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Impact of flow pulsatility on arterial drug distribution in stent-based therapy

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Abstract

Drug-eluting stents reside in a dynamic fluid environment where the extent to which drugs are distributed within the arterial wall is critically modulated by the blood flowing through the arterial lumen. Yet several factors associated with the pulsatile nature of blood flow and their impact on arterial drug deposition has not been fully investigated. We employed an integrated framework comprising bench-top and computational models to explore the factors governing the time-varying fluid dynamic environment within the vasculature and their effects on arterial drug distribution patterns. A custom-designed bench-top framework comprising a model of a single drug-eluting stent strut and a poly-vinyl alcohol-based hydrogel as a model tissue bed simulated fluid flow and drug transport under fully apposed strut settings. Bench-top experiments revealed a relative independence between drug distribution and the factors governing pulsatile flow and these findings were validated with the in silico model. Interestingly, computational models simulating suboptimal deployment settings revealed a complex interplay between arterial drug distribution, Womersley number and the extent of malapposition. In particular, for a stent strut offset from the wall, total drug deposition was sensitive to changes in the pulsatile flow environment, with this dependence increasing with greater wall displacement. Our results indicate that factors governing pulsatile luminal flow on arterial drug deposition should be carefully considered in conjunction with device deployment settings for better utilization of drug-eluting stent therapy for various arterial flow regimes.

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1 Introduction

Drug-eluting stents (DES) are now routinely used for the treatment of coronary artery disease [1] and are increasingly being considered for other vascular beds [2]. The efficacy of these devices is determined based on delivering therapeutic concentrations of drug to the underlying tissue for a sustained period. These desirable drug levels can be achieved by maintaining uniform arterial distribution patterns that are in turn modulated by, amongst other factors [3–6], the hemodynamic environment surrounding the stent [7–9]. Previous work has indicated that stent implantation intervenes with the blood flow milieu by introducing perturbations into the boundary layer of the flow, causing drug-rich recirculating pools proximal and distal to stent struts [7–9]. These regions effectively extend the contact area of drug with the tissue-lumen (or mural) interface and thereby enhance drug uptake into the underlying tissue; flow-mediated transport of drug from non-contacting surfaces of the strut surface accounts for almost 40% of total drug uptake [7].

As the impact of luminal flow on arterial drug uptake is being increasingly characterized, several aspects associated with blood flow need to be understood. In particular, the time-varying patterns of blood flow caused by the cardiac pulse creates a dynamic flow environment that may influence overall arterial drug distribution patterns. It is now known that net luminal flow governed by mean Reynolds number determines the extent of flow-mediated drug uptake [9], but the mechanisms by which parameters governing the pulsatile nature of blood flow modulate arterial distribution are not completely understood. Given that the transient arterial pressure gradient and the associated fluid flow are dynamically changing and vascular-bed dependent, the question arises as to how one could systematically quantify the flow pulsatility affecting the arterial drug distribution patterns.

Pulsatile flow can be represented by a steady component and its oscillating harmonics that is characterized by an amplitude and a frequency. The properties of the harmonics of blood flow are dependent on the cardiac output and rate, blood viscosity, visco-elastic properties of the arteries and vascular architecture. In his 1955 paper, J. R. Womersley numerically derived a solution to the flow harmonics for a short, straight, unbranched rigid vessel under a known driving pressure gradient [10]. Through these pressure-flow relations, Womersley was able to demonstrate sensitivities of instantaneous arterial flow to changes in the frequency of the driving pressure gradient, vessel size, and the viscous properties of the blood. For instance, an increase in the frequency of the driving pressure gradient will yield simultaneously a decrease in the amplitude of the flow rate and a decrease in the timescale of these changes. Conversely, a decrease in frequency will yield large, instantaneous changes in flow over a longer period. Given that flow pulsatility is intricately connected with the frequency of the oscillating pressure harmonics, we sought to understand these frequency-dependent effects on arterial drug distribution. By employing the Womersley’s framework, we simulated three distinct scenarios of pulsatile flow patterns wherein the frequency of the oscillating pressure harmonics was varied to quantify the drug distribution patterns under various degrees of strut apposition to the lumen-tissue (or mural) surface.

Our results indicate that model and experimentally derived drug distribution patterns are relatively independent of flow pulsatility when stent struts are fully apposed to the mural surface. Contrastingly, when struts lose contact with the arterial wall, drug uptake is dependent on the dynamic flow environment and varies with the relative amount of
malapposition. The finding that pulsatile flow affects arterial drug distribution patterns in a
dependent on the deployment settings adds to our understanding of the complex
physiological aspects associated with stent-based delivery and paves way for careful
consideration of this therapy to several vascular flow regimes.

2 Methods
2.1 A model of flow pulsatility

The relationship between pressure and flow in a single straight arterial segment is given by
Womersley’s pressure-flow relations, where the \( n \)th harmonic of oscillating laminar flow,
given a complex oscillating pressure gradient \( A_n e^{i \omega_n t} \) [10] is:

\[
\begin{align*}
Q_n(t) &= \text{Real} \left\{ \frac{\pi R^4}{4 \mu} \left( \frac{1}{\alpha_n^2} - \frac{2}{\alpha_n^2} J_1 \left( \frac{\alpha_n}{\alpha_n^2} \right) \right) A_n e^{i \omega_n t} \right\}
\end{align*}
\]

where, \( J_0 \) and \( J_1 \) are respectively, the zero and first order Bessel functions of the first kind, \( R \)
is the radius of the vessel and \( \rho \) is the density of blood. Angular frequency is given as
\( \omega_n = 2\pi f \), where \( f \) is the frequency of the \( n \)th harmonic. As part of this solution, a
dimensionless frequency parameter (\( \alpha_n \)), now referred to as the Womersley Number, was
introduced, where \( \alpha_n = \sqrt{\frac{\omega_n^2}{\mu/\rho}} \), and \( \mu \) is the dynamic viscosity.

