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Arterial Mass Transport Behaviour of Drugs from Drug Eluting Stents

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1. Introduction

Coronary artery disease (CAD) is the foremost cause of morbidity in the worlds industrialised nations. Consequently our ability in understanding the treatments available and the mechanisms of their success/failure is of particular importance as we strive to improve procedural success rates through the evolution of existing and the innovation of new interventional technologies. Today, the gold standard for treating CAD is to deploy a drug eluting stent (DES) in the blocked artery to first restore luminal blood flow and second to resist the body's tendency to block the artery once more through its overly aggressive healing response known as restenosis. Intrinsically, the understanding of mass transport is elemental to all aspects of DES design from the type of drug used and the polymer release characteristics to the shape and thickness of the stent struts. Design optimisation of DES is vital to achieving increases in procedural success rates as the technology evolves, as is the case for its newest embodiment, the biodegradable DES.
This chapter addresses issues fundamental to drug mass transport from DES, starting with an overview of CAD and associated interventional procedures. DES mass transport theory is then presented and followed by accounts of mass transport problem classifications employed by researchers under a number of deployment scenarios. The importance of experimental mass transport validation is highlighted and a computational investigation is developed to demonstrate how differences in DES deployment conditions alter drug concentrations in the artery wall.

2. Coronary artery disease

Atherosclerosis is a degenerative disease that affects coronary, carotid and other peripheral arteries in the body. Disease formation can occur as early as childhood with the development of fatty streaks within the artery wall. As the aging process progresses, these fatty streaks accumulate to become larger lipid deposits within the artery. This gradual propagation of plaque can be detrimental to the smooth operation of the vasculature. Occlusions ensuing from aggressive atherosclerotic plaque progression can often culminate in an ischemic attack, such as a stroke or a heart attack. CAD pertains to a blockage or narrowing of the coronary arteries that provide oxygen and nutrients vital to the smooth

operation of the heart muscle. Once identified as such, there are a number of interventional procedures available to the cardiologist but the successful emergence of stents, and more recently DES, has seen them become the preferred choice of treatment for CAD, so much so that by the beginning of 2006 more than 8 out of 10 coronary stents were DES (Head et al., 2007) at a cost of between $4 and $5 billion annually (Kaul et al., 2007).

CAD has been intrinsically linked to atherosclerosis since the early 20th century (Chen et al., 2005) and refers to the localisation of disease within the coronary arteries. It is generally asymptomatic and those afflicted often only realise they have the condition when it manifests itself in the form of a heart attack. For this reason CAD is the foremost cause of mortality in the world's industrialised nations (Khakpour &Vafai, 2008). CAD alone is reportedly responsible for approximately 700,000 deaths in the United States of America annually (Kaazempur-Mofrad et al., 2005). Lifestyle choices made by an individual, such as not smoking, regular exercise and a balanced diet, have been shown to influence CAD development but it is the concentration of lipid rich cholesterol in the blood that is considered the most important factor (Sun et al., 2006).

2.1 Traditional interventional procedures

Numerous ways exist to alleviate a stenosis in a coronary artery once detected. The first such interventional procedure commonly practiced was coronary artery bypass graft (CABG) surgery. CABG surgery was successfully performed first by Robert H. Goetz and his team in 1960 at the Albert Einstein College of Medicine (Haller & Olearchyk, 2002). Prior to surgery an angiogram is conducted in order to locate the occlusion within the artery, after which a median sternotomy is performed, which exposes the heart and enables the blocked coronary arteries to be bypassed. This procedure is traumatic for the patient with extensive recovery times and significant scarring to the chest. Furthermore, the long term patency rates of these grafts were moderate and several efforts have been made in vain to optimise downstream graft artery junctions. Despite this, CABG remained the gold standard in the treatment of CAD until 1977 when Andreas Gruntzig first performed percutaneous transluminal coronary angioplasty (PTCA) (Kukreja et al., 2008). CABG is a procedure still used today as not every patient is eligible for minimally invasive surgeries such as PTCA due to highly tortuous or extensively blocked arteries.

Initially PTCA was welcomed by the clinical community due to its minimally invasive approach to arterial stenosis alleviation. A balloon catheter is introduced through an incision in the femoral artery and is manoeuvred through the vasculature until it reaches the stenosis. Once inflated, the balloon pushes the plaque back against the artery wall and enables blood flow to recommence after it has been deflated. The initial success of PTCA was short lived as investigators soon discovered that a substantial percentage of patients, reported to be anywhere between 30% and 60%, experienced recurrent ischemia due to the re-blocking of the artery (restenosis) within the first 6 months. This was attributed to mechanical injury caused by over dilating a device within the vessel (Head et al., 2007).

The next major advance in the field of minimally invasive interventional cardiology came in the early 1990's with the advent of the coronary artery stent (CAS). Prior to surgery a cylindrical metallic scaffold, or stent, is placed on the end of an existing balloon catheter and deployed in the same way as traditional PTCA. Initially, these stents were mounted on the balloon catheter by the physician, however, in more recent times the manufacturers supply the catheters with a stent already in situ. After deployment the stent remains within the artery in an attempt to retain arterial patency. CAS reduced failure rates tobetween 10% and 40% (Duraiswamy et al., 2007; Mongrain et al., 2007) through the elimination of elastic recoil and negative remodelling of the artery associated with PTCA (Costa and Simon, 2005).

2.2 Restenosis and the advent of the drug eluting stent era

Restenosis can best be described as an overly aggressive inflammatory healing response in the artery wall due to the mechanical injury inflicted by balloon/stent expansion. It can be quantified by the reduction of lumen size after an intravascular interventional procedure. The development of restenosis can be described by three processes after PTCA; 1) elastic recoil, 2) arterial negative remodelling and 3) neointimal hyperplasia (Rajagopal&Rockson, 2003). Elastic recoil can occur within an hour of PTCA and is due to passive recoil of the elastic medial layer of the artery. Arterial remodelling on the other hand can be both positive (vessel enlargement) or negative (vessel shrinking) and is characterised as such by a change in vascular dimension. Investigators report contrasting views on the mechanisms behind negative remodelling but whatever the underlying pathology behind vascular remodelling, it is believed to be virtually eliminated when angioplasty is used in conjunction with a stent.

Over inflation of a balloon catheter can result in the fracture of atherosclerotic plaque and in some cases can cause partial fracture of the artery wall (Schwartz et al., 2004). The same crushing/fracturing effect is witnessed when a stent is used in conjunction with an over inflated balloon. However, a stent can also cause excessive injury by penetrating the media which in turn increases neointimal formation. In some extreme cases stents have been known to penetrate as deep as the adventitial layer of the artery (Costa and Simon, 2005). The introduction of the DES to market has gone someway to alleviating the issue of arterial restenosis and excessive vessel injury via stent expansion. Variations of anti-restenotic drugs have been used to coat the stent in order to prevent post-operative in stent restenosis (ISR) and these modern stents can have strut profiles in the order of 80μm which would minimise the possibility of adverse artery wall penetration.

It is generally accepted that one of the main causes of restenosis following BMS implantation is SMC proliferation from the medial artery layer to the injured site. Attempts at systemic drug delivery to inhibit restenosis after stenting failed because effective dosing levels had a toxic effect and could not be tolerated by the patients (Waksman, 2002). Therefore the concept of local drug delivery was developed to redress the issue through the application of a drug eluting coating to the stent platform. This enables site specific local delivery of drugs that can be applied to the injured vessel at the exact location and time that damage occurs. The anti-restenotic coating on DES inhibits the formation of neointimal hyperplasia via suppression of the inflammatory reaction, platelet activation and SMC proliferation, curbing the overly aggressive healing response. Most of the early drugs explored originally were those used as agents for anti-transplant rejection or immunosuppressive drugs (van der Hoeven et al., 2004).

In April 2003 the first DES to gain commercial approval from the Food and Drug Administration (FDA) in the United States was the Cypher stent, which was developed by Cordis Corporation (Miami, FL. USA). The drug used on the Cypher stent is called sirolimus. Boston Scientific's (Natik, MA. USA) TAXUS family of stents were the second DES platform approved by the FDA in March of the following year. The drug employed on the TAXUS stent is called paclitaxel (Venkatraman and Boey, 2007).The first generation DES had a profound effect on reducing restenosis rates compared to bare metal stent (BMS) models. Clinical trials carried out on the Cypher stent (SIRIUS-1) showed restenosis rates of 8.9% after 8 months compared to 36.6% for BMS in the same study. Likewise the TAXUS IV trials heralded a dramatic reduction in restenosis rates when compared to BMS after 9 months, 7.9% versus 26.6% respectively (Venkatraman and Boey, 2007).

