Drug Eluting Stent Modelling

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Abstract:
Improvement in biocompatibility is a major step forward in the development of implementable medical devices, such as stents. Recently, a new type has emerged called "Drug Eluting Stent" (DES), which releases antiproliferative agents like Sirolimus in order to prevent restenosis. Nevertheless, complexity of *in vivo* studies implementation has led to resort to numerical modeling. Combined with data from the literature, we have developed a numerical model capable of assessing whether the drug concentration contained by stent is sufficient to prevent restenosis. Our results demonstrate the ability of Sirolimus to slow down but not fully prevent restenosis. After further investigations, we have assessed the minimal concentration that should be deposited on stents in order to eradicate this phenomenon.

Keywords: Sirolimus eluting stent, coronary artery restenosis, numerical modelling, COMSOL.

1. Introduction [1]

Coronary arteries are substantial for life since they supply the heart with blood. Therefore any impairment can lead to a dramatic ending, death. Indeed coronary artery disease (CAD), also known as ischemic heart disease (IHD) or coronary heart disease (CHD), is the first cause of mortality in developed countries and is induced by aggregation of plaques in the artery lumen, which in turn retain cells, lipids and other deposits, resulting in atherosclerosis and stenosis of the artery. Hence, the coronary flow is reduced at the emplacement of the plaques, which provokes an insufficiency in oxygen supply to the heart muscle. Coronary artery disease presents several types of symptoms: angina, myocardial infarction, rhythm disturbance or myocardial ischemic disorders.
Treatment consists in two phases: a pharmaceutical therapy and a surgery. The former performs the function of slowing the progression of the disease and of easing the symptoms, whereas the latter aims to cure the disease by restoring the initial coronary artery efficiency. There are three possibilities to achieve this revascularization:

1. coronary balloon angioplasty
2. stenting
3. coronary artery bypass grafting (CABG)

For the first case of surgery, a balloon is inserted inside the lumen of the coronary artery and once it has reached the impaired area, the balloon is inflated. Thus the diameter of the artery is restored and blood flow can (almost) normally circulate.
Concerning the stenting procedure, it is similar to the previous one except that the balloon is surrounded by a stent, which is a small metallic tube-like structure with a mesh pattern. The inflation of the balloon results in the opening of the stent, which applies force on the arterial wall and thus restores the original diameter size of the artery by maintaining a constant walls pressure towards the outside. Then, the balloon is deflated and removed while the stent remains in the artery.
The last option is generally a more invasive technique than the two others. The procedure consists in the removal of a patient blood vessel coming from the leg, chest or arm and then in the grafting of this vessel to the coronary artery. The two vessel connections, which are performed during the surgery, surround the area where the blood flow is restricted in order to bypass it.
In the scope of this project, we have decided to focus on stenting and more precisely, the immune response generated by the insertion of a foreign body, the stent. In fact, a phenomenon called restenosis has been observed in response to stenting and therefore new types of stent have emerged. Starting with bare-metal stent, the medical device has evolved in a drug eluting stent covered with a polymer coating incorporated with drug. Heparin was formerly used to prevent blood clot generation but since then antiproliferative agents like Sirolimus have replaced it. The latter are molecules, which act on immune and smooth muscle cells and stop them in their cellular cycle in order to cease their proliferation otherwise giving rise to inflammation and scar tissues formation and thus to restenosis.
Therefore we formulate a research question by wondering if the Sirolimus concentration released by the stent is sufficient to eradicate restenosis phenomenon. Furthermore, in the case of a negative answer, then we would like to assess the minimal concentration required for this.

2. Methods

Since our project is at the edge of several physics, we take advantage of the models coupling functionality offered by COMSOL and thus create three models instead of one, all bound to each other with a coupling operator. In a nutshell, the first model serves the purpose to obtain the fluid – *in our case, blood* – behaviour in a coronary artery. The second one aims to characterise the diffusion and the transport of the drug at the interspace between the stent framework. And finally the third model attempts to simulate the smooth muscle cells proliferation. For each step, we

have taken parameters from the literature but we have not come across a paper including the whole process.

