NUMERICAL SIMULATIONS FOR THE EVALUATION OF MATERIAL DIFFUSION CHARACTERISTICS IN ELUTING CORONARY STENTS

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INTRODUCTION

Percutaneous Transluminal Coronary Angioplasty (PTCA) has become the standard for treatment of stenotic coronary arteries. In applicable cases, PTCA is performed because it is less invasive than alternative procedures, resulting in greatly reduced recovery times and reduced overall patient risk, however restenosis and the need for repeat surgery remains a major shortcoming with the basic PTCA procedure.

The use of coronary stents, which act as scaffolding in diseased coronary arteries, has been shown to reduce the likelihood of restenosis following PTCA (1), however in the long-term in-stent restenosis has been shown to affect up to 35% of patients three to six months after initial treatment (2). Stent-based local drug delivery in diseased coronary arteries, using either a simple pharmaceutical tissue growth inhibitor, low-energy brachytherapy, or a combination of the two, shows promise in preventing in-stent restenosis. This process involves coating the surface of the stent with a suitable smooth-muscle proliferation inhibitor prior to apposition. The success of this method is contingent on a homogeneous distribution of the drug in the vascular wall. Such a distribution would fulfill the following requirements; it would limit excess dose in the arterial wall (especially critical in brachytherapy), it would facilitate the selection of the initial drug concentration, and it would ensure that, with sufficient dose, there would be no untreated regions resulting in isolated areas of restenosis.

This study considers a coronary stent coated with a drug-infused polymer. The polymer coating retains its mechanical characteristics while delivering the dose, and some control over the rate of elution can be achieved through appropriate polymer selection. In these preliminary simulations, computational fluid dynamics (CFD) is used to investigate the dependence of dose homogeneity on polymer and arterial wall diffusion coefficients in two dimensions, which will ultimately provide theoretical limits for the ideal diffusion characteristics of both the polymer coating and the eluting drug. Blood is considered an incompressible Newtonian fluid and the arterial wall and polymer coating are considered non-porous, purely diffusive media. The ultimate goal of this study will be to use CFD to model local drug delivery in three dimensions using a coronary stent currently in development[1] with the hopes of optimizing drug concentration homogeneity by modifying stent geometry, diffusion parameters, polymer layer thickness and initial drug concentrations.

MODEL DESCRIPTION

Geometry and Meshing

Three two-dimensional geometries modeled after elements of the stent of interest were investigated. Figure 1a shows five half-embedded struts, unevenly distributed in the z-direction, corresponding to one typical cylindrical section of the stent. Figure 1b shows the section through the long axial component of the stent, which supports the transverse struts of figure 1a. Figure 1c shows the plane perpendicular to flow, with the strut distribution representing a typical cross-section of the stent. Dimensions of note in the model are: lumen diameter, 0.3 cm, strut thickness, 63.5 μm, polymer layer thickness, 50 μm, and arterial wall thickness, 400 μm. Finite element meshes were generated for the geometries using quadrilateral elements. In all cases the limited computational domain and square struts allowed for uniform quad meshes. These FEM mesh files were created using FLUENT's Gambit meshing package, and were read into FIDAP for CFD simulations.

