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Krogh-cylinder and infinite-domain models for washout of an inert diffusible solute from tissue

Timothy W. Secomb

Department of Physiology, University of Arizona, Tucson, Arizona

Abstract

Objective—Models based on the Krogh-cylinder concept are developed to analyze the washout from tissue by blood flow of an inert diffusible solute that permeates blood vessel walls. During the late phase of washout, the outflowing solute concentration decays exponentially with time. This washout decay rate is predicted for a range of conditions.

Methods—A single capillary is assumed to lie on the axis of a cylindrical tissue region. In the classic “Krogh-cylinder” approach, a no-flux boundary condition is applied on the outside of the cylinder. An alternative “infinite-domain” approach is proposed that allows for solute exchange across the boundary, but with zero net exchange. Both models are analyzed, using finite-element and analytical methods.

Results—The washout decay rate depends on blood flow rate, tissue diffusivity and vessel permeability of solute, and assumed boundary conditions. At low blood flow rates, the washout rate can exceed the value for a single well-mixed compartment. The infinite-domain approach predicts slower washout decay rates than the Krogh-cylinder approach.

Conclusions—The infinite-domain approach overcomes a significant limitation of the Krogh-cylinder approach, while retaining its simplicity. It provides a basis for developing methods to deduce transport properties of inert solutes from observations of washout decay rates.

Keywords

Solute transport; diffusion; microvessels; mathematical models

INTRODUCTION

The transport of solutes by convection in the blood and diffusion in the tissue is fundamental to normal physiological functions and to the delivery and removal of drugs and diagnostic agents in tissues. For example, when an inert diffusible tracer substance is injected into the bloodstream, the subsequent time course of its concentration in the blood depends on its transport properties including the diffusivity in the tissue and the permeability of the vessel walls to the tracer. In principle, the dependence of blood concentration on time can provide information about the transport properties of the circulatory system and the tissue [2].

However, the interpretation of such washout curves is difficult, due to the complexity of vascular network structure and flow, and the interaction between convective and diffusive transport processes. Theoretical models and simulations provide a potential approach for gaining insight into this problem, and there is a long history of such investigations [3, 4, 6, 8, 10, 26].

A number of analyses have been based on the Krogh cylinder model [20, 22, 23], which was originally proposed for analyzing oxygen transport to tissue. In this model, a capillary exchanges oxygen or other solutes only with a surrounding finite cylindrical tissue region. The condition of zero radial solute flux is imposed at the outer edge of the cylinder. The rationale for this assumption is that the tissue cylinder is surrounded by an array of equivalent parallel units (Figure 1A), such that solute levels in adjacent units are identical and no solute exchange would occur. This approach was motivated by the observation that capillaries in skeletal muscle form a parallel array, aligned with the muscle fibers. However, the actual arrangement of capillaries in skeletal muscle shows non-uniform spacing [14, 15], and the points of connection to feeding arterioles and draining venules are not typically aligned across multiple adjacent capillaries [13]. Countercurrent arrangements of vessels may lead to diffusional shunting [9]. In other non-muscle tissue types, parallel alignment of adjacent vessels is largely absent [24, 28]. These features are illustrated schematically in Figure 1B. Therefore, the appropriateness of the Krogh cylinder model is questionable. In particular, the condition of zero diffusive flux on the outer surface of the Krogh cylinder depends on the assumption that the cylinder is surrounded by an array of equivalent tissue regions, which is not typically the case.

