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A structure-sensitive continuum model of arterial drug deposition

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ABSTRACT

The successful function of drug-eluting devices used in the treatment of atherosclerosis relies on the concentration and retention of the drug in the vessel wall. While drug deposition necessarily depends on the underlying tissue structure, conventional models do not account for the intrinsic structural complexity of arterial tissue and its impact on deposition. By employing only average bulk material properties, the capability to predict the potential for local toxicity or therapeutic failure is limited. To address these limitations, we have developed a model that accounts explicitly for variations in the tissue structure. The approach uses a laminate approximation of the underlying microscopic structure to specify an expression for the continuous spatial dependence of the effective macroscopic material properties. Based on this continuum description, we derive an analytic expression for drug uptake into arterial tissue under typical *ex vivo* experimental conditions. This expression is used to extract relevant material properties for paclitaxel in bovine arteries based on available literature data. The best fit parameters are then used as the basis for numerical simulations of long-term deposition behavior from a stent with a pure paclitaxel coating. The results of these simulations are quantitatively consistent with previously reported *in vivo* observations. We also demonstrate that significant errors can arise in both the interpretation of experimental data and the prediction of drug deposition when structural heterogeneities are ignored. Establishing a robust deposition model can ultimately reduce empiricism in the design of drug-eluting devices, providing a facile means to guide the development and refinement of these technologies.

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1. Introduction

Drug-eluting coatings are featured in a relatively new class of medical products that incorporate controlled-release technologies combined with more traditional devices to improve functionality and performance. A prime example of this technology is the drug-eluting stent (DES), where the presence of cytotoxic or cytostatic drug reduces proliferation of smooth muscle cells (restenosis) after angioplasty compared to bare metal stents [1–3]. Much of the success of DES is attributed to the enhanced concentration and retention of hydrophobic drugs, such as paclitaxel and rapamycin, because they tend to segregate preferentially to specific structural elements in the vessel wall [4]. However, detailed *ex vivo* characterization of drug deposition behavior suggests the segregation can depend strongly upon drug chemistry, animal model, and disease state [4–7]. It is, therefore, important to elucidate and quantify the impact of variations in the underlying tissue structure on arterial drug deposition. A promising, relatively facile method to establish these relationships is to employ computational models of drug deposition. The ability to predict accurately and quantitatively the impact of tissue structure on deposition behavior would enable rapid development and refinement of drug-eluting coating technologies. With a robust model, it may be possible to replace much of the current empiricism used in the design of drug-eluting coatings by a more directed approach, tailoring the design to obtain a desired deposition profile while accounting for potential variations in the target patient population.

In conventional models of arterial drug deposition, it is proposed that the heterogeneous distribution of drug in equilibrium is due to binding sites associated with particular structural elements of the tissue [7–14]. Drug binding at these sites is typically modeled as a reversible, first-order chemical reaction. To date, most of these efforts approximate the artery wall as a monolithic entity with homogeneous properties, which is inconsistent with *ex vivo* studies that have characterized the spatial distribution of drug in the artery wall at equilibrium [4–7]. In certain cases, the wall has been discretized into three or four primary layers, each with different properties [13,14]. However, existing data suggest

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not only that tissue properties vary on a much smaller length scale than can be captured by these primary layers, but also that the magnitude of variation within a layer is on the order, or in excess, of the inter-layer variation [4–7]. Thus, utilizing a simplified model geometry, which necessarily employs only averaged properties, can lead to erroneous predictions. Most notably, neglecting local extrema in the tissue properties limits the ability to capture localized accumulation or absence of drug, which are critical to predicting the potential for local toxicity or therapeutic failure, respectively. While these potential drawbacks are recognized, addressing the intrinsic geometric complexity of arterial tissue by explicitly incorporating all structural elements within the tissue would require establishing a large number of physical properties [14]. Also, incorporating detailed structural geometry would result in analytical solutions that are exceedingly cumbersome, and the experimental data capable of informing such a detailed model are quite limited.

To address these shortcomings, we employ a coarse-grained continuum representation of the variation in the microscopic tissue constituents that comprise the arterial tissue. This enables us to capture explicitly the impact of the underlying structure on transport properties, while requiring only a small, finite set of parameters. We start with a conventional model for tissue binding under the assumptions that the drug is dilute and in local equilibrium. These assumptions result in a relatively simple expression for the spatiotemporal evolution of drug concentration in terms of familiar material properties. Based on this governing equation, we employ standard composite theory for laminate structures that yields a relationship between the macroscopic properties and the properties and distribution of the microscale tissue constituents [15]. By expressing the property variations as a truncated polynomial expansion, we find that the resulting expression is amenable to analytic solution under experimentally relevant conditions, thus providing a closed-form expression that can be used in the analyses of observations typically made in *ex vivo* tissue characterizations.