2.1. System

Even though, in the end, we are interested in smooth muscle cells evolution through time, it cannot be dissociated from the drug concentration along the stent, which in turn is related to blood flow. Therefore we try to give the appropriate weight to each of this phenomenon with the help of three distinct models.

For the first model, we assume a very simplified artery shape consisting in a hollow cylinder where we define the stent as being a line (see Figure 1). The rectangle that is drawn represents the area of interest, which we focus on in the second model. Thanks to the symmetry along the artery, the system is 2D axisymmetric. Furthermore, the only parameter we are willing to extract from this model is the blood flow and hence the single material properties required are the blood ones. We simply assume arterial walls to be non-elastic.

Concerning the second model, a segment of the stent as well as the surrounding bulk are modelled in 3D. We approximate the interspace created by the stent armature to be rhombus shape-like. We model half of three rhombuses in the y-direction, along blood flow, using the symmetry tool to have complete interspaces (see Figure 1). We proceed so in order to determine whereas the stent framework drug release influences only the interspace nearby or also the ones located further away. In continuation of model 1, the stent is represented as being extremely thin compared to the studied bulk, which is filled with blood and where Sirolimus according to its properties (see Table 1) diffuses freely.

Eventually, the third and last model is a representation of one interspace formed by the stent armature. We are interested in the smooth muscle cells proliferation at the stent surface, therefore a 2D model is suitable. Similarly to the second model, symmetry is set in the y-direction.

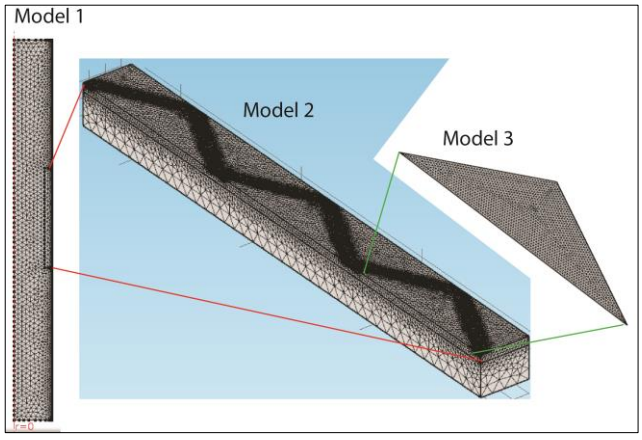

Figure 1: Whole system comprising the three models and their respective meshes

	Description	Name in COMSOL	Value
MODEL 1	Artery Segment length	-	25 [mm]
	Artery radius	R_artery	2.5 [mm]
	Stent segment length	-	6.6 [mm]
	Rectangle height	-	0.5 [mm]
MODEL 2	Bulk width	-	0.6 [mm]
	Bulk depth	-	6.6 [mm]
	Block height	-	0.5 [mm]
	Stent thickness	Th_stent	0.08 [mm]
	Rhombus edge	-	1.1 [mm]
	Rhombus big diagonal	-	2 [mm]

Table 1: Parameters used for the models geometry

2.2. Physical laws

The insertion of a stent into a coronary artery engenders several phenomena, which are described by different physics. Indeed, in this project, each model has its own physics, which are respectively laminar flow, transport of diluted species and an ordinary differential equation (ODE).

In the first model, the blood flow, considered as an incompressible flow, is described by the Navier-Stokes equation:

$$\rho(u_{fluid} \cdot \nabla)u_{fluid} = -\nabla \mathrm{p} + \mu\nabla^2 u_{fluid}$$

$$\mathrm{p}\nabla \cdot u_{fluid} = 0$$

where blood density ρ and viscosity μ are given in Table 2. To stick to reality, we implement a truncated series of Fourier function mimicking the physiological pulse flowrate [2] at the inlet, while the pressure is set to zero at the outlet.

