Computational Modeling of Local Intravascular Drug Delivery

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Abstract

Drug-eluting stents (DES) virtually eradicate the clinical phenomena of vessel restenosis; yet, they also increase the short and long term risks for stent thrombosis. To improve their safety and efficacy, it is critical to examine factors that alter local biologic outcome. The central hypothesis of this thesis is that local efficacy and toxicity are in part determined by the duration of drug exposure and local arterial drug concentrations. This thesis investigates how factors both intrinsic and extrinsic to the device impact local intravascular drug delivery. Computational models of local fluid mechanics and drug transport were formulated to study how arterial drug uptake is modulated by local blood flow, stent placement, administered drug dose and release kinetics, and the evolving local vascular response to the device. Lumenally flowing blood around stent struts was capable of transporting drug to the arterial wall in the presence of both single and multiple configurations of drug eluting stent struts. The extent of blood flow mediated arterial drug delivery depended upon the rate of drug release and administered dose. Slow drug release led to sustained, low magnitude drug uptake; exceedingly fast release resulted in transient and minimal tissue absorption due to rapid drug depletion. Drug release over several minutes maximized peak arterial drug concentrations, though arterial drug levels were not sustained. Mural thrombus did not alter the rate of drug release from a stent; however, clots increased local drug availability and reduced the extent of drug washout. Subsequently, variability in mural thrombi formation caused fluctuations in arterial drug levels. Computational modeling revealed that free diffusion of hydrophobic drugs was slower than experimental arterial drug absorption. Subsequently, a novel mechanism for arterial drug transport has been proposed in which drug diffuses faster through the arterial wall due to its association with carrier proteins. Within this thesis, we have elucidated that device, patient, and physician-dependent device implantation are among the factors governing arterial drug deposition; these subsequently dictate local efficacy and toxicity. Thus, rational design of improved local therapeutics requires consideration of how multiple interrelated factors intrinsic and extrinsic to the device determine local efficacy and toxicity.

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Chapter 1: Background and Motivation

1.1 Thesis Overview

In-stent restenosis has been a significant problem in cardiovascular medicine. In 2003, drug-eluting stents emerged in the US after clinical trials demonstrated that they virtually eradicated in-stent restenosis. When drug-eluting stents were approved for clinical use, they were intended for the treatment of de novo coronary lesions in patient subsets with few complicating medical problems. At that time, they had only been examined for a relatively short duration. However, the patient population requiring coronary intervention possesses complex coronary lesions and co-morbidities. Thus, drug-eluting stents were rapidly adopted for treating a number of complex lesions and patient populations, and they have often been used in circumstances that have not been examined within the original clinical studies. As longer follow-up and larger patient populations came to be treated, clinical evidence has evolved suggesting that these devices especially when used outside of their FDA guidelines have an increased risk for stent thrombosis. As a result, drug-eluting stents are undergoing significant scrutiny. The clinical experience gained from implementing this technology illustrates the importance of understanding mechanistically how these devices strike a balance between local toxicity and efficacy.

The central hypothesis for this thesis is that local drug toxicity and efficacy are due in large part to the cumulative drug exposure to the arterial wall. On this basis, we examined factors both intrinsic and extrinsic to the drug-eluting stent that alter local arterial drug deposition, distribution, and retention. This investigation included three specific aims:

- **Specific Aim 1 (Chapter 2):** Examine the impact of local blood flow around the drug-eluting stent struts on arterial drug deposition and distribution by using a 2-dimensional steady state computational fluid mechanics and mass transport framework.
- **Specific Aim 2 (Chapter 3):** Define the role of drug release kinetics and drug dose on arterial drug deposition, distribution, and retention using a 2-dimensional transient fluid mechanics and mass transfer model.
- **Specific Aim 3 (Chapter 4):** Investigate the role of mural thrombus in contributing to experimentally observed variability in arterial drug deposition by applying the previously developed transient computational model.

By systematically elucidating how factors interact to govern local arterial drug delivery, it is hoped that the lessons gained from this study can contribute to the rational development of improved local drug delivery strategies.
1.2 Arterial Ultrastructure and Atherosclerosis

Arteries carry blood away from the heart. They are comprised of many cell types such as endothelial cells, smooth muscle cells, and fibroblasts, as well as extracellular matrix components such as elastin, collagen, and proteoglycans. These components are organized in tunics, meaning layers (Fig 1-1). The innermost tunic adjacent to the lumenally flowing blood is the intima, consisting of a fibroelastic connective tissue lined on the lumenal side by a monolayer of endothelium which is oriented parallel to the flowing blood. The endothelium is an active and adaptable entity that is capable of processing and responding to mechanical and chemical cues from its environment. Among the many important purposes of the endothelium are maintaining hemostasis, regulating vascular tone, serving as a gatekeeper for vascular permeability, and modulating inflammatory response. The intima is separated from the adjacent arterial tunic, the media, by the internal elastic lamina (IEL), a concentric fenestrated sheet of elastin. The media consists of concentric elastin laminations between layers of smooth muscle cells. The media is separated from the third and final arterial tunic by the external elastic lamina, which is analogous to the IEL. The adventitia, the outermost arterial tunic, consists of nerves, adipose tissue, and vasa vasorum (small vessels the serve the outer layers of larger vessels).

The size and relative composition of the artery depends on its location and function. Large arteries, such as the aorta and its major branches such as the...
carotid arteries, experience fluctuating systolic-diastolic blood pressure and carry the largest blood volume, thus they have a significant elastin content which allows them to accommodate the cycling volume loads. Medium sized arteries such as coronary arteries are muscular in nature having less elastin in the tunica media and many layers of smooth muscle cells. Their muscular content enables these vessels to autoregulate blood flow by dilation or constriction based on local metabolic factors.

Atherosclerosis is a diffusely occurring progressive, degenerative disease affecting primarily elastic arteries (i.e. aorta and carotid arteries) and large to medium sized muscular arteries (i.e. coronary arteries). This process, typically involving the arterial intima and media, progresses over many decades asymptptomatically. Within the first two decades of life, it is initially characterized by formation of a fatty streak. This early lesion develops over time into a complex and heterogeneous diffuse fibrous plaque containing foamy macrophages, lipid pools, calcifications, proliferating smooth muscle cells, extracellular matrix, and necrotic core (Fig 1-2). The response-to-injury hypothesis posits that atherosclerosis is caused by chronic endothelial injury which initiates a chronic inflammation within the arterial wall. Endothelial injury is thought to be caused by factors such as hyperlipidemia, hypertension, smoking, elevating homocysteine levels, hemodynamic factors, toxins, viral infections, and immune mediated mechanisms. Injury leads to dysregulation of the endothelium. As a result, vascular permeability increases, lipid accumulates, and inflammatory cells are recruited to the arterial wall. Nonmodifiable risk factors for atherosclerosis are advancing age, male gender, family history of atherosclerosis, and genetic
abnormalities. Additional, risk factors such as diabetes mellitus, obesity, tobacco abuse, elevated blood cholesterol, hypertension, and sedentary lifestyle may be controlled to slow the progression of disease. Atherosclerosis typically causes symptomatic problems at or beyond the 5th decade of life when it obstructs blood flow, either via gradual occlusion or sudden plaque rupture. The consequences of arterial occlusion depend on the tissue it perfuses: coronary arterial occlusions cause myocardial infarction (i.e. “heart attack”), carotid arterial occlusions cause stroke, and peripheral arterial disease can lead to limb loss.

1.3 Coronary Artery Disease and Treatments

Cardiovascular disease affects 1 in 3 adult Americans according to the 2007 American Heart Association Report on Stroke and Heart Disease Statistics. Coronary artery disease accounts for 20% of cardiovascular diseases, and is estimated to accrue combined direct and indirect costs of $151.6 billion in 2007. The clinical manifestations of coronary artery disease manifest when myocardial oxygen demand exceeds the blood supply due to coronary arterial narrowing or occlusion. Clinical symptoms include chest pain (i.e. “angina pectoris”), difficulty breathing (“dyspnea”), or fatigue. These symptoms may occur predictably with exertion and resolve with rest (i.e. stable angina) or occur unpredictably (i.e. unstable angina). When atherosclerotic plaques rupture, acute thrombosis partially or totally occluding the affected artery results in acute insufficiency of coronary blood supply resulting in an acute coronary syndrome (ACS) with attendant myocardial necrosis and release of cardiac specific proteins (biomarkers) that correlate with the degree of injury. The diagnosis of myocardial infarction (MI) is confirmed with clinical, electrocardiographic, and biomarker evidence of myocardial injury.

Cardiac catheterization is a useful tool for both diagnosing arterial obstructions and treating them. Cardiac catheterization involves introducing a catheter into the arterial circulation over a wire and passing it retrograde via the aorta to the coronary arteries. A coronary angiogram is obtained by injecting radio-opaque contrast agent via the catheter into the coronary circulation.
an obstructive lesion is found, there are a number of medical and revascularization treatment options. Human cardiac catheterization was first demonstrated in 1929 by Dr. Werner Forssmann in Germany after which it was used as a diagnostic tool for measuring cardiac output by Andre F. Cournand and Dickinson W. Richards. Forssmann, Cournand, and Richards later shared the Nobel Prize in Medicine in 1956. The applications for cardiac catheterization have increased substantially in the intervening decades. From 1979 to 2004, cardiac catheterizations increased 334% for use in the diagnosis and treatment of obstructive coronary artery disease.

Coronary artery disease may be treated either medically or by mechanical revascularization. Revascularization procedures are indicated for unstable angina and myocardial infarction. Revascularization therapies include coronary artery bypass graft surgery (CABG) and percutaneous coronary interventions (PCI). CABG requires harvesting a vessel from a distal site from the heart (usually internal mammary or saphenous vein) and creating an anastomosis around the occluded coronary vessel. By contrast, percutaneous intervention involves immediate restoration of blood flow through a number of local mechanical interventions such a percutaneous translumenal balloon angioplasty (PTCA), and stent implantation. CABG has demonstrated mortality benefits and longer term vessel patency for patients with 3-vessel disease, left main coronary artery disease or the equivalent, low ejection fraction with 3-vessel disease, and patients with diabetes mellitus. PCI is the preferred method of revascularization in the setting of acute myocardial infarction and is the dominant modality for elective symptomatic relief of coronary artery disease.

Percutaneous interventions have been fraught with the problem of maintaining luminal patency in the long term. PTCA involves immediately restoring blood flow by guiding a balloon tipped catheter to an occluded vessel and inflating the balloon, causing plaque compression and ideally restoring the lumen for blood flow. Balloon expansion simultaneously disrupts the arterial endothelial lining, and potentially causes medial dissection. As a result, the vessel wall is weakened and prone to recoil in the short term. In the long
term, arterial tissue grows inward toward the lumen eventually leading to vessel re-occlusion, clinically termed restenosis.

To circumvent the drawback of vessel recoil with PTCA, endovascular stents, which are metallic mesh scaffolds, were permanently implanted either by balloon-expansion or by self-expansion to mechanically support long-term vessel patency\(^{14-16}\). Yet, stent implantation imposes both acute and chronic mechanical injury to the arterial wall. Acute injury with stenting includes endothelial denudation, stent penetration and laceration of the arterial media, compression of the media, and potential atherosclerotic plaque fracture. Chronic injury is imposed by the persistent burden of mechanical tension and compression occurring within the arterial wall around and beneath stent struts\(^{17}\). The combined effects of these mechanical injuries lead to vessel re-occlusion either via stent thrombosis or restenosis. Due to improved procedural technique and the introduction of antiplatelet therapy with cyclooxygenase antagonists (i.e. aspirin) and thienopyridines (i.e. ticlopidine or clopidogrel)\(^{18, 19}\), the incidence of acute, subacute and late stent thrombosis is less than 1% per year for metal stents\(^{18}\). However, stent thrombosis has extremely high associated risk for death. Risk factors for stent thrombosis include as stent length, arterial dissection, and small final lumen diameter\(^{18}\). By contrast, restenosis has not been shown to decrease mortality, but it is accompanied by return of ischemic symptoms\(^{20}\). Risk factors for restenosis include placement of multiple stents\(^{21}\), lesions in small diameter vessels\(^{21, 22}\), long lesions\(^{21, 23, 24}\) and lesions located at bifurcation sites\(^{25}\), and patients with co-morbidities such as diabetes mellitus\(^{21, 26-29}\). After improving stent design\(^{30, 31}\) and operator skill\(^{32}\) related to stent deployment, restenosis persists at a rate of 15-30% \(^{15, 22, 27, 33, 34}\). Thus, prevention and inhibition of restenosis has emerged as the holy grail of interventional cardiology.
1.4 In-Stent Restenosis

1.4.1 Process of Intimal Hyperplasia

Restenosis is a clinical term assigned when >50% diameter stenosis is observed angiographically after an initial PCI. Restenosis is caused by the arterial wall orchestrating a complex response to the stent induced injury. Welt and Rogers\textsuperscript{35} have proposed an integrated mechanism for in-stent restenosis involving inflammation and injury. The injury begins with disruption of the endothelial monolayer lining the arterial wall after PTCA/stenting, which dysregulates local hemostasis. Platelets aggregate along the arterial wall leading to thrombus formation, which is the earliest vascular response to injury. In turn, platelets recruit inflammatory cells to the vascular injury site. Leukocytes, smooth muscle cells (SMCs), and platelets elaborate cytokines which activate SMCs, leading to SMC migration from the media into a neointima, where these cells produce extracellular matrix. The latter proliferative process is termed intimal hyperplasia (Fig 1-3), which once again impinges upon blood flow, and symptoms related to inadequate cardiac blood perfusion return such as angina pectoris\textsuperscript{35}.

1.5 Drug-Eluting Stents (DES) Era

1.5.1 Drug Selection Characteristics

Failed attempts to inhibit intimal hyperplasia with heparin coated stents and mixed results of oral drug delivery demonstrated that biologic potency is not sufficient for biologic efficacy. Drugs must be targeted to and retained within the arterial wall at therapeutic levels to be efficacious. Careful consideration of the drug's physicochemical properties such as hydrophobicity and/or binding affinity to vascular tissue are required to observe sustained effect. Such is the case with
the compounds released from the two commercially available DES, paclitaxel\textsuperscript{36}, \textsuperscript{37} and sirolimus\textsuperscript{38} derivatives.

Paclitaxel has been used as a chemotherapeutic for cancer and is now also used as an anti-proliferative agent on drug-eluting stents. Paclitaxel binds dimerized beta-tubulin to prevent microtubule assisted cellular functions such as migration and proliferation\textsuperscript{39}.

Rapamycin is a macrolide antibiotic having immunosuppressant properties. Originally used to prevent rejection in renal transplantation, rapamycin is now coated on commercially available drug-eluting stents to prevent restenosis. The mechanism by which rapamycin exerts its anti-proliferative action is by binding to FK506-binding protein-12 (FKBP12), which is upregulated in human smooth muscle cells. The complex of rapamycin and FKBP12 binds to and blocks the activation of the mammalian target of Rapamycin (mTOR), a regulator of cell cycle progression\textsuperscript{40}. Both rapamycin and paclitaxel not only share biologic potency to prevent cellular proliferation but they are also incredibly hydrophobic compounds, partitioning at equilibrium within the arterial wall 30 to 40 times more than aqueous solution\textsuperscript{41}. These drugs associate nonspecifically with tissue elements other than their biologic targets, which enhances their tissue retention beyond that of hydrophilic compounds such as heparin\textsuperscript{41, 42}.

1.5.2 Clinical Experiences with Sirolimus and Paclitaxel Eluting Stents

In the early days of drug-eluting stents (DES), they held a promise for being the panacea for the problem of in-stent restenosis. The first-in-man clinical trial of CYPPHER\textsuperscript{©} sirolimus-eluting stent (SES) implantation into de novo coronary lesions (RAVEL) revealed a remarkable 0\% angiographic restenosis at 6 months\textsuperscript{43} and though revascularization rates increased over time, the reduction compared to bare metal stents was maintained at 5-year follow-up where SES had 10.5\% target lesion revascularization compared to 26\% in bare metal counterparts \textsuperscript{44}. In the SIRIUS clinical trials, treatment of de novo coronary lesions with sirolimus eluting stents corroborated the benefit of SES compared to bare metal stents\textsuperscript{38, 45, 46}. In the TAXUS trials, similar successes were
demonstrated for paclitaxel eluting stents (PES), which also had 0% angiographic restenosis at 6 month follow-up, where the reduction in restenosis with PES compared to bare metal stents was maintained at 2-year follow-up\textsuperscript{36, 37}. Subsequent to the RAVEL, SIRIUS, and TAXUS trials, sirolimus and paclitaxel eluting stents were approved by the FDA for use in patients with discrete de novo lesions of less than 28-30 mm in length in native coronary arteries with reference vessel diameter of between 2.5 and 3.75 mm\textsuperscript{47}.

Because the populations of patients requiring coronary intervention have more complex lesion characteristics than those described for "on-label" DES use, these devices have approximately 60% "off-label" use\textsuperscript{48}. Patients with risks factors for restenosis continue to be treated with DES such as those with long lesions, lesions at bifurcations or in small vessels\textsuperscript{49}, and patients with diabetes mellitus\textsuperscript{50}. With additional complexity in the patient population, implantation strategies become more complex requiring potentially multiple adjacent or overlapping devices to cover long lesions or lesions in bifurcations. These modified stenting strategies raised questions regarding how proximate devices with increased drug load density may impact vessel toxicity. Thus, though the early term evidence concerning DES seems to demonstrate safety and efficacy\textsuperscript{36, 37, 43, 45}, our understanding of factors governing local drug delivery with DES in the setting of complex lesion subsets and higher risk patients is rudimentary and incomplete.

As implantation frequency of DES has increased and long term follow-up has been performed, a growing concern has developed that DES are associated with a low incidence and potentially fatal risk of stent thrombosis that actually increases over time by 0.6% per year for 3 years after implantation\textsuperscript{51}. In December 2006, the increasing appreciation of DES risk for stent thrombosis was discussed at an FDA panel meeting during which manufacturers of DES convened with academic, government, and industrial experts to discuss risks for DES thrombosis. Meta-analysis of 3 years drug-eluting stent use revealed that "on-label" use of DES might have a slightly increased risk of stent thrombosis, but what was more concerning was the possibility that the "off-label" use, which
is prominent in the clinical setting, would have a more pronounced increased risk of stent thrombosis\textsuperscript{48}. A recent flurry in clinical trial data re-analysis has revealed differing rates of death, thrombosis, and myocardial infarction with DES \textsuperscript{52-56}, which likely arises from differences in patient populations and lesion characteristics, devices, and clinical protocol (i.e. inconsistent definitions for stent thrombosis). It remains to identify the true incidence, risk factors, and mechanism for DES thrombosis in order to reduce its occurrence.

While drug-eluting stents remain an important component in the interventional cardiologist's armamentarium, indications for their use must be more clearly defined. Local drug delivery of current pharmacologic agents could in theory cause both the desired inhibition of smooth muscle cell migration and proliferation as well as the potentially undesirable inhibition of endothelial cell growth\textsuperscript{39}. Thus, to maximize the established clinical benefit of reduced restenosis and simultaneously minimize toxic sequelae such as stent thrombosis, it is essential to identify and study the factors governing local arterial drug delivery.
1.6 Thesis Theme

The emerging evidence that drug-eluting stents (DES) are associated with late occurrences of toxic sequelae combined with the increasing treatment of more complex patient populations requires a close examination of factors governing device safety and efficacy. The hypothesis governing the direction of this thesis was that toxicity and therapeutic effect of drugs eluted from endovascular stents is determined by arterial drug exposure. To its greatest degree the impact of this exposure is determined by the net amount of arterial uptake and retention, and the duration of exposure. Among the many unanswered questions regarding arterial drug delivery from stents are: How does the local mural flow disruption induced by intravascular drug-eluting stents impact their arterial drug delivery? Do multiple adjacent or overlapping drug-eluting devices increase arterial drug deposition such that there may be a risk for local toxicity? Does stent apposition with the arterial wall impact arterial drug distribution? To what extent do drug dose and release kinetics impact arterial drug delivery and possibly clinical efficacy? As drug-eluting stents become surrounded by mural thrombus, how do arterial wall reactions around devices impact drug release and arterial drug distribution?