A successful DES procedure is defined by its ability to transport the right amount of an appropriate drug within the correct timeframe that will ultimately deem the operation a success through the prevention of ISR. There are aspects of the performance of a DES that can be controlled by the manufacturer which has led to considerable reductions in the instances of ISR, such as the type of drug used and the characteristics of the coating that the drug is stored in. Even the stent shape, thickness and width of the struts can all influence the manner in which the drug is transported. However, the ability for drug uptake within the artery wall is also governed by its interaction with the patient specific arterial environment, making it near impossible to completely eradicate ISR. The degree of initial stenosis, the presence of luminal and abluminal thrombus on the stent and even the advent of re-endothelialisation will all contribute to the DES ability to transport drugs throughout the artery wall.

3. Mass transport theory of drug eluting stents

Mass transport refers to the movement of mass, i.e. the species of interest which is drugs in the case of a DES, within a defined system. This transport of species may be provoked by concentration gradients between two points, but quite often in systems, especially in the vasculature, overpowering complex flow dynamics will ultimately be responsible for the mass transport outcome. In the absence of a free flowing system the presence of these concentration gradients induces diffusion, e.g. between the DES and the artery wall. Mass transport can be broken up into two types within the human vasculature. Firstly blood side mass transport (BSMT) refers to species transport within the vessel lumen and is subject to the haemodynamics therein. Often evanescent due to haemodynamic washout, BSMT can only be effective in transporting anti-proliferative agents to the wall in regions of high recirculation.
The second, and most important, mode of mass transport is in relation to transport within the wall of the artery, referred to as wall side mass transport (WSMT). Along with the properties of the species being transported within the artery wall, WSMT depends on the structural condition of the wall itself, whereby a damaged intimal layer could facilitate accelerated mass transport through to the medial layer. WSMT can be governed by two transport forces, a pressure driven convective force and a diffusive force. The Peclet number (Pe), see equation 11, is a dimensionless parameter that can be used to determine the relative influences of these two forces. A small Pe (i.e. Pe<1) is representative of transport which is dominated by diffusion, while a higher Pe (i.e. Pe>1) indicates convection dominated mass transport (Friedman, 2008).

3.1 Governing equations

Computational Fluid Dynamics has emerged as one of the most powerful numerical tools for engineers, scientists and mathematicians alike. Its foundations are based on theoretical analysis drawn from experimental observations over various branches of physics. The starting point for any computational analysis is the appropriate allocation of the governing equations. These equations are then substituted with equivalent numerical descriptions that are then solved using appropriate mathematical techniques. There are a number of numerical techniques available that will return a solution to a specified problem. Two of the more popular methods are the Finite Volume Method and the Finite Element Method. The assumptions generally applied when modelling fluid flow problems of this nature are as follows:

- The flow is incompressible and isothermal
- The fluid is Newtonian and possesses constant physical properties
- Flow is considered to be laminar

3.1.1 Conservation of mass: Continuity equation

The conservation of mass is a form of continuity equation which states the net mass flow into a control volume is equal to the rate at which mass leaves the control volume. That is providing there are no sinks or sources within the control volume. The differential form of the equation can be obtained by simply considering the flow into and out of elementary control volume. For the Cartesian co-ordinate system, having coordinates x, y, z referenced to a stationary frame with the corresponding velocity components u, v, w (m/s), the continuity equation can be written as:

$$\frac{\partial \rho}{\partial t} + \frac{\partial (\rho u)}{\partial x} + \frac{\partial (\rho v)}{\partial y} + \frac{\partial (\rho w)}{\partial z} = 0 \tag{1}$$

Where the density (ρ, kg/m^3) is a constant, as is the case of incompressible flow, this reduces further to a volume continuity equation.

$$\frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} + \frac{\partial w}{\partial z} = 0 \tag{2}$$

3.1.2 Balance of momentum: Navier-Stokes Equations

The balance of momentum is derived from Newton's second law of motion, which states that the rate of change of momentum of a fluid particle is equal to the sum of the forces on the particle. The Navier-Stokes Equations describe the full three dimensional, viscous nature of fluid motion in a control system:

$$\begin{aligned}
\rho \frac{\partial u}{\partial t} &= -\frac{\partial P}{\partial x} + \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) \\
\rho \frac{\partial v}{\partial t} &= -\frac{\partial P}{\partial y} + \mu \left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2} \right) \\
\rho \frac{\partial w}{\partial t} &= -\frac{\partial P}{\partial z} + \mu \left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2} \right)
\end{aligned} \tag{3}$$

Where μ(Pa s) is dynamic viscosity and P(Pa) is pressure. Due to the porous nature of the artery wall, flow within it must consider the influence of the tissues permeability. Therefore the flow within the wall is assumed to follow Darcy's law and is demonstrated (in the x direction) by the inclusion of the permeability term in equation 4, where K(m^2) is the permeability of the arterial tissue.

$$\rho \frac{\partial u}{\partial t} = -\frac{\partial P}{\partial x} + \mu \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) - \left(\frac{\mu}{K} \right) u \tag{4}$$

3.1.3 Fick's laws of diffusion

Species transport via diffusion is a process driven by concentration gradients between two locations. Fick's first law can be used to describe the diffusional flux (J_x, mol/m²s) of such species, shown in 1D in equation 5, where D(m²/s) is diffusivity and c is concentration (mol/m³):

$$J_x = -D\frac{\partial c}{\partial x} \tag{5}$$

The negative term in equation 5 indicates that the flux is positive in the presence of a negative concentration gradient. Biological mass transport often requires the application of a time-dependent mass transport process that can predict variations in concentration over time. Fick's second law (equation 6) can provide such a relationship and is defined here in one dimension:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \tag{6}$$

3.1.4 Conservation of species: Convection-diffusion equation

The addition of a convective term, equal to the product of the fluid velocity and the local concentration, to equation 6 demonstrates the 3D transport of species in a flowing solution. This is known as the convection-diffusion equation.

$$\frac{\partial c}{\partial t} + u\frac{\partial c}{\partial x} + v\frac{\partial c}{\partial y} + w\frac{\partial c}{\partial z} = D\left(\frac{\partial^2 c}{\partial x^2} + \frac{\partial^2 c}{\partial y^2} + \frac{\partial^2 c}{\partial w^2}\right) \tag{7}$$

3.1.5 Ratio of convective to diffusive forces

The Peclet number (Pe) is a dimensionless number that determines the relative contribution of convective and diffusive forces to species transport within a defined system. It can be defined as a product of the Reynolds number (Re) and the Schmidt number (Sc).

$$Pe = Re.Sc \tag{8}$$

The Reynolds number is a non-dimensional parameter concerning fluid forces due to viscosity and inertia and is essentially used to determine whether a flow is laminar, transitional or turbulent in nature. For example a Reynolds number of approximately 90 can be obtained for a mean arterial velocity (u) of 0.1m/s in an artery with a diameter (a) of 3mm. When considering transmural flow through the porous artery wall the value $a$would represent the thickness of the porous wall.

$$Re = \frac{\rho u a}{\mu} \tag{9}$$

The Schmidt number (Sc) is defined as the ratio of kinematic viscosity (υ, m²/s) to diffusivity (D).

$$Sc = \frac{\upsilon}{D} = \frac{\mu}{\rho D} \tag{10}$$

Substituting equations 9 and 10 into 8 describes how convective and diffusive forces can influence the outcome of the Peclet number.

$$Pe = \frac{ua}{D} \tag{11}$$

3.1.6 Diffusion in porous materials

When considering diffusion in a fluid saturated porous media, as is the case with the artery wall, diffusion takes place over a tortuous path. Because these pores are not straight, the distance over which diffusion takes place becomes effectively longer than for a homogenous material of the same thickness. The effective diffusivity (D_{eff}) can therefore be deduced by considering the impact of the materials structure on the species free diffusivity (D_{free}). The effective diffusivity of a porous material is a function of its porosity (ε) and tortuosity (τ).