Regarding the second model, drug distribution is based on two principles: diffusion and convection, thereby the selected physics is transport of diluted species. Diffusion is described by Fick's law and coupled to convection phenomenon, it results in the following mass balance:

$$\frac{\partial c}{\partial t} + u \cdot \nabla c = \nabla \cdot (D\nabla c)$$

where c represents the concentration of Sirolimus given in [mol/m^3], D is the diffusion coefficient of Sirolimus given in Table 2 and u is the velocity vector of blood in [m/s]. To this end, we define a

constant input of drug on the stent framework given in Table 2. In addition to this, boundaries are defined according to blood flow circulation, inlet at the blood entry and outlet at the exit.
Finally, the third model consists in the implementation of a function relating smooth muscle cells proliferation with the concentration of Sirolimus. Thence, the appropriate physics is domain ODEs and DASs and assuming steady state in healthy case, we define our as the following:

$$\frac{dN}{dt} = k \cdot DrugEffect(c) \cdot N$$

where N is the concentration of smooth muscle cells given in [mol/m^3], k represents smooth muscle cells (SMCs) growth rate in case of immune response, and DrugEffect(c) is a function that modulates the cellular growth rate with respect to the Sirolimus concentration. Based on in vitro studies found in the literature [3], the inhibitory effect of Sirolimus can be described by the following equation:

$$DrugEffect = 1 - \frac{(7.5 \cdot 10^{-1})}{(10^{-4} - 10^{-7})} \cdot (c - 10^{-7})$$

where the drug concentration c is given in [mol/m^3]. We consider the rhombus interspace to be fully covered with smooth muscle cells at the beginning of the simulation and hence compute the initial smooth muscle cells concentration N_0 [mol/m^3] (see Table 2) from the number of cells contained in half a rhombus (2702), the thickness of one cell (4 µm) and the number of Avogadro ($6.022 \cdot 10^{23}$). Eventually, we notice that the drug diffusion and transport start stabilising after 14 periods of the pulse flowrate function, so we inject drug concentration values corresponding to this time in the third model.

	Description	Name in COMSOL	Value
MODEL 1	Blood viscosity	mu_b	$3.5 \cdot 10^{-3}$ [Pa·s]
	Blood density	rho_b	1060 [kg/m^3]
MODEL 2	Diffusion coefficient of Sirolimus	Sirolimus_D	1e-8 [cm^2/s]
	Initial Sirolimus concentration	-	$6.23 \cdot 10^{-7}$ [mol/m^3]
MODEL 3	SMCs growth rate in unhealthy case	k	$1.71 \cdot 10^{-2}$ [1/h]
	Initial concentration of SMCs	N_0	$2.24 \cdot 10^{-9}$ [mol/m^3]

Table 2: Parameters used for material properties and physics description

2.3. Numerical model

The project is conducted on COMSOL Multiphysics 4.3a (Classkit license).
Based on convergence analysis we select an optimal mesh, which is a compromise between time of computation and accuracy for the results, for each model independently. For the first model, where we are interested in the flow rate, we use the predefined coarser mesh (element size between 0.01 and 0.217 [mm]). Whereas, to solve model 2, we design three specific meshes: at the stent armature, at the near surrounding of the stent and along the remaining part of the bulk. Indeed, a higher precision is required for the structure of the stent, a little bit less for the nearby area and finally even less for the remaining bulk. To serve this purpose, the finest mesh with element size between 0.02-0.119 [mm] is located at the stent framework, while the second mesh has an element size varying from 0.04-0.119 [mm]. Eventually, the last mesh is going from 0.119 to 0.2 [mm]. Concerning model 3, for the computation of the smooth muscle cells proliferation, a predefined extremely fine mesh is suitable. In the three models and their respective meshes, triangular elements were used.
Coupling is a critical point of our project since the three models need to be bound. For this purpose, we use the general extrusion operator between model 1 and model 2 as well as between model 2 and model 3. Indeed, from the first model, we extract the obtained velocity profile and inject it in model 2 in order to add the convection phenomenon and see the impact on drug transport. Then, the second coupling consists in the extraction of the drug concentration distribution at the surface of the stent and its insertion in the third model where ODE is applied computed thanks to this value. Hence, we can observe the inhibitory effect of Sirolimus on smooth muscle cells proliferation.
For each model, we implement a time-dependent study. This strategy is beneficial in terms of computation power since, for instance, we do not have to redo the first and second steps when evaluating the third model.

