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# An effective time-constant algorithm for drug transport to capillaries and surrounding tissues

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ABSTRACT

Expressions for a single time constant were developed in Maple (Waterloo Maple, Inc.) to calculate the rate at which a drug reaches steady-state levels in the blood capillaries and neighboring tissues. The solute concentration in the capillary region was represented by a one-dimensional convection-diffusion model. In a first case study, the plasma and the tissue reached equilibrium very quickly. Within the dynamic regime, the amount of drugs collected in both compartments increased with the Peclet number while the relaxation time to a steady-state value decreased. A similar conclusion was drawn, in a second case study, when axial and radial diffusive transports were considered important in the lungs or the skin. Also, as the mass transfer Biot number decreased, a larger amount of medication was delivered to the tissue at a given time during the transient period. Additional applications of the approach included the analysis of oxygen transport in peripheral nerves and the design of hollow fibre bioreactors.

## 1. Introduction

The Krogh tissue cylinder has been used to describe oxygen transport to a tissue [1,2]. According to this representation, the capillary bed is surrounded by a homogeneous cylindrical tissue layer. The work of Krogh serves as a basis for building systems that explain how drugs and nutrients reach specific sites in the body [3] and for designing hollow fibre membrane bioreactors to grow tissues [4]. These models assume plug, parabolic or more complex flow profiles in the blood vessel [5]. It is a common practice to write the transport equations in two dimensions (2-D) to provide a detailed description of drug concentrations [6]. This depiction may help increase delivery to specific organs or tissues and provide more accurate information than what can be obtained from traditional physiologically-based pharmacokinetic (PBPK) models. A clearer understanding of solute transport to the brain, for example, can be gained from this strategy.

Currently, the full benefit of the 2-D framework is not exploited effectively because closed-form solutions are not readily available for Krogh cylinder models. Numerical techniques, such as finite-element methods, are routinely applied. Such approaches have notable merit and help predict the level of drug in tissues. However, it is difficult to develop analytical design equations and the estimation of critical physicochemical parameters may be impossible. In particular, no expression exists to determine the time it would take to reach equilibrium concentrations in the blood or tissues. Influences of the Peclet number on the effective time constants ($t_{eff}$) have not been reported. This contribution developed expressions for $t_{eff}$ when radial diffusion in the capillaries is neglected. The limiting case of 1-D perfusion-limited transport is also considered. The algorithms were written in Maple (Waterloo Maple, Inc.).

The advantages of the proposed approach, compare to direct simulation, are:

i) The closed-form expression can be shared easily with scientists who may not be well versed in solving PDEs. They can use a spreadsheet program, such as Microsoft Excel, to study the effects of key design parameters on $t_{eff}$. The tool is attractive to experimentalists with inadequate background in Mathematics, because it does not require the programming of numerical techniques, such as the methods of orthogonal collocations or the numerical method of lines, to solve a system of PDEs.
ii) It is fairly straightforward to use a closed-form expression for $t_{eff}$ to solve optimal design problems. The analytical result is computationally less expensive to apply than a regression algorithm involving partial differential equations.

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## 2. Model

The Krogh cylinder is shown in Fig. 1. In this study, drug transport in the capillaries is governed by a one-dimensional convection-diffusion model:

$$\frac{\partial c_b}{\partial t} + u\frac{\partial c_b}{\partial z} = D_b\frac{\partial^2 c_b}{\partial z^2} \tag{1}$$

or

$$\frac{\partial c_b}{\partial t} + u\frac{\partial c_b}{\partial z} = D_b\frac{\partial^2 c_b}{\partial z^2} + \frac{2\kappa}{R}(c_t|_{r=R} - Kc_b) \tag{2}$$

where $c_b$ is the drug concentration, $u$ is the mean blood velocity and $D_b$ is the diffusion coefficient in the capillary. Plug flow is assumed in this representation [7,8]. Equation (1) represents a case in which the blood flow rate is relatively low. Equation (2) is obtained after taking a control volume and performing a shell balance on the solute in the capillary. In this formulation, the solute flux at the capillary wall is proportional to the concentration difference $(c_t|_{r=R} - Kc_b)$; $\kappa$ is the overall mass transfer coefficient and is a function of the solute permeability across the capillary and a blood side film mass transfer coefficient. The constant $K$ is the partition coefficient.