[1] Symbiotech Expandable Intravascular Stent, Patent Document Number 2201001

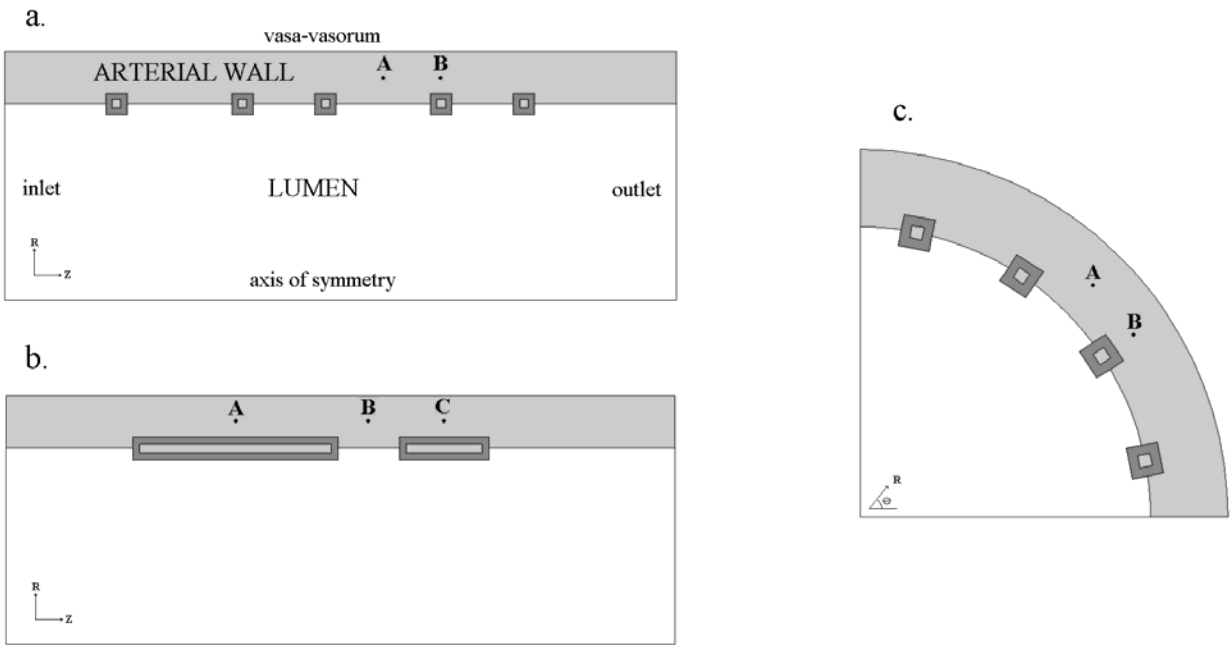

Figure 1: Model geometries with points of concentration measurement A, B and C.

Physical constants and Boundary Conditions

The governing equations for this problem are as follows: In the vessel lumen, we have the 2D advection-diffusion equation coupled with the Navier-Stokes equation (equations 1, 2 and 3), and in the arterial wall and polymer coating, diffusion is the only transport mechanism, leading to equations 4 and 5 in these regions.

$$(u \cdot \nabla)u = -\nabla P + \frac{1}{\mathrm{Re}}\nabla^2 u \tag{1}$$

$$\nabla \cdot u = 0 \tag{2}$$

$$\frac{\partial C}{\partial t} + (u \cdot \nabla)C = \frac{1}{\mathrm{Pe_l}}\nabla^2 C \tag{3}$$

$$\frac{\partial C}{\partial t} = \frac{1}{\mathrm{Pe_p}}\nabla^2 C \tag{4}$$

$$\frac{\partial C}{\partial t} = \frac{1}{\mathrm{Pe_w}}\nabla^2 C \tag{5}$$

where C is the drug concentration, and subscripts l, p and w on the Peclet numbers (Pe) indicate lumen, polymer, and arterial wall, respectively. It should be noted that since there is no convection in the polymer and arterial wall, the Peclet numbers in these regions are effective Peclet numbers scaled by the characteristic velocity of blood in the lumen. Blood is considered a Newtonian fluid, with density 1.051 g/cm^3 and viscosity 0.035 g/cm·s (Poise).

The vasa-vasorum are assumed to be continually replenished with blood, which leads to dilution of the drug at the outer radial boundary. This is translated as a Dirichlet boundary condition for concentration at the outer arterial wall. Since any dose in the blood would be diluted to near zero values upon recirculation, concentration at the lumen inlet boundary is also set to zero. An initial polymer concentration of 1 is imposed.

In preliminary trials, the characteristics of the inlet boundary flow were shown to have little effect on concentration values in the polymer and arterial wall. This is expected since any drug entering the lumen from either the polymer or the arterial wall through diffusive processes would immediately be transported out of the area, and would have no subsequent effect on concentrations in the polymer and arterial wall. As a result, the model can be divided into two regions; a flow region in which no dose collects, and a non-flow region with purely diffusive drug transport mechanisms. It should be noted that this approach is not valid in cases where recirculation zones near the intima exist. In the simulations discussed here no such features occurred, and in a more realistic pulsatile-flow model it is unlikely that stagnation areas would survive for a sufficient number of cycles to affect concentration values in those areas. A mean flow velocity of 15 cm/s was applied in the lumen, and a no-slip boundary condition was imposed on the intima and polymer. The lumen outlet boundary was not constrained.