An alternative approach for simulating mass transport in the microcirculation is to use experimentally observed three-dimensional structures of microvessel networks. In principle, this approach avoids the limitations of the Krogh model. However, its application requires detailed data on not only the geometrical structure but also the flow and hematocrit distribution of the microvessel network. This approach also requires the solution of a computationally difficult convection-diffusion problem, for which a number of different methods have been used [10, 12, 17, 30]. We developed a Green's function method for the simulation of steady-state transport of oxygen and other solutes [18, 27, 29, 30]. In the course of these studies, it became evident that the choice of boundary condition on the outer surface of the simulated domain has a major impact on the results obtained. Specifically, the use of a zero-flux boundary condition led to an exaggerated occurrence of tissue hypoxia near the boundaries. This resulted from the fact that a zero-flux condition is equivalent to a condition of mirror symmetry in the solution, so that any region not containing a vessel is effectively magnified, particularly when it lies near an edge or corner of the domain. Therefore, we proposed an alternative “infinite-domain” approach, in which the vascular network of interest and associated solute-consuming tissue regions are assumed to be embedded in an infinite domain with which it can exchange solute, with the condition that the net exchange is zero [30]. The infinite-domain approach is also applicable to the case of a single capillary embedded in a cylindrical tissue region.

The goal of the present study is to analyze the washout of an inert diffusible solute from a tissue cylinder with a single central capillary, using both the Krogh-cylinder and the infinite-

domain approaches. It is assumed that the solute is initially introduced in the blood as a brief bolus. After an initial transient behavior that may include a rapid spike of concentration in the outflowing blood, the solute concentrations in the blood and in the tissue eventually approach equilibrium spatial profiles that decay with a single exponential rate. The rate constant of this washout decay provides a useful parameter that characterizes the washout process. It should be noted that washout curves from heterogeneously perfused tissues involve a range of decay rates, which may combine to give power-law behavior of the outflow concentration with time [11]. The present study considers a single vessel with its surrounding tissue, and does not represent this aspect of tissue washout behavior.

This work has several motivations. Firstly, the infinite-domain approach provides a model for capillary-tissue exchange that retains the simplicity of the Krogh-cylinder approach while avoiding the imposition of the zero-flux condition on the outer boundary. The infinite-domain approach is also applicable to simulations with realistic heterogeneous microvascular network structures [30]. Secondly, comparison of the Krogh-cylinder and infinite-domain approaches demonstrates the effects of the assumed boundary conditions on predicted solute washout from a tissue cylinder. Thirdly, these analyses provide reference cases for testing methods designed to simulate solute washout from more complex vascular network structures. Fourthly, the results provide insight into the dependence of the washout decay rate on solute transport parameters.

METHODS

The system to be analyzed consists of a cylindrical capillary containing flowing blood, surrounded by a concentric tissue cylinder, with uniform isotropic diffusion in both regions. We consider an inert solute, whose transport through tissue occurs by passive diffusion with uniform diffusivity D . Within the blood, solute is also transported by convection. Fick's law of diffusion and the principle of conservation of mass lead to

$$\frac{\partial C}{\partial t} - D\nabla^2 C + \mathbf{u} \cdot \nabla C = 0 \quad (1)$$

where C is the concentration in blood or tissue and $\mathbf{u}$ is the blood flow velocity, with $\mathbf{u} = 0$ in the tissue. We assume that a capillary with radius r_c flows through the center of a cylinder of tissue with radius r_t and length L . With cylindrical polar coordinates (r, θ, z) where z is distance along the vessel in the flow direction, and symmetry about the z -axis, eq. (1) gives

$$\frac{\partial C}{\partial t} - D\nabla^2 C + u(r) \frac{\partial C}{\partial z} = 0 \quad \text{where} \quad \nabla^2 C = \frac{1}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C}{\partial r} \right) + \frac{\partial^2 C}{\partial z^2} \quad (2)$$

where $u(r)$ is the velocity. A Poiseuille velocity profile is assumed within the vessel:

$$u(r) = \begin{cases} 2u_0 (1 - r^2/r_c^2) & \text{if } r \leq r_c \\ 0 & \text{if } r > r_c \end{cases} \quad (3)$$

so that the flow rate in the vessel is $Q = \pi r_c^2 u_0$. The vessel wall is assumed to have a permeability P to the solute. The radial diffusive flux in the tissue at the wall equals the rate of solute permeation through the wall:

$$-D \frac{\partial C^t}{\partial r} \Big|_{r=r_c} = -P[C]_{r_c} \quad (4)$$

where $[C]_{r_c}$ denotes the jump in concentration at $r = r_c$, i.e., $C(r_c^+) - C(r_c^-)$. Here, differences of diffusivity or solubility between blood and tissue are neglected for simplicity, but can readily be introduced into the analysis.