3. Results

Starting with the initial Sirolimus concentration value of $6.23 \cdot 10^{-7}$ [mol/m^3] found in the literature [4], the pattern of drug concentration evolution along the stent segment is shown in Figure 2. Several time points are evaluated and thus allow to determine when the equilibrium is reached, in other terms when the concentration does not fluctuate radically within one pulse cycle. The stabilisation is visible after 14 periods corresponding to 11 [s]. From this preliminary result, not only we set the number of the cycle to further import in the third model, but we can observe a net increase in concentration downstream. Therefore we decide to further investigate by always

comparing the first rhombus – *located upstream* – to the third rhombus – *located downstream*.

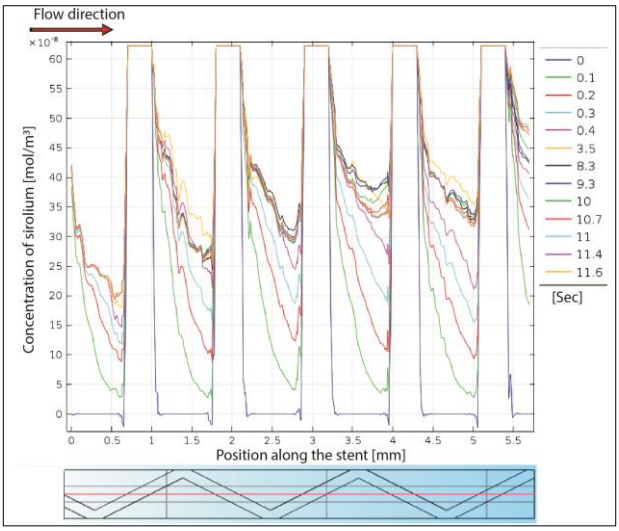

Figure 2: Distribution of the sirolimus concentration ($6.23 \cdot 10^{-7}$ [mol/m^3]) along the stent segment for different time points

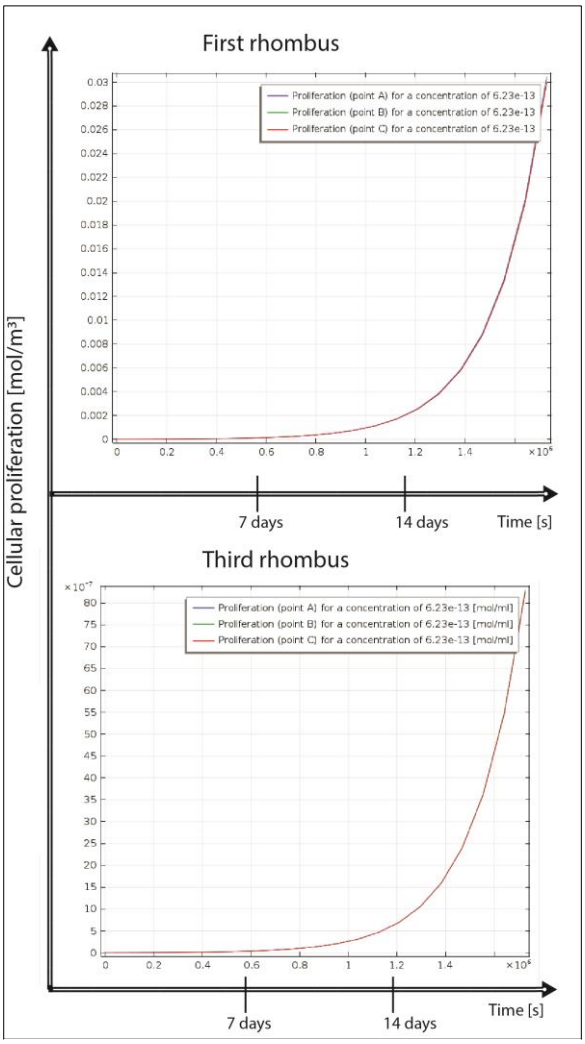

Figure 3: Smooth muscle cells concentration over time for three spatial points in the first and the third rhombuses for an initial Sirolimus concentration of 6.23·10-7 [mol/m3]

Then we shift to the third model and plot the cellular growth with the initial Sirolimus concentration of $6.23 \cdot 10^{-7}$ [mol/m^3] in function of the time for the two referred rhombuses in Figure 3. Three spatial points are selected within the rhombuses and represented on the graph with their associated cellular growth over a period of a few days.