Based upon the emergent questions, the goal of this work has been to define factors both intrinsic and extrinsic to the drug-eluting stent that govern arterial drug deposition, distribution, and retention. Examples of stent characteristics that govern drug delivery include stent design features such as inter-strut spacing, release kinetics, and drug load. Factors extrinsic to the device include the physician's decision to place overlapping devices, stent apposition against the arterial wall, device disruption of lumenally flowing blood, and the resultant arterial wall reaction to the in-dwelling drug eluting stent.
1.7 Thesis Goals and Specific Aims
This thesis explores the multiple and interacting factors that govern arterial drug delivery from intravascular stents through the pursuit of three specific aims:

Chapter 2: Describes how blood flow and stent strut position interact to dictate arterial drug deposition and distribution.

Chapter 3: Identifies that drug release kinetics from the stent and applied drug dose impact arterial drug deposition, distribution and retention.

Chapter 4: Examines the interplay between mural thrombus, drug physicochemical properties, and drug release kinetics.

By understanding the interplay of device specific and local extrinsic factors governing arterial drug delivery, this work contributes to the ongoing investigation of local drug delivery from stents. The hope is that rational design of intravascular drug delivery strategies can be devised using this collective knowledge to simultaneously maximize clinical benefit while minimizing toxic sequelae.
1.8 References


Chapter 1: Background and Significance


Chapter 1: Background and Significance


Chapter 2: Strut Position, Blood Flow, Arterial Drug Deposition

2.1 Abstract
The intricacies of stent design, local pharmacology, tissue biology and rheology preclude an intuitive understanding of drug distribution and deposition from drug eluting stents (DES). A coupled computational fluid dynamics and mass transfer model was applied to predict drug deposition for single and overlapping DES. Drug deposition appeared not only beneath regions of arterial contact with the strut but surprisingly also beneath standing drug pools created by strut disruption of flow. These regions correlated with areas of drug-induced fibrin deposition surrounding DES struts in porcine coronary arteries. Fibrin deposition immediately distal to individual isolated drug-eluting struts was twice as great as in the proximal area, and for the stent as a whole was greater in distal segments than proximal segments. Adjacent and overlapping stent struts increased computed arterial drug deposition by far less than the sum of their combined drug load. In addition, drug eluted from the abluminal stent strut surface accounted for only 11% of total deposition, whereas, remarkably, drug eluted from the adluminal surface accounted for 43% of total deposition. Thus, local blood flow alterations coupled with the location of drug elution upon the strut were far more important in determining arterial wall drug deposition and distribution than were drug load or arterial wall contact with coated strut surfaces. Simulations that coupled strut configurations with flow dynamics correlated with in vivo effects and revealed that drug deposition occurs less via contact between drug-coating and the arterial wall than via flow-mediated deposition of blood-solubilized drug.
2.2 Introduction

Drug penetration into the tissue is critical for drug efficacy \(^5\), and yet drug-eluting stents (DES) “lose” a good portion of their load into the flowing blood stream. Thus, in previous analyses drug deposition was envisioned as localized to regions beneath the struts contacting the arterial wall, and blood flow was modeled as a perfect sink for luminal drug \(^4\), \(^5\). However, luminally-protruding struts alter flow, thereby creating areas of separation, recirculation and stagnation \(^5\), \(^6\) where drug can pool with minimal dilution from flow \(^6\) and substantial drug deposition could occur from these pools of blood-solubilized drug. The impact of flow alterations around struts may vary as the number and/or spacing of struts and stents change \(^5\)-\(^6\). Sophisticated stent designs contact the wall asymmetrically and establish a variable circumferential drug load \(^6\), with complex, nonuniform flow alterations along the wall \(^6\). Furthermore, multiple adjacent or overlapping DES add to the amount of local drug, degree of strut protrusion into the lumen, depth of strut penetration into the artery, area of contact with the arterial wall, and alterations in flow. When these effects are coupled with the complexity of drug delivery \(^6\) and tissue binding \(^6\) an intuitive understanding of drug-tissue interactions becomes impossible.

To assess the importance of fluid dynamics on drug deposition, we applied a coupled computational fluid dynamics and mass transfer model to variable stent designs and overlapping regions of DES. The computational methods allowed us to study effects of flow on arterial drug delivery while varying strut position, shape and coating under rigorous conditions that can not be controlled \textit{in vivo} even when using the most refined methods for animal tissue analysis. Mathematical modeling of this and like problems is indispensable precisely because clinical and animal studies increasingly define areas of concern but are not able to fully characterize them. In this paper the spatial distribution of fibrin accumulation as a footprint of drug that was rapidly eluted off
a paclitaxel DES into the tissue matched predictions and validated this approach. The results of this study have important implications for the clinical approach to DES use, and provide a new paradigm by which to consider the design and evaluate future generations of stents.
2.3 Methods

2.3.1 Mathematical Model

The computational domain comprised a long axial arterial section idealized as a rectangle, nondimensionalized relative to strut dimensions (Fig 2-1). Struts were assumed square. The arterial wall thickness was ten times the strut thicknesses and lumen 30 fold wide. Luminal drug distribution was modeled by coupling the steady state convection-diffusion equation (Table 1, Eq 6) with the steady state Navier-Stokes (Eq 2,3) and continuity equations (Eq 1). Drug concentration was set to zero at the luminal inlet (Eq 8) and, an open boundary condition was applied at the distal boundary (Eq 9). The Navier-Stokes equation was solved using no slip boundary conditions at the blood-tissue and blood-stent strut interfaces. A Poiseuille parabolic profile was applied at the luminal inlet (Eqs 4). A zero pressure boundary condition was applied at the outlet (Eq 5). Drug transport within the tissue was modeled as a simple diffusion process (Eq 7), with an impermeable boundary condition at the perivascular wall (Eq 10), continuity of flux at the tissue-blood interface (Eq 11), and symmetry boundary conditions on the proximal and distal walls (Eq 12). Stent drug release was simulated as a Dirichlet boundary condition, with a drug concentration of unity at strut surfaces (Eq 13,14). Drug transport parameters, tissue, blood and flow properties were based upon standard values.

Figure 2-1: Schematic of Computational Domain
Schematic representation of an implanted endovascular stent strut residing in the blood flow field and overlying the arterial wall. \( \Omega_{\text{Tissue}} \) and \( \Omega_{\text{Lumen}} \) represent the tissue (shaded gray) and lumen (shaded pink) regions.
Governing Equations and Boundary Conditions

<table>
<thead>
<tr>
<th>Equation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eq1</td>
<td>( \frac{\partial v_r}{\partial t} + \frac{\partial v_r}{\partial r} = 0 )</td>
</tr>
<tr>
<td>Eq2</td>
<td>( \mu \left( \frac{\partial^2 v_r}{\partial r^2} + \frac{\partial^2 v_r}{\partial r \partial z} \right) = \frac{\partial P}{\partial r} \left( v_r \frac{\partial v_r}{\partial r} + v_z \frac{\partial v_r}{\partial z} \right) )</td>
</tr>
<tr>
<td>Eq3</td>
<td>( \mu \left( \frac{\partial^2 v_z}{\partial r^2} + \frac{\partial^2 v_z}{\partial r \partial z} \right) = \frac{\partial P}{\partial r} \left( v_r \frac{\partial v_z}{\partial r} + v_z \frac{\partial v_z}{\partial z} \right) )</td>
</tr>
<tr>
<td>Eq4</td>
<td>( v_r(r=-L_d) = 1-r^2, \quad v_z(r=-L_d) = 0 )</td>
</tr>
<tr>
<td>Eq5</td>
<td>( P(L_d, r) = 0 )</td>
</tr>
<tr>
<td>Eq6</td>
<td>( P \left( \frac{\partial C_f}{\partial z} + \phi \frac{\partial C_f}{\partial r} \right) = \frac{\partial^2 C_f}{\partial r^2} + \frac{\partial^2 C_f}{\partial z^2} )</td>
</tr>
<tr>
<td>Eq7</td>
<td>( 0 = \frac{\partial^2 C_f}{\partial z^2} + \frac{\partial^2 C_f}{\partial r^2} )</td>
</tr>
<tr>
<td>Eq8</td>
<td>( C_f(r=-L_d, r) = 0 )</td>
</tr>
<tr>
<td>Eq9</td>
<td>( \frac{\partial C_f}{\partial z} \bigg</td>
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<tr>
<td>Eq10</td>
<td>( \frac{\partial C_f}{\partial r} \bigg</td>
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<tr>
<td>Eq11</td>
<td>( \bar{D}_{f/}\frac{\partial C_f}{\partial r} \bigg</td>
</tr>
<tr>
<td>Eq12</td>
<td>( \frac{\partial C_f}{\partial z} \bigg</td>
</tr>
<tr>
<td>Eq13</td>
<td>( C_f = 1 \quad \text{on} \quad \Gamma \cap \Omega_{\text{lumen}} )</td>
</tr>
<tr>
<td>Eq14</td>
<td>( C_f = 1 \quad \text{on} \quad \Gamma \cap \Omega_{\text{tissue}} )</td>
</tr>
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</table>

**Table 1.** Governing equations and boundary conditions for the geometry shown in Fig 2-1. The radial and axial coordinates, \( r \) and \( z \), are normalized to arterial luminal radius (\( R \)). The velocities in the radial and axial directions, \( v_r \) and \( v_z \), are normalized to the arterial lumen centerline velocity, \( V_c = 46 \text{ cm/s} \). Tissue and fluid concentrations, \( C_f \) and \( C_t \), are normalized to the strut drug concentration, \( C_s \). \( \phi \) is the ratio of radial to axial velocities; Peclet number (\( Pe \)), defined as \( V_c R / D_f \), is \( 1 \times 10^5 \); Ratio of drug diffusivity in the fluid and tissue, \( \bar{D}_{f/} \), is \( 1 \times 10^4 \). The dimensionless pressure, \( P \), is normalized by \( V_c \mu / R \); \( \mu \) is blood viscosity; \( D_f \) is drug diffusion coefficient in blood.
2.3.2 Numerical Solution

Computational fluid dynamics software (CFD-ACE+, ESI-CFD, Huntsville, Al) was modified to solve Eqs 1-14 in a coupled manner. A finite volume scheme generated a steady state solution for blood velocity, and blood- and tissue-phase drug concentration profiles. The geometry was meshed with 44,472 voxels. A tolerance of $1 \times 10^{-4}$ guaranteed that overall error for any variable was four orders of magnitude less than the bulk, systemic variable values. Discretization of the diffusion term in the mass balance equation was handled in standard fashion. Potential instabilities at high Peclet numbers required special handling of the discretization of the convective term. A second-order limiter spatial differencing scheme with a blending factor of 0.1 was applied to the convective term. This scheme set drug concentration at the boundary of voxels to the concentration at the center of the upwind voxel plus 90% of half the difference between the center concentration of the upwind voxel and the voxel upwind to that. The limiter restricts the voxel boundary value to the range of surrounding voxel center values. A first-order upwind spatial differencing scheme was applied to the velocity variable setting the velocity at each voxel boundary to the center velocity of nearest proximal voxel. The spatially discretized velocity and drug concentration variables were solved iteratively using a conjugate gradient squared algorithm with a preconditioning linear equation solver. All simulations were executed using a Peclet number of $10^5$ to insure stability and coincide with expected values. Sensitivity analysis confirmed that the average drug tissue concentration was stable and changed by less than 1% when the mesh density was doubled.

2.3.3 In Vivo Stent Implantation

Coronary arteries of farm swine (Animal Biotech Industries, Inc., 35.8 ± 4.6 kg) were stented with two bare metal stents (BMS) (ML-Penta, 8 mm long x 3 mm diameter, Guidant Corp.) or with two stents coated on the abluminal and side faces with paclitaxel (Achieve, 8 x 3 mm Guidant Corp.) with an intended 3 mm overlap length and 10% oversizing compared to the baseline vessel diameter.
(stent : artery ratio 1.1:1), using methods previously described. Injury scores were correspondingly low, in the range of 0 – 0.3). Although the Achieve stent did not demonstrate marked clinical efficacy in human clinical trials, its rapid drug elution and coating coverage made it an ideal tool in preclinical and pilot clinical studies. The rapid early delivery of a drug (paclitaxel) provides a histopathological early marker of drug presence, namely fibrin; it is for this reason rather than clinical use that this device was chosen for validation of the mathematical model inferences. Because other standard techniques for spatial drug mapping within the arterial wall, such as radiolabeling and fluorescence labeling of the drug, do not allow for sufficiently high spatial resolution drug detection or for differentiation between drug on the strut and drug within the tissue, fibrin was used as a biologic marker for drug deposition. Animal care and procedures were in accordance with the guidelines of the American Association for the Accreditation of Laboratory Animal Care and the National Institutes of Health.

Arteries were harvested 28-days after implantation, fixed in 10% neutral buffered formalin, embedded in methacrylate resin, then sawed and microtome sectioned, radiographed in two orthogonal planes, then sawed and microtome sectioned. A total of 10 pairs of stents were evaluated in each group. Five bare metal stent pairs and five DES pairs were cross sectioned proximal to, distal to and at overlap of the two stents. The remaining five stent pairs were sectioned in a longitudinal plane and individual struts examined. Fibrin content detected with Carstair’s fibrin stain (Fig 2-2) was used as a marker for drug effect within the arterial wall and quantified by color.

Figure 2-2: Fibrin Deposition
Photomicrographs show histological sections of isolated DES (top) and DMS (bottom) struts in procine coronary arteries 28 days after stent implantation (Carstair’s Fibrin stain, D = Distal, P = Proximal, S = Strut, F = Fibrin)
segmentation using Adobe Photoshop v5.0. Fibrin content in cross sections was determined as a percent of the total vessel wall area, and in longitudinal sections as the linear extent proximally or distally from the stent strut normalized to strut width. Data were evaluated with two-tailed, paired Student’s t-test.
2.4 Results

2.4.1 Single Isolated Stent struts

Simulations predicted that two distinct recirculation regions form proximal and distal to single struts; the latter significantly larger than the former (Fig 2-3a). These zones create pockets of stagnant drug-laden blood, which allow drug accumulation at the luminal-arterial wall interface and subsequent entry into the arterial wall. Drug deposition is highest when all strut surfaces elute drug, surprisingly, lowest when only the bottom or abluminal, contacting surface is drug-eluting, and only reduced by 11% when the drug-coating is removed from the contacting surface. Unexpectedly, the non-
contacting top and distal strut surfaces individually account for 30 and 43% of total drug deposition, respectively. Even when the strut is unapposed to the arterial wall, residing one strut height above the arterial wall, drug deposition drops by only 19% compared to an apposed strut. The location of drug-coating also determines the concentration profile. When only the contacting strut surface is drug-coated, drug concentration peaks directly beneath the strut; when only the contacting surface is drug-free, the peak drug concentration occurs distal to the strut and is of greater magnitude (Fig 2-3b).

### 2.4.2 Multiple Struts

The concentration profile for multiple struts depends on interstrut spacing. A single peak profile was noted when multiple struts were placed consecutively one strut width apart (Fig 2-4). The profile width was \((d+1)^n\), where \(d\) is the interstrut distance measured in strut lengths and \(n\) is the number of evenly spaced consecutive stent struts. As the interstrut distance increases the peak concentration falls and discrete peaks form over each strut (Fig 2-4). Increasing separation results in lower peak drug concentrations (Fig 2-4), but higher average arterial drug concentrations (not shown). When the interstrut distance is seven strut widths, typical for clinical stents, the proximal peak magnitude is 7% greater than that from a single
isolated strut while the distal peak magnitude is 40% greater than that from a single isolated strut (Fig 2-4). In all cases tissue segments beneath distal struts have greater peak magnitudes than those beneath proximal struts.

Overlapping DES increase local drug load, alter blood flow, and potential increase strut:tissue direct contact. The resultant effects on drug deposition depend upon relative strut configurations. The flow fields associated with side-by-side and stacked configurations are equivalent to those of single struts of twice the width or height, respectively. When stacked struts are staggered relative to each other a third region of stagnant flow is formed bordered by the bottom surface of the topmost strut and a side surface of the bottom (Fig 2-5). Peak concentrations resulting from different overlapping strut configurations rise by 22-34% compared to the single strut case (Fig 2-6a). If drug is removed from one of two overlapping struts the counterintuitive and dominant role of flow is even more evident. If the DES strut remains in contact with the arterial wall but is covered on the luminal aspect by a BMS strut, total deposition is reduced more than 50% (Fig 2-7b). When the configuration is reversed, with the DES superior to the BMS and without arterial wall contact, the peak concentration is displaced distally four strut lengths (Fig 2-6b) but remarkably drug deposition is only reduced by 16% (Fig 2-7b).

Figure 2-5: Contour Map for Two Overlapping DES
Two DES struts in which the top strut is staggered upstream relative to the bottom. Visual representation of drug concentration distribution (in color) and blood flow profiles (black curves). The white line separates the lumen (above) and the tissue (below).
In practice, stent placement invariably leads to some degree of strut embedding in the arterial wall. In our simulations, embedding struts into the arterial wall increased the peak drug concentrations with increased local arterial wall contact, but reduced the distal deposition as less strut surface area is exposed to blood and a lesser degree of flow disruption and subsequent flow-mediated drug delivery ensues (not shown). These effects were most pronounced when in an overlapping two-strut case the bottom strut was entirely embedded within the wall of the artery and the top strut was flush against the arterial wall. The peak concentration increased by 45% but total arterial drug deposition decreased by 6.8% compared to the case where the bottom strut was flush against the wall.

Figure 2-6: Drug Distribution from DES and BMS Struts
a. Arterial drug concentrations for a single DES strut and different configurations of two DES.
b. Arterial drug concentrations when the top strut is staggered proximal/upstream to the bottom strut, in which either one or both struts are drug eluting. The boxes illustrate the specific strut configuration, where drug-coating is designated by colored strut sides. Concentration profiles (colored according to drug-coated surfaces) as a function of axial distance along the arterial wall were taken at a depth of 1.5 strut lengths into the arterial wall.
2.4.3 In Vivo Stent Implantation

The peri-strut deposition of fibrin in paclitaxel-eluting Achieve stents 28 days after implantation was used as a marker for drug effect and model predictions of flow-mediated drug delivery. In cross sections, the zone of the arterial wall rich in fibrin was quantified as a percent of total arterial wall area and was 20 fold higher for DES (18 ± 3% of the area) than BMS (0.9 ± 0.3%, p < 0.0002). Sections with overlapping DES (14 ± 2%) had 2.8 fold more fibrin than single-stent distal sections of the same arteries (5 ± 1%), and, in turn, distal sections had six fold more fibrin than single-stent proximal sections (0.8 ± 0.3%, p < 0.05) of the same arteries. In longitudinal sections, fibrin extended twice as far distally from isolated struts (1.27 ± 0.2 strut lengths) than proximally from the same struts (0.73 ± 0.2 strut lengths, Fig 2-2, p = 0.02).