We consider the final phase of the washout process, in which the concentration field has an equilibrium spatial profile that decays with a single exponential rate, and seek solutions of the form

$$C = C_0 e^{-\lambda t} \quad (5)$$

where λ is the washout decay rate. Eqs. (2) and (4) give

$$-\lambda C_0 - D \nabla^2 C_0 + u(r) \frac{\partial C_0}{\partial z} = 0 \quad (6)$$

$$D \frac{\partial C_0}{\partial r} \Big|_{r=r_c} = P[C_0]_{r_c} \quad (7)$$

For the analysis of washout, we assume that the inflowing blood contains no solute, i.e. $C_0 = 0$ when $z = 0$ and $r = r_c$.

In the standard Krogh-cylinder approach (Figure 1A), the zero-flux condition is applied on the outer boundaries of the tissue cylinder, i.e. $C_0 / r = 0$ when $r = r_t$, and $C_0 / z = 0$ when $r > r_c$ and $z = 0$ or $z = L$. In the “infinite-domain” approach (Figure 1C), the tissue cylinder is considered to be embedded in a cylindrical “outer region” of radius r_t' , chosen to be much larger than r_t , with zero-flux conditions applied on its outer boundaries. In the outer region ($r_t \leq r \leq r_t'$), the effect of perfusion by other vessels is represented in an approximate, spatially homogeneous way by assuming continuous removal of solute throughout the tissue outer region at a rate proportional to the local concentration. Eq. (5) then becomes

$$-\lambda C_0 + \rho C_0 - D \nabla^2 C_0 = 0 \quad \text{when} \quad r_t \leq r \leq r_t' \quad (8)$$

where the proportionality constant ρ determining the rate of solute removal is chosen to satisfy the condition of zero *net* solute flux across the boundary of the tissue cylinder ($r = r_t$). This approach allows non-zero fluxes across the boundary, as long as they integrate to zero. The main effect of including the outer region is to enhance axial redistribution of solute, which results in reduced axial concentration gradients in the tissue. Application of

the divergence theorem to the outer region shows that $\rho = \lambda$. This condition ensures that the rate of solute removal from the outer region by the homogenized uptake process corresponds to the rate of solute removal from the tissue cylinder by convection in the capillary. Eq. (8) simplifies to

$$D\nabla^2 C_0 = 0 \quad \text{when} \quad r_t \leq r \leq r'_t \quad (9)$$

Solutions for both the Krogh-cylinder approach and the infinite-domain approach were obtained with a general purpose finite-element package (FlexPDE 6, PDE Solutions Inc, Spokane Valley, WA), using an option that allows solution of eigenvalue problems to estimate λ . The problem descriptor file is included in the Supporting Information. Parameter values were chosen to correspond to the case examined by Beard [10] for a single vessel in a cuboidal tissue domain, with the tissue cylinder radius r_t here chosen to give equal tissue cross-section area and the capillary flow velocity chosen to give equal perfusion: $r_t = 28.21 \mu\text{m}$, $r_c = 2.5 \mu\text{m}$, $D = 500 \mu\text{m}^2 \text{s}^{-1}$, $L = 400 \mu\text{m}$, $P = 10 \mu\text{m s}^{-1}$, $u_0 = 424.4 \mu\text{m s}^{-1}$. The assumed values of D and P represent a highly permeable low-molecular-weight solute. The large outer radius was $r'_t = 10r_t$, so that the volume of the outer cylinder was 100 times that of the tissue cylinder. Effects of varying flow velocity were examined.

