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MULTISCALE MODELLING OF DRUG RELEASE FROM STENTS

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ABSTRACT

Drug eluting stents (DES) are apparently simple medical implanted devices used to restore blood flow perfusion into stenotic arteries. However, the design of such devices is a very complex task because their performance in widening the arterial lumen and preventing further restenosis is influenced by many factors such as the geometrical design of the stent, the mechanical properties and the bio-compatibility of the metal struts, the bio-compatibility of the stent outer surface and finally by the chemical properties of the drug that is released. All these topics are relevant for an effective stent design, as discussed in [1,2].

In this framework, numerical simulation techniques play a relevant role in understanding what are the most appropriate choices for the optimal design of DES. Indeed, several mathematical models have been developed to address the fundamental questions of pharmacokinetics, i.e. to estimate the total amount of drug to be released and the characteristic time scale of the release process. The model proposed by Higuchi, see [3], is a milestone in this field. However, the drug release rate has been studied by Higuchi in one space dimension and for the case of constant coefficients, exploiting the analytical solutions of the governing equations in this simplified setting. For this reason, the Higuchi model and its variants are not suitable to address directly problems with complex geometries, such as the case of stents. Recently, see [4], a more advanced model has been proposed for the study of the drug dose, namely the cumulative concentration along the release period, on an axialsymmetric geometrical setting. The work presented in [4] definitely overrides the main limitations of the original Higuchi model, but the fully three-dimensional and time dependent problem is not considered yet. This is the aim of the present work, that we address by means of a multiscale approach putting together the main ideas at the basis of the Higuchi model together with a general treatment of the geometrical setting. The resulting problem is then efficiently addressed by means of suitable numerical approximation techniques.

The main computational difficulties arise from the need to deal with phenomena that take place on multiple scales in space and time. Concerning the space scales, we remind that DES for cardiovascular applications are miniaturized metal structures that are coated with a micro-film containing the drug that will be locally released into the arterial walls for healing purposes. The thickness of this film generally lays within the range of microns. As regards the time scales, we observe that the release of drug is deliberately very slow. In general, it persists until a few weeks after the stent implantation. However,

the local phenomena that influence the drug release take place within much shorter time scales, typically minutes or even seconds.

To address these topics, we start from a general model for mass transfer through heterogeneous media, consisting on an advection-diffusion-reaction equation for each different layer of material or tissue into the stent and the arterial walls, see for instance [5,6]. Such model has already been applied in [7] for computational studies about drug release from stents. However, we point out that simulation studies based on this model involve extremely high computational costs and by consequence, to our knowledge, only studies concerning simplified stent geometries have been pursued so far. Starting from this point, we present a reduced model for mass transfer from a thin layer, developped in [8], which significantly cuts down the computational cost for the simulation of the drug release from stents because the diffusion equation governing the drug release form the stent is condensed into a boundary condition applied on the stent surface. Furthermore, the study of reduced models turns out to be particularly effective to determine the dynamics of the drug release with respect to time. This allows us to set up an a priori adaptivity strategy for the time steps in order to control of the increment of the amount of drug that is released.

To sum up, combining the reduced model for mass transfer with suitable numerical discretization methods, it is possible to obtain simulations involving realistic expanded stent geometries, obtained in [9], and long time scales. The efficacy of our approach is demonstrated by means of numerical results concerning realistic situations.

REFERENCES

[1] J. Garasic, E.R. Edelman, J. Squire, P. Seifert, M. Williams, C. Rogers, Stent and artery geometry determine intimal thickening independent of arterial injury. *Circulation*, 101:812–8, 2000.

[2] C. Hwang, D. Wu, and E.R. Edelman. Physiological transport forces govern drugdistribution for stent-based delivery. *Circulation*, 104(5):600–605, 2001.

[3] T. Higuchi. Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharmac. Sci.*, 50:874–875, 1961.

[4] M.C. Delfour, A. Garon, and V. Longo. Modeling and design of coated stents to optimize the effect of the dose. *SIAM J. Appl. Math.*, 65(3):858–881 (electronic), 2005.

[5] G. Karner and K. Perktold. Effect of endothelial injury and increased blood pressure on albumin accumulation in the arterial wall: a numerical study. *J. Biomech.*, 33:709–715, 2000.

[6] M. Prosi, P. Zunino, K. Perktold, and A. Quarteroni. Mathematical and numerical models for transfer of low-density lipoproteins through the arterial walls: a new methodology for the model set up with applications to the study of disturbed lumenal flow. *J. Biomech.*, 38:903–917, 2005.

[7] D.R. Hose, A.J. Narracott, B. Griffiths, S. Mahmood, J. Gunn, D. Sweeney, and P.V. Lawford. A thermal analogy for modelling drug elution from cardiovascular stents. *Comput. Methods. Biomech. Biomed. Engin.*, 7:257–264, 2004.

[8] C. Vergara and P. Zunino. Multiscale modeling and simulation of drug release from cardiovascular stents. Technical Report 15, MOX, Department of Mathematics, Politecnico di Milano, 2007. Submitted.

[9] F. Migliavacca, F. Gervaso, M. Prosi, P. Zunino, S. Minisini, L. Formaggia, and G. Dubini. Expansion and drug elution model of a coronary stent. *Comput. Methods. Biomech. Biomed. Engin.*, 10:63–73, 2007.