Consider a realistic pulsatile profile in the renal artery, where the Womersley number at the
fundamental frequency is approximately 4, \( (\alpha_1 \approx 4) \), at basal conditions \( (\omega_1 = 2\pi) \) (Figure
1a). We first derive the pressure waveform for the first twelve harmonics using Equation 1,
and then scale the fundamental frequency of the driving pressure gradient, \( \omega_n \) and each of its
harmonics by the same factor in Equation 1. Figure 1b shows that as \( \alpha_n \) increases with
frequency, the amplitude of the unsteady flow rate (measured as the ratio of maximum
instantaneous flow rate, \( \max\left( \sum_{n=1}^{N} Q_n(t)/Q_{\text{mean}} \right) \)) decreases, and thus the unsteadiness of
the flow decreases as well. A large \( \alpha_n \) implies an inertially driven flow, and so as frequency of
the pressure gradient increases, accelerating the inertia is made more difficult. Increasing
frequency and thus \( \alpha_n \) from the nominal renal arterial case shows an instantaneous flow
that has a significantly damped flow rate, decreasing the unsteady component of the
instantaneous Reynolds number. This implies that in this case, high frequency renal arterial
flow reflects a fluid mechanic effect that can serve as a close approximation to steady
luminal flow (Figure 1b). By decreasing \( \alpha_n \) from the nominal renal arterial case via this
frequency change, the flow becomes highly viscous with large changes in the amplitude of
the unsteady flow (Figure 1b), including periods of reverse flow as the flow moves in phase
with the instantaneous pressure gradient.

Thus by changing the frequency from the nominal pressure gradient of a renal arterial flow,
both the unsteady magnitude \( (Q(t)/Q_{\text{mean}}) \) and the time scale of changes (time period) vary,
acting to scale the overall unsteadiness of the system. As \( \alpha_n \) increases to 16 with \( \omega_n \), there is
effectively no pulsatility (only steady flow) while as \( \alpha_n \) decreases with \( \omega_n \), we introduce an
unsteady component that is far larger than the steady one and is therefore dominantly
unsteady, resulting in periods of flow reversal. Taken together, the cases \( \alpha_n = 1 \) (truly
unsteady), \( \alpha_n = 4 \) (physiologic) and \( \alpha_n = 16 \) (approximately steady), prescribe a range of
dynamic fluid mechanic environments that allowed us to determine the sensitivity in arterial
drug to the relative pulsatility of luminal flow. Accordingly, changes in the unsteady flow
environment in both our computational and bench-top models were simulated by changing
the cardiac frequency (ω) of a nominal renal arterial pressure gradient (Figure 1a), yielding unsteady flow profiles each characterized in terms of their associated Womersley number.

2.2 In vitro model

A bench-top model was previously constructed, simulating drug release from a model stent strut into compartments housing a controlled, pulsatile flow and a tissue mimic (Figure 2a). The details of the methodology were presented elsewhere [12], however we discuss some of the key features here for completeness. Model components include a flow channel made using an acrylic material with square cross-sections (3×3 mm²) and a length (120mm) sufficient for fully developed flow at the region of interest. Arterial tissue was modeled using a poly-vinyl alcohol (PVA) hydrogel (20% PVA, 16kDa, 98% hydrolyzed), functionalized with 7-methacrylate cross-linkers located in a recess along the acrylic channel. A glycerol-water mixture (40/60 vol%, 0.01% surfactant) held constant at 23°C (μ=0.0044 Pa.s [13], and ρ=1101 kg/m³) yields a kinematic viscosity 0.04 cm²/s, similar to that of blood. System properties were maintained by ensuring that the channel was primed with cleaned working solution prior to the experiment. A thermocouple downstream of the outlet confirmed temperature fluctuations throughout the experiment to be less than 0.2°C. Fluorescein-Sodium (400Da, λex= 490nm / λem=512nm) used as a marker drug was released from a strut coating made using polyurethane film, and was housed in a sealed chamber where the blood analogue and the tissue mimic were present. All the system components - fluid, hydrogel, and channel - were designed to be optically clear and make the system amenable for fluorescent imaging.

By changing the frequency of a pulsatile flow-generating pump, time-varying flow reflecting a change in the Womersley number was simulated. Two flow waveforms were prescribed as inputs to the pump (CompuFlow 1000 MR, Shelley Medical Imaging Technologies, London, ON, Canada) (Figure 2b). The first profile was based on the nominal pressure gradient of the computational model (f=1Hz) and corresponded to α≈2. The frequency (ω) was then adjusted in Equation 1 to the maximum allowable pump speed of 12 Hz, yielding the second profile, representing a higher vessel Womersley number (α≈6). Note that the two values α≈2 and α≈6 simulate approximately unsteady and steady flow regimes, which allowed us to systematically quantify the effects of pulsatility on arterial drug deposition. Changes to the steady flow environment were simulated by changing the mean vessel flow rate, Qmean, and characterized in terms of the mean vessel Reynolds number Re0=427.