In addition, an analytic solution was derived for the Krogh cylinder approach. Briefly, solutions to the time-dependent diffusion equation in the tissue were sought by separation of variables, in the form

$$C = (aJ_0(\mu r) + bY_0(\mu r)) e^{\kappa z} e^{-\lambda t} \quad (10)$$

where J_0 and Y_0 are Bessel functions. For given λ , a sequence of solutions for κ and μ was found. A superposition of the three solutions with the values of κ of smallest complex modulus was shown to approximately satisfy the boundary conditions at the ends of the cylinder, when λ was set to a unique specific value. The analytic solution is described in detail in the Supporting Information.

RESULTS

Figure 2 illustrates the axial (z -dependent) variation of concentration in the vessel and tissue regions during the exponential phase of washout, as computed using the Krogh-cylinder approach and the finite-element method. These solutions are multiplied by $e^{-\lambda t}$ where λ is the exponential decay rate. For the assumed parameter values, the vessel wall provides the main barrier to blood-tissue exchange, and the radial variation within the tissue (from $r = r_c$ to $r = r_t$) is small. For low flow velocity ($u_0 = 100 \mu\text{m/s}$), the intravascular concentration equilibrates with the surrounding tissue within a short distance from the entrance, whereas for higher flow velocity ($u_0 = 2000 \mu\text{m/s}$), a substantial gradient across the capillary wall persists for the entire length of the capillary. A notable feature of these results, for both low and high flow velocities, is the presence of a significant axial gradient in concentration within the vessel and the tissue, with higher concentrations at the downstream end.

Figure 3 illustrates the concentration fields in the vessel and tissue regions, as computed using the infinite-domain approach. As in the Krogh-cylinder approach, the radial gradients in concentration increase with increasing capillary flow velocity. In contrast to the Krogh-cylinder approach, however, the infinite-domain approach predicts small axial gradients in concentration in the tissue region. Exchange of solute with the outer region leads to an almost uniform concentration at $r = r_t$. This reflects the averaged effect of surrounding vessels. If the effects of discrete neighboring vessels were included, the concentration would show spatial variations around this level.

Predicted values of the washout decay rate λ are shown in Figure 4, for both models and for a range of capillary flow velocities. These results are expressed relative to the perfusion p , i.e., the blood flow rate divided by the volume of the tissue cylinder:

$$p = \frac{r_c^2 \mu_0}{r_t^2 L} \quad (11)$$

When $u_0 = 424.4 \mu\text{m/s}$, the perfusion is 0.5/min, as assumed by Beard [10]. In the case of solute washout from a single well-mixed compartment, a simple analysis shows that the washout decay rate would equal the perfusion, i.e., $\lambda = p$. Therefore, deviations of λ/p from 1 reflect the effects of factors limiting transport within in the cylindrical domain. As shown in Figure 4, λ/p depends on the assumed velocity. In the limit that the flow velocity goes to zero, the ratio must approach 1, since diffusion then dominates convective effects, leading to a uniform concentration within the domain [8]. An interesting feature of the results is that both models predict $\lambda/p > 1$ for a range of velocities. This can be understood in terms of the axial concentration gradients shown in Figures 2 and 3, with higher tissue concentrations at the downstream end of the cylinder, such that the concentration in the outflowing blood can exceed the average concentration in the tissue, resulting in λ/p values greater than 1. The effect is more pronounced for the Krogh-cylinder approach, due to the steeper axial concentration gradients. This effect occurs in the flow-limited regime, where the diffusivity and permeability are large enough that they do not significantly limit the washout rate [8]. At higher capillary flow velocities, the λ/p ratio declines as a result of disequilibrium between intravascular and tissue concentrations, representing permeability-limited or diffusion-limited regimes [8].

For the Krogh-cylinder approach, Figure 4 shows results from three independent computational methods: the finite-element method, the analytic method (see Supporting Information), and the numerical method of Beard [10] (for $u_0 = 424.4 \mu\text{m/s}$). In the last case, the washout decay rate was estimated by fitting an exponential curve to the published results. Close agreement among all three methods is shown, giving confidence in the finite-element simulations.

