use of a single-compartment, flow-limited, well-stirred tank (WST) tissue model is of concern, as the WST model has less biophysical detail than a two-subcompartment permeability-limited model having both vascular and extravascular tissue spaces. (Here, the flow-limited model of Eq. 1 is referred to as the WST model, though in the literature it is also referred to as the venous equilibrium model.)

The other standard PBPK tissue compartment model is for use in tissues where mass transfer out of the vascular space is limited by a permeability barrier. Tissues possessing a permeability barrier are therefore modeled with a permeability-limited equation that requires consideration of two tissue subcompartments. Two ordinary differential equations, with permeation between the vascular and extravascular spaces, define the standard permeability-limited two-subcompartment (PLT) model (Fig. 1b) with

$$\frac{dc_1}{dt} = \frac{F}{V_1} (c_{in} - c_1) - \frac{PS}{V_1} \left(c_1 - \frac{c_2}{\lambda} \right) \quad (2a)$$

and

$$\frac{dc_2}{dt} = + \frac{PS}{V_2} \left(c_1 - \frac{c_2}{\lambda} \right) \quad (2b)$$

where c_1 is the concentration of drug in the vascular subcompartment, c_2 is the concentration of drug in the extravascular subcompartment, V_1 is the vascular volume, V_2 is the extravascular volume, and PS is the permeability-surface area product. Equations 2a and 2b can be thought of as an extension of the WST model (Eq. 1) with addition of permeation between two well-stirred subcompartments. The PLT model invokes two state variables rather than the one of the WST model. Furthermore, the PLT model requires identification of four parameters (F/V_1 , PS/V_1 , PS/V_2 , and λ) while the WST model requires two (λ and F/V). Thus while the PLT model may capture more biophysically realistic behavior, it is more computationally expensive.

Herein, the development, assumptions, and limitations of the WST and PLT equations are reconsidered, revealing the conditions under which the WST model fails to approximate the PLT model. A novel two-region asymptotically reduced (TAR) PBPK tissue compartment model is developed that accounts for vascular and extravascular regions for both the permeability-limited and flow-limited regimes, invoking only a single state variable in both cases. The WST, PLT, and TAR equations are then analyzed to show how drug-specific and tissue-specific properties influence model behavior and selection.

Methods: model theory and development

General cases of tissue compartment models

Models of drug transport ideally (1) meet defined objectives; and (2) achieve balance between a detailed, mechanism-based framework and application appropriateness [6]. There are three general cases of PBPK tissue models to consider, each having its own assumptions and inherent limitations. The following cases are based largely on the need to model processes occurring over a range of time scales: Case I, spatially distributed; Case II, spatially homogenized, lumped compartmental; and Case III, well-stirred tank. While Case III is the model upon which PBPK most heavily relies, Case I is discussed leading to Case II and subsequently, the novel TAR PBPK tissue compartment model.

Case I: spatially distributed—Pharmacokinetic modeling is generally considered to have begun with Teorell in 1937 [7, 8]; yet, not until the 1970s and 1980s did Bischoff et al. [9] and Anderson and coworker [10] begin using computational approaches to develop physiologically based kinetic models to investigate drugs and toxins. However, even preceding Bischoff et al., studies of mass transport had been carried out using the advection–diffusion equation, where two physical processes for transport predominate: advection—the bulk movement of fluid—and diffusion—the random thermal motion of molecules down a concentration gradient. A mathematical solution for a one-dimensionally treated two-region model with advection and permeation was first presented by Sangren and Sheppard in 1953 [11].

In cases where transport processes lead to the formation of spatial concentration gradients, there is a need to use a distributed model [12–14]. Accounting for spatial gradients along a capillary, mass flux out of the capillary is given by the advection equation

$$\frac{\partial c_1}{\partial t} = -v \frac{\partial c_1(x, t)}{\partial x} - \frac{J_{\text{out}}(x, t)}{V_1}, \quad (3)$$

where v is the velocity along the major axis, x is the position along the length of the capillary, J_{out} is the mass flux out of the capillary, and axial diffusion is ignored. Assuming passive permeation of solute through the endothelial barrier and into the tissue in a concentration-dependent manner,

$$J_{\text{out}} = PS \left(c_1 - \frac{c_2}{\lambda} \right), \quad (4)$$

where PS is the permeability-surface area product. To model changes in concentration in both regions, we have the model studied by Sangren and Sheppard [11]:

$$\frac{\partial c_1}{\partial t} = -v \frac{\partial c_1(x, t)}{\partial x} - \frac{PS}{V_1} \left(c_1 - \frac{c_2}{\lambda} \right), \quad (5a)$$

$$\frac{\partial c_2}{\partial t} = + \frac{PS}{V_2} \left(c_1 - \frac{c_2}{\lambda} \right), \quad (5b)$$

where there is no consumption term for non-eliminating tissues and advection in the tissue space is neglected (Fig. 1a). The spatially distributed case is often not used in PBPK modeling but situations do exist where spatial gradients in tissue arise with drug treatment [15]. In other areas of physiological modeling, such as oxygen transport and metabolism, spatially distributed models are necessary [16, 17].

Case II: spatially homogenized, lumped compartmental—The lumped compartmental model may be obtained via spatial averaging of Eqs. 5a and 5b. Defining mean capillary concentration as

$$\bar{c}(t) = \frac{1}{L} \int_0^L c(x, t) dx, \quad (6)$$

where L is the vessel length, and based on the relationship $F = vA$, where A is the vessel cross-sectional area, $V_1 = LA$, and thus $F/V_1 = v/L$, the governing equations for the mean concentrations in the two regions are obtained:

$$\frac{d\bar{c}_1}{dt} = \frac{F}{V_1} \left(c_{in} - \bar{c}_1 \right) - \frac{PS}{V_1} \left(\bar{c}_1 - \frac{\bar{c}_2}{\lambda} \right), \quad (7a)$$

$$\frac{d\bar{c}_2}{dt} = + \frac{PS}{V_2} \left(\bar{c}_1 - \frac{\bar{c}_2}{\lambda} \right). \quad (7b)$$

In this lumped model, the arterial concentration is the input concentration $c_{in} = c_1(0, t)$. The venous outflow concentration is approximated as being equal to the average concentration along the vascular subcompartment with $c_1(L, t) = c_{out}(t) \approx \bar{c}_1(t)$. In Fig. 1b, Eqs. 7a and 7b for Case II are presented with c in place of $\bar{c}$ and are therefore identical to Eqs. 2a and 2b for the PLT model. However, these sets of equations were developed with different assumptions, i.e., spatial averaging versus instantaneous mixing, respectively.

In the distributed model of Case I, there is a time delay between solute entry at the arterial end and exit from the venous end of the vascular subcompartment, whereas the lumped model assumes instantaneous transport to the venous end. The assumption that no axial gradient of drug exists along the capillary length is a simplification [14]; however, averaging the concentration (Eq. 6) is a reasonable approximation if $c_{in}(t)$, the arterial drug concentration, remains constant over the timescale of the vascular transit time, given by V_1/F , when permeation is low ($PS/F \ll 1$). When permeation is higher, tissue transit time, given by $(V_1 + V_2)/F$, provides a timescale for the validity of the lumped approximation. Since most drugs have half lives on a timescale of hours, not seconds, the lumped approximation of Case II is usually reasonable for drug transport.

Case III: well-stirred tank—The WST model is formulated based on a single compartment having instantaneous mixing; and therefore, concentration throughout the

whole tissue space is assumed to be homogeneous. Assuming constant volume, the rate of mass change in a tissue compartment is given by

$$V \frac{dc}{dt} = F_{in} c_{in} - F_{out} \frac{c}{\lambda}, \quad (8)$$

where the outflow concentration is the overall tissue concentration divided by the partition coefficient (Fig. 1c). Because Case III has been effectively implemented in modeling a range of drugs and toxins, it remains the default PBPK tissue compartment model. Historically [18], the WST model is used assuming: (1) the vascular and extravascular spaces are well-stirred with rapid equilibration and no mass transfer limitation between the tissue and blood; and (2) that when $V_2 \gg V_1$, V_2 approximates the total tissue compartment volume thus leading to an approximation that the entire organ/tissue is treated as a single compartment. More accurately, accounting for the partitioning, the use of the WST model requires that V_1 is much smaller than λV_2 .