Figure 2-7: Average Arterial Drug Concentration from DES & BMS
a. Average arterial drug concentrations resulting from two DES struts in different strut configurations. b. Average arterial drug concentrations resulting from one drug-eluting strut and one bare-metal strut in different strut configurations. The boxes below each bar illustrate the specific configuration. A gray-filled box represents a drug-eluting strut and a white-filled box represents a BMS strut.
2.5 Discussion

Intuition dictates that drug released from stents enters an artery in meaningful amounts only if present at the DES-arterial interface. Conventional wisdom has therefore held that flowing blood is detrimental to drug delivery, siphoning drug off stents and diluting it in the blood stream before arterial entry. Hence, thinner struts ought to be more effective than thicker struts carrying the same drug payload, and only abluminal coatings are required on DES. On the contrary, our mathematical model that couples computational fluid dynamics and mass transfer in an idealized stented artery and in vivo spatial mapping of drug-effect after coronary arterial implantation of DES (Fig 2-2) demonstrated that the role of flow is complex and even counterintuitive. Flow elevates arterial drug deposition beyond levels achieved exclusively via arterial wall contact. Drug deposition is determined by a complex interplay between strut-arterial wall contact, amount and location of drug release, and flow profiles which depend on strut size and position. These findings explain the emerging and expanding information as to limitations and challenges of DES and will have potential impact on the clinical use and evaluation of this technology.

2.5.1 Single Struts

If only contacting surfaces deposited drug one might optimize DES design for delivery by broadening struts, inducing deeper stent penetration where the sides, not simply the abluminal face, contact the wall, or coating only the abluminal surface of each strut. Yet, simulations predict that direct strut contact accounts for only 38% of peak (Fig. 2-3b), and 11% of total arterial drug, suggesting that another process actually dominates. The complex role of flow in stent-based drug delivery becomes apparent when examining cases in which drug load and/or flow profiles are altered. For instance, doubling the DES strut thickness increased the drug supply and flow disruption and consequently increased total arterial drug deposition by 20%. In contrast, doubling the strut thickness without increasing the drug load resulted in the same flow disruption
but because less drug was eluted into the recirculation zones, drug deposition decreased by more than 30% (Fig 2-7a,b). Strut protrusion disrupts blood flow and creates stagnation zones which, when fed drug from non-contacting strut surfaces, establish standing drug pools along the vessel surface. Flow profiles around struts, dictated by strut shape, and the location of the drug-eluting surfaces determine whether drug solubilized within the blood is convectively washed away or instead is trapped in stagnant zones for subsequent deposition.

The fraction of drug convectively delivered to the arterial wall is responsible for elevating both local peak and non-local distal arterial drug concentrations (Fig 2-3b). The overall tissue uptake is therefore determined by both partitioning from drug sources in direct contact with the tissue, and flow-mediated convective transport of drug pools into the arterial wall. Indeed, the deposition profile established by struts with all surfaces coated is the algebraic sum of the profiles obtained from struts with drug only on the abluminal surface and struts with every other strut face coated (Fig 2-3b). Non-contacting strut surfaces can contribute up to 90% of arterial drug deposition, and the top (adluminal) surface provides half of this. Thus, even non-apposed struts removed a full strut thickness from the wall can deliver the greatest bulk of drug to the vessel wall explaining perhaps the remarkably predictable and uniform efficacy of clinical use of DES. Intravascular ultrasound reveals that many struts remain incompletely apposed to the vessel even after high pressure deployment 43. If only apposed struts could deliver drug one would expect more frequent focal restenotic failure and restenosis rates that correlated with stent length, as is the case with BMS 24. On the contrary, however, even arteries with malapposed struts have no substantial neointimal growth, 43, 75 and there is minimal correlation of stent length with restenosis 45, 76.
2.5.2 Multiple Struts

Struts do not reside in isolation. They surround the lumen in a ring and extend along the length of the blood vessel. The concern for non-uniform drug deposition with the variable strut spacing of modern stent designs $^{63,77}$ was seen to be justified when struts were spaced more than two strut distances apart (Fig 2-4). Strut spacing is critical to drug deposition. A section underlying a fixed number of closely adjacent struts is effectively exposed to a wider single strut (equal to the width of the struts and their intervening space) while the remainder of the artery is without exposure. As struts are spaced farther apart total drug deposition rises, as does the variability of interstrut drug concentration. Peaks and troughs are evident and an ascending distribution is observed proximally to distally (Fig 2-4). Indeed our in vivo experiment showed that fibrin deposition was twice as large on the distal as on the proximal aspect of DES struts, and significantly higher in distal than proximal sections of stented arteries. This flow-dependent spatial distribution may explain in part why some DES reduce late lumen loss at their distal edges $^{78}$.

When stents overlap one must consider strut positioning in two dimensions. A second stent presents twice as much drug but also alters flow around struts. As a result peak arterial drug concentrations vary with extent of flow alterations and only increase significantly compared to the single stent case when positioning of struts is optimized (Fig 2-6a,2-7a). Flow disruption created by the close proximity of struts in any overlapping strut configuration diminishes the ability of the additional drug-eluting struts to contribute to drug deposition, increasing the fractional drug washout. Although total deposition depends non-linearly on drug load, when stents overlap the arterial surface area receiving high doses of drug is greater, and extends beyond the strut contact area into drug-laden stagnation regions. As delayed vascular healing follows high drug dosages $^{74}$, overlap regions may alter vascular healing not only by increasing drug under or adjacent to struts, but also in distal tissue segments or in interstrut zones. These issues coupled with the temporal development of intimal
hyperplasia increase the complexity of drug deposition further and amplify the dependence of tissue deposition on strut position and flow.

The role of flow disruption is further validated by examining the case where DES and BMS are used together. When only one device has drug, deposition is always less than with two DES and never higher than with a single DES (Fig 2-7b). Moreover, when the BMS is expanded into an artery which contains a previously implanted DES drug delivery suffers. If however the DES is expanded into an artery where a previously implanted BMS resides and is in contact with flowing blood the added flow disruption from increased strut height combined with drug availability on the innermost strut extends the flow stagnation zones and area to which drug could be delivered (Figs 2-6b and 2-7b). Of more clinical relevance is the extension of these observations to anticipated drug delivery from overlapping DES delivering different drugs. Even if the transport parameters of both drugs are equal, one would anticipate differential deposition, with the innermost DES contributing far more drug to the wall than the outer, more abluminally apposed DES. In every case strut positioning has a complex effect. Strut spacing determines flow disruptions, drug load, and degree of injury imposed on the artery. Situations that increase peak concentrations may actually reduce total drug deposition and vice versa.

2.5.3 Embedded struts

Minimizing vascular injury often conflicts with minimizing luminal flow disruption; the more superficial the strut, the greater the impact on flow; the deeper the strut, the greater the vascular injury. Closely apposed stent struts or overlapping stents create the worst of both situations and significantly change drug delivery. The outermost struts are driven deeper and the innermost struts protrude more. Deeper penetration increases direct contact and drug delivery, but increases injury and reduces the surface area of stent that can deliver drug distally. Increased flow disruption increases the standing zones and resultant
drug delivery. Consequently, the deeper the struts the more localized drug deposition. Peak drug concentrations rise but total deposition falls (Figs 2-8, 2-9 in supplement). The impact of embedding and the role of protrusion on formation of stagnation zones suggest that stent designs with thinner struts may actually deliver less drug in a nonuniform distribution than thicker struts.

2.5.4 Strut Geometry

Stent struts are not often square, most are trapezoidal, some rounded. To test how strut geometry alters our findings for square struts we conducted an additional series of simulations. By placing a range of differently shaped non-eluting bare metal tops atop of the square DES constant drug load was maintained while the effect of different flow profiles on arterial drug deposition was studied. These simulations illustrate that strut geometry only slightly affects the extent of drug spread (Fig 2-10 in supplement), and has minimal effect on the maximum degree of drug deposition. Strut protrusion into the flow field and aspects of the strut coated with drug are more important than overall shape. Strut shape extends the area of the artery exposed to low levels of drug but only downstream of the strut. Shape has no impact on the amount of drug proximal to the stent which is still splayed out by disruption of flow by the struts. The site of maximum concentration is similarly nearly the same for all the tested shapes, but square struts result in a smaller area of total distribution (Fig 2-10 in supplement). As an example, the total deposition was 17% higher for the triangular top strut than the square strut alone although the concentration profiles do not show significant changes in the peak profile.

Moreover, the single strut simulations show that blood flow can carry drug downstream to be deposited well beyond the stent strut and that the degree of this extension of distribution is a function of strut shape. When a stent of many struts is examined in this model there is a small degree of superposition of drug effect from serial struts and distribution increases downstream (Fig 2-11 in
supplement). Here too strut shape plays as an affect albeit subtle. When multiple struts were modeled we observed a 10% increase in total drug deposition with only a slight increase in peak concentration for the triangular top strut compared to the square top strut.

2.5.5 Clinical Implications

This paper uses computational and animal models to address important clinical issues at the interface of stent design, tissue pharmacology and vascular biology. The findings raise a number of immediate clinical issues. The most timely of these concerns for DES systems are those that force changes in our perception of drug distribution after elution, the impact of strut overlap and the importance of stent design. The idea that drug can be delivered to the vessel wall only if stent struts are in contact with the wall is incorrect. Hence, for example, malapposition of struts is not by necessity counterproductive to drug delivery. Even stents not directly apposed to the vessel wall can deliver drug. Similarly, the increasing use of multiple stents in an intervention will mean that struts abut other struts and not just the wall. Conventional wisdom holds that two struts over one arterial segment provide "double the dose" of delivered drug, raising the possibility of double the effect or double the toxicity. Our data show that the addition of a second DES abutting or overlapping a first only modestly increases the dose delivered and actually detracts from the dose if one of the stents is bare metal (Fig 2-7a,b). If overlapping stents provide increased toxicity it is not from heightened dose alone. Rather the safety of overlap is determined by the extent of additional mechanical injury induced by insertion of multiple proximate stents and the spatial extension of drug over the exacerbated injury. The mass of added and overlapping stents create flow disturbances that deliver drug farther beyond where a single strut covers an artery. These data are critical at a time when the approach to overlapping stents is unclear, when clinicians must choose between long stents and overlapping stents, and when there continues to be occasional use of drug-eluting stents in combination with bare metal stents.
Finally, our paper shows that central precepts which drive current DES development must now be called into question. It has been assumed that abluminal coating alone can ensure optimal delivery of drug to the wall while minimizing loss of drug into the bloodstream, and that thinner struts are better than thicker struts for reasons of enhanced deliverability, etc. We show that abluminally-coated drug accounts for less than 50% of the drug which ends up in the arterial wall. The addition of drug on one other face significantly increases the amount of drug that can be delivered to segments of a stented artery. Addition of drug to non-apposed strut faces greatly enhances drug delivery in areas adjacent to, but not underneath, the struts. This finding, coupled with the impact of stent design on flow-mediated stagnant pools, and the demonstration that the thinner the struts, the less drug delivered to the vessel wall, emphasizes the idea that in addition to its recognized importance for mechanical injury and procedural success 31, 63 stent design is also of paramount importance in dictating drug therapy.

2.5.6 Limitations and Future Directions

Mathematical modeling is indispensable precisely where clinical and animal studies increasingly define areas of concern but cannot fully characterize them. The predictions of these models are becoming increasingly important as our experience with DES emerges in increasingly challenging clinical environments. Computational methods are valuable in isolating and understanding mechanisms for drug delivery, and yet idealized models do not account for all possible clinical variables. In our mathematical model simplifications were made such as neglecting drug metabolism and binding, assuming homogeneous, healthy tissue composition, assuming negligible arterial drug transport via vasa vasorum, and considering only 2-dimensional flow. Substantial work remains to include drug-specific pharmacokinetics 64, 79, unique vascular ultrastructure such as vessel disease 80, and topographies 81, and even
the impact of intimal hyperplasia and thrombosis on DES function. The results of this study motivate further study of the relationship between the complex 3-dimensional flow generated over the stent mesh and total arterial drug deposition. We would hypothesize that the longitudinal patterns we describe in this paper will also provide the dominant effects in more complex settings.

Further limitations exist in analyzing *in vivo* data due to the paucity of high resolution techniques for detecting drug deposited within the tissue and differentiating it from drug adherent to the strut. Thus, fibrin was used in this study for its advantage in being able to differentiate between tissue deposited drug and that adhering to the strut surface. The mathematical model does not include drug specific properties so as to focus the study on the effects of blood flow on arterial deposition of drug for a generic drug, though the *in vivo* validation was confined to a specific drug. The properties of rapamycin that increase its tissue retention include its specific binding to a complex of proteins and general binding to plasma and tissue proteins. Thus, broad generalization beyond drugs like rapamycin which do not share similar physico-chemical properties would be unwarranted.

The coupling of fluid dynamics with stent design and pharmacology of local delivery creates a powerful tool by which to evaluate DES. Using a combined approach which mixes mathematical and animal-based modeling we now show that direct contact of DES struts with target tissue is important but not essential, as drug deposition does not necessarily scale linearly with drug load or stent-artery contact area. The relative positioning of struts and flow over the stent determines tissue concentration. As we define the kinetics of drug release and tissue uptake, computational models may suggest even more creative and efficient means of delivering drugs for a range of vascular indications and patients.
Figure 2-8: Arterial Drug Deposition and Strut Embedding
Total arterial drug deposition depends on the degree of strut embedding. The average drug content in the wall drops as these fully-coated DES struts are embedded into the arterial wall to greater extents and removed from flow. Typically a stent strut indents the elastic lamina and bows the underlying tissue but is still subject to flow and very much surrounded by areas of flow separation.
The axial concentration profile at a plane 1.5 strut heights deep into the artery is changed by DES strut embedding. As the strut is driven deeper into the wall, the local concentration rises and extent of higher concentration propelled down stream drops. Typically a stent strut indents the elastic lamina and bows the underlying tissue but is still subject to flow and very much surrounded by areas of flow separation.
Figure 2-10: Arterial Drug Distribution and Strut Shape

The concentration profile of drug along the length of the artery at an arterial depth of 1.5 strut heights is subtly changed when the shape of the strut tops are changed. To isolate the effect of shape from dose only the base of each strut (color outline) and not the tops (black outline) were coated with drug. This effectively maintained the dose constant as each strut had an identical surface area of coating, which can not be similarly controlled with the different shapes. Flow in the blood vessel is from left to right and the bottom left edge of the strut is aligned with the origin of the Cartesian coordinate system. Drug concentration on the ordinate within the arterial wall (colored curves that correspond to respective colored struts) is plotted against longitudinal position on the abscissa. In all cases the arterial drug concentration rises before the strut and peaks slightly beyond the strut. While the proximal concentration is unaffected by the geometry of the strut, the down stream concentration is extended, likely as a result of differential effects on flow by different shaped struts.
The axial concentration profile at a plane 1.5 strut heights deep into the artery is only subtly changed by strut shape. In this depiction flow runs from left to right, and drug-eluting strut surfaces are depicted in color (pink for triangular and blue for squared strut tops). In both cases drug concentration, is lowest in the tissue at the most proximal upstream portion of the artery, and increases along the length of the stented vessel. The triangular top strut increases the distal spread of drug beyond the strut and minimal level of drug between struts but in barely discernible quantities.
2.7 Acknowledgements
The authors thank Mr. Kartik Shah of ESI-CFD, and Dr. Chao-Wei Hwang.
2.8 References


Chapter 2: Blood Flow, Strut Position, and Arterial Drug Deposition


Chapter 3: Release Kinetics, Drug Dose, and Arterial Drug Deposition

3.1 Abstract
Millions of patients worldwide have received drug-eluting stents to reduce their risk for in-stent restenosis. The efficacy and toxicity of these local therapeutics depends upon arterial drug deposition, distribution, and retention. To examine how administered dose and drug release kinetics control arterial drug uptake, a model was created using principles of computational fluid dynamics and transient drug diffusion-convection. The modeling predictions for drug elution were validated using empiric data from stented porcine coronary arteries. Inefficient, minimal arterial drug deposition was predicted when a bolus of drug was released and depleted within a few seconds. Month-long stent-based drug release efficiently delivered nearly continuous drug levels, but the slow rate of drug presentation limited arterial drug uptake. Uptake was only maximized when the rates of drug release and absorption matched, which occurred for hour-long drug release. Of the two strategies for increasing the amount of drug on the stent, drug concentrations potently impacted the magnitude of arterial drug deposition, while thicker coatings prolonged duration of release. This work demonstrates the importance of drug release kinetics and administered drug dose in governing arterial drug uptake and suggests novel strategies for controlling spatio-temporal drug distribution.

Keywords: Stents, Drug Delivery, Release Kinetics, Arterial Drug Deposition, Restenosis
3.2 Introduction

Blood flow through atherosclerotic vessels is restored by balloon angioplasty and/or stent implantation, but vessel patency is frequently short-lived. In a process termed intimal hyperplasia, proliferating cells grow radially inward to re-occlude the vessel, which results in a clinical phenomena termed restenosis. The burden of restenosis has been alleviated in part by delivering anti-proliferative drugs to the arterial wall via local and systemic drug delivery modalities. While drug biologic potency\(^1\) and physicochemical properties\(^2,3\) have been identified as critical determinants of biological effect, the impact of dosage and timing of arterial drug presentation is not clear. In the O-SIRIS trial, orally delivered sirolimus only inhibited intimal hyperplasia if administered at high doses for 2 days prior to the procedure\(^4\). In the ELUTES clinical trial\(^5\), paclitaxel delivered from stents significantly reduced the percent diameter stenosis at 6 months only when delivered at the highest applied drug dose. That biologic success could be achieved by vastly different drug delivery modalities, such as oral delivery\(^4\), drug release from coated stents\(^6,7\) or coated angioplasty balloons\(^8\), suggests that different combinations of drug dosage and release kinetics potentially elicit the same arterial response. Both clinical and in vitro data motivated our hypothesis that applied drug dose and kinetics of drug release modulate arterial drug uptake. In turn, drug distribution and retention within the arterial wall likely dictate biologic outcome. In an era of potentially fatal toxic sequelae, such as stent thrombosis, which may occur concomitantly with inhibition of cellular proliferation, understanding how administered dose and release kinetics impact arterial drug uptake is critical to ensuring device safety and efficacy.

Computational techniques were ideal because they enabled rapid consideration of a range of drug doses and release kinetics followed by precise monitoring of arterial drug deposition, distribution, and retention. We employed an experimentally validated finite volume based computational model in which drug diffused from a drug laden strut to and through the arterial wall with simultaneous diffusive-convective drug washout into flowing blood.
computational model predicted that release kinetics and applied drug dose do in fact modulate arterial drug deposition, distribution, and retention. But surprisingly, when our data were compared to outcomes from human clinical studies, we found that predicted variations in arterial drug uptake may not necessarily correspond to gradual variations in biologic outcome. These findings indicate that though biologic response may be related to arterial drug uptake it is potentially controlled independently of the device.
3.3 Methods

3.3.1 Mathematical Model

Drug transport was modeled using a 2-dimensional transient model (Fig 3-1). The luminal diameter, 3 mm, was 3 times greater than the arterial wall thickness; and, the axial distance along the artery was determined by the fluid mechanic entry length required to reach fully developed flow. The strut and coating dimensions were based upon representative dimensions of the CYPHER© Bx Velocity drug-eluting stent (Cordis Corporation, a Johnson & Johnson Company).