The dependence of the ratio λ/p on both the diffusivity D and the permeability P is shown in Figure 5, for a fixed capillary velocity $u_0 = 424.4 \mu\text{m/s}$, using the infinite-domain approach. The axes are also labeled in terms of two dimensionless parameters:

$$N_P = \frac{2LP}{r_c \mu_0} \quad (12)$$

$$N_D = \frac{2LD}{r_c^2 u_0} \quad (13)$$

where N_P and N_D characterize vascular permeability and tissue diffusivity respectively, relative to convective solute transport. For fixed values of N_P and N_D , λ/p is relatively insensitive to the assumed geometrical parameters, decreasing with increasing r_t/r_c and increasing very slightly with L/r_c over relevant ranges of these ratios (results not shown). The wide gray lines indicate an approximate subdivision of the D - P plane into regions where the rate of washout is limited primarily by the blood flow rate (flow limited), by the tissue diffusivity (diffusion limited) and/or by the wall permeability (permeability limited). Diffusivities and permeabilities of biologically relevant solutes range over orders of magnitude, depending on solute size, charge and solubility characteristics, so that both flow-limited and diffusion or permeability-limited regimes can occur.

DISCUSSION

Developed almost a century ago, the Krogh cylinder model [20] provides the theoretical foundation for understanding exchange of oxygen and other solutes between capillaries and tissue. Krogh-type models continue to be used to the present [19]. Several limitations of the Krogh cylinder model have been recognized and a number of modifications have been proposed [16, 19, 21-23, 25]. However, most modifications of the Krogh model retain the assumption of zero radial flux on the outer boundary of the tissue cylinder. In reality, this condition is not satisfied due to the typically irregular arrangement of other vessels surrounding a given capillary. In the “infinite-domain” approach proposed here, the Krogh cylinder is retained, but the condition of zero flux is relaxed to one of zero *net* flux on the outer boundary of the tissue cylinder, by the introduction of a large outer cylindrical region that can exchange solute with the tissue cylinder. As shown by the results presented here, this model leads to significantly different results for the washout behavior of an inert solute. In particular, the axial concentration gradient in the tissue is strongly reduced because the outer region facilitates diffusion from the downstream end of the region to the upstream end. An analogous effect can be achieved by artificially increasing the axial diffusivity within the tissue region, as discussed by Bassingthwaite et al. [7]. The infinite-domain approach represents a potential improvement on the classic Krogh-cylinder approach, while retaining its simplicity.

In this approach, it is assumed that the washout rate of solute throughout the external region is equal to that in the simulated tissue domain. This approach does not include effects of spatial variations in perfusion that are likely to occur in the tissue external to a given tissue cylinder. Such variations can be represented by expanding the modeled tissue domain to contain multiple vessels [30].

An unexpected finding of this study is that the washout rate in the flow-limited regime can exceed the perfusion rate of the tissue. This effect is more prominent with the Krogh-cylinder approach than with the infinite-domain approach (Figure 4), but can exceed 10% even in the infinite-domain model (Figure 5). Although previous studies have noted the development of a standing gradient of concentration within the tissue [5], the elevation in washout decay rate appears not to have been mentioned previously.

Theories for solute washout have the overall goal of allowing interpretation of washout behavior in terms of perfusion and solute transport characteristics. The results shown in Figure 5 represent a step towards this goal. For solutes with high diffusivity and high permeability, such that the flow-limited regime applies, the model predictions imply that the decay rate of the washout tail gives a relatively accurate estimate ($\pm 10\%$) of the tissue perfusion. In contrast, the Krogh-cylinder approach would imply that the discrepancy could be as much as 30% (Figure 4). In the infinite-domain model, diffusive exchange with the outer region results in behavior that more closely approaches the well-mixed case, relative to the Krogh-cylinder approach. The present results support the interpretation of the washout decay rate λ of a highly permeable and diffusible solute as a measure of tissue perfusion p . (If necessary, the estimate of p should be multiplied by the ratio of solubility in tissue vs. blood.)

