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Numerical modelling of the physical factors that affect mass transport in the vasculature at early time periods

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ABSTRACT

Coronary artery disease results in blockages or narrowing of the artery lumen. Drug eluting stents were developed to replace bare metal stents in an effort to combat re-blocking of the lumen. A key element in determining the therapeutic success of a drug eluting stent is an in-depth understanding of the physical factors that affect mass transport of the drug into the arterial wall, over early time periods. The numerical models developed within this study focus on assessing the influence of a host of physical factors that either facilitate or impede therapeutic drug delivery into the arterial wall from the unit cell of an idealised stent. This study demonstrates that model reduction strategies to 2D and 1D can still adequately represent a 3D curved arterial wall and strut polymer coating, respectively, using an idealistic stent geometry. It was shown that the level of strut compression can have a significant impact on therapeutic drug delivery in the arterial wall.

1. Introduction

Coronary artery disease (CAD) that results in inadequate blood flow to the heart is responsible for 2150 deaths in the US each day, an average of 1 death every 40 s [1]. A key advancement in the treatment of coronary artery disease in recent years has been the introduction of drug eluting stents (DES). These devices enable the controlled delivery of anti-proliferative drugs to the smooth muscle cells (SMC) of the medial layer of the arterial wall. However, these implantable, polymeric-based drug delivery systems have been associated with foreign body reaction and the incidence of late stent thrombosis (LST) [2,3]. No-one is yet certain what specifically causes LST, but there are two main potential culprits: the trace presence of anti-proliferative drug long after the therapeutic time period which can delay endothelialization and hypersensitivity reactions to the polymer, which remains coated to the stent once it has released the majority of its drug loading [4,5]. Furthermore, the long-term sustained drug release from DES has been identified as a culprit of delayed healing, which does increase the risk of LST [6,7]. It has been experimentally shown that after only a 1–3 min exposure time, Paclitaxel can remain detectable in porcine arteries after 180 days [8–10]. In a study by Axel et al. (1997) [11] it was found that even after 20 min of direct cell exposure, Paclitaxel caused a complete and prolonged inhibition of SMC growth. Creel et al. (2000) [12] demonstrated that after Paclitaxel delivery, most of the drug is bound to fixed hydrophobic binding sites, and a smaller quantity is transported via diffusive and convective mechanisms [12,13]. The partitioning of Paclitaxel into the tissues and drug binding slows transport, which explains the accumulation of drug in sites adjacent to drug delivery. Therefore it can be suggested that the long term sustained release of Paclitaxel from a DES over days and months is unnecessary due to its ability to partition slowly in the vessel and long-term tissue levels are regulated by its inherent physicochemical properties.

A key element in determining the therapeutic success of a DES is an in depth understanding of the factors that affect mass transport of the drug to the injured region of the arterial wall.

Some assumptions and simplifications need to be made in order to represent the problem numerically. The endothelium, tunica intima and internal elastic lamina layers are often neglected on the basis that the stent strut penetrates these layers upon deployment [14–19].

However, while the stent may very well penetrate these layers, uncompressed areas that lie in - between struts may still have an intact intima layer. Different authors have made the following assumptions in an effort to simplify their numerical models, such as; modelling the media layer as a homogeneous, one-dimensional layer [15,20]; modelling the media layer as a two-dimensional,

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homogeneous layer in which the effects of tissue cells were evenly distributed [16,21,22]. An examination of histology images taken by Finkelstein et al. (2003) demonstrates that the assumption of strut-media contact does hold some validity, but also cautions that compression of the vascular tissue is also present [23]. Some studies have incorporated strut embedment in the arterial wall into the 2D geometries of numerical models [14,16,17,19,24]. Other studies have developed 3D models that focus on modelling structural deformation of the arterial wall [25–27]. These models provide representations of arterial wall deformation with resulting regional changes in haemodynamics at the strut–luminal interface. However, these models do not account for changes to directional dependent transport properties, as a result of the applied compression.

Drug delivery from a DES is mainly governed by two fundamental mass transport processes which are referred to as blood-side-mass-transport (BSMT) and wall-side-mass-transport (WSMT). BSMT is generally dominated by convection due to the momentum of blood particles through the lumen and numerous studies have shown that in the absence of the intima layer, luminal flow can amplify BSMT into the arterial wall under both steady and periodic flow profile assumptions [28–30]. In addition, convective forces also exist within the arterial wall, as a result of transmural flow set up by the presence of a pressure gradient across the wall [31]. Nonetheless, a more recent study concluded that its effect is negligible and therefore transport within the medial layer can be assumed to be diffusion dominated [30].

Examinations conducted in the current study are; the use of a 1D model to simulate simple diffusion within a stent polymer coating, the choice of boundary condition at the mural surface and representing a 3D idealised stent model in 2D for subsequent numerical modelling of a host of physical factors. Such physical factors that were examined are; the polymer diffusion coefficients, WSMT alone, WSMT coupled with BSMT, compression of the medial layer from stent struts whilst accounting for regional effective diffusivity changes from the applied compression.