As in previous work, the blood was assumed Newtonian and non-pulsatile, and its fluid mechanics were described with continuity and steady state Navier-Stokes equations (Fig 3-2, Eq 1-3). The inlet profile, applied at axial position \( z = -L_{\text{Proximal}} \) (Fig 3-1), was assumed unidirectional and parabolic (Fig 3-2, Eq 4) and the outlet, located at axial position \( z = L_{\text{Distal}} \) (Fig 3-1), was assumed to have zero pressure (Fig 3-2, Eq 6) boundary conditions. Blood velocities were zero at all solid-fluid interfaces (Fig 3-2, Eq 5). The fluid mechanical blood properties and volumetric flow rate were obtained from standard reference values.
### Governing Equations, Boundary & Initial Conditions

#### Navier-Stokes Equations & Boundary Conditions

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<thead>
<tr>
<th>Equation</th>
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<td>Eq 1</td>
<td>( \frac{\partial v_x}{\partial t} + \nabla \cdot (v_x v) = 0 )</td>
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<td>Eq 2</td>
<td>( \left( \frac{\partial^2 v_x}{\partial z^2} + \frac{\partial^2 v_x}{\partial r^2} \right) + \frac{v_x}{r} = \frac{\partial P}{\partial r} )</td>
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<td>Eq 3</td>
<td>( \left( \frac{\partial^2 v_y}{\partial z^2} + \frac{\partial^2 v_y}{\partial r^2} \right) + \frac{v_y}{r} = \frac{\partial P}{\partial r} )</td>
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<td>Eq 4</td>
<td>( v_x(r_{-L_{proximal}}) = V_c \left( 1 - \frac{(r-R)^2}{R^2} \right), \quad v_x(r_{+L_{proximal}}) = 0 )</td>
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<td>Eq 5</td>
<td>( v_y(r_{-L_{proximal}}) = v_c(2R,x) = 0 ), ( v_y(r_{+L_{proximal}}) = v_c(2R,x) = 0 )</td>
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<td>Eq 6</td>
<td>( P(r,L_{coat}) = 0 )</td>
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#### Drug Transport Equations

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<td>( \frac{\partial C_r}{\partial t} = D_r \left( \frac{\partial^2 C_r}{\partial z^2} + \frac{\partial^2 C_r}{\partial r^2} \right) )</td>
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<td>Eq 8</td>
<td>( \frac{\partial C_{tissue}}{\partial t} + v_z \frac{\partial C_{tissue}}{\partial z} + v_r \frac{\partial C_{tissue}}{\partial r} = D_{tissue} \left( \frac{\partial^2 C_{tissue}}{\partial z^2} + \frac{\partial^2 C_{tissue}}{\partial r^2} \right) )</td>
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<tr>
<td>Eq 9</td>
<td>( \frac{\partial C_{coat}}{\partial t} = D_{coat} \left( \frac{\partial^2 C_{coat}}{\partial z^2} + \frac{\partial^2 C_{coat}}{\partial r^2} \right) )</td>
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#### Drug Transport Boundary Conditions

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<td>Eq 10</td>
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<td>Eq 11</td>
<td>( \frac{\partial C_{blood}}{\partial z} \bigg</td>
</tr>
<tr>
<td>Eq 12</td>
<td>( \frac{\partial C_{blood}}{\partial r} \bigg</td>
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<td>Eq 13</td>
<td>( D_b \frac{\partial C_{blood}}{\partial r} \bigg</td>
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<td>Eq 14</td>
<td>( \frac{\partial C_{tissue}}{\partial z} \bigg</td>
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<td>Eq 15</td>
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<td>( D_{tissue} \frac{\partial C_{tissue}}{\partial z} \bigg</td>
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<td>Eq 17</td>
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#### Drug Transport Initial Conditions

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<td>( C_{coat} = 1 ) at ( t = 0 )</td>
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<tr>
<td>Eq 19</td>
<td>( C_{tissue} = C_{blood} ) at ( t = 0 )</td>
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**Figure 3-2:** 2-Dimensional, Transient Model Equations

Governing equations and boundary conditions describing the physics of fluid dynamics and transient drug transport. The arterial luminal radius (R) is 1.5 mm and the arterial wall thickness (L.) is 1 mm. The velocity map in the radial and axial directions, \( v_r \) and \( v_z \), were calculated based on the inlet parabolic profile with centerline velocity \( (V_c) \) of 46 cm/s. Tissue and blood drug concentrations, \( C_t \) and \( C_b \), were normalized to the strut drug concentration, \( C_c = 1 \). The \( P \) is dynamic pressure; \( \mu \) is blood dynamic viscosity; \( D_p, D_r, D_{t} \) are drug diffusion coefficients in blood, \( 10^{15} \) um\(^2\)/s, in the arterial wall, 1 um\(^2\)/s, and in the coating, ranging from \( 10^{-5} \) to \( 10^{-9} \) um\(^2\)/s.

Drug transport parameters in the tissue were based upon experimental measurements of transmural drug diffusivity\(^\text{12}\), while drug diffusivity within the coating was calculated based on the desired duration of drug release and the coating thickness, \( D_{coat} = L_{coat}^2/t_{release} \).\(^9\) Drug release ranged from bolus to intra-arterial drug infusion to continuous, 30 day release. The time-dependent drug transport from the coating was assumed to occur solely via transient diffusion of drug through the coating (Fig 3-2, Eq 7), where the initial drug concentration was unity throughout the coating (Fig 3-2, Eq 18). In this model,
the blood and tissue were initially devoid of drug (Fig 3-2, Eq 19). The process of drug diffusion from the coating was handled using a continuity of flux boundary condition at the interfaces between the coating and the tissue/blood (Fig 3-2, Eqs 16,17). Upon leaving the coating, the drug transport through the blood was described by the transient diffusion and convection equation (Fig 3-2, Eq 8), where the luminal inlet boundary drug concentration was assumed zero (Fig 3-2, Eq 10)\textsuperscript{10}. These conditions are valid because in the convection dominated arterial lumen it is virtually impossible for drug to diffuse 34 strut widths in the direction opposing blood flow\textsuperscript{9}. As it is unlikely that drug would diffuse 20 strut heights perpendicular to the direction of blood flow to the opposite arterial wall, the tissue wall above the stent strut had a no flux boundary condition (Fig 3-2, Eq 12). The outlet was an open boundary condition (Fig 3-2, Eq 11), because blood flow carries drug solubilized in the blood downstream. Finally, drug transport through the arterial wall with the apposing-strut was approximated using the transient diffusion equation (Fig 3-2, Eq 9), where the perivascular wall (R = -W_{tissue}, Fig 3-1) was assumed to be impenetrable to drug transport (Fig 3-2, Eq 15), and the up- and downstream bounds of the tissue had symmetry boundary conditions (Fig 3-2, Eq 14)\textsuperscript{10}. Drug transport between the tissue and blood compartments occurred via a continuity of flux condition (Fig 3-2, Eq 13) applied to the interface\textsuperscript{10}.

### 3.3.2 Numerical Methods

Commercially available geometry/mesh generation and computational fluid dynamics software (GAMBIT v2.3.16, FLUENT v6.3.17, Fluent Inc., Hanover, NH) were used to apply the mathematical model. The geometry was discretized into approximately 200,000 rectangular mapped mesh elements. To ensure that the discretized geometry had sufficient resolution to detect changes induced by model parameters, a mesh sensitivity study was performed. Results show that doubling local mesh density resulted in less than 2% change in local and average arterial and coating drug concentrations. The discretized geometry
was imported into Fluent, a finite volume based software. Second order discretization schemes were used for all velocities and concentration variables. The momentum and continuity equations were solved iteratively using SIMPLEC algorithm\textsuperscript{13} for pressure-velocity coupling; the diffusion-convection equations were handled with upwind differencing.

3.3.3 Experimental Methods

CYPHÉR\textsuperscript{©} Bx velocity stents (Cordis Corporation) were deployed to a target balloon artery ratio of 1.1:1 into porcine coronary arteries. At the designated time points of 1, 8, 14, 30, 60 and 90 days post-implantation, the stented arteries (n = 6 per time point) were harvested and the stent was carefully separated from the surrounding arterial tissue. Sirolimus was extracted from the stents in 10 ml of HPLC grade methanol and quantified using standard LC/MS/MS methodology.
3.4 Results

3.4.1 Release Rates are Modulated by Drug Coating Diffusivity and Affect Arterial Drug Deposition and Retention

The validity of the transient 2-dimensional diffusion-convection computational model was confirmed by comparing predicted drug release from stent strut coatings with actual release from devices implanted in porcine coronary arteries. The model accurately predicted fractional drug release over a 90 day interval detected in vivo with a root mean squared error of < 0.1. In both the model and in vivo experiment, at 2 weeks post-implantation, the stent had released half of its initial load into the tissue and the surrounding lumenally flowing blood (Fig 3-3). Drug release, which was governed primarily by drug diffusivity within the coating, was initially faster than first order exponential release.

Drug diffusivities modulated drug elution from the coating within the extremes of bolus to continuous drug delivery. At high drug coating diffusivity, e.g. $10^5$ um$^2$/s, drug was depleted from the coating within seconds post-implantation, operating analogous to true bolus drug administration (Fig 3-4a). As release was prolonged, e.g. with coating drug diffusivity of 1 um$^2$/s, the timescale for drug elution and depletion was prolonged to hours post-implantation, similar
to intravenous bolus drug delivery (Fig 3-4a). Finally, drug release was prolonged most dramatically to weeks and months post-implantation for coating diffusivity around $10^{-5}$ um$^2$/s, which was akin to local stent based drug delivery (Fig 3-4a). Even within the class of slow stent based drug delivery, release could be made to vary from 10 days to more than 1 month of drug release (Fig 3-5a).

![Figure 3-4: Coating Drug Diffusivity Alters Arterial Drug Uptake](image)

**Figure 3-4:** Coating Drug Diffusivity Alters Arterial Drug Uptake
Impact of varying drug release rate from the coated strut by changing drug diffusivity within the coating within a 10 log range. A. Average coating drug concentration vs. time, B. Average arterial drug concentration vs. time, C. Arterial drug concentration vs. longitudinal position along the arterial wall at a location <1 strut depth within the arterial wall at 110s and 1 day post-implantation. All data were acquired using a transient computational model with equivalent initial drug load conditions.

Arterial drug uptake was predicted to follow drug release. The magnitude of arterial drug deposition over time was determined by a balance between drug availability and the rates of drug release from the coating and tissue uptake. At the extremes of drug diffusivity within the coating, drug was released so rapidly that it exceeded the tissue absorption rate, or so slowly as to limit the amount of
drug presented to the artery (Fig 3-4a-b). The former represents an inefficiency wherein drug is diluted systemically prior to arterial uptake and the latter is an efficient, but release rate-limiting state. True bolus drug administration resulted in a low peak in arterial drug uptake that was transient and rapidly lost as the model drug did not significantly enter the target tissue and local stent drug concentrations were insufficient to maintain arterial drug delivery (Fig 3-4b). When drug was administered over several hours akin to intravenous infusion, peak arterial drug deposition was maximized, although arterial drug retention only lasted for a few days post-implantation (Fig 3-4b). Without binding, readily diffusible drugs like heparin may achieve high peak arterial drug concentrations that rapidly decay when delivered quickly from the stent. Finally, when drug release was prolonged for weeks and months, the arterial drug uptake was submaximal, due to slow drug presentation to the arterial wall, but uptake was efficient. Continuous, long term drug release enabled arterial drug retention which decayed after more than a month post-implantation (Fig 3-4b). Even increasing drug diffusivity marginally by 3 fold translated into 3 times faster release (Fig 3-5a), resulting in peak arterial drug uptake increasing by 70%, which subsided after two weeks post-implant (Fig 3-5b). Clearly fluctuations in release rate are responsible for potentially large shifts in the dynamics of arterial drug uptake.

Figure 3-5: Drug Release Duration and Stent Drug Concentration
Impact of modulating release rate both independently of drug load and as a consequence of increased applied drug concentration. A. Average coating drug concentration vs. time. B. Average arterial drug concentration vs. time.
The distribution of drug within the arterial wall also depended on the drug release rate from the coating. Bolus release allowed transient drug accumulation within the blood. Subsequently, more drug deposited asymmetrically downstream from the stent strut than upstream in the arterial wall (Fig 3-4c) within less than 2 minutes post-implantation. Conversely, when the release rate was slow, there was limited drug release and minimal luminal drug accumulation. Thus, the asymmetric arterial drug deposition was not prominent. In all cases, asymmetric arterial drug deposition was undetectable beyond 1 day post-implantation (Fig 3-4c).

3.4.2 Release Rate Affects Arterial Drug Deposition and Retention Independently of Drug Load

Two coated struts possessing the same initial drug loading were modified so that they released drug at different release rates. Release rates could be modulated either independently of applied dose or as a result of altered drug dose. Release rate was altered independently of drug load not only by changing coating drug diffusivity but also by decreasing (increasing) drug concentration with a commensurate increase (or decrease) in coating thickness. The release rate from thinner, high concentration coatings was initially fast, leading to rapidly declining coating drug concentration (Fig 3-6a) as compared to thicker, lower drug concentration coatings. Due to the large fractional drug release for thinner coatings, arterial drug deposition peaked and remained elevated for 20 days post-implantation (Fig 3-6b). Once the fast releasing thin coatings were nearly depleted, the arterial wall lost drug faster than it received drug from the coating, leading to brief arterial drug retention (Fig 3-6b). By contrast, thicker coatings possessing the lower drug concentration released their load slowly and relatively steadily, which resulted in more gradually declining coating drug concentrations (Fig 3-6a). Slow release reduced the extent of arterial drug deposition in the short term, but by 30 days post-implantation, the continued drug infusion from the thicker coating sustained a more constant level of arterial drug deposition and
retention, compared to that occurring from its thinner coated counterpart (Fig 3-6b).

![Graph](image)

**Figure 3-6:** Coating Thickness and Coating Drug Concentration Impact of altering release rate independently of initial drug load by simultaneous and opposite variations in coating drug concentration and thickness for coating drug diffusivity of $10^{-5}$ $\text{um}^2/$s. A. Average coating drug concentration vs. time. B. Average arterial drug concentration vs. time.

### 3.4.3 DES Strut Dimensions and Drug Concentration Impact Initial Drug Load and Arterial Drug Deposition

Often release rates are affected by changes in stent strut characteristics such as drug load. Variable drug loading on stents is achieved either by increasing the relative amount of drug in the polymer formulation or by increasing both the drug and polymer proportionally on the stent strut. The former was simulated by increasing drug concentration in the coating, and the latter was achieved by increasing drug coating thickness on the stent strut. Increasing the coating drug concentration increased the drug load but not the duration of drug release, leading to faster drug release rate (Fig 3-5a, 3-6a). In response, arterial drug deposition increased proportionally with the increase in drug concentration (Fig 3-5b, 3-6b), resulting in 3-fold increased stent drug concentrations causing 3-fold increased arterial drug uptake (Fig 3-5b).
Alternatively, increased drug load was also achieved through thicker drug-laden coatings. Thicker coatings with the same drug concentration as their thinner counterparts had greater drug diffusion distance and consequently released drug more slowly, leading to gradually declining coating drug concentration (Fig 3-7a). Thicker coatings possessed a larger initial drug load and therefore released more drug over time than thinner coatings (Fig 3-7b). The slower release rate of the thicker coating combined with its larger drug mass induced 10-20% increase in peak arterial drug deposition that remained elevated over time (Fig 3-7c). Conversely, thin coatings had smaller drug load (Fig 3-7b) that was released faster (Fig 3-7a), and also led to lower arterial drug deposition (Fig 3-7c). The impact of redistributing the coating thickness from the inner diameter (ID) to outer

Figure 3-7: Drug Coating Thickness and Arterial Drug Deposition
Impact of altering release rate by changing initial drug load via increased coating thickness using coating drug diffusivity of $10^{-5}$ um$^2$/s. A. Average coating drug concentration vs. time for different coating thicknesses and distributions of coating around the strut, B. Drug released from the stent normalized by the initial drug load on the “x” coating thickness strut, C. Average arterial drug concentration vs. time. All coating drug concentrations were unity.
diameter (OD) of the stent strut was tested with no change in total coating thickness or peri-strut fluid dynamics. When the OD coating was 3-fold thicker than the ID, drug release was slightly slower and arterial drug uptake increased minimally, which are all insignificant compared to the effects of increasing total coating thickness (Fig 3-7a,c).

Strut size is dependent upon stent design, which often varies dramatically. Stent strut sizes were tested, representing potential stent design changes. When 5-10% longitudinally wider struts were simulated, the strut surface area contacting the arterial wall increased. Drug release in our model was negligibly impacted (Fig 3-8a), though peak arterial drug deposition increased 10-20% within 2 days (Fig 3-8b) due to greater surface area drug exposure. A 15% taller strut carrying more drug did not alter release rate or drug uptake compared to a shorter strut carrying a smaller drug load (Fig 3-8b). These model findings illustrate that arterial drug uptake is more sensitive to strut-arterial wall contact area than it is to equivalent changes in strut height.

![Figure 3-8: Coated Strut Size and Arterial Drug Deposition](image)

Impact of variations in coated strut size on drug release kinetics and arterial drug uptake using coating drug diffusivity of $10^{-5}$ um²/s. A. Average coating drug concentration vs. time, B. Average arterial drug concentration vs. time for different strut sizes. All coating drug concentrations were initially unity. Brackets around legend entries indicate curves overlap as designated by arrow.
3.5 Discussion

Initial restoration of blood flow through atherosclerotic vessels is lost in part as intimal hyperplasia encroaches on luminal patency. Local drug delivery platforms have successfully inhibited intimal hyperplasia, yet the factors governing biologic effect remain incompletely understood and are likely multifactorial. As the toxic sequelae associated with local drug delivery become more severe it is imperative to characterize the relationship between biologic outcome and arterial drug uptake. In addition to biologic potency, it has been established that physicochemical properties dictate biologic effect. Hydrophobic drugs, for example, traverse the arterial wall more slowly, and once penetrated are retained better than hydrophilic compounds\(^4\). Yet, these properties alone do not ensure a biologic effect.

From the first identification of restenosis after angioplasty, questions have been raised regarding the impact of drug dosage and release kinetics on inhibition of intimal hyperplasia. Restenosis following balloon angioplasty was curtailed by oral drugs but only if begun days to weeks before the procedure\(^15,\,16\). More recently, oral sirolimus reduced angiographic restenosis post-stent implantation only when the drug was ingested at high doses and if given at least two days before the procedure\(^4\). Yet, a single drug presentation kinetic must not dominate biologic outcome, as evidenced by vastly different modalities successfully reducing post-stent intimal hyperplasia despite releasing their individual drug dosages for different durations. Restenosis has been reduced by a number of modalities such as administration of drugs in a sustained fashion over months from the stents themselves\(^5,\,6,\,17-19\), drug delivery over a few minutes from coated angioplasty balloons\(^8\), intra-coronary injections in the presence of angiographic contrast media\(^20,\,21\), and infusion from microporous catheters\(^1\). Despite the range of drug delivery modalities, there has yet to be a definitive demonstration of a dose response in animal models or clinical experience\(^5,\,22,\,23\); drugs work at some dose and do not below this level.
One interpretation of these observations is that the arterial wall is insensitive to differences in the device modality. The many failed attempts at eradicating restenosis however make this idea remote\textsuperscript{5, 23, 24}. Alternatively, seemingly disparate modes of local drug delivery may appear biologically indistinguishable. Either the complexities of the arterial wall may preclude a dose response, or the actual kinetics of drug delivery amongst the different modalities may be too similar to achieve varied response. Our findings are consistent with both explanations. In some instances, the predicted patterns of drug penetration, distribution and retention achieved with devices in successful clinical trials are more like each other than not, even with seemingly different modes of delivery. Thus, biologic response may in fact be dose and kinetics dependent but we have yet to stress the system across the full range of possible drug concentrations and patterns of presentation. On the other hand, it is likely that arterial wall drug metabolism is far more dynamic than the amount and rate of drug release from the formulations considered to date.