In this manuscript, we describe the development of the structure-sensitive model for arterial drug deposition and its application to not only extract the salient material properties from experimental observations using the closed-form solution, but also to predict numerically the local drug concentration *in vivo*. We first detail the derivation of the model, relevant boundary conditions, and both analytical and numerical solution methods in the following section. In the subsequent Results section, we describe the application of the model to extract material parameters for paclitaxel, a drug commonly used in DES, from *ex vivo* measurements available in the literature. Also, we present the outcome of numerical predictions based on the extracted parameters under actual use conditions and provide a comparison with previously reported *in vivo* observations in this section. This is followed by a brief discussion of our findings, including the potential drawbacks of neglecting the variation of properties within arterial tissue, before giving a brief overview in the Summary section.

2. Materials and methods

2.1. Model formulation

To develop the model, we begin with the conventional binding site reaction approach [7–14]. In this approach, the vessel tissue is assumed to be comprised of two compartments, one in which the drug can freely flow and one in which the drug is bound. The molar drug concentration in the former compartment will be denoted as F and B in the latter. The conversion between these two drug states is assumed to be controlled by a reversible chemical reaction. Further, the flux of the free drug is assumed to be Fickian and independent of the bound drug, while the flux of the bound drug is assumed to be zero. Based on these assumptions, the following system of equations has been proposed [7–14]:

$$\frac{\partial F}{\partial t} = \nabla \cdot \mathbb{D}\nabla F - R_F F + R_B B, \tag{1a}$$

$$\frac{\partial B}{\partial t} = R_F F - R_B B, \tag{1b}$$

where $\mathbb{D}$ is the diffusion coefficient of the free drug and R_F and R_B are the forward and backward reaction rates, respectively. If the binding reaction is fast relative to the rate of diffusion, i.e. the system is in *local* equilibrium, the concentrations of free and bound drug are no longer independent, and one need only specify the evolution of the total amount of drug, C, to uniquely describe the spatiotemporal behavior of the system. Summing Eq. (1a) and (1b), we can write:

$$\frac{\partial C}{\partial t} = \nabla \cdot \mathbb{D}\nabla F(C). \tag{2}$$

In local equilibrium, i.e. $R_i \gg \mathbb{D}/\lambda^2$ where λ is the characteristic diffusion length scale, the relationship between C and F is given trivially by an equilibrium partition coefficient $S = C/F = (1 + R_F/R_B)$. We further assume the system is dilute, and therefore, R_i and $\mathbb{D}$ are independent of concentration. This is where we begin our analysis, under the assumptions that the system is dilute and in local equilibrium. Although the system properties are assumed independent of concentration, R_i and $\mathbb{D}$ will still depend on the local tissue structure and, therefore, position $\mathbf{r}$ within the tissue. We then let $D \equiv \mathbb{D}/S$ and Eq. (2) can be rewritten as [8]:

$$\frac{\partial C}{\partial t} = \nabla \cdot D\left[\nabla C + CS\nabla\frac{1}{S}\right] = \nabla \cdot DS\nabla\frac{C}{S}. \tag{3}$$

Thus, one need only specify how S and D vary with position, $S = S(\mathbf{r})$ and $D = D(\mathbf{r})$, to completely determine the spatiotemporal dependence of drug concentration. Note that because we assume local equilibrium, there is a well-defined chemical potential μ at each position, and the same expression emerges from irreversible thermodynamics arguments [16] at constant temperature and pressure using the standard definition of μ if the activity coefficient of the drug is given by $1/S$. Therefore, drug molecules will tend to drift away from regions of high potential (low S) and accumulate in regions of low potential (high S), e.g. in regions with high binding affinity. Note that the equation reduces to Fick's law in regions of constant S, gradients in S result in a local drift in drug concentration, and equilibrium requires $\nabla(C/S) = 0$ everywhere.

2.2. Effective material properties

From histology of tissue equilibrated in drug solution *ex vivo*, S has been shown qualitatively to vary at length scales on the order of a few micrometers [6]. These variations are attributed to distinct structural components or micro-phases in arterial tissue, such as elastin, fibrin, collagen, and lipids, that exhibit a lamellar structure parallel to the lumen, e.g. [17,18], and give rise to spatial variations in S [6]. Although it is possible to explicitly incorporate discrete phases into the model, quantitative measurements that can be used to inform the model are taken on a much coarser scale, averaging over these local variations [4–7]. Further, the complexity of analytical solutions that account for the discrete phases can severely limit their utility [19]. Thus, adopting effective macroscopic material properties that are spatially varying on the length scale of the experimental measurements appears to be in order.

To derive expressions for the effective material properties, we first approximate the underlying lamellar structure of the vessel wall as a first-rank laminate, with two alternating discrete phases corresponding to regions of minimum and maximum S oriented