Drug diffusion coefficients through the glycerin/water solution at 23°C and through the solution-swollen membrane were calculated as 1.67±0.51×10⁻¹¹ m²s⁻¹ and 1.72±0.36×10⁻¹¹ m²s⁻¹, respectively [12]. Their similarity in magnitude indicates the microstructure of the hydrogel offers no significant barrier to the diffusion of marker drug like that found in vivo with Paclitaxel. Furthermore, the diffusivities of marker drug in the working solution and hydrogel are approximately 2.4-fold smaller than that of Paclitaxel in blood at 37°C (3.89 × 10⁻¹¹ m²s⁻¹) [6] and 4.2-fold larger than the Paclitaxel diffusivity in tissue (3.65×10⁻¹² m²s⁻¹) [4], respectively. Despite these variations, the relative magnitude of these coefficients indicate they approximately match the time scale of the diffusion processes and hence were determined to be adequate for modeling purposes.

The design of the bench-top apparatus was not amenable to the modeling of the hydraulic convection gradients found in vivo [14]. Drug release was simulated using a polyurethane film loaded with Fluorescein-Sodium (1% wt/wt), cut to dimensions, 0.24 × 0.35 × 1.5 mm³. Release over 3 hours was found to be proportional to the square root of time and therefore was approximated well by Higuchi’s model of drug release [15]. A diffusion coefficient calculated as 2.83±0.04×10⁻¹⁶ m²s⁻¹ and was determined to be similar to that calculated for
stent-based drug delivery [16, 17]. Details of the preparation of this film and its release kinetics can be found in our earlier work [12].

After an experimental run-time of 180 minutes, the hydrogel was removed from the channel and bisected. Cross-sectional images of marker drug distribution in the hydrogel were captured with an epifluorescent microscope (Nikon Eclipse TE2000), equipped with a 100-W mercury lamp (Carl Zeiss) and a long pass filter (510–560 nm). Images (CCD camera, SPOT) were taken at a 4× magnification and at an exposure time of 159 ms. Experiments were performed in triplicate (n = 3) and shown in units of concentration mg/m². Results are presented with mean ± standard deviation.

2.3 Numerical simulations

The computational domain comprised of two rectangular channels simulating the arterial lumen and the wall. Arterial wall thickness was prescribed as A_w = 1mm and the radius of the lumen was set at R= 3mm for the nominal case of a model renal arterial flow [18]. Both channels were of length L = 3R (Figure 2c). A single strut of unit aspect ratio (S_H X S_H = 0.1 × 0.1 mm²) was placed at the lumen-wall interface. The artery was assumed to be symmetric with respect to a centerline. Blood was modeled as a laminar fluid with a shear-dependent dynamic viscosity, used to systematically account for the non-Newtonian characteristics [8] and a density of 1060 kg/m³. Transient luminal blood flow was modeled by utilizing the continuity and momentum relations

$$\nabla \cdot \mathbf{v}_f = 0, \quad (2)$$

$$\rho \left[ \frac{\partial \mathbf{v}_f}{\partial t} + \mathbf{v}_f \cdot \nabla \mathbf{v}_f \right] = - \nabla p + \nabla \left( \mu \nabla \mathbf{v}_f \right), \quad (3)$$

where \( \mathbf{v}_f \) is the normalized velocity field of the fluid, \( P \) is the pressure field and \( \rho \) and \( \mu \) are the density and dynamic viscosity, respectively. The arterial wall was assumed to behave as a homogeneous porous medium. Transport of interstitial fluid was modeled numerically using the continuity as well as the momentum equations and by employing a correction for Darcy’s permeability,

$$\nabla \cdot \mathbf{v}_i = 0, \quad (4)$$

and

$$\rho \left[ \frac{\partial \mathbf{v}_i}{\partial t} + \mathbf{v}_i \cdot \nabla \mathbf{v}_i \right] = - \nabla p + \nabla \left( \mu \nabla \mathbf{v}_i \right) - \frac{\mu}{K} \mathbf{v}_i, \quad (5)$$

where \( \mathbf{v}_i \) is the tissue velocity vector and permeability coefficient \( K = 1.43 \times 10^{-18} \text{ m}^2 \) [19]. A scalar transport model was employed to simulate drug transport

$$\frac{\partial C_i}{\partial t} + \mathbf{v}_i \cdot \nabla C_i = D_i \nabla^2 C_i, \quad (6)$$

where \( C_i \) is the normalized concentration, \( D_i \) is the diffusion coefficient of the model drug Paclitaxel, and \( \mathbf{v}_i \) is the normalized velocity vector, for both tissue and blood, with diffusivities in fluid and tissue set to \( D_f = 3.89 \times 10^{-11} \text{ m}^2/\text{s} \) and \( D_t = 3.89 \times 10^{-12} \text{ m}^2/\text{s} \), respectively [4, 6, 9]. Flow in a straight vessel was assumed to be axisymmetric with respect to its centerline. At the lumen-tissue and lumen-strut interfaces, a no-slip condition was
imposed. Drug release was handled with a Dirichlet boundary condition on the surface of the strut with flux prescribed by the Higuchi Model for drug release [15]

$$J(t) = \frac{D_C C_0^2}{\pi t}, \quad (7)$$

with diffusion coefficient prescribed as $D_C = 1.0 \times 10^{-15} \text{m}^2/\text{s}$ [17]. The Higuchi model assumes a release rate that is constant with respect to the square root of time and is commonly used to describe the initial release of drug from diffusion controlled membranes [20]. The initial concentration was set at unity, $C_0 = 1 \text{ mol/m}^3$ and tissue upstream and downstream and perivascular wall aspects with a zero flux boundary condition. A zero concentration was applied at the inlet, and a continuity of flux was assumed at the lumen-tissue domain interfaces. The sensitivity of arterial drug deposition to the steady and unsteady flow environments was investigated independently. This was achieved by imposing an inlet velocity boundary condition based on either a frequency change of the oscillating pressure gradient using Womersley’s framework (Equation 1) to represent a change in the unsteady flow environment or a decrease in the nominal inlet flow rate $Q_{\text{mean}}$ by a nominal factor representing a change in the steady flow component.