3.5.1 Experimental Validation of Computational Model

Computational models of drug transport and target penetration are only valid if the release kinetics achieved by the simulation realistically recapitulates \textit{in vivo} release from a stent. Drug release from a coated stent is a complex process wherein drug must navigate through a complex porous polymeric coating. Passive diffusive forces are governed by effective diffusivity and the porosity and tortuosity of the polymer coating\textsuperscript{25}. We therefore approximated this complicated mechanism by using a Fickian diffusion model within the coating, where constant effective drug diffusivity characterized the drug-polymer interaction. Simultaneously, we measured drug release from a stent implanted into porcine coronary arteries for up to 30 days. This computational model can simulate drug release over a range of seconds to days by modulating the drug diffusion coefficient in the coating (Fig 3-3b). Predicted drug release faithfully matched 30 day \textit{in vivo} release (Fig 3-3a), implying that stent based drug release in aggregate behaves like concentration gradient driven drug transport. With these
resources in hand one can precisely define the impact of release on arterial wall uptake.

3.5.2 Rapid Drug Release and Arterial Drug Uptake

Our model examined the resultant drug levels for short and long term drug exposure following vascular injury. We examined release of drug that was instantaneous and resembling true bolus release, slightly more prolonged release over a matter of minutes and sustained release over days to weeks (Fig 3-4a). Arterial drug uptake was predicted to vary significantly from different release kinetics. True bolus release, which releases and clears drug from the local milieu within seconds post-implantation, results in negligible arterial drug uptake (Fig 3-4b). Yet, clinical delivery modalities likely achieve a slightly more prolonged release that is not as strictly speaking a bolus.

In experiments, intra-coronary injection of paclitaxel reduced diameter stenosis and raised minimal lumen diameter compared to no drug control\(^{20, 21, 26}\), but only when used with contrast media. The media prolongs circulation time beyond the true bolus profile and enhances drug penetration to achieve detectable arterial wall drug concentrations. Similar effects were achieved with stented porcine coronary arteries preinflated with paclitaxel coated balloons\(^{27}\). Human studies validated the possible long term benefit from relatively transient drug exposure if formulations extended release even by minutes\(^{28}\). Paclitaxel coated balloons expanded within the femoral artery reduced mean late lumen loss and binary restenosis at 6 months compared to plain balloon angioplasty\(^{8}\). Our mathematical models suggest that when release is prolonged, even over several minutes, high magnitude peak arterial drug uptake can be obtained that only subsides within a day (Fig 3-4). These computational data verify that transient drug delivery over a relatively short duration of minutes may actually result in brief but significant arterial drug uptake and exposure. The experimental and computational studies combined imply that transient arterial drug exposure on the order of days is sufficient to sustain a relatively longer term favorable biological response when
initiated shortly after injury. These findings hint toward the existence of a temporal window for biologic efficacy that begins immediately after procedure induced injury.

3.5.3 Slow Drug Release and Arterial Drug Uptake

In contrast to the fast drug release kinetics, polymer matrix-based stent arterial drug delivery is prolonged for weeks and even months. The question then arises as to whether this same model of arterial wall kinetics can explain the absence of a dose response within clinical trials in which dose and release kinetics were changed\textsuperscript{5, 22, 29, 30}. In the 3D study\textsuperscript{30}, doubling the dose of sirolimus from the Cypher stent also did not alter neointimal hyperplasia detected by IVUS in diabetics between 6 months and 2 years. Several potential reasons explain the absence of a dose response. Our computational studies predict that a double drug dose achieved by doubling drug coating thickness on the stent most notably prolonged drug release from the stent (Fig 3-7a) but increased peak arterial drug deposition by at most 20\% (Fig 3-7b). As demonstrated by both paclitaxel and sirolimus clinical studies and computational predictions, dose doubling in this manner should produce minimal changes in peak arterial drug uptake and therefore elicit indistinguishable biologic effect. In fact, most possible modifications of stent design, such as the possible range of coating distribution around the strut (Fig 3-7a,c), or strut dimensions (Fig 3-8a-b) cannot be changed enough to significantly impact release kinetics or arterial drug uptake. Design may dictate arterial wall injury but within the limits of the formulations considered design does not change release features.

In other clinical trials, it is possible that a dose response was not observed despite significant fluctuations in release kinetics and arterial drug uptake. In this situation it is postulated that the arterial wall regulated either its drug absorption or its response to absorbed drug. In this paradigm the arterial wall is possibly nearly incapable of displaying a dose response because the tissue-based drug metabolism and clearance create an exceedingly narrow dose response range.
which practically leads to threshold, binary behavior. In the ELUTES clinical trial\(^5\), paclitaxel was precipitated directly onto bare metal stents at four doses that spanned a 10-fold range. Only the highest dose had a statistically significant reduction in angiographic restenosis at 6 months compared to the bare metal stent. Computational predictions demonstrate that a ten-fold drug dose achieved by increasing stent drug concentration resulted in faster drug release and 10-fold increased transient peaks in arterial drug deposition, which gradually taper (figure not shown). Thus, arterial drug deposition can fluctuate dramatically without demonstrated dose response, implying that the potential dose response range is narrower than the range of stent-based drug presentation kinetics.

In the PISCES clinical trial, where drug release was more finely controlled, paclitaxel was effective when released over 10 or 30, but not 5 days \(^{22}\). Furthermore, tripling drug dose had a modestly improved response if released over 10 days but not 5 or 30 days. Computational predictions show that extending the release of a fixed dose from 10 to 30 days creates a relatively more constant arterial drug infusion (Fig 3-5a). By deduction from previous findings (Fig 3-4a), the fast 5-day release would result in initial elevation in arterial drug deposition followed by abbreviated drug retention due early depletion compared to 10 and 30 day release. Delivering three fold more drug, by increased drug concentration, within a fixed duration predicted a transient 3-fold increase in peak arterial drug uptake which subsequent declined rapidly (Fig 3-5). Thus, for 10 day release, the arterial wall potentially elicits graded response to dose because the dose and duration of administration fall with the sensitivity range of the tissue. Together, the computational and PISCES data suggest that within the drug doses and durations investigated, arterial drug exposure duration is a primary determinant of biologic response. Given the evidence that even short term drug release from drug coated angioplasty balloons may inhibit intimal hyperplasia, these findings indicate that there may exist multiple arterial drug dose and retention time pairings that are therapeutic. Abbreviated release likely requires substantially larger arterial drug dose while sustained release does not.
Despite wide variations in arterial drug uptake after local release the arterial response predominantly exhibits threshold behavior. The arterial wall may be controlling biologic outcome independently of arterial drug uptake through control of drug binding. Specific and nonspecific tissue binding sites are known to exist for drugs used in eluting-stents with clinical approval\textsuperscript{14}. The dose response range could be easily missed if the applied drug concentration exceeds the receptor density and if the receptors have strong binding affinity for the drug. In this case, the receptors would rapidly saturate and display nearly binary biologic response.
3.6 Conclusions and Future Directions

Drug release kinetics and applied dose are responsible in part for the duration and magnitude of arterial drug uptake. Surprisingly, the clinical data in conjunction with computational predictions suggest that biologic effect exhibits a threshold response despite wide variations arterial drug uptake. It is likely that drug delivery modality and arterial wall jointly govern the biologic effect of drugs on stent-induced vascular repair. It remains for future work to fully characterize the arterial wall and the relationship between drug uptake and biologic outcome. Computational models are valuable and expedient tools for understanding the impact of specific physical phenomena on arterial drug delivery, yet they necessarily employ simplifications. In this computational model only diffusive drug transport forces within the arterial wall were considered. In reality, the arterial wall is a heterogeneous complex milieu in which drug diffuses passively, travels via pressure-driven radial flow, and also binds to drug-specific arterial components. It remains for future work to assess the aggregate impact of additional physical phenomena upon arterial drug uptake.
3.7 Acknowledgements

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3.8 References


Chapter 4: Thrombus-Induced Fluctuations in Arterial Drug Deposition and Retention

4.1 Abstract
Arterial drug concentrations determine local toxicity. As such the emergent safety concerns surrounding drug-eluting stents mandates an investigation of the factors contributing to fluctuations in arterial drug uptake. Drug-eluting stents were implanted into porcine coronaries with minimal variation from stent to stent in release kinetics but with up to 114% variability in arterial drug deposition 2 weeks after stent implantation. While intimal hyperplasia was not significantly different amongst stented specimens the extent of adherent mural thrombus was. A 2-dimensional, transient computational drug transport model predicted that focal and diffuse thrombi elevate arterial drug deposition by increasing local drug availability and reducing drug washout. Arterial drug uptake was observed experimentally at a rate faster than that expected from free drug diffusion. Carrier-mediated drug transport was identified as a potential novel mechanism for increasing arterial drug transport. The results of this investigation highlight that thrombus induces fluctuations in arterial drug uptake without altering the rate of drug release from the stent. The mural thrombus effects on arterial drug deposition may be circumvented by forcing slow, rate limiting arterial transport that cannot be further hindered by mural thrombus.
4.2 Introduction

There is increasing concern for the risk of thrombosis of drug-eluting stents later after implantation. These stents clot at a rate of 0.6% each year after implantation up to 3 years\(^1\) and remain an issue even years after implantation\(^2,3\). Documentation of delayed healing and re-endothelialization suggest that the unhealed tissue state could be providing a nidus for thrombosis\(^4-6\). Other studies found that drug-eluting stents delay recovery of endothelial function compared to their bare metal counterparts even 6 months after implantation\(^7,8\). Local arterial drug levels are likely responsible for these observations, because of the narrow therapeutic window within which paclitaxel and sirolimus offer selective inhibition of cultured smooth muscle cell growth and migration without affecting endothelial cell proliferation\(^9,10\). Complete appreciation of the role and limitations of drug eluting stents requires understanding and control of factors governing local arterial drug delivery. In this manner unwarranted fluctuations in tissue drug levels can be minimized to achieve an acceptable balance between local efficacy and toxicity.

We hypothesized that local thrombus formation is responsible for observed variation in local arterial drug uptake. This hypothesis is supported by previous studies showing that specific compositions and distributions of mural thrombus can act as a capacitive reservoir and transport barrier, for locally administered drug. Mural thrombus interposed between the arterial wall and the drug source decreased arterial drug deposition in animal models of vascular injury\(^11\). Mural thrombus is a natural consequence of percutaneous intervention\(^12\). Its formation is probably highly variable within the heterogeneous patient populations receiving drug-eluting stents, because clot is affected by many factors both architectural and biological. For example atherosclerotic plaque disruption\(^13,14\), induced by patient specific lesion morphology and device implantation strategy, increases tissue factor exposure to the luminal blood which can lead to mural thrombus formation. In addition, differences in anti-platelet regimens\(^3\) or even patient insensitivity to anti-platelet therapies\(^15\) promotes
variability in the risk of clot formation. Finally, mural clots may actually be a self-perpetuating phenomena as indicated by the finding that arterial levels of sirolimus and paclitaxel\(^8,16\) upregulate tissue factor expression. Because mural thrombus is likely to form in patients to varying extents, it is important to understand mechanistically how thrombus alters drug release kinetics from a stent and arterial drug deposition.

We investigated the interrelated roles of peri-strut thrombus formation, drug release kinetics, and drug physicochemical properties in contributing to fluctuating local arterial drug deposition. We used a combination of \textit{in vivo} experiments and computational modeling analysis to demonstrate that variability in mural thrombus formation may significantly alter the time course and magnitude of arterial drug uptake and retention. The findings from this work highlight novel pathways for arterial drug transport and mechanisms by which mural thrombus alters drug release kinetics and arterial drug uptake.
4.3 Methods

4.3.1 Mathematical Model

Drug transport was modeled using a 2-dimensional transient model (Fig 4-1). The luminal diameter, 3 mm, was 3 times greater than the arterial wall thickness; and, the axial distance along the artery was determined by the fluid mechanic entry length required to reach fully developed flow. The coated strut 150 μm height and width were based upon representative dimensions of the CYPHER® Bx Velocity drug-eluting stent (Cordis Corporation, a Johnson & Johnson Company). As in previous work, blood was assumed Newtonian and non-pulsatile, and its fluid mechanics were described with continuity and steady state Navier-Stokes equations (Fig 4-2, Eq 1-3). The inlet profile, applied at axial position \( z = -L_{\text{Proximal}} \) (Fig 4-1), was assumed parabolic (Fig 4-2, Eq 4) and the outlet, located at axial position \( z = L_{\text{Distal}} \) (Fig 4-1), was assumed to have zero pressure (Fig 4-2, Eq 6) boundary conditions. The interfaces between the blood and any solid (i.e. stent coating, thrombus, and tissue) were assumed impenetrable to blood flow (Fig 4-2, Eq 5). Blood velocity was also assumed to be zero at any fluid-solid interface (Fig 4-2, Eq 5). The fluid mechanical blood properties and volumetric flow rate were obtained from standard reference values.
Governing Equations, Boundary & Initial Conditions

Navier-Stokes Equations & Boundary Conditions

\[ \begin{align*}
\text{Eq 1} & \quad \frac{\partial v_x}{\partial z} + \frac{\partial v_z}{\partial r} = 0 \\
\text{Eq 2} & \quad \mu \left( \frac{\partial^2 v_x}{\partial z^2} + \frac{\partial^2 v_z}{\partial r^2} \right) = \frac{\partial p}{\partial z} + \rho \left( \frac{\partial v_x}{\partial z} + \frac{\partial v_z}{\partial r} \right) \\
\text{Eq 3} & \quad \mu \left( \frac{\partial^2 v_y}{\partial z^2} + \frac{\partial^2 v_r}{\partial r^2} \right) = \frac{\partial p}{\partial r} + \rho \left( \frac{\partial v_y}{\partial z} + \frac{\partial v_r}{\partial r} \right) \\
\text{Eq 4} & \quad v_y(r,-L_p) = V_c \left( \frac{(r - R)^2}{R^2} \right) \\
\text{Eq 5} & \quad V_d(\Omega_{\text{solid}}(\text{tissue,coating,thrombus}) \cap \Omega_{\text{blood}}) = v_y(2R,z) = 0, \\
\text{Eq 6} & \quad \rho(r,\text{L_dial}) = 0
\end{align*} \]

Drug Transport Equations

\[ \begin{align*}
\text{Eq 7} & \quad \frac{\partial C_j}{\partial t} = D_j \left( \frac{\partial^2 C_j}{\partial z^2} + \frac{\partial^2 C_j}{\partial r^2} \right) \\
\text{Eq 8} & \quad \frac{\partial C_h}{\partial t} + \frac{\partial C_b}{\partial z} + \frac{\partial C_h}{\partial r} = D_h \left( \frac{\partial^2 C_h}{\partial z^2} + \frac{\partial^2 C_h}{\partial r^2} \right) \\
\text{Eq 9} & \quad \frac{\partial C_l}{\partial t} = D_l \left( \frac{\partial^2 C_l}{\partial z^2} + \frac{\partial^2 C_l}{\partial r^2} \right) \\
\text{Eq 10} & \quad \frac{\partial C_th}{\partial t} = D_{th} \left( \frac{\partial^2 C_{th}}{\partial z^2} + \frac{\partial^2 C_{th}}{\partial r^2} \right)
\end{align*} \]

Drug Transport Boundary Conditions

\[ \begin{align*}
\text{Eq 11} & \quad C_j(r,-L_{\text{proximal}}) = 0 \\
\text{Eq 12} & \quad \frac{\partial C_h}{\partial z} \Big|_{r,z=\text{L_dial}} = 0 \\
\text{Eq 13} & \quad \frac{\partial C_l}{\partial r} \Big|_{r=2R,z} = 0 \\
\text{Eq 14} & \quad \frac{\partial C_l}{\partial z} \Big|_{r,z=\text{L_proximal} \text{L_dial}} = 0 \\
\text{Eq 15} & \quad \frac{\partial C_l}{\partial r} \Big|_{r=-W_{\text{tissue}-z}} = 0
\end{align*} \]

Drug Transport Initial Conditions

\[ \begin{align*}
\text{Eq 19} & \quad C_j|_{\text{L_border}} = 1 \quad @ \quad t = 0 \\
\text{Eq 20} & \quad C_l|_{\text{tissue}} = C_b|_{\text{blood}} = C_{th}|_{\text{thrombus}} = 0 \quad @ \quad t = 0
\end{align*} \]

Figure 4-2: Equations for Model with Thrombus

Governing Equations and Boundary Conditions for Local Fluid Mechanics and Drug Transport within the Drug Laden Coating (c), Arterial Tissue (t), Lumenal Blood (b), and Peristreut Thrombus (th).

We compared mechanisms of local drug transport using arterial drug diffusivities obtained from two independent assays: (1) drug transport parameters in the tissue were obtained from experimentally measured values for anisotropic transmural and planar free drug diffusivities\textsuperscript{20, 21}, and (2) arterial drug diffusivity...
was fit to the experimental data of arterial drug uptake in stented porcine coronaries. Drug diffusivity within the coating was determined from the duration of drug elution observed from the retrieved porcine implanted devices. The time-dependent drug transport from the coating was assumed to occur solely via transient drug diffusion through the coating (Fig 4-2, Eq 7). The initial drug load was assumed to be uniformly dispersed throughout the coating (Fig 4-2, Eq 19). In this model, all domains except the coated strut were initially devoid of drug (Fig 4-2, Eq 20). The process of drug diffusion from the coating was handled using a continuity of flux boundary condition at the interfaces between the coating and the tissue/blood/peri-strut mass (Fig 4-2, Eqs 17,18). Drug transport through the blood was described by the transient diffusion and convection equation (Fig 4-2, Eq 8), where the luminal inlet boundary drug concentration was assumed zero (Fig 4-2, Eq 11). These conditions are valid because in the convection dominated arterial lumen it is virtually impossible for drug to diffuse 5 mm, which is approximately 35 times the stent strut width, in the direction opposing blood flow. The outlet was an open boundary condition (Fig 4-2, Eq 12), because blood flow carries drug solubilized in the blood downstream. As it is unlikely that drug would diffuse perpendicular to the direction of blood flow to the opposite arterial wall, a distance equivalent to more than 20 times the stent strut thickness, the tissue wall above the stent strut had a no flux boundary condition (Fig 4-2, Eq 13). Drug transport through the arterial wall from the apposing-strut was approximated using the transient diffusion equation (Fig 4-2, Eq 9), where the perivascular wall was assumed to be impenetrable to drug transport (Fig 2, Eq 15), and the up- and downstream bounds of the tissue had symmetry boundary conditions (Fig 4-2, Eq 14). Drug transport between the tissue and blood compartments occurred via a continuity of flux condition (Fig 4-2, Eq 16) applied to the interface.

Peri-strut thrombus was simulated by placing a solid mass of nearly any size and distribution around the stent strut at specific time point (Fig 4-1b). The size of the mass was based upon the average peri-strut thrombus size and
distribution observed histologically at 3, 14, and 30 days post-implantation. Drug diffusivity through the thrombus was based on experimentally measured values for a whole blood clot\(^{11}\). Once the solid peri-strut mass was placed, first the local blood flow around the engulfed strut was recalculated using non-slip conditions at the interfaces between the blood and mural thrombus (Fig 4-2, Eq 5). After re-establishing the local fluid mechanics, drug was allowed to diffuse to and through the peri-strut mass (Fig 4-2, Eq 10). By iteratively solving for local fluid mechanics and drug transport, the computational simulations were able to capture for the first time the dynamics of drug transport within a setting of growing mural thrombus. At the edges of the thrombus where it formed interfaces with the blood, coating, and arterial wall, a continuity of flux boundary condition was applied (Fig 4-2, Eq 16, 18) so that drug transport could occur from the coating through the peri-strut mass to the arterial wall or to lumenally flowing blood.