Two situations are considered in this work:

1. Equilibrium is reached quickly between the capillary and the tissue:

$$R \le r \le aR,\ c_t = Kc_b \tag{3}$$

The equilibrium is achieved instantaneously in the radial direction at each point along the z-axis. In this case, drug transport in the tissue is represented by Eq. (1)

2. The transport rate across the capillary is considered (i.e., Eq. (2)). Axial and radial solute transports are important in the tissue and governed by diffusion [3]:

$$\frac{\partial c_t}{\partial t} = D_t\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial c_t}{\partial r}\right) + \frac{\partial^2 c_t}{\partial z^2}\right] \tag{4}$$

Case 1 (rapid equilibrium with the blood) is often considered in the literature and is referred to as a perfusion-limited model. The analysis assumes a high diffusion coefficient ($D_t$) in the tissue. Case 2 (slow equilibrium with the blood) makes it possible to evaluate the effects of $D_b$ and $u$ on the amount of drug that reaches the tissue. The influence of relevant dimensionless numbers on the time it takes a tissue to become saturated with the drug is of particular interest.

### 2.1. Case 1 (rapid equilibrium with the blood): model and solution

The governing equations in the two compartments are Eqs. (1) and (3). The boundary and initial conditions are [7]

$$z = 0,\ D_b\frac{\partial c_b}{\partial z} = u(c_b - c_{b0}) \tag{5}$$

$$z = L,\ \frac{\partial c_b}{\partial z} = 0 \tag{6}$$

and

$$t = 0,\ c_b = 0 \tag{7}$$

where $c_{b0}$ is the concentration in the blood upstream of the tissue cylinder. Eq. (6) is the Danckwerts' condition, which assumes a zero gradient in the solute concentration at the exit section [9]. It is based on arguments, presented by Danckwerts in his original paper, which led to a continuity in the solute concentration. The equation is not applicable when there is variation in some key properties at the outlet, which would result in a discontinuity.

The variables are made dimensionless:

$$\tau = \frac{tu}{L},\quad Z = \frac{z}{L},\quad C_b = \frac{c_b}{c_{b0}},\quad C_t = \frac{c_t}{c_{b0}},\quad Pe_L = \frac{uL}{D_b} \tag{8}$$

These transformations lead to

$$\frac{\partial C_b}{\partial \tau} + \frac{\partial C_b}{\partial Z} = \frac{1}{Pe_L}\frac{\partial^2 C_b}{\partial Z^2} \tag{9}$$

$$1 \le \rho \le a,\quad C_t = KC_b \tag{10}$$

$$Z = 0,\quad \frac{\partial C_b}{\partial Z} = Pe_L(C_b - 1) \tag{11}$$

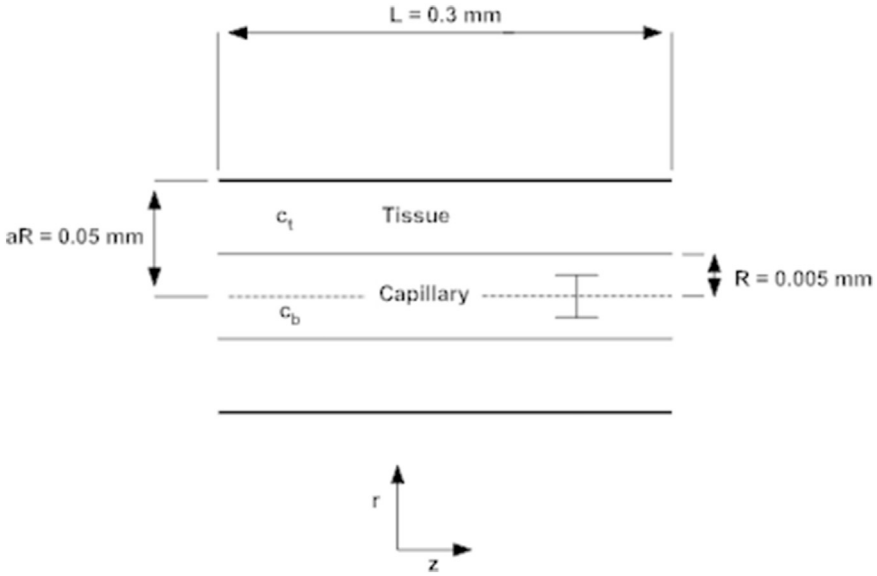


**Fig. 1.** Krogh tissue cylinder model. The concentration in the tissue (radius $R$) and capillary regions (radius $aR$) are represented by $c_t$ and $c_b$, respectively. The figure is not drawn to scale.