Summary of prior approaches

As demonstrated by these three cases, pharmacokinetic model selection is largely dependent on whether a model sufficiently handles the relative time scales of drug-related ADME and retains adequate biophysical detail for a given tissue. Case I is rarely encountered or required in pharmacokinetics as long as (1) no significant spatial gradients exist; and (2) the mixing/transit time is small compared to the timescale of changes in arterial input concentration, c_{in} . If these conditions are met, Case I can be reduced to Case II. Case II is likewise reduced to Case III (well-stirred), if V_1 is small relative to λV_2 .

Development of TAR model equations

In this section, the lumped two-region case (Case II) is used to develop the permeability-limited (P-TAR, Fig. 1d) and flow-limited TAR (F-TAR, Fig. 1e) PBPK tissue compartment models. The equations presented here are for non-eliminating organs and tissues. Additional equations that account for inputs, metabolism, and excretion can be developed using different dynamic mass balance equations, with an example provided at the end of this section.

Singular perturbation analysis—To simplify the second order system of Eqs. 7a and 7b (or Eqs. 2a, 2b), a singular perturbation analysis may be applied. Equations are expressed as scaled dimensionless concentration and time variables:

$$\begin{aligned} \tau &= tF/(\lambda V_2) \\ s_1 &= c_1/c_o \\ s_2 &= c_2/c_o \\ s_{in} &= c_{in}/c_o \\ \varepsilon &= V_1/(\lambda V_2) \end{aligned} \quad (9)$$

where c_o is an arbitrary reference concentration. With substitution, Eqs. 7a and 7b become

$$\varepsilon \frac{ds_1}{d\tau} = s_{in} - s_1 - \frac{PS}{F} \left(s_1 - \frac{s_2}{\lambda} \right), \quad (10a)$$

$$\frac{ds_2}{d\tau} = +\frac{PS}{F} (\lambda s_1 - s_2). \quad (10b)$$

In the limit $\varepsilon \rightarrow 0$, Eq. 10a becomes singular, with the leading order derivative becoming unbounded and the right hand side finite. Taking $\varepsilon = 0$, we obtain

$$s_1 = \frac{s_{in} + \frac{PS}{F} \frac{s_2}{\lambda}}{1 + \frac{PS}{F}} \quad (11a)$$

and

$$\frac{ds_2}{d\tau} = \frac{PS/F}{(1+PS/F)} (\lambda s_{in} - s_2), \quad (11b)$$

or in terms of the original variables,

$$c_1 = \frac{c_{in} + \frac{PS}{F} \frac{c_2}{\lambda}}{1 + \frac{PS}{F}}, \quad (12a)$$

$$\frac{dc_2}{dt} = \frac{F}{V_2} \left(\frac{PS/F}{1+PS/F} \right) \left(c_{in} - \frac{c_2}{\lambda} \right). \quad (12b)$$

These P-TAR equations represent the long timescale solution where the change in c_1 is slow ($dc_1/dt \cong 0$), i.e. drug inflow concentrations are relatively constant compared to the tissue transit time of the drug.

Matched asymptotic expansions—As a result of reducing a second-order system (Eqs. 7a, 7b) to a first-order system (Eqs. 12a, 12b), arbitrary initial conditions for c_1 and c_2 cannot both be satisfied [19]. Because ε is finite, the quasi-steady state approximation ($dc_1/dt \cong 0$) breaks down on a relatively rapid timescale. Therefore, another set of equations may be defined for the short timescale

$$\frac{ds_1}{d\theta} = s_{in} - s_1 - \frac{PS}{F} \left(s_1 - \frac{s_2}{\lambda} \right), \quad (13a)$$

$$\frac{ds_2}{d\theta} = +\varepsilon \frac{PS}{F} (\lambda s_1 - s_2), \quad (13b)$$

where $\theta = Ft/V_1$. When $\varepsilon PS/F \ll 1$, s_2 remains essentially constant over the timescale defined by $t \approx < V_1/F$ as long as $\lambda = O(1)$. With $s_2 = \text{constant}$, the equation for s_1 has the solution

$$s_1(\theta) = \frac{s_2}{\lambda} \left(\frac{PS/F}{1+PS/F} \right) \left(1 - e^{-\beta\theta} \right) + e^{-\beta\theta} \int_0^\theta e^{+\beta u} s_{in}(u) du + s_1(0) e^{-\beta\theta}, \quad (14)$$

where $\beta = (1 + PS/F)$. In terms of the original variables,

$$c_1(t) = \frac{c_2}{\lambda} \left(\frac{PS/F}{1+PS/F} \right) \left(1 - e^{-\alpha t} \right) + e^{-\alpha t} \int_0^t e^{+\alpha u} c_{in}(u) du + c_1(0) e^{-\alpha t}. \quad (15)$$

where $\alpha = F(1 + PS/F)/V_1$. When $c_2(t)$ is constant, over the timescale $t \gg 1/\alpha$, c_1 becomes the quasi-steady state solution over the longer timescale:

$$c_1(t \gg 1/\alpha) = \frac{c_{in} + \frac{PS}{F} \frac{c_2}{\lambda}}{1 + \frac{PS}{F}}. \quad (16)$$