2. The physical model

Fig. 1(a) shows a 2D model that was used to represent the unit cell of the 3D idealised curved stented arterial model. Fig. 1(b) shows a side view of the arterial wall and luminal domains in direct contact with a single square stent strut. Also shown in Fig. 1(b) is a 1D schematic that is representative of the polymer coating domain. The models explored in this study are a variation of the 2D schematic presented in Fig. 1(b) previous.

Geometry creation in both 2D and 3D was carried out using commercially available computer aided design software (Creo Elements/Pro 5.0, PTC, MA). In order to deform the uncompressed 2D model presented in Fig. 1(b), the layers of the artery wall were modelled as a single entity in an idealised 2D model [32,33]. Nonlinear elastic Mooney–Rivlin model properties were taken from Feenstra and Taylor (2009) and the model was computed by using prescribed displacements of 100% strut and 50% strut thicknesses respectively using the commercially available Abaqus FEA platform (ABAQUS, Providence, Rhode Island, USA). Aother finite element platform (COMSOL Multiphysics 4.3a, Sweden) was used for mesh generation and to compute solutions to the mathematical models of coupled mass transport. Grid independence was established at

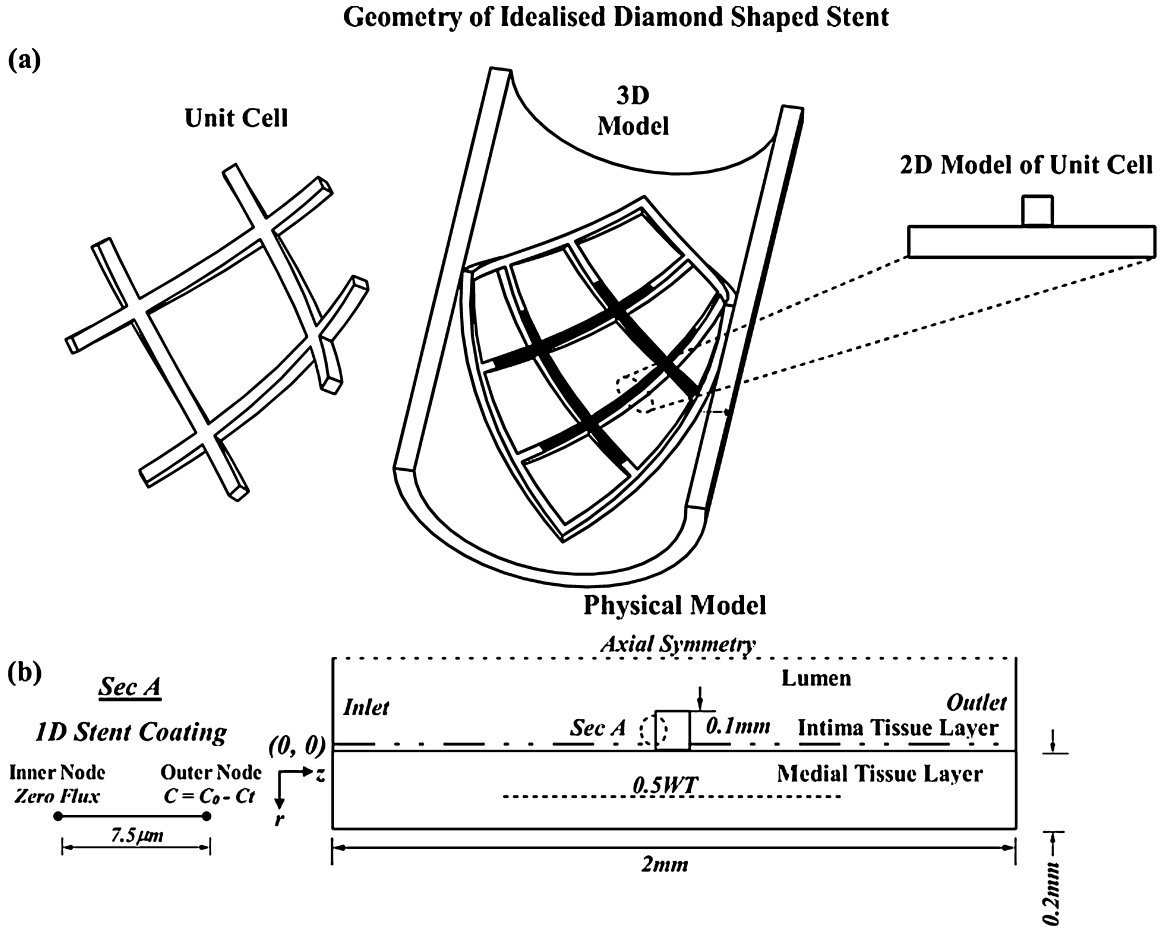

Fig. 1. (a) Model reduction of the unit cell of an idealised diamond shaped stent. (b) Schematic side view diagram of the physical model including a 1D model representing the stent coating.