$$D_{eff} = \frac{\varepsilon}{\tau} D_{free} \tag{12}$$

One of the more common ways to determine the free diffusivity of a species in a solvent is to use the Stokes-Einstein equation (13), where k(J/K) is the Boltzmann constant, T(K) is temperature and R(m) is the radius of the solute. For the purpose of diffusion in the artery wall, this solvent is considered to be plasma.

$$D_{free} = \frac{kT}{6\pi\mu R} \tag{13}$$

The radius of the solute can be calculated from equation 14 assuming that the particle is spherical in shape, where M(Kg/mol) is the solute molecular weight and Na(mol^{-1}) is Avogadro's number.

$$R = \left(\frac{3M}{4\pi\rho Na} \right)^{1/3} \tag{14}$$

The structure of the porous medium is defined by the tortuosity(τ) of its porous network (15) and by the porosity(ε) (16) of the material itself.

$$\tau = \frac{L}{X} \tag{15}$$

Where L = pore path length and X = distance between beginning and end of the pore path.

$$\varepsilon = \frac{Pore\,Volume}{Total\,Volume} \tag{16}$$

4. Problem classification

In reality the classification of problems of this nature are inherently patient specific and as such no one representation of the problem is correct. However, there are innate similarities between patients. Blood flow within the vasculature is a highly complex 3D process to model given the pulsatile nature of arterial haemodynamics. Coupled with this pulsatile

process, the coronary arteries are situated on the surface of the heart and as such are subject to cyclic motion due to the beating of the organ. Therefore the modelling of drug transport from a DES in these arteries is multifaceted in nature, comprising of both luminal and artery wall mass transport, the latter of which may also be subject to a reaction giving that some drug may bind to the arterial tissue. The introduction of a multi-layered artery wall to the model increases the complexity of the domain even further. So to what extent does one go to when modelling DES mass transport?

Comprehensively modelling the behaviour of a DES computationally over a given time period would require the application of the following *in vivo* conditions experience by the device.

- The DES would have to be placed in multi-layered diseased artery.
- Both BSMT and WSMT would have to be considered.
- The real time occurrence of thrombus formation and re-endothelialisation under pulsating flow conditions would need to be modelled.
- The structural deformation of the artery wall due to DES deployment would need to be taken into account.
- Also the movement of the vessel in space due to its location on the surface of the beating heart and how this may alter depending on the extent of the patient's physical activeness would have to be considered.

In light of the computational requirements to undertake such a model it is possible, and almost necessary, to make certain assumptions in order to simplify both BSMT and WSMT models whilst retaining enough detail of the actual model to draw relevant conclusions from the analysis.

The implementation of an arterial pulse and a beating heart are neglected by most researchers. Often the artery is modelled as rigid in space in order to analyse mass transport post DES deployment. This is an effective assumption but one must consider the deformation of the artery wall due to the dynamic expansion of the stent, as this can have an impact on the mass transport outcome due to the porous nature of the wall and the compression it incurs upon stent expansion. As for the application of laminar blood flow, it can be seen that the majority of drug that enters the artery wall from the DES does so via physical contact with the wall and the drugs emanating from the areas of the stent exposed to flow, be it laminar or pulsatile, are predominantly carried downstream.

4.1 Artery wall classification

Arteries transport oxygen rich blood around the body providing essential nutrients to vital organs. The artery wall consists of a complex multilayer porous substructure with an interstitial phase comprising predominantly of plasma. In a healthy artery this substructure (Figure 1) is comprised of three concentric layers; the tunica intima, the tunica media and the tunica adventitia. The tunica intima is the innermost layer, consisting of a single layer of endothelial cells and a subendothelial layer mainly consisting of delicate connective tissues and collagen fibres. The outer boundary of the tunica intima is surrounded by an elastic tissue with fenestral pores known as the internal elastic lamina (IEL). The medial layer consists primarily of concentric sheets of smooth muscle cells (SMC) within a loose connective tissue framework. This configuration of SMC enables the artery wall to contract and relax. The tunica media and the tunica adventitia are separated by another thin band of elastic fibres known as the external elastic lamina (EEL). The outermost layer of the artery, the tunica adventitia, is comprised of connective tissue fibres and some capillaries. These

fibres blend into the surrounding connective tissues and aid in stabilising the arteries within the body (Khakpour and Vafai, 2007).

The target layer for the anti-restenotic drugs is the tunica media, where the SMC reside, and quite often computational studies will consider just this arterial layer not only because of this fact but also due to the possible erosion of the tunica intima upon stent deployment. Regardless of the level of complexity modelled, the artery wall is porous in composition and drug transport is facilitated through the surrounding plasma not only via diffusion but there is also the presence of a transmural velocity due to a pressure gradient observed across the artery wall. However, the presence of arterial plaque will reduce the magnitude of this transmural velocity and can even stem it altogether. As DES are deployed in highly occluded arteries it is reasonable to reduce the complexity of the problem by neglecting convection in the wall. Equation 12 gives us an indication of how arterial properties such as porosity, tortuosity and free diffusivity can influence the transport of drugs within the respective artery wall layers. The compression of these layers will alter these properties which in turn may inhibit the transport of species as governed by the mass transport equations. The compression of a porous structure not only reduces the materials porosity but it results in the creation of a more arduous pore path over which mass transport would normally occur. The combination of a reduced porosity with an increased tortuosity, when the artery wall has been compressed, has a net effect of reducing the effective diffusivity thus hindering mass transport within the vessel.

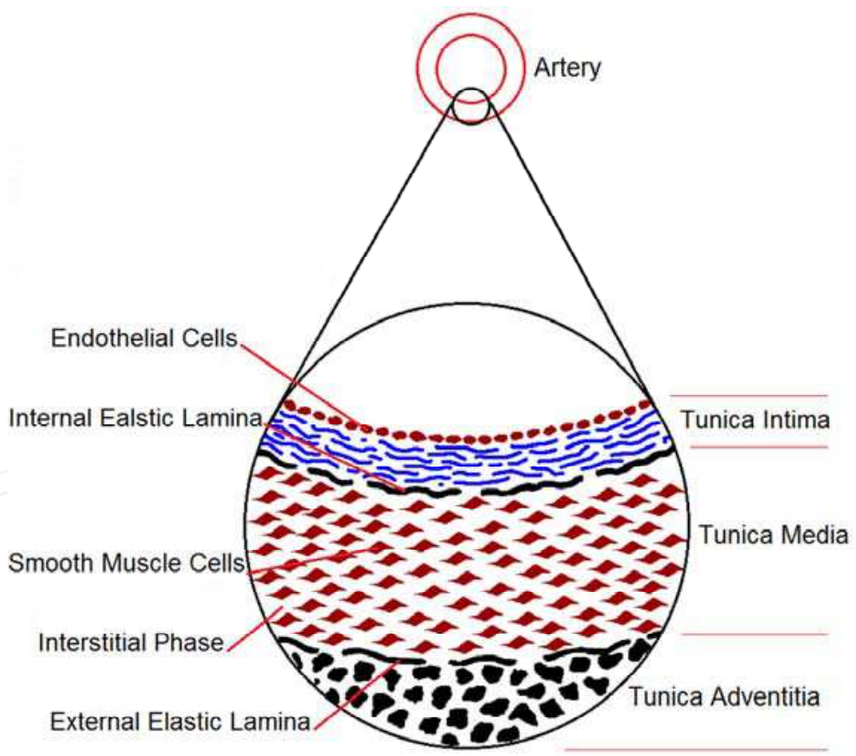

Fig. 1. Illustration of the cross-sectional structure of a healthy artery wall.