Flow-limited approximation—In the limit where PS is arbitrarily high and therefore permeability is not limiting ($PS/F \rightarrow \infty$), Eqs. 12a and 12b reduce to

$$c_1 = \frac{c_2}{\lambda} \quad (17a)$$

and

$$\frac{dc_2}{dt} = \frac{F}{V_2} \left(c_{in} - \frac{c_2}{\lambda} \right). \quad (17b)$$

These are the flow-limited, two-region asymptotically reduced (F-TAR) equations. The validity of this approximation depends on drug-specific permeation relative to tissue blood flow, as well as the timescales of mixing and transport processes in the tissue relative to changes in arterial input concentration.

To summarize the basic TAR models, Eqs. 12a and 12b are the P-TAR equations for a tissue compartment under a permeability-limited regime and Eqs. 17a and 17b are the F-TAR equations for a tissue compartment under a flow-limited regime. Both sets of equations describe a two-region model reduced to a single state variable, and though they are slightly more complex than the standard equations (Eqs. 2a, 2b and 1, respectively), they do not introduce additional adjustable parameters. The form of Eq. 17b is identical to the WST model of Eq. 1. However, the proper implementation of this model equation in PBPK differs from its standard use, as seen below.

Implementation of TAR model equations for whole-body PBPK modeling

Tissue outflow concentrations—In PBPK, model structure is based on the vascular connectivity of organs and tissues. In this whole-body approach, the flow-weighted sums of tissue outflow concentrations provide the inputs into the venous pool. To develop a global model that conserves mass, a dynamic mass balance given by

$$F(c_{in} - c_{out}) = V_1 \frac{dc_1}{dt} + V_2 \frac{dc_2}{dt}, \quad (18)$$

is used to compute the outflow concentration, $c_{out}(t)$, from a given organ. Rather than identifying the outflow concentration as the mean capillary concentration, outflow concentrations are more accurately obtained by solving Eqs. 12a, 12b and 18 for c_{out} ,

$$c_{out} = c_{in} - \frac{1}{F} \left[\frac{V_1}{1+PS/F} \frac{dc_{in}}{dt} + \left(\frac{V_1 PS/F}{(1+PS/F)\lambda} + V_2 \right) \frac{dc_2}{dt} \right]. \quad (19)$$

For the flow-limited case, the outflow concentration is

$$c_{out} = \left(1 + \frac{V_1}{\lambda V_2} \right) \frac{c_2}{\lambda} - c_{in} \frac{V_1}{\lambda V_2}. \quad (20)$$

Using these equations, additional conditions must be considered to avoid computing negative values for c_{out} when a PBPK model is initiated at zero concentration of a drug. Using the flow-limited TAR model as an example: If $c_{out} = 0$,

$$F c_{in} = \left(\frac{V_1}{\lambda} + V_2 \right) \frac{dc_2}{dt}. \quad (21)$$

Solving for dc_2/dt yields

$$\frac{dc_2}{dt} = \frac{F c_{in}}{V_2 + V_1/\lambda}. \quad (22)$$

Development of dynamic mass balance equations for three compartments undergoing input, excretion, or metabolism—Though a two-compartment model is appropriate for simple non-eliminating organs and tissues, modeling organs with more than two compartments and/or metabolism and excretion requires a more general mass balance. For example, a three compartment model can be constrained to satisfy the general mass balance equation:

$$F(c_{in} - c_{out}) + I - E = V_1 \frac{dc_1}{dt} + V_2 \frac{dc_2}{dt} + V_3 \frac{dc_3}{dt}, \quad (23)$$

where I is input and E is excretion or loss.

