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Does anisotropy promote spatial uniformity of stent-delivered drug distribution in arterial tissue?

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ABSTRACT

In this article we investigate the role of anisotropic diffusion on the resulting arterial wall drug distribution following stent-based delivery. The arterial wall is known to exhibit anisotropic diffusive properties, yet many authors neglect this, and it is unclear what effect this simplification has on the resulting arterial wall drug concentrations. Firstly, we explore the justification for neglecting the curvature of the cylindrical arterial wall in favour of using a Cartesian coordinate system. We then proceed to consider three separate transport regimes (convection dominated, diffusion dominated, reaction dominated) based on the range of parameter values available in the literature. By comparing the results of a simple one-dimensional model with those of a fully three-dimensional numerical model, we demonstrate, perhaps surprisingly, that the anisotropic diffusion can promote the spatial uniformity of drug concentrations, and furthermore, that the simple analytical one-dimensional model is an excellent predictor of the three-dimensional numerical results. However, the level of uniformity and the time taken to reach a uniform concentration profile depends on the particular regime considered. Furthermore, the more uniform the profile, the better the agreement between the one-dimensional and three-dimensional models. We discuss the potential implications in clinical practice and in stent design.

1. Introduction

Local drug delivery to the arterial wall is becoming an increasingly common method of tackling restenosis (re-narrowing of the lumen) following percutaneous coronary interventions (PCIs). These PCIs, commonly known as angioplasty, are non-surgical procedures used to treat narrowed arteries as a result of coronary heart disease (CHD). The most common of these PCIs is the insertion of a small mesh-like device called a stent [1], to act as a scaffold and widen the lumen. Some of the methods of reducing restenosis include directly coating the stent with a drug (the so-called drug-eluting stent) and, more recently, by inflating a drug-coated balloon at the required site [2,3]. Modelling the transport of drug from the device through the arterial wall is extremely challenging given the multitude of factors that influence drug distribution. For example, a portion of drug will likely be carried away by the pulsatile flowing blood in the lumen and the drug that enters the arterial wall is subject to diffusion, convection and binding, while at the same time the artery is under the influence of contraction and relaxation. To complicate matters further, the arterial wall is a heterogeneous structure, consisting of three distinct layers with possibly different anisotropic properties in each layer. Notwithstanding, many models of differing dimensionality and different simplifying assumptions have been proposed for modelling the transport through these tissue layers. These models have emanated from the substantial body of work on mass transport in biological tissue which has featured heavily in the literature over the past few decades. We refer the interested reader to the review by Khaled and Vafai [4] for background reading and to the recent work by the same group [5] on mass transport in mammary glands which is an excellent exemplar of a different application of mass transport in biological tissue.

Whilst some authors explicitly account for the curvature of the arterial wall (see e.g. [3]), in the literature it is standard to neglect the curvature so that the resulting model may be written in a Cartesian coordinate framework (see e.g. [6–8]). However, this assumption is never justified mathematically. Tzafriri et al. [7] did, however, state that they had carried out numerical simulations

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Nomenclature

a	arterial inner radius
b	arterial outer radius
c	volume averaged drug concentration
c_0	initial stent drug concentration
D	radial diffusion coefficient
D_1	axial/circumferential diffusion coefficient
Da_1	non-dimensional first Damkohler number
Da_2	non-dimensional second Damkohler number
K	drug absorption rate
L	arterial wall thickness
L_1	half strut separation
L_2	half strut thickness
r	cylindrical radial coordinate
Pe	non-dimensional Peclet number
R	reaction term
t	time
T	non-dimensional time
v	magnitude of transmural velocity
x	Cartesian spatial coordinate
X	non-dimensional spatial coordinate
y	Cartesian spatial coordinate
Y	non-dimensional spatial coordinate
z	Cartesian/cylindrical spatial coordinate
Z	non-dimensional spatial coordinate
α	ratio of arterial wall thickness to half-strut separation
γ	ratio of radial to axial diffusion coefficient
Γ	computational domain
Γ_1	drug containing region of abluminal facing plane
Γ_2	drug containing region of abluminal facing plane
Γ_3	drug-free region of abluminal facing plane
ϵ	ratio of arterial wall thickness to arterial radius
θ	cylindrical circumferential coordinate
$\theta^\star$	wedge angle with abluminal-facing arc length equal to the half strut separation
λ	drug release rate