The nominal driving pressure gradient from which the frequency ($\omega = 2\pi f$), was derived from literature values for renal artery flow waveform [11, 18] (Figure 1), with cardiac frequency for fundamental harmonic of this nominal case was set to 1 Hz. Frequency of this pressure gradient was then varied yielding those unsteady flow rates ($Q(t)/Q_{\text{mean}}$) (Figure 1b). The steady component of flow, $Q_{\text{mean}}$, was scaled for a mean vessel Reynolds number $Re_0=427$, consistent with flow in a renal vessel [18].

The presence of an oscillating component of flow means that Poiseuille inlet velocity profiles can no longer be assumed. Thus fully developed transient velocity profiles were derived by letting a time varying plug flow (uniform velocity)

$$u(t) = \frac{Q(t)}{\pi R^2}, \quad (8)$$

to develop over an entrance length. A conservative estimate of the entrance length for the range of $\alpha$ was based on the vessel radius and peak instantaneous Reynolds number ($Re = 2Ru_m/\nu$), where $u_m$ is the mean velocity of the cross-section of the channel and $\nu$ is the kinematic viscosity of blood [21]. A zero pressure condition was applied at the outlet.

A Streamline Upwind/Petrov-Galerkin method [22] with second order accurate time integration [23], was used to solve for the momentum and mass transport variables using a finite element method (COMSOL 4.0a, Comsol Inc.). Delaunay triangulation scheme was used to mesh the interior regions of the lumen and the arterial wall with quadrilateral elements on the domain boundaries and local refinement in areas of expected high concentration gradients. A fixed time step chosen was required to be sufficiently small so that both transient drug release and cyclical changes in flow for each time period were properly resolved. The solution was found to be independent of the time-step when $\Delta t$ was the maximum value of either 0.06s or $T_{\text{period}}$. Numerical simulations were run for a total solution time of 50s regardless of position in cycle. Given the small time scale of change in the high frequency case, the total solution time served as the best compromise between computational time and accurate representation of the physiology. Iterations at each time-step were performed until there was a $10^{-8}$ reduction in the relative error. A solution was determined to be mesh-independent when there was less than 2% change in the area-weighted average concentration (AWAC) within the tissue at five strut widths either side of
the stent strut at a solution time of 50s, for a further sequential refinement. The total number of elements for a mesh independent solution was found to be \(2.8 \times 10^4\) elements corresponding to \(1.12 \times 10^5\) degrees of freedom.

3 Results

Our in vitro system comprising a synthetic arterial bed was exposed to controlled flow conditions that simulated frequency-dependent changes in the Womersley number (Figure 2b). After exposure, the synthetic bed was sectioned to yield a spatial map of the marker drug in the cross-sectional plane (Figure 3a). The spatial distribution of drug shows large concentrations at the centre top, where the strut is in contact with the hydrogel \((x=0, z=0)\), with this quantity decreasing with distance away from the strut.

When \(\alpha\) increased from 2 to 6, little change in the drug distribution was observed. First, spatial distribution of drug was similar for both cases (Figure 3b), indicated quantitatively with a consistently higher concentration at an axial location downstream compared to the same point upstream \((29.9\pm6.82\%\) for \(\alpha=2\), and \(28.3\pm5.08\%\) for \(\alpha=6\)). Secondly, total drug uptake (measured as mean concentration in the hydrogel) varied by only \(7.3\%\) \((\pm17.3\%)\) with a change in \(\alpha\) (Figure 3c). Furthermore, the impact of \(\alpha\) was small compared to that from a change in the Reynolds number, \(Re\), where a two-fold reduction in the inlet flow rate \((Q(t))\) increased total marker-drug uptake by \(28.8\%\) \((\pm18.0\%)\) (Figure 3c), indicating a relationship already determined from previous computational studies [9]. These results for a single stent strut underscore the dependence on flow rate but offer no significant evidence of a relationship with the pulsatility of the flow environment. One possible inference from these findings may be that local drug distributions in flowing fields may be independent of flow pulsatility when stent struts are placed apposing the wall.

Computational modeling of an ideally apposed single stent strut residing in a standardized renal vascular bed confirmed experimental findings. For the nominal case of renal arterial flow \((\alpha \approx 4)\), large drug concentrations are evident immediately below the stent strut with variations in the areas proximal and distal to the strut (Figure 4a). Net amount of drug on either side of the strut is shown to be approximately equivalent but while the spread of drug extends further in the distal aspect, drug concentration is higher in the proximal portion of the tissue. This difference arises because though the mass released from both aspects of the stent strut is equivalent at each time point, the two-fold greater distal recirculation region dilutes the drug relative to the more concentrated drug that remains in the smaller proximal recirculation region. Net flow directionality determines this variability as drug is carried from the adluminal surface of the strut into a concentration boundary layer downstream of the strut so that the overall effect for a net downstream luminal flow is a distribution of drug skewed towards the distal segment [7–9].

A change in the Reynolds number of the flow alters deposition in both the proximal and distal aspects of the tissue and lumen. Instantaneous recirculation lengths fall with flow creating a larger pooling and less washout of the drug into the bulk flow (Figure 4b). A similar pattern of drug is observed in the tissue but at a higher concentration in both aspects for smaller Reynolds numbers (Figure 4c). Average drug uptake measured as the area-weighted average concentration (AWAC) in the tissue increases by a third for unit decrease in Reynolds number (Figure 4d).