Methods: model behavior and selection

Comparing behavior of PLT, WST, P-TAR, and F-TAR tissue compartment models

To assess whether the TAR tissue compartment models are comparable to or perform better than the standard models, an isolated PBPK tissue compartment model is simulated with an input function determining drug inflow concentration. To evaluate the four models (PLT, WST, P-TAR, and F-TAR), rapid and slow time courses of inflow drug concentration are simulated using the ordinary differential equation

$$\frac{dc_{in}}{dt} = k_a c_{dose} - k_{el} c_{in}, \quad (24)$$

where k_a is the absorption rate constant and k_{el} is the elimination rate constant. Arbitrary units of concentration (a.u.) are used throughout, with c_{dose} set to 1 a.u. for rapid kinetics and 2 a.u. for slow kinetics. To simulate rapid changes in inflow concentration and assess the ability of the TAR model regimes to match standard PLT model behavior on a rapid

timescale, initial input concentration is set to zero, $k_a = 1 \text{ s}^{-1}$, and $k_{el} = 0.05 \text{ s}^{-1}$ (simulating kinetics over 200 s). For the slower timescale, initial input concentration is set to zero, $k_a = 0.001 \text{ s}^{-1}$, and $k_{el} = 0.0005 \text{ s}^{-1}$ (simulating kinetics over 4 h). Physiological parameter values for volumes are selected based on a typical vascular space comprising ~5% of total tissue/organ volume, though values certainly can vary from this [20]. A value for flow is chosen that gives a 3 s vascular transit time and a 60 s tissue transit time. Though other physiological parameter values could also have been selected, altering the observed kinetics, analysis over a wide range of parameter values does not change the conclusions regarding the comparability of standard and TAR models. Drug-specific parameters for the partition coefficient and PS/F are provided with each simulation. The four tissue compartment models are used to simulate time courses for c , c_1 , c_2 , and c_{out} . The solutions for the WST model are compared to the overall concentration for the PLT and F-TAR models, as given by

$$c = \frac{c_1 V_1 + c_2 V_2}{V_1 + V_2}. \quad (25)$$

Results and Discussion

Behavior of permeability-limited tissue compartment models over different timescales

To evaluate the behavior of PLT and P-TAR models, simulations are performed for rapid and slow changes in inflow concentration (c_{in}). In Fig. 2, PLT and P-TAR tissue compartment models are compared with rapid inflow kinetics. Plots of simulated kinetics show the result of perturbing the system on a timescale of seconds. P-TAR model solutions (c_1 , dashed light gray line; c_2 , dashed dark gray line) agree with the PLT model (c_1 , solid light gray line; c_2 , solid dark gray line) once the quasi-steady state is achieved. Substantial differences between the full PLT and the reduced P-TAR model are apparent only over the first 5 s. In most PBPK applications, timescales on the order of seconds are not encountered, and the PLT and P-TAR models would yield nearly identical results for simulated drug transport. The result of the additional conditions placed upon the P-TAR solutions (Table 1) requiring both mass conservation and non-negative concentrations are observed in the insets. In Fig. 2a (inset), the concentration in the vascular space (c_1) goes up more rapidly for the P-TAR model than the PLT model solution, reaching its peak several seconds before the PLT model. During this early phase, the P-TAR outflow concentration (dashed gray line), as shown in Fig. 2b (inset), is initially zero as opposed to the outflow concentration in the PLT model (solid gray line) which immediately rises. The P-TAR model solution then has a slight overcompensation seen around 5 s, achieving mass balance, before simulations nearly overlap for the remainder of the simulation time.

Though the P-TAR model is able to produce solutions similar to the PLT model when inflow concentration is rapidly changing, the TAR models perform even more closely to the standard models when inflow kinetics operate on a slower timescale (e.g. hours). In Fig. 3, PLT and P-TAR tissue compartment models are compared with this slower inflow kinetics. The main plots of Fig. 3 show the inflow concentration (c_{in} , solid black line) leading the vascular and extravascular concentration curves for both models. Because the duration of the simulation is 4 h, the insets better show the degree of agreement between the models. In Fig. 3 (insets), the P-TAR simulations (dashed gray lines) closely approximate the PLT model solutions (solid gray lines) for c_1 , c_2 , and c_{out} . The P-TAR model solution at onset of simulation (Fig. 3, bottom inset, slow kinetics) shows enhanced agreement compared to Fig. 2 (bottom inset, rapid kinetics) due to the slower rate of change in inflow concentration relative to transit time. Therefore, in contrast to the rapid kinetics, all portions of the P-TAR simulated curves—initial rise, peak, and tailing concentrations—demonstrate no substantial

deviation of behavior from the PLT model solution when using slower changing inflow concentrations. In summary, the one-variable P-TAR model effectively captures the overall kinetic behavior of the two-variable PLT model, especially for drugs with slower kinetics (e.g. hours).