The present theory applies only to the final decaying phase of the washout process, under the assumption that the solute is delivered as a brief bolus in the inflowing blood. It does not address the time course associated with convective transport of the initial bolus and diffusion of solute into the tissue, or situations in which the inflowing blood contains a persistent solute concentration. The infinite-domain approach could be applied to describe such behavior, but a single exponential decay rate would not generally be applicable.

For solutes that are not highly permeable or not highly diffusible, the present results can in principle be used to provide information about their transport properties, given estimates of the washout decay rate λ and the perfusion p . For a given ratio λ/p , possible D and P values lie on a specific curve in the P - D plane. Observed values of λ/p close to 1 imply flow-limited conditions and place lower bounds on the values of both P and D . In this example, perfusion $p = 0.5/\text{min}$ is assumed. For the assumed geometry, the results depend only on the ratios P/p and D/p , and results for other perfusion levels can be obtained by a simple scaling. The actual geometry of the microvascular system is, of course, much more complex and heterogeneous than can be represented by a single cylinder-type model, and the degree of heterogeneity can affect the washout characteristics [1, 11]. The results presented here provide a prototype and a reference for future analyses using more realistic vascular geometries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PERSPECTIVES

- When a bolus of an inert diffusible tracer is injected into arterial blood, the time course of its washout (concentration in venous blood) can be used to deduce information about tissue perfusion and transport properties.
- Here, a new theoretical model based on the Krogh-cylinder concept is developed and used to predict the exponential decay rate of washout concentration and its dependence on perfusion, solute diffusivity and vessel wall permeability to the solute.
- This model provides a theoretical basis for quantitative assessment of solute washout behavior.

Figure 1.

Schematic illustration of cylinder-type models for exchange of solutes between blood and tissue. In each case, the central tissue cylinder (dark gray) contains a capillary flowing along its axis. A. Krogh cylinder model. The central tissue cylinder is surrounded by an array of equivalent cylinders, such that the condition of zero radial solute flux can be imposed at each point on the outer edge of the cylinder. B. In many tissues, adjacent vessels are not typically aligned with a given capillary. Even vessels that are aligned with the capillary are not fed and drained at the same axial location. C. Infinite-domain approach. The tissue cylinder is assumed to be embedded in an infinite domain with which it can exchange solute, with the condition that the net exchange is zero. This configuration can be approximated by introducing an outer region that is much larger than the tissue region (dashed outline).

Figure 2.

Axial variation of solute concentration during the exponential phase of washout in the vessel ($r = 0$) and in the tissue ($r = r_c$ and $r = r_t$), computed using the Krogh-cylinder approach, for mean capillary flow velocities as indicated, and other parameters as stated in the text.

Figure 3.

Axial variation of solute concentration during the exponential phase of washout in the vessel ($r = 0$) and in the tissue ($r = r_c$ and $r = r_t$), computed using the infinite-domain approach, for capillary mean flow velocities as indicated, and other parameters as stated in the text.

Figure 4.

Predicted values of the ratio of washout decay rate to perfusion (λ/p), for both Krogh-cylinder and infinite-domain models, over a range of capillary flow velocities. Solid curves: results of finite-element calculations. Short dashed curve: results of analytic solution for Krogh model (see Supporting Information). Triangle: numerical result of Beard [10]. Long dashed line: $\lambda/p = 1$, corresponding to the well-mixed case.

Figure 5.

Dependence of the ratio of washout decay rate to perfusion (λ/p) on solute permeability (P) and diffusivity (D) according to the infinite-domain model, for $u_0 = 424.4 \mu\text{m s}^{-1}$. The dependence of λ/p on the dimensionless parameters N_P and N_D , as defined in the text, is also shown. Contours are labeled with the value of λ/p . Wide gray lines represent the approximate boundaries between flow-limited, permeability-limited and diffusion-limited regimes.