4.2 Influence of thrombus

Hwang et al. (2005) were among the first to explore the influence of thrombus height, width and type on the arterial drug uptake. Stents can be deployed at sites of thrombus and after

implantation a clot will inevitably develop once the struts become covered with plasma proteins. In most cases this will not be angiographically present or clinically evident but even a fine layer of clotting blood deposited on the surface of the DES can alter drug distribution within the wall. The presence of clot alters the local environment of the stent strut and the physiological transport forces that regulate arterial uptake and retention. Balakrishnan et al.(2008) reported that drug eluting stents clot at a rate of 0.6% each year after implantation for up to 3 years. Strut position within a clot also has a major influence on the arterial uptake. The greater the volume of clot covering the strut, and the closer the strut is to the wall, creates improved conditions for greater drug delivery. Hwang et al. (2005) discovered that in this configuration concentration distribution in the wall can be 30 fold higher than situations where no clot is present. Similarly thrombus or plaque between the strut and the artery wall act as a buffer layer and reduce wall concentrations. Clot diffusivities higher than that of the artery wall will result in drug transfer to the blood at a rate faster than can be absorbed by the wall. Clots with diffusivities equal to or lower than the artery wall can transport drugs to the wall at a rate where the wall can effectively absorb the drugs, thus reducing drug loss to the bloodstream.

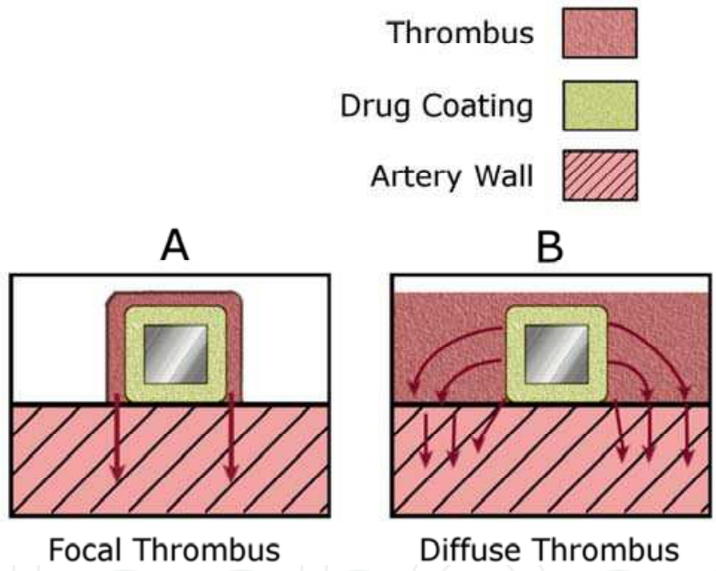

Fig. 2. An illustration of how Focal (A) and Diffuse (B) thrombus, surrounding a DES strut, contribute to drug mass transport within the artery wall.

In 2008, Balakrishnan et al. demonstrated how variations in thrombus size and distribution contribute to fluctuating arterial drug intensities (Figure 2). Their simulations indicate that thrombus cannot influence the slow rate of drug release from the stent because the polymer resistance to drug transport is significantly greater than that of the thrombus, which is consistent with *in vivo* experimental drug release. Focal thrombus, with a thickness of 0.1mm, increased peak average drug concentration by 80%. Greater clot formation between stent struts will also have an effect on arterial concentrations because once the species is transported within the clot it effectively increases the surface area from which the artery wall can absorb drugs. The formation of this interstrut thrombus, described as diffuse thrombus, acts as a shield from drug washout and culminates in an increase in arterial concentration by up to 3.5-fold.

The variability of thrombus can have a major impact on arterial drug concentrations. It can aid in drug uptake and retention within the wall when it covers the stent, but too much thrombus will effectively block the artery, thus creating a problem that the DES aimed to alleviate. Also it can act as a barrier in preventing drugs from reaching the wall when it is located between the strut and the wall. The likely scenario following DES implantation within the vasculature is that at some location along the length of the stent each of these situations will be present. In addition to issues arising from the development of thrombus, the presence of plaque in a freshly stented artery will have a similar effect on mass transport but does so immediately upon implantation, as opposed to thrombus which develops with time. The initial presence of the plaque coupled with the time dependent formation of thrombus, and even the occurrence of re-endothelialisation, would create a realistic stenting scenario if modelled but the volume and formation of these will be different for each person. So to what extent does one model this?

4.3 Polymer and drug characterisation

Stent coatings play a vital role in the regulation of drug release from the stent. Careful consideration must be observed when allocating a polymer as a drug carrier for a DES. If the polymer is not biocompatible an inflammatory response ensues. It has been shown that the development of neointimal hyperplasia can be doubled when certain polymer configurations are used compared with a controlled substance (Granada et al., 2003). Each biologically viable polymer must be able to endure the stresses exerted when stents are deployed, resist cracking, peeling and maintain their physiochemical properties after sterilisation. Drug release rates can be altered with the addition of an extra layer of polymer coating to modulate between slow and fast release formulations. This adds an extra degree of complexity when designing functional DES and indeed analysing them computationally.

Sirolimus, everolimus and paclitaxel were among the first anti-restenotic agents used in DES. Sirolimus, or rapamycin, is a naturally occurring macrocyclic lactone. It was approved by the FDA in 1999 for the prophylaxis of renal transplant rejection because of its potent immunosuppressive properties (Costa & Simon, 2005). Essentially sirolimus inhibits the activation of multiple kinases, associated with cell proliferation, resulting in the cessation of cellular division between the G1/S phases and is said to be cytostatic in nature (Burt & Hunter, 2006). Everolimus is an analogue of the sirolimus immunosuppressant which binds to cytosolic immunophillin FKBP12. It is very similar to sirolimus in that it prevents the cellular division between the G1/S phases of the cell cycle therefore inhibiting SMC proliferation (Stone et al., 2008).

Paclitaxel is a naturally occurring drug that was originally extracted from the pacific yew tree Taxusbrevifolia. It was initially used to treat several types of cancer such as breast and ovarian cancer (Tanabe et al., 2004). Like sirolimus and everolimus, paclitaxel is effective in reducing restenosis but it does so in a manner that results in cell death, suggesting that it works through a cytotoxic mechanism (Parry et al., 2005). Paclitaxel achieves its anti-proliferative effects by binding to aminoterminus β-tubulin thus disrupting microtubule dynamics. This results in the arrest of cells at the M stage and even G2 stages of the cell cycle, leading to cell death (Hara et al., 2006). Due to its lipophilic properties paclitaxel has been known to be loaded directly onto stents without a polymer coating but there could be potential implications with regards to a lack of controlled release (Burt & Hunter, 2006).

4.4 DES problem design and deployment

This problem can be approached in one of two ways, do you a) want to compare the mass transport capabilities between different stent designs or b) want to analyse arterial mass transport for a single stent design under various stenting and artery wall conditions. The latter of which is of more initial interest because a comprehensive understanding of a multifaceted mass transport study with a generic stent design will give a greater understanding of the interactions between drug/polymer characteristics and the arterial condition. Once these interactions are better understood the researcher can revert to comparing stent designs for a predetermined deployment configuration.

The main goal of a DES is to prevent the onslaught of arterial restenosis, which occurs in part due to damage inflicted on the artery during stent deployment. However, researchers to date have generally neglected the artery wall damage induced and its influence on mass transport. An exploratory DES mass transport computational study, even if it is only 2D modelling, should consider both cause and effect. A stent should not just be placed flush with the artery wall, there is going to be some wall indentation and intimal damage, the extent of which is a study onto itself. To this end the resulting artery wall compression will alter the effect that is the transport of the anti-restenotic drugs throughout the artery wall. Stent design and drug/polymer properties, although of significant importance, should be a secondary consideration until these fundamental issues have been addressed.

5. Typical computational boundary conditions for DES models

Once the governing equations have been applied to the model domain the boundary conditions need to be allocated. Often with biological modelling it is necessary to make assumptions when applying boundary conditions. For example treating the artery wall as rigid (Mongrain et al., 2007; Devereux, 2005; Kaazempur-Mofrad and Ethier, 2001) or assuming that mass transport within the wall is modulated solely by diffusion (Balakrishnan et al., 2008, 2007, 2005; Mongrain et al., 2007, 2005) are two examples of ways commonly employed to simplify what is in reality a very complex problem. However, as previously mentioned the fundamental *in vivo* issues should be taken into account as much as possible when applying such simplifications.