Behavior of flow-limited tissue compartment models over different timescales

The behavior of WST and F-TAR tissue compartment models is also comparable over the two different timescales (seconds and hours). Inspection of the rapid kinetics in Fig. 4 shows nearly overlapping WST (solid light gray lines) and F-TAR (dashed dark gray lines) model solutions for c (Fig. 4a). Close agreement is also observed for outflow concentration (Fig. 4b) except for the initial 4 s of the solution. The WST model is a single well-stirred compartment where only the overall tissue concentration, c , and the partition coefficient, λ , impact outflow concentration. This is in contrast to the F-TAR model where outflow concentration is dependent on the partition coefficient, the physiological parameter values for volumes, and the concentrations in each region (Eq. 20). Substantial deviations of F-TAR model solutions from WST do occur when the partition coefficient is not 1.

The WST and F-TAR models (Eqs. 1 and 17a, 17b, respectively) have the same basic form but differ in how drug-specific (e.g., partition coefficient) and tissue-specific (e.g., vascular volume) parameters influence outflow concentration and hence mass and concentration of drug within the tissue. To compare and contrast the WST and F-TAR models, flow-limited behavior of the PLT model is used as the reference tissue compartment model possessing both vascular and extravascular subcompartments. Figure 5 shows results for $\lambda = 0.5$ (Fig. 5a) and $\lambda = 2$ (Fig. 5b). Solutions from the PLT model (solid light gray line) (flow-limited regime, $PS/F = 100$) are plotted along with WST (solid dark gray line) and F-TAR (dashed dark gray line) model solutions; all simulations use the slow input, c_{in} (solid black line). The F-TAR and PLT models are indistinguishable in these plots while the WST peak height can differ from these solutions by ~3–5%. Figure 6 demonstrates that when vascular volume is increased ($V_1/V_2 = 0.25$), the WST model becomes an even worse approximation of flow-limited transport. In this case, the F-TAR remains an excellent approximation, but the WST model differs by ~11 and ~17% from the flow-limited two subcompartment/region models for $\lambda = 2$ (Fig. 6b) and $\lambda = 0.5$ (Fig. 6a), respectively.

In summary, the WST model will only match model solutions for the more biophysically detailed flow-limited PLT model or F-TAR model when $\lambda = 1$. Historically, the WST model approximates V_2 as the total tissue compartment, simplifying the determination of outflow concentration to c/λ ; however, this simplification of the tissue compartment under a flow-limited regime is no longer required. Where the WST model fails to adequately handle a range of partition coefficients, the F-TAR model may now be used in PBPK tissue compartment modeling, potentially having broad implications for the field.

Additional considerations

Supplementary materials can be found online (<http://www.springerlink.com/content/1567-567X>). The supplement contains additional discussion of the validity of the TAR approximation and the limiting behavior of PLT and P-TAR models with a number of supplementary figures for rapid and slow inflow kinetics.

Implications for research in pharmacokinetics and toxicokinetics

Herein, a simple formal analysis of a two-region model is carried out to yield quasi-steady state (asymptotic) approximations for the permeability-limited and flow-limited regimes. The derived permeability-limited equations provide the means of simulating permeability-limited transport with a single state variable representing a two-region system (P-TAR),

equivalent to the standard permeability-limited case (PLT). The derived flow-limited equations (F-TAR) are shown to be a first-order improvement over the commonly used well-stirred tank model (WST), without introducing additional parameters or computational complexity and maintaining the distinction between the vascular and extravascular spaces. As a result, the F-TAR model more accurately captures the behavior of a two-region system in the high-permeability limit than the WST model. Though the WST model has been the default PBPK tissue compartment model for decades because it could fit experimental data sufficiently, it may provide less insight compared to F-TAR, particularly given certain drug-specific and tissue-specific properties. As such, avoiding use of the WST model, in favor of the F-TAR model, may be warranted. As demonstrated through the development of the TAR equations and reconsideration of standard tissue compartment models (PLT and WST), careful selection of equations for permeability-limited and flow-limited transport is important to gain the most insight when evaluating the in vivo kinetics of drugs, toxins, nutrients, and endogenous metabolites.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