EXPERIMENTAL APPROACH

The active period of cell growth following stent apposition, called the "proliferative phase", lasts up to two weeks. As a result, an ideal dose delivery would need to a) achieve the therapeutic threshold concentration throughout the treatment region during the proliferative phase, b) show a gradual decrease in concentration over time in the treatment region, and c) achieve a high degree of dose homogeneity in the treatment region. The key parameter in deciding the success of these aspects of treatment is the diffusion coefficient ratio (DCR), which is the ratio of polymer diffusion coefficient to arterial wall diffusion coefficient. In a clinical setting the diffusion characteristics of blood and arterial wall are not easily controlled, and as such the diffusion coefficients of blood (10^{-7}cm^2/s) and arterial wall (10^{-8}cm^2/s) were kept constant, and the polymer diffusion coefficient was varied from 10^{-8} to 10^{-11} cm^2/s. Simulations were run with time steps of $5x10^4$ seconds (about 12 hours) for 12 steps. The total time period is then $6x10^5$ seconds (about one week). Final concentration values are the dimensionless quantity C/C_o since the initial concentration in the polymer was set to 1.

RESULTS

Simulations were carried out for four DCRs in the range from 0.001 to 1.0, and the concentration values at points of interest directly above and between struts at a distance of 200 μm from the intima were plotted against time. The results were evaluated based on three criteria:

C1. The averaged differences in concentration from one time step to the next. If this value is low, then initial concentration selection is made much simpler because potentially harmful excessive doses are minimized.
C2. The ratio of final concentration to concentration at 10^5 seconds. If this ratio is high, then concentration has been maintained over the simulation period.
C3. The ratio of final dose concentration between points above and between struts, giving a simple dose homogeneity index. A favourable result would be a value of 1, indicating equal dose at both points.

Figures 2 to 4 show result for geometries a and b, and evaluation criteria results are presented in table 1.

DCR	Geometry *a*					Geometry *b*						
	Point A		Point B		C3	Point A		Point B		Point C		C3
	C1	C2	C1	C2		C1	C2	C1	C2	C1	C2	
1	0.42	1.08	0.44	0.06	0.52	0.15	0.55	0.24	0.99	0.20	0.32	0.15
0.1	0.44	1.86	0.32	0.14	0.33	0.13	0.75	0.25	1.42	0.17	0.56	0.17
0.01	0.38	1.97	0.24	0.25	0.21	0.08	0.82	0.20	1.40	0.10	0.65	0.17
0.001	0.39	1.32	0.34	0.12	0.29	0.14	0.48	0.21	0.87	0.19	0.35	0.19

Table 1: Three evaluation criteria taken at measurement points for model geometries a and b.

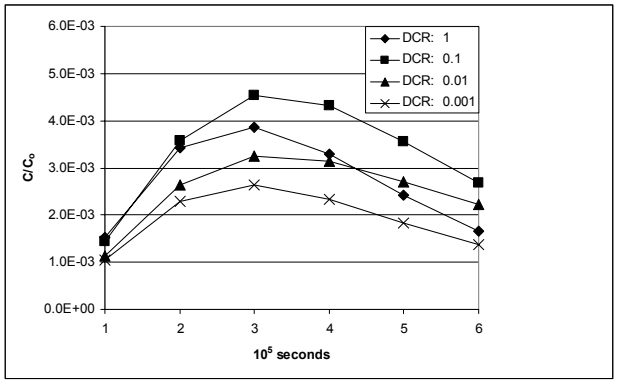

Figure 2: Geometry *a*, Point A.