5.1 Application of momentum boundary conditions

5.1.1 Inlet: Velocity

The heart is a muscular organ that undergoes repetitive contraction and relaxation of its walls in order to propel blood through the circulatory system. Coupled with the complex geometry of the coronary arteries, the pulsating blood velocity profile is an integral part in the mass transport behaviour of blood borne species. However, when considering the transport of drugs from a DES a common assumption to make is the presence of a steady fully developed flow profile within the lumen (Balakrishnan et al., 2008, 2007, 2005; Mongrain et al., 2007, 2005). When modelling BSMT it may be necessary to incorporate the time-dependent pulsatile nature of blood flow. However, the transient nature of blood side drug transport enables the assumption of a steady flow inlet boundary condition that in most cases will not have a considerable impact on WSMT. Arterial flow can be replicated by applying a pulsatile parabolic velocity profile at the vessels inlet.

5.1.2 Outlet: Pressure

A pressure of zero can be applied to the outlet of DES computational models which reduces the likelihood of encountering backflow through the outlet. The application of such a boundary condition is prevalent in mass transport studies of this nature (Kolachalama et al., 2009; Balakrishnan et al., 2008, 2007, 2005; Rajamohan et al., 2006).

5.1.3 Lumen-wall interface: No-slip

The no-slip boundary condition is standard for a model with a stationary wall and states that the velocity of the fluid is zero relative to the boundary (O'Brien et al., 2005; Walsh et al., 2003).

5.1.4 Axial-symmetry

Due to the idealised nature of some arterial computational models the use of an axial-symmetry boundary condition can greatly reduce the number of degrees of freedom that need to be solved for. This will reduce the computational demand without having to sacrifice the accuracy of the analysis. The Reynolds number for blood flow in DES computational models is normally small (Re<100), indicating laminar flow and as such the application of the axial-symmetry boundary condition should not influence the fluid flow solution.

5.2 Application of mass transport boundary conditions

5.2.1 Luminal inlet: Concentration

Because mass transport within the artery's lumen is convection dominated, it would be virtually impossible for drugs to diffuse in the direction opposing blood flow. Therefore it can be assumed that the luminal inlet concentration has a constant value equal to zero. This boundary condition has been used extensively in mass transport studies on DES (Balakrishnan et al., 2008, 2007, 2005; Mongrain et al., 2007, 2005).

5.2.2 Luminal outlet: Convective flux

A convective flux outflow condition is generally imposed on the outlet of a models lumen, resulting in a zero concentration gradient at the outlet. This boundary condition assumes that all the mass passing through the boundary is convection dominated.

5.2.3 Lumen-stent-wall interface: Continuity

A common assumption for DES mass transport studies is that the intimal layers of the artery are denuded and that the stent is in direct contact with the medial layer of the artery wall (Kolachalama et al., 2009; Balakrishnan et al., 2008, 2007, 2005; Mongrain et al., 2007, 2005). This negates the need to model the endothelial, intima and internal elastic lamina layers. Regardless of the inclusion or exclusion of these layers the continuity equation should be the default setting for all interior boundaries. This condition states that in the absence of sources or sinks, the flux in the normal direction is continuous across the boundary, i.e. the concentration is equal on both sides of the boundary.

5.2.4 External faces: Insulation/symmetry

This condition is specified at the perivascular wall and at the up- and down-stream wall boundaries, which should be a sufficient distance away from the stent. It specifies where the domain is well insulated or it can reduce the size of a model by taking advantage of

symmetry. Intuitively this condition states that the gradient across the boundary must be zero, therefore it is impermeable to mass transport.

6. Experimental validation of mass transport behaviour

Historically, experimental validations have been necessary to prove researchers hypotheses across all paradigms of science. In order to validate a theory one must not only be mindful of their goal but also their ability to achieve it. For instance, trying to validate a computational DES model using excised arterial DES would be nice in theory but in practice may prove fruitless because it would be near impossible to obtain the site specific drug concentrations within the artery wall, necessary for the researcher to examine the nuances of stent design that they are interested in analysing. It is often useful to validate a single aspect of the model if possible. With regards to DES, a solitary WSMT model may be acceptable,as a vast body of knowledge pertaining to fluid flow problems already exists, unlike the as of yet mature understanding of WSMT and how the behaviour of the porous artery wall and other pertinent features influence the mass transport therein.

Figure 3 illustrates an example of a validation flowchart for a study of mass transport from DES. The first process in designing a validation experiment is to analyse the problem as a whole and see what you would like to prove. Then certain aspects of the problem that are relatively rudimentary can be neglected from the validation, providing they won't have a fundamental impact on the outcome of the test. The flowchart is divided up into two streams that are developed jointly in order to achieve a desired validation. The experimental mass transport validation is on the left and the development of the corresponding computational mass transport model is on the right. In both streams BSMT is not highlighted for inclusion in this example's validation procedure. This may be due to the readily available examples of validations of this nature in literature or its minimal impact on the outcome of the results. This study was designed to investigate instances of WSMT in relation to DES design and deployment.

How accurate do you want your computational model to be and what assumptions are going to be made? The flowchart (Figure 3) describing this example validation decided to neglect convection-diffusion mass transport in the artery wall and concentrate on validating a diffusion only model. The reason for such a decision could be threefold; 1) an artery requiring a DES would be highly calcified and therefore the plaque can act as a buffer to stop or considerably reduce the flow in the porous wall, 2) an analysis of the Peclet number (equation 8) demonstrates diffusion dominated transport for a give drug or 3) the inability to create and obtain tangible results from an applicable experimental model with both convection and diffusion. The next aspect of the computational model is the characterisation of the artery wall, i.e. should it be modelled as a porous medium. Although flow in the wall has been neglected the application of a porous wall still can have a bearing on the outcome of mass transport due to the characterisation of the effective diffusivity and its propensity to change under varying stenting conditions (equation 12).

In this example a computational model has been identified in which many of the aspects of the *in vivo* stenting conditions remain but more importantly contains the ability to develop and analyse a corresponding experimental validation. Validations of this nature are a powerful tool in a researchers arsenal because once the initial hypotheses has been validated the computational model can be changed to any geometry imaginable to create more realistic stenting scenarios, and when solving the problem using the same physics one can have full confidence in the results.

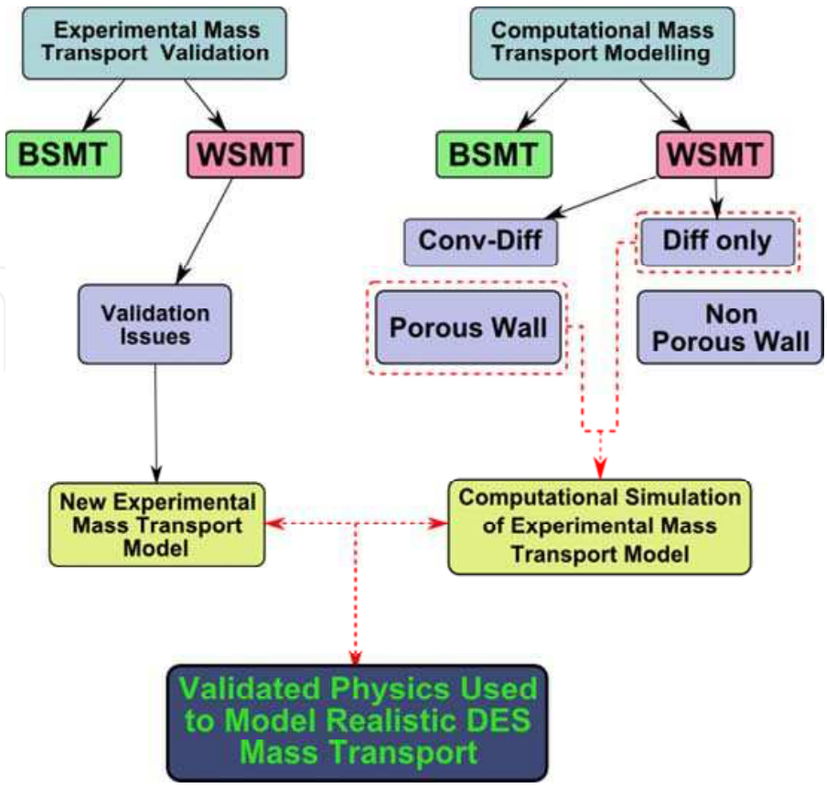

Fig. 3. Flowchart demonstrating the process of identifying an appropriate route for the experimental validation of DES mass transport.