which illustrated that maximal tissue drug content was 10% lower when neglecting the curvature dependent term. However, this was for a specific set of parameter values. Another common simplification is to treat the arterial wall as a single layer with uni-directional convection and isotropic diffusion properties (see [7,9–12] among others). Coupled with the negligible curvature assumption, this allows the transport equation in the arterial wall to be written in one-dimension as

$$\frac{\partial C}{\partial t} + v\frac{\partial C}{\partial x} = D\frac{\partial^2 C}{\partial x^2} - R, \tag{1.1}$$

where C is the volume-averaged concentration of drug in the arterial wall, v is the magnitude of the transmural convection, D is the diffusion coefficient of drug within the tissue and R is some reaction term to account for the effects of binding. A variety of models for R have been reported (see [1] for a review of these). However, there exists experimental evidence that within each layer anisotropy may be important. For example, diffusion within the tissue has been reported to be anisotropic [13,14] with the diffusion coefficient in the radial direction at least 10 times (and possibly as much as 100 or 1000 times) less than that in the circumferential and axial directions. This anisotropy cannot be captured by a one-dimensional model and it is unclear the effect this simplification has on the resulting concentration profiles.

Realising this, many authors have turned to higher dimensional models. For example, [15,8] both considered a two-dimensional model in a Cartesian geometry, and [16] proposed a two-dimensional model in a cylindrical co-ordinate system. The focus of the work in [15] was on the difference in the transport properties of two commercially available drugs (paclitaxel and sirolimus) and how this can affect the distribution of drug in the arterial wall, while [16] focussed on the influence of strut compression on the drug transport properties of the arterial wall. Zhu et al. [8], on the other hand, were more concerned with the effect of diffusion (in their two-dimensional model) on the resulting arterial wall drug levels. In each case, anisotropic diffusion coefficients were accounted for, with the diffusion coefficient in the radial direction chosen to be different from that in the circumferential direction. Being two-dimensional, these models were unable to study the effect of a different diffusion coefficient in each of the three mutually perpendicular directions.

Weiler et al. [17] provided a broad generalization of the works of [18–20]: a three-dimensional model of drug transport in the lumen and the arterial wall. However, only the steady diffusion equation (no time-dependence, convection nor reaction) was considered in the arterial wall and drug diffusion was assumed to be isotropic. Horner et al. [21] appear to be one of the first groups to provide a three-dimensional reaction–diffusion–convection model in a realistic geometry (obtained using ABAQUS software). Whilst having the advantage of allowing for a variation in the diffusion coefficient in three spatial directions, the authors only considered the case in which the axial and circumferential diffusion coefficients were the same. They also make a number of significant simplifications. Perhaps the most unrealistic assumption is that of a constant drug source: the drug concentration on the stent remains constant and does not deplete.

Whilst not explicitly considering anisotropic diffusion, Saylor et al. [22] most recently attempted to better account for the structure of the arterial wall by presenting a structure-sensitive continuum model of arterial drug deposition. Their model attempts to account explicitly for variations in tissue structure, and they are able to derive a closed form analytical solution of their one-dimensional model, after making some simplifying assumptions. Using their analytical expression, they fit for the unknown material parameters in the model based on ex-vivo experimental data, and they found that the data were well fit by the model.

In this paper, we investigate the role of anisotropic diffusion on the resulting arterial wall drug distribution following stent-based delivery. We start by exploring the justification for neglecting the arterial curvature before investigating the impact of the transport regime (convection dominated, diffusion dominated, reaction dominated) on the uniformity of drug concentrations in the abluminal-facing plane. In this context, the word "uniformity" should be interpreted loosely as the closeness of the numerical drug concentration values in the abluminal-facing plane: the more uniform the drug concentrations are, then the closer their difference is to zero. We then proceed to compare drug concentrations obtained from a one-dimensional model with those from the corresponding three-dimensional anisotropic model. Analytical solutions are derived for the one-dimensional model and the open source computational software openFoam is utilised to compute the three dimensional solution. We conclude by providing recommendations for when a one-dimensional model may reasonably be used and, further, we comment on stent design (in terms of strut thickness and strut spacing) based on our findings and desired clinical outcome.