Computationally derived arterial drug maps exhibited a small but complex sensitivity to the unsteady flow field. Specifically, a change in frequency of the cardiac pulse yielded only a small difference \((<3.5\%)\) in the net drug deposition (Figure 5a), however very different spatial patterns of drug in the tissue (Figure 5b). Specifically as \(\alpha\) is decreased from 16 to 1,
local concentration falls in the proximal region but the length by which it is spread increases by 3-fold. Furthermore, in the distal portion of the tissue, local magnitude of drug decreases with lower cardiac frequency. This phenomenon can be understood by considering the changes in strut induced flow disruptions caused by a change in the frequency described by Womersley.

Flow over a strut will yield asymmetrically sized flow recirculating regions (Figure 6a), the extent of which will be dependent on the direction and magnitude of flow. While flow is orientated in the downstream direction, the proximal flow disruption will remain at least 2-fold smaller than the distal region, however when flow reverses these regions are now reverse in aspect. This sensitivity to flow direction will be critical when we consider that a change in the pulsatile flow can induce reverse flow. For example, when frequency of the nominal pressure gradient given in Figure 1a is decreased (α = 1), viscous effects rise, yielding large instantaneous changes and periodic reverse flow (Figure 1b). Consequently for a strut residing in this flow (Figure 6c), we see significant changes in the length of the flow disruptions, including the proximal region. This is in contrast to an increase in frequency (α =16), yielding an almost static positive flow environment and with little changes observed in both proximal and distal recirculating flow lengths (Figure 6d). A change in α from 16 to 1 yielded a cycle-averaged proximal region length that varied in size by 74% (Figure 6b). Cycle-averaged lengths in the distal region do not demonstrate the same sensitivity since net flow remains positive (Figure 6b). That pulsatile flow characteristics can induce both temporal as well as changes to the time-averaged flow field surrounding a stent strut is a non-intuitive finding, yet it will be critical to appreciating of the effects of pulsatility on local drug delivery. Indeed, in our example of low frequency renal arterial flow, we see locally extended distribution of the drug into the tissue far upstream of the strut (Figure 5b). The introduction of reverse flow at this low frequency will increase the proximal region’s length, acting to dilute the instantaneous magnitude of the mural surface concentration and concomitantly, extending the length of the mural interface exposed to drug.

Arterial drug distribution in the distal aspect of the tissue shows a similar pattern however in a larger quantity for the steady equivalent case of α = 16 (Figure 5b). This trend implies that drug uptake in a dynamically changing flow field will be inferior in magnitude to that with approximately steady standing recirculation zones. Systematic dilution via instantaneous changes in the distal recirculation length when coupled with the exponentially decreasing rate of drug release from the stent coating will mean that cycle-averaged surface concentrations, and thus tissue uptake are time-dependent. In this case, larger oscillations over a longer time period (α = 1, T_{period} ≈ 17.1 s) will act to decrease the efficiency of this distal zone in its contribution to total drug uptake (Figure 5b) when compared to a flow with only small instantaneous changes in their length (α = 16, T_{period} ≈ 0.068s).

We have seen that the periodic nature of cardiac ejection induces unsteady flow and in some cases, reversal of flow, and thereby acts to increase the area of tissue exposed to drug proximally, and dilute the magnitude distally in a periodic fashion. It is therefore through a combination of time-averaged behavior in the proximal and temporal changes in the distal region that pulsatility induces variations to the spatially distributed drug. Interestingly though, when the combined proximal and distal recirculation lengths (total cycle-averaged lengths) are plotted against AWAC in the tissue (Figure 5c), we see that an inverse and approximately linear relationship exists between the cycle-averaged recirculation region and net drug deposition. That transient variations are explained well by the cycle-averaged size of the recirculation region implies insensitivity to the prevailing instantaneous changes in the flow field. Furthermore the differences in total drug uptake for a change in the unsteady flow are small in magnitude when compared to those due to a change in the steady flow.
component. This indicates a strong correlation between arterial drug distribution patterns and steady flow characteristics but only a weak correlation due to unsteady fluid forces.

So far, we have demonstrated how factors characterizing flow pulsatility play a relatively insignificant role in governing arterial drug distribution for fully apposed strut configurations. But this is a highly idealized case especially as the model system cannot include non-ideal settings such as strut malapposition. Not all stents undergo ideal deployment and moreover, arterial wall negative remodeling may occur in some cases; both leading to stent struts being positioned away from the vessel wall. It is therefore natural to quantify the effects of sub-optimal interventional settings such as strut malapposition in the context of varying Womersley number to fully appreciate the role of flow pulsatility in stent-based drug delivery.

We employed our computational model to simulate varying degrees of strut malapposition. For a given Womersley number ($\alpha = 4$), results showed that malapposed struts create unique local flow disruptions that in turn act to modulate the amount and pattern of drug absorbed within the tissue (Figure 7a–c). For instance, a strut displaced by a distance $h = \frac{R}{300}$ (equivalent to 1/10 of strut width) sees drug deposition in the tissue decreased by almost 93% (Figure 7d) yet still has drug levels in appreciable concentrations in the immediate vicinity of the strut (Figure 7a). As the strut is moved further away from the wall, these flow disruptions with pooled drug move further into the free stream and away from contact with the mural interface (Figure 7b). Accordingly, we see drug uptake into the tissue decreasing exponentially with $h$ (Figure 7d). At wall displacement of $h = \frac{R}{30}$, strut-adjacent flow disruptions were contained entirely in the free stream resulting in negligible mural surface concentrations and thus insignificant drug uptake into the tissue below (Figure 7c).