6.1 Historical experimental mass transport validations

Experimental techniques to simulate mass transport in the vasculature have been an integral part in the development of DES. Various techniques can be applied depending on the required outcome from the analysis. For example if lumen transport is to be analysed a common approach would be to introduce a dye to a flowing system. Concentrations are then measured at certain time points and locations by withdrawing fluid samples so that the optical dye intensity can be determined.

Markou et al. (1998) employed this approach when analysing the local transport of anti-restenotic agents from a novel drug delivery device. The device consisted of a porous membrane that lined the artery wall and was the location where drugs would be infused into the artery. Their experimental approach consisted of a simulated artery section with a 1cm slit around its circumference. Dye was then infused from this slit in a radial direction into the lumen at uniform speed. It was found that the radial diffusion of the species was minimal in comparison to the axial convection therefore the majority of species remain in close proximity to the wall. This experiment was validated with the commercially available finite volume solver Fluent (Lebanon, NH). The computational models predicted an increase in dye concentration at the wall with an increase in the infusion rate. The same effect was witnessed experimentally and there was good agreement between the results. This study indicates the dominance of convective transport over diffusive transport in the arteries lumen.

Lutostansky et al. (2003) adopted a similar technique when conducting an experimental analysis of mass transport in the recirculation region downstream of a sudden expansion. Dye

concentrations were determined at four equidistant locations after the sudden expansion. Experimental concentrations were taken over the course of one hour and showed very good correlation with predicted results from two numerical codes, the finite volume code Fluent (Lebanon, NH) and a finite element code FTSP (developed by Graz University of Technology). Although these experiments provided a validation of their numerical approach, they are limited in that they cannot be used to analyse mass transport within a porous wall.

In 2001, Hwang et al. found that stent based delivery, from a Palmaz-Schatz Crown stent (Cordis), resulted in large variations in concentration gradients. Drug concentrations were found to vary from zero to several times the mean over a few micrometres. The aforementioned stents were spray coated with a fluorescein sodium/ethylene vinyl acetate copolymer and deployed in excised bovine carotid arteries. The arteries were positioned in an *ex vivo* perfusion apparatus and immersed in a perivascular bath where coronary flow was simulated. After 3 hours the arteries were removed and cut into slices. The fluorescein concentration was then measured with a spectrofluorometer. Although the experiment was not used to validate a computational model, the effects witnessed experimentally were compared to variations in simulated drug physicochemical properties. They concluded that the proximity of the device does not necessarily ensure adequate targeting because transport forces can cause local concentrations to deviate from the mean concentration.

In a later paper Hwang et al. (2005) evaluated the paclitaxel uptake in stented abdominal aortas of adult male Sprague-Dawley rats in the presence and absence of controlled mural thrombus. The in vivo clot dimensions were determined and used as boundary conditions and input parameters for the computational model. The computational analysis predicted an arterial drug ratio of 0.56 which correlates with the 50% decrease in arterial uptake ascertained from the animal experiments. Hwang et al. (2005) discovered that by varying clot size and location, large variations in arterial uptake were witnessed.

In 2007, Balakrishnan et al. deployed a Cypher sirolimus eluting stents in porcine arteries. At the desired time points of 1, 8, 14, 30, 60 and 90 days after implantation the stents were harvested and analysed. In each case the stents were carefully removed from the artery and the remaining drug within the polymer was determined. When subtracted from the amount of drug prior to implantation the release fraction can be calculated. At each time point this fractional drug release was compared to numerical predictions using Fluent (Lebanon, NH). A good correlation validated the Fickian diffusion analysis applied with the numerical solver to approximate the drug transport from the coating. However, validating drug release from the polymer coating does not elucidate subsequent drug uptake within the porous artery wall.

In 2010, O'Connell and Walsh developed an analogous model of artery wall mass transport, examining the hypothesis of how compression of a porous media alters mass transport within. Due to the difficulty in measuring site specific concentrations within the artery wall they developed a scaled up experiment. It consisted of a bed of pH paper that was saturated in a neutral pH solution in order to fill the pore space of the material, similar to that of the artery walls interstitial fluid. The wall is then compressed, in increments up to a maximum of 23.75% of its initial thickness, and then the species of interest, an acid of pH 2.0, is introduced to the system and the resulting colour change was used as a marker for concentration. This enabled the site specific measurement of concentration at different depths throughout the porous wall. These experimental results were then validated computationally using the finite element solver COMSOL Multiphysics. The authors concluded that compression of a porous artery wall contributes significantly to the modulation of arterial WSMT and should be considered in future DES computational studies.

7. Computational modelling of mass transport from drug eluting stents

The following computational models were created to illustrate how changes in stenting deployment conditions can influence drug concentrations within the artery wall, analysed after 30 and 60 minutes for each model. Figure 4 describes the five 2-D axis-symmetric computational models that were analysed. Model 1 in figure 4 depicts the locations of drug concentration measurement through the depth of the artery wall and axially down the artery at a depth of 25% and 50% of the wall thickness (WT) beneath the strut. The models are described as follows:

Model 1. In the absence of a lumen and subsequent BSMT, this model only considered WSMT from a single DES stent strut (150μm) deployed flush against a single layer artery wall (200μm). In this instance WSMT is purely diffusive.

Model 2. Similar to Model 1 but with the inclusion of a steady blood flow profile (mean velocity = 0.1m/s) through the arterial lumen. Here WSMT is purely diffusive and BSMT is modelled using the convection-diffusion equation.

Model 3. Similar to Model 2 but with the inclusion of a 20μm thick layer of plaque along the artery wall.

Model 4. Similar to Model 2 only the stent strut becomes embedded in the artery wall as it compresses it by 25% of the wall thickness.

Model 5. Similar to Model 4 except upon compression of the wall the stent strut doesn't become embedded.

A hypothetical drug was used in the analysis with effective diffusivity values in each respective media defined in table 1. It is the combination of both the drug used and the characteristics of the media within which transport takes place that determines the effective diffusivity value. This fact becomes evident as the effective diffusivity of the drug in the compressed wall is determined. The drug remains the same but, as described in equation 12, changes to the tortuosity (τ) and porosity (ε) of the wall alters the effective diffusivity within.

From equation 15 the pore path (L) remains the same length but the distance (X) has reduced due to the 25% compression of the artery wall. Therefore the tortuosity of the compressed wall (τ_{CW}) can be described as a function of the tortuosity of the wall in its original state (τ_W).

$$\tau_{CW} = \frac{L}{0.75X} = 1.333\frac{L}{X} = 1.333\tau_W$$

Similarly, as the wall is compressed the total volume and pore volume of the wall under compression reduces but the fibre volume remains the same. To this end ε_{CW}= $0.787\varepsilon_W$ and the effective diffusivity of the compressed wall (D_{CW}) can be described as follows:

$$D_{CW} = \frac{\varepsilon_{CW}}{\tau_{CW}} D_{free} = \frac{0.787\varepsilon_w}{1.333\tau_W} D_{free} = 0.59D_W = 0.59\times10^{-12} m^2 / s$$

Diffusivity in Lumen	$D_L = 1\times10^{-10}$ m²/s
Diffusivity in Stent Coating	$D_S = 1\times10^{-14}$ m²/s
Diffusivity in Plaque	$D_P = 1\times10^{-13}$ m²/s
Diffusivity in Wall	$D_W = 1\times10^{-12}$ m²/s
Diffusivity in Compressed Wall	$D_{CW} = 0.59\times10^{-12}$ m²/s

Table 1. Effective diffusivity values of the different layers of arterial DES models.