4.3.2 Numerical Methods

Commercially available geometry/mesh generation and computational fluid dynamics software (GAMBIT v2.3.16, FLUENT v6.3.17, Fluent Inc., Hanover, NH) were used to apply the mathematical model. The geometry was discretized into approximately 200,000 rectangular mapped mesh elements, which was most densely distributed around the stent strut. The smallest mesh element was 0.0375 \(\text{um}^2\) (.15 x .25 um). To ensure that the discretized geometry had sufficient resolution to detect changes induced by model parameters, a mesh sensitivity study was performed. Doubling local mesh density resulted in less than 2% change in local and average arterial and coating drug concentrations. The discretized geometry was imported into Fluent, a finite volume based software. Second order discretization schemes were used for all velocities and concentration variables. The momentum and continuity equations were solved iteratively using SIMPLEC algorithm\(^{22}\) for pressure-velocity coupling; the diffusion-convection equations were handled with upwind differencing.
4.3.3 Experimental Methods

Sirolimus eluting stents were placed in the coronary arteries of Yucatan miniswine. These pigs were fasted for 24 hours prior to stent implantation, and received oral 650 mg aspirin, 300 mg clopidogrel and 30 mg Procardia XL, for cardiac spasm. Twenty-four hours later, at the time of stent implantation, animals received 150-300 IU/Kg intraprocedural heparin, I.V., to achieve a target activated clotting time (ACT) of >300 sec. Additional heparin was administered as necessary to maintain ACT. Post-implantation, animals received 325 mg oral aspirin daily for the remainder of the study and 75 mg oral clopidogrel daily for 2 months. Under general anesthesia, animals received CYPHER® sirolimus-eluting stents (Cordis Corporation) which were deployed within the LAD, LCX and RCA coronary arteries to a target balloon-to-artery ratio of 1.1-1.3:1. A subset of stented arteries (n = 6 per time point) was harvested at 1, 8, 14, 30, 60, and 90 days post-implantation. The stents were carefully separated from the surrounding arterial tissue. Sirolimus was extracted from the stents in 3 ml of HPLC grade methanol. The extracted sirolimus was determined as the amount of drug remaining on the stent at each time point and was quantified using a validated LC/MS/MS method. The fresh arterial tissue segments were frozen on dry ice and maintained at –70 °C until analysis. Tissues were homogenized in PBS and the aqueous phase extracted into methyl-t-butyl ether/n-butyl chloride (1:1), evaporated to dryness and reconstituted in 0.5 ml HPLC grade methanol. Sirolimus in the arterial wall samples was also quantified using a validated LC/MS/MS method.

A second subset of arteries was harvested at 3, 14, and 30 days post-implantation for histological analysis. Hearts were harvested and immediately perfusion fixed with 10% neutral buffered formalin. Vessels were carefully dissected from the hearts and embedded with methyl methacrylate after dehydration in graded ethanol. Four serial plastic cross-sections were obtained.
proximally to distally from within each stent (approximately equally spaced) and were cut and stained with a metachromatic stain for histological analysis.

4.3.4 Histological Quantification of Mural Thrombus and Neointima
Histomorphometry measurements were made on H&E and pentachrome stained porcine coronary sections. The internal (IEL) and external elastic (EEL) laminae were traced using Adobe Photoshop version 5.0 to separate the arterial media from the lumenal neointima/thrombus and the adventitia. The local thrombus / neointima formation at 3, 14, and 30 days was quantified by tracing the boundary around the peristrut mass and measuring its area.

4.3.5 Statistical Analysis Methods
Quantification from porcine stented coronary arteries of drug release, arterial drug uptake, and peri-strut thrombus area were calculated for each time point using the arithmetic mean and the corresponding standard deviation. Statistical comparison of thrombus change between different time points was determined using a two-tailed Student’s t-Test assuming two samples with unequal variance. The agreement between the experiments and computationally predicted time course for stent drug release was measured using a root mean square analysis.
4.4 Results

4.4.1 In Vivo Variability in Arterial Drug Deposition and Mural Thrombus Formation

To quantify fluctuations in drug release, tissue drug uptake, and thrombus in relation to a mean value, variability was defined as the standard deviation of a data set normalized by its sample arithmetic mean. Stents implanted into porcine coronary arteries released 93% of their drug load within 90 days. Drug release from the stent strut reached its maximum variability of 30% after 1 day of drug elution. Stent release variability subsequently diminished over time as drug release decreased (Fig 4-3a). By two weeks post-implantation variability had decayed to 5% of the mean. In contrast, arterial drug uptake fluctuated more substantially, reaching peak drug levels within a day after implantation and decaying to 75% of its peak value by 30 days. The maximum variability in arterial drug uptake was 114%, which occurred two weeks after implantation (Fig 4-3b).

Figure 4-3: Experimental Drug Release and Tissue Uptake
Experimental drug release and arterial drug uptake data obtained from drug-eluting stent implants within porcine coronary arteries. (A) Fractional Drug Release from the Stent, (B) Average Arterial Drug Concentrations. Quantification of drug released from the stent and absorbed by the arterial wall was obtained for 1, 8, 14, 30, 60, 90 days post-implantation. (Note: all error bars represent the standard deviation from the mean.)
Histological analysis of explanted porcine coronary arteries revealed that foci of mural thrombus formed around stent struts as early as 3 days after implantation, and the thrombus size ranged from 0.3% to 70% of the 0.02 mm² strut area (Fig 4-4a,d). The peri-strut mass grew over time to become on average 5 times larger in area by 14 days post-implantation, ranging in size from 70%-250% of the strut area (Fig 4-4b,d). By 30 days, the peri-strut region was surrounded by a diffuse neointimal covering that was on average more than 25-fold larger than the 3 day thrombotic mass (Fig 4-4c-d). Interestingly, the variability was maximized at 120% at 3 days after stent implantation, and declined over time reaching 60% at 14 days (Fig 4-4d). By 30 days, the extent of variability in neointimal area was reduced to 45%. The overlapping duration of maximal variability in the peristrut mass (thrombus and neointima) and arterial drug deposition (Fig 4-3b, 4-4d) suggests that they are related.

### 4.4.2 Computational Predictions of Thrombus Formation

Transient, 2-dimensional computational simulations were performed to examine drug transport from the coated strut through the surrounding thrombus and finally to the underlying arterial wall. The goal was to test how dynamic variations in mural thrombus of physiologic size and distribution contribute to
fluctuating arterial drug levels. The simulations indicated that the slow rate of drug release from the stent cannot be altered by either diffuse or focal, peri-strut thrombi (Fig 4-5a), because the stent release is rate limiting. This prediction is consistent with the experimental drug release in vivo that appears well-controlled with little variability in fractional release (Fig 4-3a). The simulated drug release from the stent matches in vivo drug release with a root mean square value of <0.1. In contrast, models predicted that the size and distribution of peri-strut thrombi determines the extent of variability in arterial drug uptake and retention (Fig 4-5). Focal, peri-strut thrombi of 0.1 mm² (Fig 4-1) increased the maximum average drug concentration and cumulative drug exposure within the arterial wall by 80% without protecting drug from washout (Fig 4-5b). Focal thrombus increased the residence time of drug eluted from the stent within the local arterial milieu. As a result, more drug was available at arterial interface where it was absorbed by the artery from the thrombus (Fig 4-5c). In this way, focal thrombus acted as an extension of the stent strut, increasing the footprint of the strut-thrombus complex along the arterial wall. When the drug traveled even more slowly through the thrombus, which was approximated using drug diffusion characteristics within a heterogeneous clot¹¹, simulations predicted that thrombus elevated arterial drug levels to an even greater extent (Fig 4-5d). The role of the diffusely distributed thrombus (Fig 4-1) was to shield drug from washout (Fig 4-5c). When drug transport was simulated in the presence of a diffuse thrombus, arterial drug uptake was predicted to increase 3.5-fold. Thus, thrombus induced elevations in arterial drug uptake and exposure was predicted as a consequence of better local arterial drug availability and reduced drug washout into the luminal blood.

When the peri-strut mass was simulated to grow dynamically, arterial drug uptake was predicted to increase. As the focal thrombus grew around the strut, the size of the transport barrier increased, simultaneously extending the effective strut size and reducing the surface area for drug washout. Interestingly, within 2 weeks, arterial drug levels reached levels predicted from instantaneous thrombus
formation upon implantation, indicating a “catch-up” phenomena in arterial drug deposition (Fig 4-5e).

4.4.3 Drug Physicochemical Properties Govern Thrombus Induced Arterial Drug Deposition

It was predicted that drug physicochemical properties within the arterial wall and thrombus influence the extent to which thrombus increases arterial drug deposition. Drugs that were rapidly transported in the arterial tissue relative to thrombus, with arterial drug diffusivity of 50um²/s compared to thrombus drug diffusivity of 20um²/s, were predicted to exhibit thrombus-induced increases in

Figure 4-5: Thrombus-Induced Variability Depends on Physicochemical Drug Properties

Drug physicochemical transport properties in the arterial wall impact the extent of thrombus-induced elevations in arterial drug deposition and distribution (A) Fractional release of drug from the stent (Note: curves with and without thrombus overlap) and (B) Average arterial drug concentration for drugs with different transport properties in the arterial wall (C) Transmural and (D) Axial Arterial Drug Distributions resulting from extremely fast (50um²/s) and slow (0.02 um²/s) arterial drug diffusivities. (Note: black curve = without thrombus, pink curve= with focal thrombus 0.1mm²; Strut width and height = 150um.)

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drug deposition and distribution by more than 2-fold (Fig 4-6b-d). In contrast, drugs that moved exceedingly slowly through the arterial wall compared to the thrombus, with an arterial drug diffusion coefficient of 0.02um²/s compared to thrombus drug diffusivity of 20um²/s, were not predicted to be associated with thrombus-induced fluctuations in arterial drug deposition. In these cases, the slow nature of drug entry and exit from the tissue was rate limiting, thus additional thrombus could not slow an already hindered rate of tissue drug transport (4-6b-d).

In reality, most drugs interact with the layered arterial ultrastructure so that they travel faster axially and circumferentially than transmurally. Preferential axial transport enables spreading along the arterial wall but minimizes radial penetration. Two different anisotropic drug transport diffusivities were simulated. In one instance, a previously measured diffusion coefficient for anisotropic free paclitaxel\(^{21}\) (Fig 4-6b, \(D_{\text{transmural}}=0.02 \text{ um}^2/\text{s}, \ D_{\text{axial}}=50 \text{ um}^2/\text{s}\) was used. Thrombus increased average arterial drug levels by only 20% when free paclitaxel transport was simulated, which is small compared to the thrombus effect on faster moving agents (Fig 4-6b). Hydrophobic drugs were found to diffuse faster through the arterial wall than expected from free drug diffusion alone (Fig 4-4b, 4-5b), which suggests that an alternative faster arterial hydrophobic drug transport modality exists. As a result, an empiric anisotropic drug diffusion coefficient value was obtained by fitting the computations with the experimental arterial drug uptake data. The subsequent rate of arterial drug diffusion matched the arterial diffusion properties of carrier proteins, such as albumin (Fig 4-5b, \(D_{\text{transmural}}=1 \text{ um}^2/\text{s}, \ D_{\text{axial}}=10 \text{ um}^2/\text{s}\)). The faster rate of drug transport hypothesized from computational fitting of experimental data is carrier-protein mediated transport. Focal thrombus in the setting of faster anisotropic drug diffusion caused 80% increase in the average arterial drug concentration (Fig 4-5b).
Though potentially a rare event, a compound may traverse preferentially in transmural penetrating direction compared to axial transport, for instance due to transmural pressure driven flow from porous catheter drug delivery\textsuperscript{23}. Such anisotropically transported compounds spread minimally, so the available surface area for washout is also minimal (Fig 4-6b). As a result any mural thrombus only minimally impacted arterial drug uptake.

4.4.4 Impact of Rapid Drug Release Kinetics on the Thrombus-Induced Variation in Arterial Drug Uptake

Peristrut thrombus was predicted to slow drug release kinetics when release was sufficiently rapid compared to drug transport through the thrombus. When drug was released within minutes or hours, mural thrombus hindered drug diffusion from the coated stent strut and through the surrounding thrombus, which subsequently slowed the overall rate of drug release (Fig 4-7a). The thrombus induced deceleration in drug release increased local drug availability for arterial uptake, leading to elevated arterial drug deposition (Fig 4-7b). Thus, when drug transport through thrombus and not drug release was rate limiting, the extent of arterial drug deposition was governed by the mass, distribution and transport properties of peristrut thrombus. By contrast, when the stent strut eluting drug over several weeks was surrounded by a thrombus, the release from the stent was so slow that the thrombus was predicted to impose a negligible barrier for drug transport. As a result, mural thrombus around a slowly eluting stent was predicted to have no effect on drug release, because drug release from the stent and not transport in the thrombus was rate limiting (Fig 4-5a, 4-6a).
Figure 4-6: Thrombus Effects on Drug Release Kinetics
Thrombus slows drug release kinetics and subsequently increases local drug availability leading to elevated arterial drug levels. (A) Fractional release of drug from the stent, (B) Average arterial drug concentration. For all these cases, the arterial drug diffusivity in the transmural direction was $10 \text{um}^2/\text{s}$ and in the axial direction was $1 \text{um}^2/\text{s}$; the drug diffusivity within the stent coating was $10 \text{um}^2/\text{s}$; drug diffusivity within the mural thrombus was $20 \text{um}^2/\text{s}$. (Note: black curve = without thrombus, pink curve = with focal thrombus 0.1mm$^2$; (A) and (B) are plotted on different time scales on the x-axis)
4.5 Discussion

4.5.1 A Novel Mechanism for Arterial Drug Transport

Computational predictions of free hydrophobic drug diffusion did not immediately agree with experimental observations and their discordance has prompted speculation over a novel paradigm for arterial drug transport. Hydrophobic drugs such as sirolimus and paclitaxel diffuse exceedingly slowly through the arterial wall, which permits their high arterial retention and subsequent superior biologic efficacy over biologically potent hydrophilic agents\(^{21,24}\). The rate of arterial drug transport is dictated by drug interactions with the local arterial ultrastructure, which is a layered structure of smooth muscle cells residing between sheets of elastin. This laminate tissue structure hinders drug diffusion transmurally but does not impose much resistance to circumferential or axial diffusion\(^{20,21}\). Thus, computations predicted that hydrophobic drugs penetrate through the arterial wall poorly, but spread axially and circumferentially with greater ease, achieving the highest drug concentrations near the arterial-lumenal interface.

The first indication of a paradox became evident when the computational prediction of arterial drug uptake was much slower than that observed from experiments (Fig 4-4b, 4-6b). This indicated that the mechanism for \textit{in vivo} arterial drug uptake is faster than that predicted by diffusion alone. Another major inconsistency was that the addition of mural thrombus of any size or distribution around the stent and arterial wall was not predicted to elevate arterial drug deposition or distribution. The inability of local clot to alter arterial drug deposition occurred because drug transport within the arterial wall was so much slower than that in the mural thrombus that the clot imposed a negligible barrier to drug diffusion. However, the prediction that thrombus elicits no change in arterial drug deposition contradicts previous experimental findings, where thrombus was proven to significantly alter arterial drug deposition\(^{11}\). These two discrepancies indicate that the computational model must not be fully capturing the dominant transport forces within the arterial wall.
Consequently, the computational arterial drug diffusion coefficients were fit to the experimental data, and were found to be 5 fold larger than the free drug diffusivities measured experimentally (Fig 4-5b). Interestingly, the faster drug diffusion coefficients corresponded well with previously measured transport parameters of carrier proteins within the arterial wall\textsuperscript{20}. The implication of this finding is that hydrophobic drugs, which move slowly in their free state, may actually associate with carrier proteins in the arterial wall and subsequently diffuse faster. In support of a carrier-mediated mechanism for arterial drug transport, prior experimental data show that carrier protein, albumin, penetrates the arterial wall, especially when the endothelium is denuded\textsuperscript{25}, which occurs during stent implantation\textsuperscript{26}. Additionally, hydrophobic drugs such as paclitaxel bind albumin, with potentially strong affinity\textsuperscript{27}. This computational model did not treat the arterial wall as a porous medium through which convective drug transport may occur, but by analogy to hydrophilic drug transport\textsuperscript{28}, transmural drug convection could also be a dominant transport force for hydrophobic compounds within the arterial wall.

4.5.2 Mural Thrombus Accounts for Variability in Arterial Drug Deposition

The causative role of thrombus in modulating arterial drug levels was identified previously when mural thrombus interposed between the tissue and drug source decreased arterial drug levels\textsuperscript{11}. On this basis, variable mural thrombus formation was investigated as an initiator of fluctuating arterial drug deposition. Healthy pig coronary arteries implanted with drug-eluting stents were associated with significant variability in arterial drug deposition (Fig 4-3b). A component of variability is always attributable to experimental error. Such error can arise from the technical difficulty of harvesting tissue and separating it from the stent, as well as from drug quantification methods and detection instruments. However, if random errors were the only source of variability, one would expect data deviation to remain either constant over time or at a fixed percentage of the value at specific points in time. Yet, the variability in arterial drug deposition was greatest within the first two weeks post-implantation after which it declined. A
similar trend of maximal arterial drug deposition variability occurring at 2 weeks post-implantation was reported in another study and corroborates our experimental observations\textsuperscript{29}. The early variation in arterial drug deposition was hypothesized to arise from an identifiable and predictable source. If stent release kinetics fluctuated substantially, one might attribute the varying arterial drug deposition to release kinetics. However, experimental data did not reveal substantial variability in drug release from the stent (Fig 4-3a), and modest variation in drug release was not predicted to induce significant variation in drug uptake. Thus, stent release kinetics was an unlikely perpetrator of the transient fluctuations in arterial drug levels.

The role of thrombus was suspected when observations revealed that the onset and duration of maximal fluctuations in thrombus formation overlapped with that of variability in arterial drug deposition (Fig 4-4). Computational results confirmed that physiologically sized thrombus could elevate arterial drug uptake in a manner comparable to experimental observation (Fig 4-5). Thus, uncontrolled formation of mural thrombus around the stent strut was concluded to be a significant contributor to the observed variability in arterial drug deposition.

4.5.3 Mechanisms of Thrombus-Induced Arterial Drug Uptake Fluctuations and the Drug Transport Properties that Modulate Thrombus Effects

Thrombus-induced fluctuations in arterial drug deposition may increase the risk for local toxicity due to the narrow therapeutic window of the current hydrophobic agents\textsuperscript{9, 10}. To achieve uniform local therapy, one can either (1) minimize variability in local thrombus formation, or (2) minimize the effect of thrombus on arterial drug levels. The former can be achieved by minimizing local thrombus formation either pharmacologically or via improvements in procedural and device related risk factors for thrombus. Still, fine control over focal thrombi as small as 0.1 mm\textsuperscript{2} may prove difficult, considering that local tissue levels of sirolimus and paclitaxel may promote thrombus formation\textsuperscript{16, 30}. Alternatively, some degree of mural clots may be essential for efficacious drug delivery, and may be problematic only when clot is excessive and uncontrolled. Thus, it is
useful to understand the mechanisms by which thrombus induces fluctuations in arterial drug levels and possibly alter these pathways.