Simulations also demonstrated that arterial drug levels of a malapposed strut were sensitive to changes in the unsteady flow parameter $\alpha$. When $\alpha$ changed from 4 to 1, arterial drug uptake from a strut malapposed by a distance of $\frac{R}{300}$ increased by 10% (Figure 7d). Sensitivity to $\alpha$ increased further with distance between vessel wall and drug source until finally the strut-adjacent flow disruptions lost contact with the vessel wall. Since drug uptake for a malapposed strut is only via drug pooling within the flow recirculation zones, sensitivity to the unsteady flow parameter implies that the pulsatile nature of blood flow does in fact play a role in modulating arterial drug uptake, but only as a function of device deployment settings. Moreover, it is the stent-wall interaction that will define the extent to which pulsatile flow affects arterial drug deposition. Only under ideal device deployment settings can the effects of pulsatile flow on arterial drug distribution be neglected; highlighting the importance of stent deployment settings in our understanding of the dynamically changing luminal flow environment and its impact on stent-based drug delivery.

4 Discussion

Endovascular drug delivery was long assumed to be a result of arterial wall transport alone [4, 24]. Luminal flow is being accepted as an important factor modulating arterial drug distribution [7–9, 25]. Flow disruptions within the device milieu spread the exposure of drug beyond the regions of device-lumen contact and thereby allow for an extended distribution with perhaps therapeutic concentrations of drug for a sustained period. This may partially explain why some clinical endpoints were achieved in recent human trials and the success of DES therapy became unprecedented. However, issues such as stent thrombosis raised concerns about its long-term efficacy and motivated us to understand the conditions under which these devices work or fail and the factors that determine the longevity of this therapy. Our previous work has shown that arterial drug distribution is sensitive to stent design, strut...
malapposition and the mean Reynolds number within the lumen [7–9]. The manner by which pulsatility of the luminal flow affects arterial drug distribution in the context of several real world procedural settings has yet to be appreciated, and this has been the focus of our current study.

4.1 Effect of flow pulsatility in local drug delivery

Our results revealed a complex interplay between flow pulsatility and arterial drug distribution. By modeling flow pulsatility via changes in pressure pulse frequency, we could vary not only the time scale of changes in the local flow disruptions but also the magnitude of these changes. Consequently, variations in the vessel Womersley number via a change in cardiac pressure pulse frequency were shown to change the instantaneous extent of the strut-induced flow disruption as well as its time-averaged behavior. Specifically, when frequency decreases, we see larger oscillations over a longer period. This will simultaneously act to extend drug uptake proximal to the stent strut and decrease drug quantity in the distal aspect, when compared to a flow with only small instantaneous changes in their length. Together, these findings imply that drug uptake in a dynamically changing flow field will be lesser in magnitude but larger in extent to that with approximately steady standing recirculation zones. Therefore, if we define an effective stent-based drug therapy to constitute a more extended and uniform distribution of drug, our results indicate that DES efficacy may become higher with increase in flow pulsatility, as opposed to that under steady flow. However, this effect abates when stents get malapposed and drug levels drop off dramatically with displacement of the strut away from the vessel wall. These inferences may also partially explain why DES therapy has been successful in certain vascular beds such as the coronaries and not equally effective in other regions within the vasculature.

4.2 Role of computational modeling

Computational modeling allowed us to isolate and appreciate the factors governing luminal flow pulsatility under various device deployment settings at a resolution that is not feasible via bench-top or in vivo studies. Such modeling paradigm required careful design, simplifications and assumptions to model the multi-scale nature of drug release and transport under several flow regimes. For example, the highly idealized bench-top model was incapable of resolving the micro-level changes in wall displacement, and thus only computer models enabled understanding of the relationship between wall-displacement, pulsatile flow and arterial drug distribution. Further, majority of the previous studies to date have modeled luminal flow presumably in a steady state form [7, 8]. The computational burden of coupling the small time scale of luminal flow frequency with the larger time scale of drug release from the stent often necessitates such simplifications, however its implication is not fully understood. Our current study allowed us to appreciate that such compromises may very well result in meaningful conclusions under certain conditions such as fully apposed device deployment settings, where the effects of pulsatility on arterial drug distribution may be negligible.

4.3 Importance of Womersley number

The Womersley number ($\alpha$) and the Reynolds number ($Re$) appear in the non-dimensional formulation of the Navier-Stokes equations governing oscillating fluid flow, and as such are used to characterize kinematic similarities between vascular flows. Certainly one can scale $\alpha$ independently of $Re$ within the framework of the non-dimensional Navier-Stokes equation, however such a variation has little physical meaning in the context of arterial blood flow. While $\alpha$ impacts pulsatile flow, one must consider how variations in $\alpha$ physically arise. This aspect of fluid behavior is not obvious in the Navier-Stokes formulation, however it can be explained using the pressure-flow relation in Equation 1. Assuming viscosity remains fixed, it is clear that an increase in the frequency of the driving pressure gradient and therefore $\alpha$. 

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will yield simultaneously a decrease in the amplitude of the unsteady flow rate and an increase in its frequency. However, when \( \alpha \) increases as a result of the vessel size, we see an oscillating flow rate that monotonically increases with fixed frequency. These results support two intriguing aspects related to \( \alpha \) and flow pulsatility. First, \( \alpha \) is a function of both dimension and frequency, and each will have a different impact on oscillating flow.