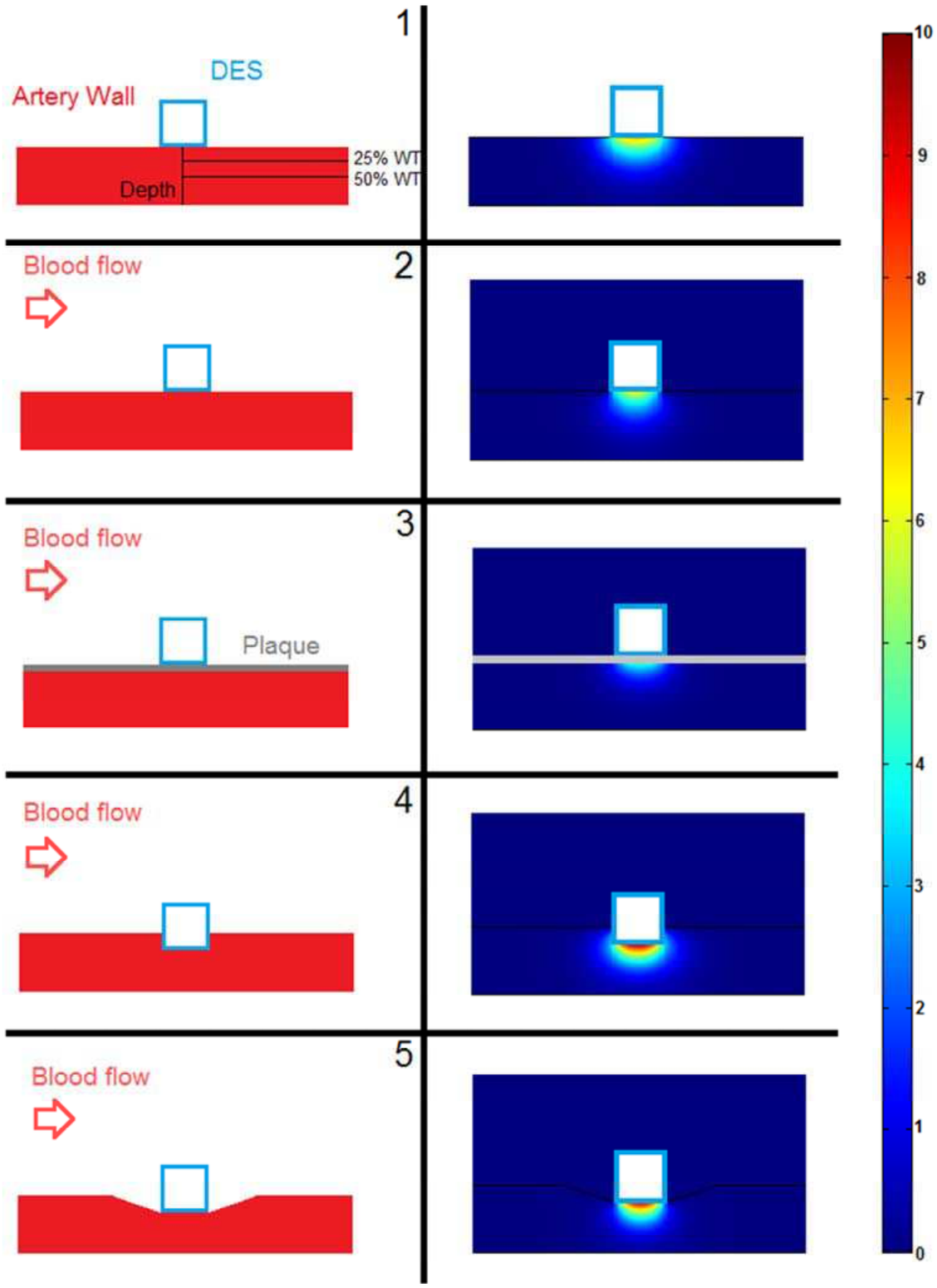

Fig. 4. Illustration of 2-D axis-symmetric computational models used in the DES mass transport analysis and their resulting drug concentration contours after 30 minutes.

7.1 Computational predictions of mass transport in the artery wall

Even though BSMT doesn't significantly contribute to the distal absorption of drugs into the artery wall, it is a necessary element of the modelling process as it provides a more realistic representation of how the drugs in the DES dissipate in the vasculature. Failure to model BSMT (Model 1) culminates in the entire reservoir of antirestenotic drug, from both the luminal and abluminal side of the stent, having no choice but to eventually transport into the wall. This as we know is not the case as a considerable amount of drug is lost to the blood stream. Figures 5-7 demonstrate that for both time points and at each location the drug concentration for Model 1 is greater than that of Model 2 due to the absence of BSMT. Model 3 examined the influence of arterial plaque, which was given a drug diffusivity of $1\times10^{-13}m^2/s$. In reality plaque size and composition will vary from patient to patient and the implication of this is a study in itself where a range of plaque types would need to be modelled in order to quantitatively predict its influence on WSMT. For the purpose of demonstrating the influence that the presence of any plaque may have on mass transport, a drug diffusivity was chosen that is an order of magnitude between the diffusivities in the DES coating and the uncompressed artery wall respectively. What Model 3 demonstrates is that even a 20μm thick layer of plaque between the stent and the artery wall can significantly reduce uptake within the artery wall, even more so than arterial compression.

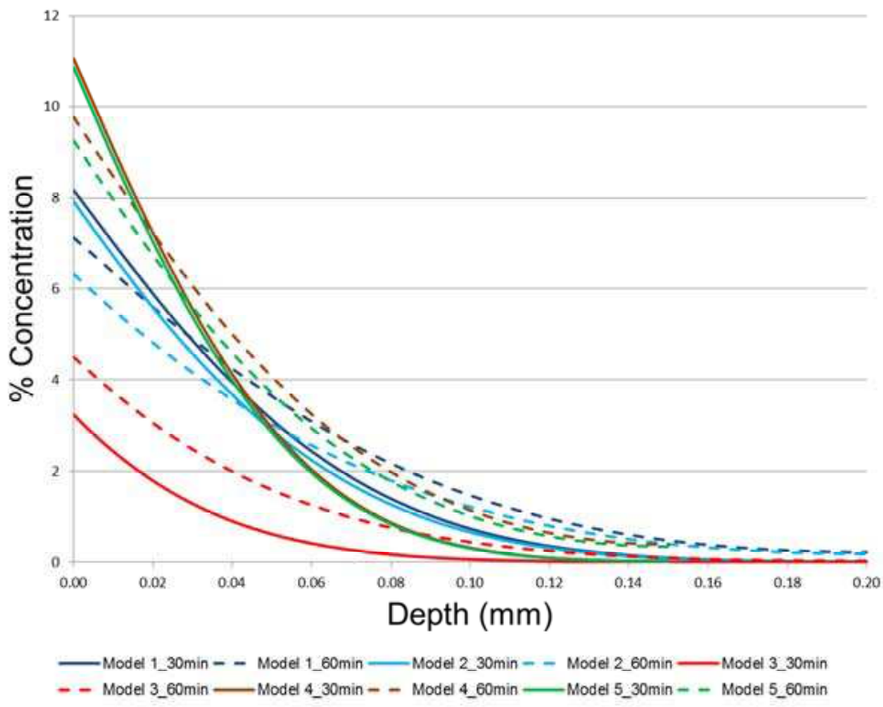

Fig. 5. Drug concentrations through the depth of the artery wall, as illustrated in Fig 4 Model 1. Concentrations are measured after 30 minutes (solid line) and 60 minutes (dashed line) respectively.

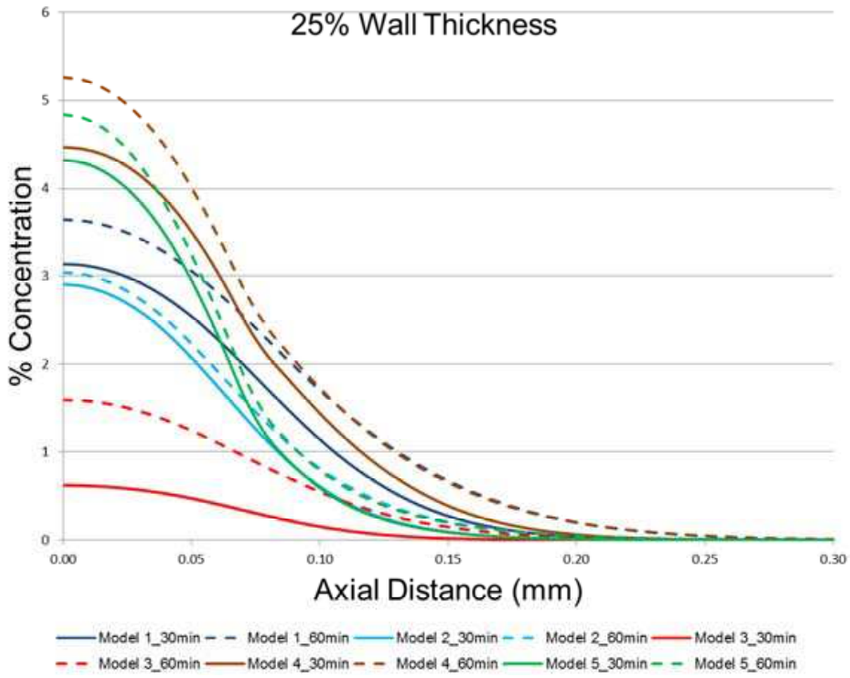

Fig. 6. Axial drug concentrations at 25% of the artery wall depth, illustrated in Fig 4 Model 1 by the 25% WT concentration line. Concentrations are measured after 30 minutes (solid line) and 60 minutes (dashed line) respectively.