Thrombus distribution determines its mechanism for increasing arterial drug levels. Local, focal thrombi formed adjacent to the stent strut and arterial wall effectively increase the footprint of the stent strut along the arterial wall, leading to elevated arterial drug deposition. These thrombi prolong local drug residence time and retention at the arterial interface long enough to enhance tissue absorption. Such local thrombi are ubiquitous even 3 days after stent implantation (Fig 4-4a), and even small thrombi 0.1 mm² were predicted to increase tissue drug deposition (Fig 4-5b). By contrast, diffusely distributed thrombus / neointima, which is observed at 14 and 30 days post-implantation, can shield arterial drug from washout into the lumen (Fig 4-4b-c, 4-5b).

The ability of thrombi to induce changes in arterial drug deposition was found to depend on the extent to which drug transport through the thrombus altered the kinetics of drug washout and retention in the local milieu (Fig 4-5, 4-6, 4-7). Thrombus was predicted to increase arterial drug deposition if it imposed a diffusion barrier to drug release (Fig 4-7) and/or drug washout (Fig 4-5). This situation is predicted to occur when arterial drug transport is enhanced by carrier-mediated drug diffusion (Fig 4-5). Local, focal thrombus near the stent increased drug absorption by enhancing the local drug residence time, while diffuse thrombus increased uptake by preventing arterial drug from washing away (Fig 4-5b-d). Similarly, when drug release kinetics was fast, which might be expected when drug delivery occurs from a coated angioplasty balloon, mural thrombus slowed the overall drug release rate (Fig 4-7). Subsequently, the drug residence time in the local milieu increased due to impeded drug transport from the stent and through the thrombus, which enabled better arterial drug absorption. Conversely, when transport in the arterial wall and stent coating were exceedingly slow relative to that in thrombus, thrombi of all sizes and distributions were powerless to retard the drug further. Thus arterial drug levels were not predicted to change because the thrombus neither increased drug availability nor decreased its washout (Fig 4-6 c,d). Stent based drug delivery is
an example of a predicted thrombus-independent process, where the slow rate of drug elution from the stent could not be further decelerated by the thrombus. This prediction is supported by the experimental observation that stent release kinetics did not vary despite mural thrombus formation (Fig 4-3, 4-4). One way to further control thrombus induced fluctuations in arterial drug deposition would be to enforce slower arterial drug transport, perhaps by steric modification of the drug. However, this approach is accompanied by the drawback that slow drug transport results in poor distribution of drug through the arterial tissue.
4.6 Conclusions

Arterial drug diffusion occurs faster than would be predicted by free drug diffusion alone. Subsequently, a novel mechanism for arterial drug transport has been postulated in which hydrophobic compounds diffuse faster through the arterial wall in association with carrier proteins. Arterial drug deposition was observed to fluctuate during periods of locally varying thrombus formation. Computations demonstrated that fluctuating amounts of mural thrombus account for varying arterial drug levels. Small, focal thrombi may be virtually impossible to prevent yet they were predicted to substantially increase local drug deposition, which may subsequently impact local toxicity. To control these effects, drug delivery systems must minimize thrombus-induced variations on drug release and tissue drug uptake. Simulations predicted that slowly releasing drug from the stent prevented thrombus from hindering drug transport further, resulting in thrombus-independent drug release kinetics. However, thrombus increased arterial drug deposition by enhancing local drug availability and reducing drug washout when arterial drug transport was faster than free drug diffusion alone. Thrombus induced fluctuations in arterial drug deposition were minimized when the rate of arterial drug transport was slower than that through mural thrombus.
4.7 Acknowledgements

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4.8 References


CHAPTER 5: CONCLUDING REMARKS

5.1 Summary of Thesis

Although drug-eluting stents have demonstrated their efficacy in reducing the incidence of restenosis, these devices appear to impose a risk for stent thrombosis that increases over time, unlike its bare metal counterpart. The balance between local toxicity and efficacy is determined in large part by arterial drug deposition, distribution, and retention. In an era of increasing scrutiny over the use of drug-eluting stents, understanding the mechanisms of local pharmacokinetics will help to rationally determine the safe circumstances for their use and develop better therapies. The findings from this thesis revealed that arterial drug deposition and cumulative exposure depend not only upon device characteristics such as drug physicochemical properties, release kinetics, and administered dose. It was also evident that local arterial drug deposition and distribution was dictated by the circumstances surrounding device implantation and the local vascular reaction to the device. The findings from this thesis imply that developing novel local therapeutics will require not only an understanding of the device itself, but also an appreciation for how arterial drug delivery may be altered by both physician and patient dependent factors.
5.2 Specific Findings

The central hypothesis of this work was that the safety and efficacy of drug-eluting stents is linked to arterial drug levels and duration of drug exposure. This thesis investigated the role of multiple factors both intrinsic and extrinsic to the drug-eluting stent that govern local arterial drug delivery.

In Chapter 2, we investigated how intravascular blood flow impacts arterial drug delivery from a stent using a 2-dimensional steady state computational fluid dynamics and mass transfer model. We identified that stent disruption of blood flow leads to areas of flow recirculation adjacent to the stent strut. Subsequently, drug was predicted to elute from the stent, become sequestered within recirculating pools of blood, and be absorbed by the arterial wall. Using fibrin deposition as a surrogate marker for arterial drug distribution, histologic observation of stented porcine coronary arteries revealed an asymmetric pattern of fibrin deposition that correlated with predicted asymmetric arterial drug deposition. The pattern of arterial drug distribution and deposition was also sensitive to the placement of multiple adjacent stent struts within the flow field.

In Chapter 3, we analyzed how drug release kinetics and applied drug dose alter arterial drug deposition using a transient computational fluid dynamics and mass transfer model. Drug release kinetics obtained from computational predictions agreed with experimental drug release observations. Using the computational model, three categories of coupled drug release and tissue drug uptake were defined: (1) rapid drug release resulted in minimal and inefficient arterial drug deposition because drug release and depletion from the stent were faster than tissue drug uptake; (2) exceedingly slow drug release resulted in minimal arterial drug deposition because drug release and availability limited arterial drug uptake; (3) moderate drug release achieved maximal arterial drug deposition because the rates of drug release kinetics and uptake matched. Increasing drug loading on the stent by applying thicker drug-laden coatings did not increase arterial drug levels substantially. Instead, thicker drug coatings prolonged the duration of drug release. In contrast, increasing drug coating
concentration linearly increased arterial drug levels without impacting the duration of drug release.

In Chapter 4, the role of mural thrombus in altering drug release and tissue uptake kinetics was examined using the previously developed 2-dimensional transient computational fluid dynamics and mass transfer model. Experimental data from stented porcine coronaries revealed that arterial drug deposition was incredibly variable within two weeks after stent implantation. Within the same time, mural thrombus formation was also maximally variable. We hypothesized that variability in mural thrombus causes fluctuations in arterial drug deposition. Computational modeling revealed that focal mural thrombi of physiologic size can significantly elevate arterial drug levels. We also predicted that mural thrombus does not impose a barrier for the slow drug release from a stent, which was consistent with the minimal experimental variability in drug release observed in the presence of thrombus. Finally, computational predictions of hydrophobic drug diffusion revealed that experimentally observed arterial drug transport occurs much faster than that predicted by free drug diffusion alone. This observation led us to hypothesize a novel mechanism for arterial drug transport involving association of hydrophobic drugs with carrier-protein in the arterial wall, leading to faster drug transport.

Within this thesis, we explored the relative impacts of local blood flow, stent position, drug release kinetics and administered drug load, and mural thrombus in governing local arterial drug deposition, distribution, and retention. Through this work, many of the local transport forces within the arterial microenvironment were characterized in a way that would have been impossible without the flexibility and control of computational modeling. In a field where experimental methodologies dominate, I hope that this work has highlighted the many advantages of using computational methods to isolate the complexities of local arterial drug delivery. Most importantly, at a time when drug-eluting stent technology is increasingly under scrutiny, I hope that the principles of drug transport elucidated within this thesis can contribute to developing better local drug delivery technology and improving the quality of patient care.
5.3 Generalizing Lessons

5.3.1 Interactions between the Device and Its Environment

A central theme of this thesis was that factors intrinsic and extrinsic to the stent influence local arterial drug delivery. Therefore, a tenet that has emerged throughout this analysis is that the safety and efficacy of these devices depends upon understanding not only the device itself, but also its placement strategy and the effects of the local microenvironment on device function. Even if the latter two external variables may not directly impact the device, they can synergize or negate the intended biologic effect. For instance, patient specific lesion characteristics may influence device implantation techniques, and the together these may determine arterial drug distribution. In addition to studying the device itself, development of reliable therapeutics requires an assessment of how extrinsic factors impact drug delivery and consideration of ways to counteract potentially detrimental extrinsic effects.

5.3.2 Dynamics vs. Steady State

The first aim of this thesis employed a steady state analysis of arterial drug deposition from an infinite source stent strut residing in a blood flow field. The second aim investigated transient drug release kinetics to an arterial geometry of fixed dimension. Finally, the last aim investigated how evolving mural thrombus altered transient arterial drug deposition. Each of these increasingly nonstationary analyses improved our understanding for how arterial drug deposition evolves within its dynamically changing environment. In addition, the advance to transient analysis dramatically improved our ability to compare computational results with quantities that are routinely measured in animal experiments. This enabled computational model validation as well as experimental comparisons that led us to hypothesize new arterial drug transport mechanisms. There is enormous potential to understand the relationship between drug distribution and exposure with efficacy by transiently mapping arterial drug distribution with computational models and correlating the finding with either local or clinical biologic outcome. For this reason, it will continue to be
important to study the dynamics of arterial drug delivery in conjunction with experiments that highlight the biologic effect.

5.3.3 Coupling Computational Modeling and Experiments

Computation provides an unparalleled local resolution and precision for tracking drug deposition and allows great control over the system being examined, yet its impact in isolation is limited without experimental data to complement or verify predictions. Validation of computational prediction with an experimentally measurable parameter is often critical to justifying future model predictions. In vitro experiments are essential for translating predicted spatial-temporal drug maps into knowledge about efficacy and toxicity. Finally, when coupling clinical studies with computational predictions, the relationship between drug deposition and clinical biologic effect can be approximated. Integration of all these modalities will be critical in developing mechanistic insight between drug delivery and deposition, local biologic effect, and clinical outcome.

5.4 Future Directions

Although a number of questions have been answered within this thesis, as many or more questions have been raised. The future directions branching from this work fall into areas of greater computational complexity and experimentation.

5.4.1 Ultrastructure Considerations

According to the central hypothesis of this work, local drug toxicity and efficacy are related to arterial drug distribution, deposition, and retention. It has previously been demonstrated that the arterial wall ultrastructure influences the local drug transport forces. Within this thesis, ultrastructure effects were approximated by applying anisotropic drug diffusivities. But the arterial wall is more complex and deserves deeper characterization within computational drug delivery models. Specifically, one important addition to the arterial wall characteristic that may be considered for future studies is drug partitioning. This
topic was only superficially examined within Chapter 6 (Appendix). A more in- 
depth analysis might seek to understand how drug deposits within the arterial 
wall when hydrophobic compounds exhibit differential affinity for extracellular, 
intracellular, and even disease state components such as lipid pools.
Experiments within the lab have shown that fluorescently labeled paclitaxel 
associates with both the hydrophobic elastin layers as well as with cellular 
microtubules (communication with Brazin J, Tzafriri AR). Separate experiments 
have revealed that hydrophobic drugs preferentially partition within the arterial 
tissue compared to depots of lipid and calcifications (communication Vukmirovic, 
N). These pieces of experimental evidence point toward a nonintuitive role of 
arterial composition on drug distribution and deposition. Such an analysis is 
incredibly timely, given that most analyses of these devices in silico and in vivo 
have focused on drug transport within healthy vessels\textsuperscript{1, 3-9}. A heterogeneous 
arterial model will also be relevant if local drug delivery is considered within 
different arterial vessels for which the composition changes. For instance, carotid 
arteries are more elastic than the muscular coronaries, and local drug delivery 
within each location would be expected to distribute drug differently.

Another important level of complexity to consider with regard to arterial 
fluid transport is the arterial wall's porous structure. It consists of both tissue 
spaces for drug diffusion and interstitial spaces through which drug convection 
may occur. Even for hydrophobic drugs that partition 30 to 40 times in the arterial 
tissue than in aqueous solution\textsuperscript{10}, the extent of interstitial drug convection might 
be significant compared to hydrophobic free drug diffusion, because free drug 
diffusion is incredibly slow. Analysis of porous flow through the arterial wall is 
relevant and is a transport modality that is enhanced by therapies such as 
microporous drug infusion\textsuperscript{2}, which deliver pressure driven flow of drug 
transmurally. Although certain volume and pressure conditions could be 
damaging to the artery, these delivery methods may improve drug targeting to 
deep smooth muscle layers.
Finally, understanding arterial transport of hydrophobic drugs in greater depth will require further experimentation. A hypothesis emerged within the final aim of this thesis (Chapter 4) that hydrophobic drugs not only diffuse freely but they also transport through the arterial wall in association with carrier proteins. The existence of such a mechanism as well as its relative important compared to porous convective flow can be tested by performing a series of experiments in which hydrophobic drug transport occurs with and without albumin in the presence and absence of transmural pressure gradient. In addition, fluorescent experiments could help visualize whether drug associated with mobile arterial proteins. When combined with experimentally determined transport parameters, multiple pathways for arterial drug transport can be studied computationally: free drug diffusion, carrier mediated transport, and porous convective transport.

Finally, because stents impose both tensile and compressive forces on the arterial wall, which surely impact local porosity and tissue density, it may be important to investigate the relationship between mechanical loading and drug transport. Such forces can potentially be controlled by the extent of balloon expansion of the stent against the arterial wall.

5.4.2 Blood Flow Considerations
This thesis work began with the hypothesis that blood flow can influence local mass transfer of drug from the stent to the arterial wall, which is a concept that may be generalized to examine how local mass transfer of blood components such as platelets influence the evolving arterial-lumenal interface. For instance, we observed that fibrin deposits asymmetrically around an isolated stent strut, which matched the pattern for local blood recirculation zones (Figures 2-2, 2-3). We posited that fibrin was a surrogate marker for local asymmetries in drug deposition. A mechanism by which this may have occurred is sequestration of platelets and clotting factors within recirculating pools of blood, which initiated asymmetric thrombus formation and fibrin deposition due to local arterial injury. It is known that blood carries its various constituents in different locations of the
flowing stream, red blood cells travel closer to the centerline and plasma travels at the margins\textsuperscript{11}. These observations may explain the histological findings of local thrombus formation and fibrin deposition adjacent to the stent strut. Thus a computational or even experimental investigation of local platelet transport near stents may help to determine how the evolving thrombotic reaction can be modified by altering local fluid mechanics.

Blood flow not only serves as a vehicle for mass transfer, but it induces local mechanical stresses on the arterial wall, which are known to impact the endothelial cells\textsuperscript{12}. A coupled computational and experimental analysis could be performed to correlate local mechanical forces with the observed behavior of cells near local areas of flow recirculation. Using computation to quantify the effects of local mechanical forces, we can understand and possibility inhibit the factors predisposing to thrombosis and intimal hyperplasia.

A particularly difficult problem in the clinical setting even with the use of drug-eluting stents is treatment of bifurcation lesions, which are at higher risk for restenosis\textsuperscript{13}. Understanding how local fluid mechanics and drug delivery change within different vascular topographies ranging from straight, curved, and bifurcated vessels may help to develop implantation strategies or devices that are specific to lesion location.

\textbf{5.4.3 Novel Therapeutics}

The increasing appreciation that drug-eluting stents must simultaneously minimize their risk of stent thrombosis and reduce in-stent restenosis highlights that the biologic response to the in-dwelling device is an orchestrated set of responses that evolves over time\textsuperscript{14}. It is likely suboptimal to manage local biology by simply interfering in one of many potentially parallel biologic pathways, in this instance, proliferation of smooth muscle cells. One could imagine that an intermediate solution to the problems of current drug-eluting stents would be to locally deliver different compounds to address each phase in the biologic
cascade: anti-thrombotic, anti-inflammatory, and anti-proliferative. Such a strategy must not hinder endothelial cell regrowth.

In fact pharmacologic intervention is probably crude compared to how healthy endothelium can regulate the local arterial milieu. Since healthy endothelium itself is a sensor and effector for hemostasis, immune regulation, and proliferation within the arterial environment, it is probably the best modulator of local biology. It has been demonstrated that in fact if endothelial factors could be delivered after arterial injury, then it would significantly inhibit intimal hyperplasia\(^\text{15}\). Therefore, the ideal local therapeutic would be one in which mechanical restoration of local blood flow is immediately followed by engraftment of a healthy endothelium along the arterial wall to prevent thrombosis, inflammation, and proliferation.

* * *

My hope is that the principles of local transport phenomena explored throughout this thesis will provide a framework with which to develop and evaluate next generation local drug delivery therapeutics.
5.5 References


Chapter 6: Appendix

Steady State vs. Transient Models: Mechanisms of Flow Mediated Arterial Drug Deposition and Local Drug Partitioning

6.1 Abstract

Within this thesis work, a significant computational improvement was made by transitioning from steady state to transient modeling. In the former model, drug source was infinite and there was no peri-strut coating controlling the rate of drug release. In the latter transient model, both a finite drug load and a coating around the stent strut were introduced. Many of the findings from Chapter 2 were re-analyzed within the context of a transient, finite drug load, and variable drug release kinetics. The appendix illustrates that flow mediated arterial drug deposition is less prominent for slow drug release kinetics, typical for stents. Therefore, the role of the stent strut width was found to be more important for drug deposition than strut height, because of increased arterial wall contact with the stent strut. In addition, the blood flow behaved more like a sink for drug washout from the arterial wall. Thus, arterial drug deposition was greatest when struts were spaced close together rather than far apart, because the interstrut length for drug washout was minimized. In addition, the role of drug partitioning within the arterial wall was examined for a transiently depleting drug source. Drug partitioning increased drug deposition especially immediately after stent placement, which appeared mediated from the strut surface contacting the arterial wall. After 1 day, the extent of arterial drug uptake increase was less than the partition coefficient.
6.2 Introduction

In transitioning between the steady state and transient computational analyses of local drug delivery, important variables were explored in greater depth than presented within Chapters 2 and 3. This Appendix includes analyses that are not within the scope of Chapters 2 and 3, but are nonetheless relevant findings. Specifically, three issues were explored: (1) the factors that modulate the extent of blood flow mediated arterial drug deposition are examined; (2) effect of stent design characteristics on arterial drug uptake which were explored using a steady state analysis (Chapter 2) are now analyzed transiently; and (3) a transient analysis of how drug partitioning impacts the arterial drug uptake is presented.

6.3 Methods

The computational framework used for this analysis used the 2-dimensional, diffusion-convection drug transport models that have previously been defined using the steady state drug transport model (Section 2.3.1) and also the transient drug transport model (Section 3.3.1). Thus, the simulations presented address a series of questions of increasing complexity that were partially deciphered using a steady state model. The questions are delineated below and individually addressed within this Appendix:

1. How does a drug-laden coated strut containing only a finite drug mass impact the magnitude of flow mediated arterial drug deposition?
2. Using a transient analysis, what is the impact of wider and taller struts on arterial drug uptake? Are the transient findings consistent with the steady state findings (Chapter 2)?
3. Within the transient setting, what is the impact of multiple consecutively spaced struts on arterial drug uptake? How does uptake change with increasing strut number and strut spacing?
4. Finally, how does transient arterial drug deposition increase for compounds that partition preferentially within the arterial wall?

6.4 Results

6.4.1 Transient Models and Flow Mediated Drug Deposition

Question: Does the placement of a finite amount of drug within a coating surrounding the stent strut alter the extent of flow mediated arterial drug deposition?