Secondly, a change in either dimension or frequency will yield changes to the magnitude of the oscillating flow harmonics, and therefore physical changes in \( \alpha \) will not in fact be independent of \( Re \). Such coupling and dependencies indicate that the relative unsteadiness in arterial flow is only partially captured by non-dimensional metrics such as the Womersley number. Nonetheless, they allow for systematic analysis and understanding of physicochemical phenomena, specifically within the context of stent-based drug delivery.

### 4.4 Frequency of the oscillating pressure harmonics as a model of pulsatile flow

Throughout this analysis, we have made use of Womersley’s framework to simulate various patterns of pulsatile flow. We now make it more clear how this was done and specifically note that for a given physiologic driving pressure gradient, we fixed the steady component while varying the frequency of its oscillating harmonics and constructed three specific scenarios of flow patterns. First, by contrasting a physiologically realistic flow in the renal artery to one operating at a high frequency (\( \alpha = 4 \) versus \( \alpha = 16 \)), we were able to consider the case of an approximately steady flow. Similarly, comparisons at low frequency (\( \alpha = 4 \) versus \( \alpha = 1 \)) allowed us to consider how large changes in the unsteady flow, including the phenomenon of instantaneous flow reversal can affect resultant drug distribution patterns. These flow settings were imposed by prescribing a boundary condition to a straight, non-bifurcating arterial segment with a single stent strut. Womersley’s pressure-flow relations served as a vehicle of analysis, where changes in pressure pulse frequency scaled both the timescale and magnitude of changes in arterial flow.

Our methodology allowed systematic quantification of unsteady flow but represents only a subset of all the permutations by which pulsatile flow regimes could be quantified within arterial vasculature. Indeed by modeling only with fixed pressure pulse amplitude, we neglected physiologic changes in pulsatile flow that yield changes to both the shape and fundamental frequency of the driving pressure gradient. That is, for a change in vascular bed the pressure pulse will undergo changes in shape as it travels with branching, changes in cross-sectional area, reflection of the wave and non-uniform arterial elasticity all giving rise to distinct pulse shapes and thus fundamentally different flow waveforms. Similarly, a change in the heart rate will yield changes in the pressure pulse, as determined by both Womersley’s pressure-flow relations at the root of the aorta and the vascular impedance of the arterial system [26, 27]. Furthermore, the high and low frequency values studied here (3.5 and 882 beats per minute, respectively) are not truly physiologic but allowed us to systematically understand the phenomena of flow pulsatility in the context of stent-based delivery.

### 5 Study Limitations and Future Work

In this study, bench-top and computational models of an idealized stent strut were used to evaluate the role of pulsatile parameters governing blood flow on arterial drug deposition. As with the case of many integrative approaches focused on obtaining mechanistic insight, inferences become relevant when they are validated with appropriate bench-top data. In this work, we have made all possible efforts to replicate a model-based setting using a bench-top approach and vice-versa, however were practically limited by the resources available and the difficulty associated with setting up these complex bench-top and computational model scenarios. For instance, the kinematic viscosity used within the bench-top setting (\( \nu = 0.04 \) cm\(^2\)/s) is similar but not equivalent to the value used in our computational model (\( \nu = 0.033 \) cm\(^2\)/s).
cm$^2$/s). Furthermore, diffusion coefficients measured earlier [12] and used within our study may not perfectly match that of a true in vivo setting. These differences limited us to establish exact correlation between the findings derived using computational and bench-top paradigms. However, we believe the inference related to the impact of flow pulsatility on arterial drug distribution as a function of strut apposition to the wall remains intact, and should be further quantified to extend our findings to various pathophysiologic settings.

We were limited in the experimental method to analyze drug distribution for long periods, while at the same time computational constraints forced us to simulate only for shorter time intervals. In particular, we saw that the time scale of unsteady blood flow (of the order of 0.1 s) required the numerical simulation to be truncated at a solution time of 50 s - so as to harness available computational power - a time far premature than the in vitro endpoint (3 hrs). We were thus prohibited from comparing equivalent amounts of drug at defined time points. However, the combined experimental and computational approach allowed us to simultaneously consider both short and long times scales of transport and observe finer aspects associated with changing flow patterns due to flow frequency as well as strut malapposition.

Theoretical aspects of pulsatile fluid mechanics have been utilized with ideal fluid and geometry assumptions to determine flow boundary conditions, whereas actual circulatory flow is a complex milieu of platelets, plasma and cells in vessels with highly irregular tissue and lumen geometries. A lack of rigorous experimental data prevented us from considering blood as a suspension. Also, there may be changes in the composition of the blood, and its associated transport characteristics as it moves through the arterial wall from one anatomical location to the other. Future work is aimed to add insight into these aspects by considering models that incorporate these settings.

6 Conclusions
Pulsatility leads to instantaneous changes in the luminal flow field. When struts releasing drugs are placed in these environments, change in flow pulsatility contributes minimally to drug deposition for a well-apposed strut, while a similar change for a strut offset from the vessel wall leads to significant changes in arterial drug uptake. These findings also suggest that one could approximate the effects of pulsatile flow on arterial drug distribution using its steady flow equivalent under ideal device deployment settings. Better appreciation of stent-based drug delivery is needed under dynamically changing physiologic and procedural settings to extend its utilization to other vascular beds.