Eventually, the impact of several concentrations of Sirolimus on cellular growth is shown in Figure 4. Similarly to Figure 3, smooth muscle cells proliferation is shown in function of time but due to visibility concerns, only one spatial point is represented for each drug concentration. The minimal concentration able to fully stop restenosis phenomenon is $1.33 \cdot 10^{-4}$ [mol/m^3].

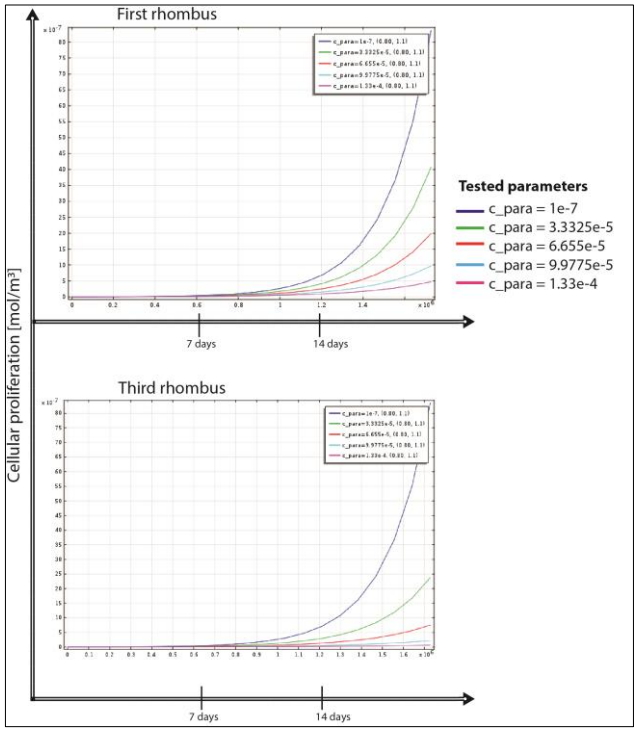

Figure 4: Smooth muscle cells concentration over time in the first and the third rhombuses for a range of initial Sirolimus concentration

4. Discussion

4.1. Interpretation of the results

From the above section, we have made interesting discoveries. As a first step, we assess the contribution of upstream stent armature on downstream rhombus. For this purpose, we have plotted the concentration of Sirolimus found in the literature along the stent (see Figure 2). Based on these results, a non-negligible amount of drug is coming from upstream stent armature, driven and carried by blood flow, increasing the downstream interspaces drug concentration. Therefore, as mentioned above, we have decided to always look at drug effect on the first and third rhombuses.

Then, we try to figure out whether the standard drug concentration detained by the drug eluting stent is sufficient to prevent restenosis. To this end, we analyse the cellular proliferation with respect to time in both rhombuses (see Figure 3). For the three spatial points selected, an exponential cellular growth is observable around day 14. Moreover, at this time-point the smooth muscle cells concentration varies from the first and the third rhombuses in agreement with our previous finding. Indeed, for the first rhombus, the concentration is of 0.002 [mol/m^3] of cells – *corresponding to* $2.45 \cdot 10^9$ *cells* – whereas it is of $5 \cdot 10^{-7}$ [mol/m^3] – *corresponding to 603'125 cells* - for the third rhombus, demonstrating a more pronounced inhibition in the third rhombus. Nevertheless, in both cases, the increase in smooth muscle cells number is huge and leads us to conclude that the initial concentration applied on stent is not sufficient to prevent restenosis.

In a second phase, we try to assess the minimal concentration required in order to prevent completely restenosis. Thanks to the parameter sweep functionality, we select a range of Sirolimus concentration and analyse their impact on cellular growth (see Figure 4). Similarly to the previous results, the proliferation is more consequent in the first rhombus rather than in the third one. In fact, for a concentration of $1.33 \cdot 10^{-4}$ [mol/m^3], while the smooth muscle cells proliferation is considerably slowed down in the first rhombus, the phenomenon is fully stopped in the third one. Since a stent includes several hundreds of rhombuses in a row, if restenosis is already blocked at the third rhombus, it seems legitimate to consider this concentration as the minimal one able to prevent restenosis.