PBPK tissue compartment model diagrams and equations. **a** Spatially distributed model (Case I; Eqs. 5a, 5b); **b** permeability-limited two-subcompartment (PLT) model (Case II—spatially homogenized, lumped compartmental, Eqs. 7a, 7b; diffusion-limited, Eqs. 2a, 2b); **c** well-stirred tank (WST) model (Case III, flow-limited, or venous equilibrium; Eq. 1); **d** permeability-limited two-region asymptotically reduced (P-TAR) model (Eqs. 12a, 12b); **e** flow-limited two-region asymptotically reduced (F-TAR) model (Eqs. 17a, 17b). Additional conditions for outflow concentrations for the P-TAR and F-TAR models are given in Table

1

Fig. 2.

Comparison of PLT and P-TAR tissue compartment models with rapid inflow kinetics. **a** Inflow concentration (c_{in} , solid black line), concentration in the vascular subcompartment/region (c_1) (PLT model, solid light gray line; P-TAR model, dashed light gray line), and concentration in the extravascular subcompartment/region (c_2) (PLT model, solid dark gray line; P-TAR model, dashed dark gray line). **b** Inflow concentration (c_{in} , solid black line) and outflow concentration (c_{out}) (PLT model, solid gray line; P-TAR model, dashed gray line). Rapid timescale is based on Eq. 24 with simulation time being 200 s, $k_a = 1 \text{ s}^{-1}$, and $k_{el} = 0.05 \text{ s}^{-1}$; physiological parameters: $V_1 = 0.05 \text{ l}$, $V_2 = 0.95 \text{ l}$, $F = 1 \text{ l min}^{-1}$; drug-specific parameters: $\lambda = 1$ and $PS/F = 1$. Arbitrary units (a.u.) of concentration are plotted versus time in seconds. Insets show initial 20 s

Fig. 3.

Comparison of PLT and P-TAR tissue compartment models with slow inflow kinetics. **a** Inflow concentration (c_{in} , solid black line), concentration in the vascular subcompartment/region (c_1) (PLT model, solid light gray line; P-TAR model, dashed light gray line), and concentration in the extravascular subcompartment/region (c_2) (PLT model, solid dark gray line; P-TAR model, dashed dark gray line). **b** Inflow concentration (c_{in} , solid black line) and outflow concentration (c_{out}) (PLT model, solid gray line; P-TAR model, dashed gray line). Slow timescale is based on Eq. 24 with simulation time being 4 h with $k_a = 0.001 \text{ s}^{-1}$ and $k_{el} = 0.0005 \text{ s}^{-1}$; physiological parameters: $V_1 = 0.05 \text{ l}$, $V_2 = 0.95 \text{ l}$, $F = 1 \text{ l min}^{-1}$; drug-specific parameters: $\lambda = 1$ and $PS/F = 1$. Arbitrary units (a.u.) of concentration are plotted versus time in hours. Black arrowheads indicate values trail inflow concentration. Top insets show simulations near peak of time course (in seconds). Bottom insets show initial 30 s

Fig. 4.

Comparison of WST and F-TAR tissue compartment models with rapid inflow kinetics. **a** Inflow concentration (c_{in} , solid black line) and concentration in the overall compartment (c) (WST model, solid light gray line; F-TAR model, dashed dark gray line). **b** Inflow concentration (c_{in} , solid black line) and outflow concentration (c_{out}) (WST model, solid gray line; F-TAR model, dashed gray line). Rapid timescale is based on Eq. 24 with simulation time being 200 s, $k_a = 1 \text{ s}^{-1}$, and $k_{el} = 0.05 \text{ s}^{-1}$; physiological parameters: $V_1 = 0.05 \text{ l}$, $V_2 = 0.95 \text{ l}$, $F = 1 \text{ l min}^{-1}$; drug-specific parameters: $\lambda = 1$ and $PS/F = 1$. Arbitrary units (a.u.) of concentration are plotted versus time in seconds. *Insets* show initial 20 s

Fig. 5.