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Figure 1.
Effects of Womersley number on different flow regimes. (a) Nominal pressure gradient derived from the renal arterial flow waveform [11] using Womersley’s framework. (b) Flow waveforms as a result of varying $\alpha$ via frequency of pressure gradient in Equation 1. Nominal case is shown for the renal artery [11]. As $\alpha$ increases from the nominal case, unsteadiness decreases while a decrease in $\alpha$ acts to increase the amplitude of the unsteady component of flow.
Figure 2.
(a) Schematic of the bench-top model used to validate computational results. Model includes marker drug release from a polyurethane strut and transport through a model tissue (hydrogel) and a solution mimicking blood flow, where varying the pump frequency changes the Womersley number. (b) Flow profiles demonstrating a change in $\alpha$ are prescribed as inputs to the pump generating pulsatile flow for in vitro validation. Changing pump frequency varies $\alpha$ and thus the frequency of the nominal driving pressure gradient changes (Equation 1) from 1 Hz, $T_{\text{period}} = 1\text{s}$, to 12 Hz, $T_{\text{period}} = 1/12\text{s}$, representing equivalent steady and physiologic flow regimes. (c) Schematic of the computational domain.
shows flow past a single stent strut of dimensions 0.1×0.1 mm², located in a luminal flow channel of radius R = 3mm, and juxtaposed to a vessel wall of thickness \( W_t = 1 \text{mm} \).
Arterial drug distribution remains invariant due to changes in the unsteady flow field. a) Spatial concentration profiles measured at a distance \( z = -0.5 \text{mm} \) into the thickness of the hydrogel, for the two waveforms demonstrating a change in the unsteady flow. Fluorescein-Sodium concentration was found to be consistently higher at an axial location downstream \( (x=+0.68\text{mm} \) or 2.0 strut widths) compared to the same point upstream \( (x=-0.68\text{mm}) \) (29.9 \( \pm \) 6.82\% for \( \alpha = 2 \), and 28.3 \( \pm \) 5.08 \% for \( \alpha = 6 \)). b) The mean concentration over the \( x-z \) plane for a change in Womersley number. Reynolds number is kept constant at \( \text{Re}_0 \). c) Mean concentration in the hydrogel was shown to decrease by 7.3\% (\( \pm \)17.3\%) when \( \alpha \) was decreased. This difference is small compared to a change in the mean Reynolds number.
where concentration was shown to increase by 28.8% (±18.0%) when Reynolds number was decreased by a factor of ½.
Figure 4.
Arterial drug deposition for a change in the steady flow parameter. a) Drug distribution and velocity contours (in black) indicating recirculating flow proximal and distal to the stent strut where drug accumulates for the nominal case of $\alpha=4$, shown at a time period of $t=50s$, with inset showing the instantaneous time point in the cycle. b) Scaling the instantaneous flow rate by a factor of $1/3$ yields an equivalent decrease in the mean Reynolds number ($Re_0$). Recirculation lengths decrease in size with decreasing flow rate, with the decrease most obvious in the distal region. Drug concentration contours also show a larger amount of drug for the lower flow rate. c) When $Re$ is decreased, the spatial drug distribution in the tissue measured at a distance $y=0.2mm$ (or $1/5W_t$) below the mural surface, shows a similar pattern but different magnitudes in proximal and distal regions of the strut. Results are shown in units of normalized concentration. The strut lies between $-0.05mm<x<0.05mm$. d) Area-weighted average concentration of the accumulated drug in
the tissue increased by 10% at 50s when Re of the nominal case (Re₀) is decreased by 1/3. α is kept constant for a Re change.
Figure 5.
Arterial drug deposition for a change in the unsteady flow parameter. a) Area weighted average concentration (AWAC) in the tissue at a time t=50s for varying Womersley number as a result of a frequency change in the driving pressure gradient (shown in units of concentration normalized to initial concentration - C<sub>0</sub>). Reynolds number is kept constant at Re<sub>0</sub> for all changes in α. b) Womersley number changes the spatial drug distribution in the tissue, measured at a distance y= −0.2mm (or 1/5W<sub>t</sub>) below the mural surface, with stent strut residing between −0.05mm<x<0.05mm. c) AWAC versus total length (proximal +distal) of the cycle-averaged recirculating region for each Womersley-Reynolds number combination (Note: Re=Re<sub>0</sub> unless otherwise signed.), showing linear relationship with
negative slope. The high $R^2$ value indicates a strong linear relationship between total drug uptake and steady flow-equivalent recirculation lengths.
Figure 6.
Instantaneous flow field surrounding a stent strut. a) Velocity magnitude contours for the nominal case of $\alpha=4$ at an instantaneous time point during systole ($t=0.3T_p$) show respective lengths of the strut-induced recirculation flow regions in the proximal and distal aspects of the strut. b) Cycle-averaged proximal and distal recirculation lengths for each Womersley number change. Note that for $Re=Re_0$ unless otherwise stated. c) Instantaneous lengths of recirculating flow in the proximal and distal segments were plotted for a decrease in frequency of the pressure gradient, and d) an increase in frequency to $\alpha=16$. Right axis in (c) and (d) indicates local velocity in the boundary layer measured using a probe placed at unit strut height into the flow stream ($y=0.1\text{mm}$) and far upstream of the stent strut.
Figure 7.
Arterial drug distribution in suboptimal interventional settings. (a–c) A single stent strut at $\alpha=4$, $Re=Re_0$ with various wall displacements ($h$) is shown that creates unique instantaneous flow fields, and varying degrees of flow stasis where drug gets accumulated. Drug contours and flow streamlines are shown at $t=50s$ and malapposition is measured as wall displacement ($h$) normalized to the radius of the vessel ($R$). (d) Drug deposition (measured as AWAC) decreases exponentially with increasing wall displacement. AWAC increased by 10% when a strut displaced by a distance $h/R=1/300$ had a change in $\alpha$ from 4 to 1, and decreased by 33% for the same $\alpha$ change when the strut was displaced by $h/R=1/100$. 

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