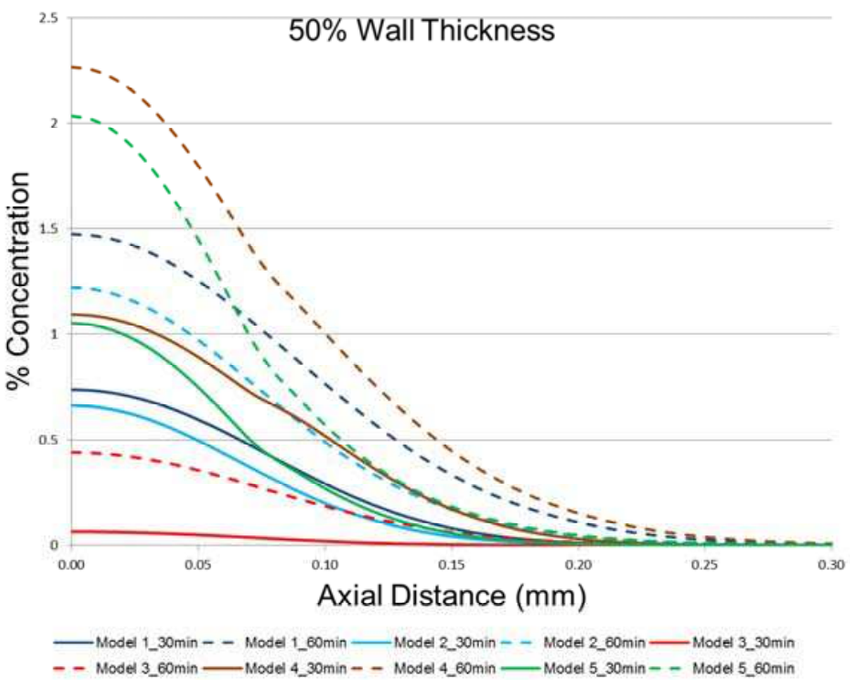

Fig. 7. Axial drug concentrations at 50% of the artery wall depth, illustrated in Fig 4 Model 1 by the 50% WT concentration line. Concentrations are measured after 30 minutes (solid line) and 60 minutes (dashed line) respectively.

The influence of compression on a porous wall in relation to mass transport has been demonstrated experimentally by O'Connell and Walsh (2010) and is evident in the results from Models 4 and 5. Histological evidence demonstrated that upon stent implantation some struts almost cut into the wall (Model 4) while others merely compress it providing gradual recovery either side of the stent strut (Model 5). Contrasting concentration profiles from these models elucidate to the inclusion of compression alone may not necessarily be adequate enough because the surrounding tissue orientation will also play a role in WSMT. Intuitively the greater the DES surface area in contact with arterial tissue the greater its ability to transport drugs into the wall. This holds true when comparing the concentration profiles of Models 4 and 5. The depth concentrations at the early time point for both models are very similar (Figure 5) but there is a notable difference in the axial concentration plots at both 25% and 50% of the wall thickness, whereby the 60% greater wall contact surface area of model 4 results in an increased concentration profile.

8. Conclusion

Understanding the behaviour of DES in the pursuit of improving device functionality is of great importance to clinicians and researchers alike. The modern application of computational techniques have greatly aided in achieving this goal, with researchers continuingly adding to the global understanding of drug mass transport from these devices. However, computational modelling isn't the complete solution because exact recreation of DES deployment and ensuing mass transport is not feasible for a number of reasons. No two patients will have identical stenosis of the coronary artery and therefore a single computational model will not provide the information required to comprehensively assess the viability of a single stent design. Instead a variety of models that will cover the spectrum of DES deployment scenarios is required and to computationally recreate these like for like with *in vivo* stenting conditions would be too computationally demanding for the same rewards that one could yield with a simplified analysis.

However, one must be mindful when simplifying the problem. The computational models developed in this chapter were created as 2-D axis-symmetric models as the study was intent on analysing the influence of relatively simple geometries. However, this may not always be the case and the need may arise where it would be necessary to model the problem in 3-D. The pitfalls of over simplification can be seen in the computational Model 1 where failure to model BSMT results in drug concentrations that are higher than that of the more realistic case, Model 2, that includes the luminal blood flow and mass transport therein.

Computational models where DES struts are flush against a bare artery wall have their merits but a greater degree of complexity needs to be implemented if an improved insight into DES mass transport within the coronary artery environment is to be gained. These arteries are heavily diseased and even a thin layer of plaque between the stent strut and the wall can inhibit WSMT. The compression of the porous artery wall upon stent expansion has an interesting effect on drug concentration within the wall. The reduction in artery wall diffusivity results in higher peak concentrations beneath the stent strut compared to the models where artery wall compression is not present. This pooling of drugs close to the stent strut is undesirable as it retards the early penetration of drugs into the wall, demonstrated in Figure 5 as the uncompressed artery wall of Model 2 recorded concentrations higher than that of Models 4 and 5 from a depth of approximately 50μm

through the rest of the artery wall. There is also the danger of potential toxicity due to prolonged exposure of high drug concentrations close to the strut.
Analysis of mass transport from DES requires a multifaceted approach in order to predict behaviour of these devices and subsequently their response to *in vivo* arterial conditions. Future research that is mindful of preoperative DES design and postoperative environmental conditions will increase our knowledge of the second generation DES and enable us as a community to prepare for the advent of biodegradable DES.

9. Acknowledgements

The authors would like to thank the Irish Research Council for Science, Engineering and Technology (IRCSET), Grant no. RS/2005/159, for funding this body of work. The authors would also like to thank the members of CABER and the MSSI.

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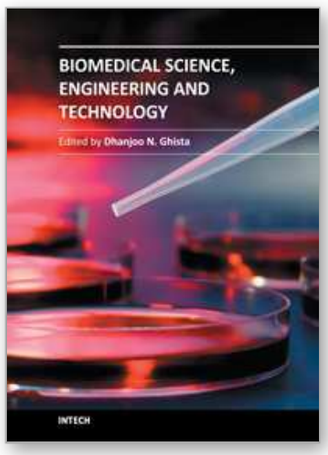

Biomedical Science, Engineering and Technology

Edited by Prof. Dhanjoo N. Ghista

ISBN 978-953-307-471-9
Hard cover, 902 pages
Publisher InTech
Published online 20, January, 2012
Published in print edition January, 2012

This innovative book integrates the disciplines of biomedical science, biomedical engineering, biotechnology, physiological engineering, and hospital management technology. Herein, Biomedical science covers topics on disease pathways, models and treatment mechanisms, and the roles of red palm oil and phytomedicinal plants in reducing HIV and diabetes complications by enhancing antioxidant activity. Biomedical engineering coves topics of biomaterials (biodegradable polymers and magnetic nanomaterials), coronary stents, contact lenses, modelling of flows through tubes of varying cross-section, heart rate variability analysis of diabetic neuropathy, and EEG analysis in brain function assessment. Biotechnology covers the topics of hydrophobic interaction chromatography, protein scaffolds engineering, liposomes for construction of vaccines, induced pluripotent stem cells to fix genetic diseases by regenerative approaches, polymeric drug conjugates for improving the efficacy of anticancer drugs, and genetic modification of animals for agricultural use. Physiological engineering deals with mathematical modelling of physiological (cardiac, lung ventilation, glucose regulation) systems and formulation of indices for medical assessment (such as cardiac contractility, lung disease status, and diabetes risk). Finally, Hospital management science and technology involves the application of both biomedical engineering and industrial engineering for cost-effective operation of a hospital.

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