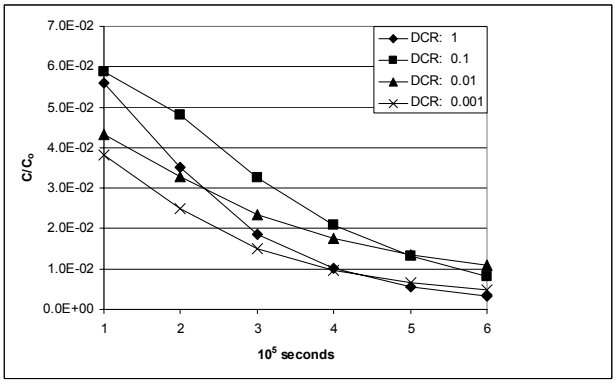

Figure 3: Geometry *a*, Point B.

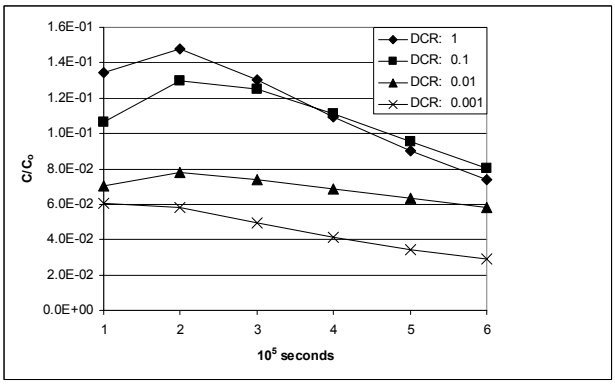

Figure 4: Geometry *b*, Point A.

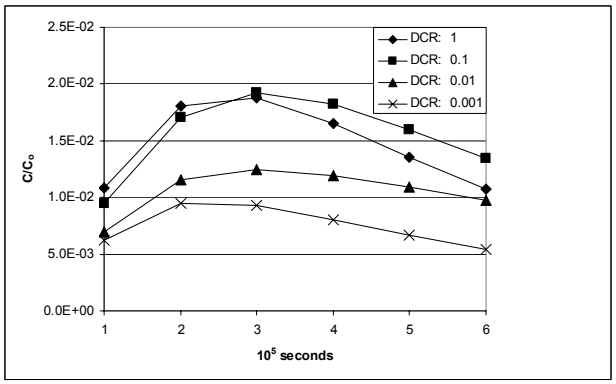

Figure 5: Geometry *b*, Point B.

DISCUSSION

A DCR of 0.01, corresponding to a polymer diffusion coefficient of 10^{-10} cm^2/s and an arterial wall diffusion coefficient of 10^{-8} cm^2/s, was shown to produce the most favourable drug release characteristics based on C1 and C2 in the previous section. In geometry *a* the dose homogeneity index, C3, shows the least desirable results for DCR 0.01, and the most favourable for DCR 1, however in light of the unfavourable results of DCR 1 in other areas, DCR 0.01 remains the most suitable choice. Homogeneity indices for geometry *b* were found to be independent of DCR. Results for geometry c were found to be very similar to those for geometry *a* owing to the close resemblance of the local strut geometry of the two models. The diffusion coefficient for blood and the flow velocity had no significant impact on the results, since any dose diffusing into the lumen is transported away immediately by convection.

CONCLUSIONS

The results obtained here for a simple 2D case are meant to provide an order of magnitude estimate for a polymer diffusion coefficient which would lead to favourable overall dose homogeneity and temporal concentration distribution characteristics. Other factors that are being studied in similar 2D models are the effects of strut apposition and polymer layer thickness on dose homogeneity. In order to render this two-dimensional model more realistic, refinements such as consideration of a porous arterial wall medium, more careful treatment of vasa-vasorum effects, and pulsatile flow dynamics could be applied. Efforts are now being focused on the development of a three-dimensional model using the same basic principles discussed here. Results from this three-dimensional model will be used to optimize dose homogeneity through the modification of stent geometry.

REFERENCES

1. **Rankin J, Spinelli JJ, Carere RG, et al.** Improved clinical outcome after widespread use of coronary-artery stenting in Canada. N Engl J Med. 1999; 341:1957-65.
2. **Wentzel JJ, Whelan DM, van der Giessen WJ, et al.** Coronary implantations changed 3D vessel geometry and 3D shear stress distribution. J Biomech. 2000; 33:1287-95.