This question is subdivided into two parts: (1) the impact of the drug release kinetics from the coating on flow mediated arterial drug deposition, which was addressed by placing a coating with different drug release characteristics around the strut and using the steady state model to solve for average arterial drug deposition; and (2) the impact of a depleting drug source on transient flow mediated arterial drug deposition.

When a coating was placed around the stent strut, the drug release rate from the stent was generally dictated by the drug isotropic diffusivity within the coating. When the coating drug diffusivity was relatively high (i.e. $10^{+5}$ um$^2$/s), then the flux of drug leaving the stent strut surface was high, because the coating essentially provided no resistance to drug transport (Fig 6-1A). Drug subsequently accumulated within the blood at high enough concentrations that arterial drug deposition and distribution was greatly increased by flow mediated arterial drug deposition, as evidenced by the asymmetric drug distribution (Fig 6-2A). The arterial drug distribution and deposition occurring after rapid drug elution from a coating was nearly identical to that obtained from the steady state model of an uncoated stent with a constant concentration boundary condition (Fig 6-1B, 6-2C, 2-3).
As the coating resistance to drug transport increased, via incremental 5 log decreases in coating drug diffusivity (i.e. from $10^{+5}$ to $10^{-5}$ um$^2$/s), arterial drug deposition decreased largely because of the disappearance of flow mediated arterial drug delivery, evidenced by the symmetric arterial drug distribution (Fig 6-1, 6-2B-C). As the role of flow mediated arterial drug deposition decreased, the arterial drug distribution became confined to the strut contacting region (Fig 6-2C). Thus, even with an infinite drug source, the flow mediated arterial drug deposition was diminished by the exceedingly slow rate of drug release.
Figure 6-2: Arterial Drug Distributions with Different Coating Resistances

Arterial Drug Distributions Predicted at Steady State for Different Drug Release Kinetics Controlled by Drug Coating Diffusivity ($D_{co}$). Drug distribution contour within the blood and arterial wall resulting from (A) rapid drug release and (B) slow drug release from a coated strut. (C) Axial arterial drug concentrations at a depth of 10 um into the arterial wall.

When rapid drug release was tested with a depleting drug laden coating using a transient transport model, fast release caused transient peaks in blood levels of drug, which is consistent with the steady state predictions (Fig 6-2A). However, the precipitous depletion of drug from the stent, not taken into account within a steady state model, resulted in the washout of drug transiently accumulated in the plasma (Fig 3-4). Because rapid blood accumulation and depletion occurred faster than it takes for arterial drug absorption, there was only brief evidence of flow mediated arterial drug deposition (Fig 3-4). At the other extreme of exceedingly slow transient drug release and depletion, the drug release kinetics was so slow that despite the slow depletion of the drug source on the stent, flowing blood diluted plasma drug concentrations too much for flow mediated arterial drug deposition to occur. This transient finding is consistent with steady state predictions for slow drug release rates (Fig 6-2B-C). As a result, there was no impact of blood flow mediated arterial drug uptake during transient slow drug release, instead the blood acted as a sink for convective washout of drug from the arterial wall. Even with a moderate rate of drug depletion from the
coated strut \( (D_{co} = 1 \text{ um}^2/\text{s}) \), which maximized average arterial drug concentrations (Fig 3-4), plasma drug accumulation was minimal and blood flow mediated arterial drug deposition remained negligible (Fig 3-4C).

6.4.2 Strut size and Arterial Drug Deposition

Question: Given that flow mediated arterial drug deposition is minimal when drug release is exceedingly slow (i.e. on the order of 30 days) what is the impact of strut dimensions on arterial drug deposition using the transient analysis?

In light of the evidence that flow mediated arterial drug deposition is minimally for slow drug release kinetics, one would presume that contact between the stent struts would become more important. Therefore, to test this idea, simulations for realistical variations in stent strut sizing were performed to assess the importance of strut width and height on arterial drug deposition.

![Graph A: Average Coating Drug Concentration vs Time (day)](image)

**Figure 6-3: Strut Dimensions and Transient Arterial Drug Uptake**

Arterial drug deposition resulting from increasing strut height \((h)\) and width \((w)\) separately. Additionally, the confounding effects of larger struts increasing both fluid mechanical disturbance and drug content were separated by comparing struts with increased size but one having only partial drug coating and the other having a full drug coating. Partial drug coating is depicted in the graph using thick black lines around the picture of the stent strut (orange curve).

Changes in strut dimension had no impact on local drug release kinetics. By contrast, when the strut was 5% and 11% wider and therefore there was more arterial-strut contact length, according to actual potential device specifications, peak average arterial drug concentration increased 10-20% (Fig 6-3). When the strut was 16% taller, average arterial drug concentration was unchanged. Increasing strut height simultaneously increased fluid disruption and local drug
loading, because of the greater strut perimeter (in 2-D model “perimeter” is analogous to “surface area” in 3-D). To deconvolve the impact of local fluid mechanics from drug loading, struts were increased in height without an increase in drug load, by selectively making specific coating regions devoid of drug (Fig 6-4). Average arterial drug concentrations were no different between tall struts with similar drug load as shorter struts, indicating that increased flow disruption insignificantly impacted local drug deposition. Taller struts with reduced drug load also had identical average arterial drug concentrations as tall struts with a higher drug load (Fig 6-3). Thus, increasing the surface area of the stent strut impacts average arterial drug concentrations only when strut width and not height changes.

Figure 6-4: Schematic for Strut Height and Width Analysis
Illustration of coated struts with different dimensions. To deconvolve the effects of increased fluid mechanical disturbance and increased local drug load, which both occur when struts increase in height, some parts of the drug coating were simulated without drug. Blackened coating regions signify coating devoid of drug.

Taken together, the results for strut dimension confirm the conclusions from Section 6.4.1: for devices that release drug slowly, the predominant modality for arterial drug deposition is strut-arterial wall contact, therefore increases in contact length increase arterial drug deposition more than increases in height.

6.4.3 Transient Analysis and Multiple Struts

Question: When stent struts are placed longitudinally along the arterial wall, how does interstrut spacing impact arterial drug deposition?
The cumulative results for single drug eluting stent struts in isolation indicate that there is insufficient blood accumulation of drug in the isolated strut cases and therefore no flow mediated arterial drug deposition occurs (Fig 6-2). Yet it is conceivable that drug accumulation within the blood could be elevated if struts are clustered closely together forming recirculation zones that connect (Fig 2-4) effectively protecting drug from washout. Thus, multiple struts with different strut spacings were analyzed for their drug distribution and deposition (Fig 6-5).

Figure 6-5: Schematic of Multiple Stent Strut Analysis Transient
Illustration of 5 struts longitudinally placed along the length of the arterial wall with different interstrut spacing (d). In some simulations only the arterial wall contacting strut surfaces were drug coated, thus blackened coating regions depict coating regions devoid of drug (bottom illustration).

When the strut number was increased from 1 to 5, drug release from the coating was unaffected by strut spacing or number of struts. In all cases, over 75% of the drug concentration in the coating was depleted by 28 days post-implantation (Fig 6-6A). The impact of 5 consecutive stent struts on average arterial drug concentration, defined as the integral of spatial arterial drug concentration for the tissue area divided by tissue area, depended on the interstrut spacing (Fig 6-6B-C). Average arterial drug concentration increased as the interstrut spacing decreased from 24 to 1 strut width, because the arterial area served by the struts decreased while applied drug load remained the same (Fig 6-6B). Struts
clustered 1 strut width apart had 5.38-fold greater average arterial drug concentration than that from a single strut at 1 day-post implantation. Struts placed 24 strut widths apart led to average arterial drug concentration only 2.26 fold higher than that from a single strut at 1 day post-implantation, because arterial area increased by 2.2-fold (Fig 6-6B). The observation that average drug concentration decreases with wider interstrut spacing indicates greater nonuniformity in drug concentrations, not surprisingly. This is supported by axially fluctuating local arterial drug concentrations measured at an arterial wall depth of 10μm (Fig 6-6D).

In order to understand how much of the initial drug load entered the arterial wall, the total arterial drug deposition, defined as the integral of spatial arterial drug concentration for the arterial area, was measured. Arterial drug deposition 1 day after implantation for 5 struts placed 24 strut widths apart was 5-fold greater than that from a single strut (Fig 6-6C), indicating that drug deposition from each strut was independent of the other struts at this interstrut spacing. When the same number of struts were clustered within 1 strut width of each other arterial drug deposition was 5.38 fold greater than that from a single strut at 1 day post-implantation (Fig 6-6C). This indicates that interstrut spacing enhanced arterial drug deposition by 8% independently of applied drug load. By mass balance, this resultant increase in arterial drug uptake could either result from increased arterial drug deposition or reduced drug washout from the arterial wall. To differentiate from the two, maximal drug washout was imposed at the arterial-blood interface by applying zero drug concentration blood-tissue
boundary condition. The magnitude of arterial drug deposition was unchanged by the forced maximal drug washout (Fig 6-6C), indicating that nearly maximal luminal washout of drug occurs within the interstrut region even without the forced boundary condition. When convective drug transport was eliminated by stopping blood flow, arterial drug deposition was substantially increased for 5 struts placed 1 strut width apart (Fig 6-6C), confirming that convective washout serves as an important sink for drug removal.

Finally to determine whether blood solubilized drug within recirculating pools of blood in the interstrut space could contribute to arterial drug deposition, drug was eliminated drug from the blood facing coated strut surfaces of 5 stent struts place 1 strut apart (Fig 6-5). When only the outer diameter (i.e. portion of the drug coating apposing the arterial wall) was drug eluting, the average drug concentration...
concentration in the coating decreased to less than 25% (Fig 6-6A) indicating that the drug mass on the strut has decreased by 75%. Despite the decreased drug load, arterial drug deposition at 1 day post-implantation was only 4% decreased relative to that of fully coated stent struts (Fig 6-6C). Because additional drug loading on the non-arterial wall contacting surfaces of the strut only increased arterial drug deposition 4%, the arterial wall contacting strut surface and not blood solubilized drug appeared to be the dominant source for arterial drug deposition. After comparing the blood and arterial local drug concentrations, blood levels were markedly lower that arterial drug levels even with closely placed struts. Thus, the blood was serving as a convective sink for drug even with clustered strut. The 4% increase in average arterial drug concentration observed for fully coated struts was caused by drug diffusing within the coating from the strut sides to the arterial wall.

Peak arterial drug concentrations measured at about 10 um depth within the arterial wall along the axial direction were identical at 1 day post-implantation for single strut and 5 struts placed 24 strut widths apart (Fig 6-6D). Clustering the 5 struts to 1 strut distance apart caused the peak concentration along the axial length of the arterial wall to increase by 10% at 1 day post-implantation (Fig 6-6D). The trajectory for arterial drug concentration decay downstream of a strut was similar for the two cases of interstrut spacings. As the interstrut spacing increased, the minimum arterial drug concentration between struts decreased. For an interstrut spacing of 1 strut width, minimum arterial drug concentration was 5% of peak concentration. Between struts placed 24 struts widths apart, minimum arterial drug concentrations were less than 0.3% of peak concentration at 1 day post-implantation (Fig 6-6D). When maximal drug washout was induced at the blood-arterial wall interface, the maximum and minimum arterial drug concentrations along the axial length of the arterial segment were nearly unchanged for 5 struts with 1 and 24 strut-width interstrut spacing, compared to the cases where maximal convective washout was not enforced numerically (Fig 6-6D). Variation in maximum and minimum arterial drug concentrations was
markedly reduced when there was no flowing blood in the arterial lumen (this was only evaluated for an interstrut spacing of 1 strut width) (Fig 6-6D).

Taken together, these data suggest interstrut spacing provides additional surface area for convective washout, but it does not contribute to arterial drug deposition. Thus, struts clustered more closely together lose less drug to the flowing blood, because though drug is maximally leaving the tissue within the interstrut length, the interface length is relatively short compared to that for farther struts. Therefore the integral of convective flux over the length of blood-tissue interface leads to less washout in the case of clustered struts.

6.4.4 Transient Analysis and Partitioning

Compounds released locally from coated stents and angioplasty balloons are incredibly hydrophobic (i.e. paclitaxel and rapamycin\(^{41}\)), thus we investigated the role of drug partitioning within the arterial wall on transient arterial drug deposition and distribution. Paclitaxel and rapamycin have demonstrated greater solubility in the arterial wall than in aqueous solution; rapamycin for instance displayed partitioning 30 times greater into the arterial wall drug relative to aqueous solution\(^{41}\). In the steady state, a hydrophobic drug that partitions is expected to increase arterial drug deposition linearly according to the partition coefficient, because drug concentrations scale linearly in the diffusion-convection model. The resultant arterial drug concentrations become less intuitive when the partitioning coefficient is applied within a transient setting of finite drug load. Thus, a partitioning coefficient was computationally applied by altering the interfacial boundary condition between the arterial wall and the blood/coating. In all previous simulations, a flux boundary condition was coupled with a continuity of concentration at the interface between the tissue and the blood/coating (applied as an equal arterial and blood/coating drug concentrations). The following study of partitioning was performed by modifying the concentration boundary condition to enable a jump in drug concentration from blood/coating to arterial wall (Fig 6-7A with jump).
Figure 6-7: Partitioning and Transient Arterial Drug Deposition

Impact of drug partitioning ($K = \frac{C_{\text{tissue}}}{C_{\text{blood}}}$). (A) Demonstration of the interfacial jump in drug concentration between the blood and tissue domains due to partitioning ($K=30$). (B) Average coating drug concentration. (C) Average arterial drug concentration with drug that does not partition preferentially within the tissue ($K=1$) and a hydrophobic drug that partitions within the tissue ($K=30$).

The results indicate that drug release kinetics are not significantly impacted by partitioning (Fig 6-7B). This is perhaps not surprising, since drug transport through the coating is slow, which subsequently slows the drug release rate. Early within the drug release duration, average arterial drug concentrations were more than 30 times larger with partitioning than without ($K=30$ vs $K=1$, Fig 6-7C). The transient peak in arterial drug deposition arises in large part from the stent surface contacting the arterial wall. This is evidenced by the longitudinal arterial drug distribution at a depth of 10um into the arterial wall, in which the area underneath the stent strut increased nearly 100 fold with drug partitioning (Fig 6-8A).
Figure 6-8: Arterial Drug Distribution with Partitioning

(A) Longitudinal Arterial Drug Distribution at a depth of 10um within the arterial wall. (B) Transmural Arterial Drug Distribution at an axial location of 4 um downstream of the stent strut. (Note: Cartoon insert with dashed black line illustrates location for arterial drug distribution.)

The transmural distribution measured just 4 um downstream of the stent strut illustrates that hydrophobic drugs, which partition in the arterial wall, penetrate better early after implantation compared to drugs that do not partition (Fig 6-8B). The distribution and deposition data reveal that the effect of drug partitioning was most significant early after implantation. After 1 day, both transmural and longitudinal arterial drug distributions were similar for drugs that partition and ones that do not. The impact of partitioning on arterial drug levels eventually declined, so that by 30 days, average arterial drug concentrations were 30% greater with partitioning. Thus, the experimental observation that drug partitioning within the arterial wall elevates arterial drug deposition is verified, and this effect appears most dramatic early after implantation.

6.5 Discussion

6.5.1 Flow mediated arterial drug deposition

Flow mediated arterial drug deposition appears to result in part from a rate matching process between the rate of drug elution from the stent into the blood, the rate of drug washout from local milieu by flowing blood, and the rate of arterial drug uptake. For an infinite drug source, when the resistance to drug elution in the coating is low, drug release is fast so that drug accumulates in the blood and enters the arterial wall (Fig 6-2). However, as the drug release rate decreases, via increasing resistance to drug transport within the coating, the rate
of drug washout exceeds drug release. As a result, lower drug concentrations reside in the blood and flow mediated arterial drug deposition is minimal (Fig 6-2C). The situation becomes more complex when the drug load depletes from the coating over time. In this case, fast release accumulates drug in the blood only transiently, but because drug is simultaneously depleting from the stent, drug accumulation in the blood is short-lived. The extent of flow mediated arterial drug deposition in this case depends on how rapidly the arterial wall can uptake the blood solubilized drug. It turned out that arterial drug uptake was too slow (using arterial drug diffusivities of $1 \text{um}^2/s$) for the transient blood solubilized bolus of drug to cause appreciable asymmetric arterial drug distribution, which is characteristic of flow mediated transport (Fig 2-3).

This analysis highlights important attributes for local release kinetics. When local release kinetics is faster than drug washout and continues long enough for arterial drug uptake to occur from the blood, then blood mediated drug deposition is feasible. But when local delivery is fast for a rapidly dwindling drug load, mimicking bolus release, blood plays a greater role in washout than contributing to arterial drug deposition. Conversely, when drug release is slower than the rate of drug washout, drug is diluted by the flowing blood and therefore independently of the amount of drug source, flow mediated arterial drug deposition is minimal (Fig 6-2A,C).

In the setting of local stent based drug delivery sustained for 30 days, fluid mechanics primarily mediate arterial drug washout, in contradistinction with steady state conclusions. Therefore, wider stent struts that contact the arterial wall over a greater length achieve higher arterial drug levels compared to tall strut that cause larger areas of local blood recirculation (Fig 6-3). Interestingly, fluid mechanics is important for arterial drug deposition as demonstrated in the setting of multiple stent struts. Closely clustered struts have enhanced arterial drug uptake, not by virtue of greater drug deposition but rather due to less drug washout (Fig 6-6). Because the arterial-blood interface is shorter between clustered struts, drug washout is reduced compared to struts spaced farther
away. Thus, smaller interstut distance is a means of shielding drug from washout through the arterial-blood interface.

### 6.5.2 Partitioning

Partitioning of hydrophobic drugs into the arterial tissue is expected to increase arterial drug deposition. In the steady state where there is no limit on the drug load, arterial drug deposition will linearly increase according to the partition coefficient. However, when the drug mass is finite and decreasing over time, the extent to which partitioning elevates arterial drug deposition is unintuitive. The computational simulations for a drug like sirolimus, which has a partitioning coefficient of $30$ in tissue relative to aqueous solution, demonstrated that arterial drug uptake is not increased $30$ fold in the long term (Fig 6-7). Arterial drug increases transiently by more than $30$ fold fold, but by less than a day post-implantation the increase in average arterial drug concentrations is $30\%$ compared to a case without partitioning ($K=1$). The effects of drug partitioning is most prominent at the interface between the stent and the arterial wall, where transient arterial drug concentrations were elevated by 2 orders of magnitude with partitioning compared to the case without partitioning. As the complexity of the arterial ultrastructure especially within disease states is explored, it will be interesting to incorporate the effects of differential drug partitioning within arterial drug components to understand the local competition for drug.

### 6.6 Conclusions

In this Appendix, the results from steady state computational models were compared with those from transient models, to elucidate the relevance of flow mediated arterial drug deposition and also to understand transient partitioning within the arterial wall. The work reveals that flow mediated arterial drug deposition is a result of a complex balance between the relative rates and duration over which drug leaves the stent, accumulates within the blood, and is absorbed from the blood by the arterial wall. Stents in their current $30$ day sustained release formulations do not exhibit much flow mediated arterial drug
deposition as previously envisioned with the steady state model, though depending on the therapeutic window, the drug effects could still be asymmetric, as illustrated previously in asymmetric fibrin deposition (Fig 2-2). Nonetheless, local fluid mechanics remains an important issue as demonstrated with strut clustering, because the blood flow mediates drug washout from the arterial wall. This study further illustrates that partitioning increases average arterial drug deposition but by less than the equilibrium partitioning value.

6.7 References