Comparison of WST, F-TAR, and flow-limited PLT models while varying λ with slow inflow kinetics. **a** $\lambda = 0.5$; **b** $\lambda = 2$. **a, b** Inflow concentration (c_{in} , solid black line) and concentration in the overall compartment (c) (WST model, solid dark gray line; F-TAR model, dashed dark gray line; flow-limited PLT model, solid light gray line). Black arrowhead indicates where WST model solution deviates from flow-limited PLT and F-TAR. Slow timescale is based on Eq. 24 with simulation time being 4 h with $k_a = 0.001 \text{ s}^{-1}$ and $k_{el} = 0.0005 \text{ s}^{-1}$; physiological parameters: $V_1 = 0.05 \text{ l}$, $V_2 = 0.95 \text{ l}$, $F = 1 \text{ l min}^{-1}$; drug-specific parameter: $PS/F = 100$. Arbitrary units (a.u.) of concentration are plotted versus time in hours

Fig. 6.

Comparison of WST, F-TAR, and flow-limited PLT models while varying λ and vascular volume with slow inflow kinetics. **a** $\lambda = 0.5$; **b** $\lambda = 2$. **a, b** Inflow concentration (c_{in} , solid black line) and concentration in the overall compartment (c) (WST model, solid dark gray line; F-TAR model, dashed dark gray line; flow-limited PLT model, solid light gray line). Black arrowhead indicates where WST model solution deviates from flow-limited PLT and F-TAR. Slow timescale is based on Eq. 24 with simulation time being 4 h with $k_a = 0.001 \text{ s}^{-1}$ and $k_{el} = 0.0005 \text{ s}^{-1}$; physiological parameters: $V_1 = 0.2 \text{ l}$, $V_2 = 0.8 \text{ l}$, $F = 1 \text{ l min}^{-1}$; drug-specific parameter: $PS/F = 100$. Arbitrary units (a.u.) of concentration are plotted versus time in hours

Table 1

Basic equations

Step	Permeability-limited TAR (P-TAR) equations
1	$\frac{dc_2^*}{dt} = \frac{F}{V_2} \left(\frac{PS}{1 + PS/F} \right) \left(c_{in} - \frac{c_2}{\lambda} \right)$
2	$c_{out}^* = c_{in} - \frac{1}{F} \left[\frac{V_1}{1 + PS/F} \frac{dc_{in}}{dt} + \left(\frac{V_1 PS/F}{(1 + PS/F)\lambda} + V_2 \right) \frac{dc_2^*}{dt} \right]$
3	$c_{out} = \begin{cases} 0, & c_{out}^* \leq 0 \\ c_{out}^*, & c_{out}^* > 0 \end{cases}$
4	$\text{If } c_{out}^* \leq 0, \frac{dc_2^{**}}{dt} = \frac{(1 + PS/F)Fc_{in} - V_1 dc_{in}/dt}{(PS/F)V_1/\lambda + (1 + PS/F)V_2}$
5	$\frac{dc_2}{dt} = \begin{cases} \frac{F}{V_2} \left(\frac{PS}{1 + PS/F} \right) \left(c_{in} - \frac{c_2}{\lambda} \right), & c_{out}^* > 0 \\ \frac{(1 + PS/F)Fc_{in} - V_1 dc_{in}/dt}{(PS/F)V_1/\lambda + (1 + PS/F)V_2}, & c_{out}^* \leq 0, \frac{dc_2^{**}}{dt} \geq 0 \\ 0, & c_{out}^* \leq 0, \frac{dc_2^{**}}{dt} < 0 \end{cases}$
6	$\text{Solve for } c_2 \text{ and compute } c_1 = \frac{c_{in} + \frac{PS c_2}{F\lambda}}{1 + \frac{PS}{F}}$
Flow-limited TAR (F-TAR) Equations	
1	$c_{out}^* = \left(1 + \frac{V_1}{\lambda V_2} \right) \frac{c_2}{\lambda} - c_{in} \frac{V_1}{\lambda V_2}$
2	$c_{out} = \begin{cases} 0, & c_{out}^* \leq 0 \\ c_{out}^*, & c_{out}^* > 0 \end{cases}$
3	$\frac{dc_2}{dt} = \begin{cases} \frac{Fc_{in}}{V_2 + V_1/\lambda}, & c_{out}^* \leq 0 \\ \frac{F}{V_2} \left(c_{in} - \frac{c_2}{\lambda} \right), & c_{out}^* > 0 \end{cases}$
4	$\text{Solve for } c_2 \text{ and compute } c_1 = \frac{c_2}{\lambda}$