4.2. Verification

As a first verification, mesh convergence analysis is performed in order to check the sensitivity of the numerical model to mesh refinement. The value of the most discriminating parameter at a certain point is plotted against the degrees of freedom of the different meshes for each of the three models. The selected parameters are maximal velocity for the 1st model, drug concentration for the 2nd one and cells concentration for the 3rd one. Models 1 and 2 reach convergence and this allows us to choose the most suitable meshes mentioned in section 2.3. Regarding model 3, convergence cannot be reached with the finest predefined mesh for the chosen point. As an alternative, we would suggest to do an averaging on a small region of interest away from this point.

The second type of verification we perform is related to the coupling operators. First, we check whether the flow of the first model is correctly applied to the second one. To do this, we plot the velocity magnitude along a cut-line identical for both models. As a result, we observe that both curves are superposed, meaning that the flow is correctly transferred to the second model (Fig. 5).
Secondly, we check whether the drug concentration of the second model is correctly applied to the third one. Similarly, we plot the drug concentration along a cut-line identical for both models. Again, both curves are superposed, meaning that the drug concentration is correctly transferred to the third model (Fig. 5).

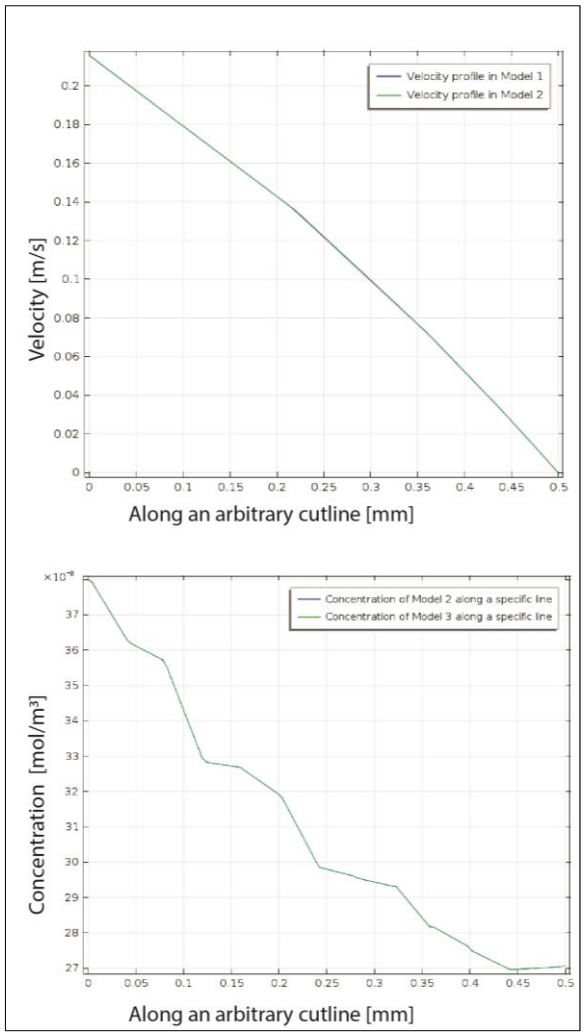

Figure 5: Verification of the coupling operators. Velocity magnitude and drug concentration along a cut-line for models 2 and 3

As a third verification, we compute the analytical solution of the ODE of the third model:

$$N(t) = N_0 \cdot e^{k \cdot drugEffect(c) \cdot t}$$

In order to verify that the ODE is correctly applied in the third model, we manually compute the cells concentration N at a time $t = 8.64 \cdot 10^4$ [s] and for a drug concentration $c = 2.44 \cdot 10^{-7}$ [mol/m^3] and we compare it with the value obtained by COMSOL. We get $3.38 \cdot 10^{-9}$ [mol/m^3] for the theoretical value and $3.38 \cdot 10^{-9}$ [mol/m^3] for the COMSOL value. This means that the equation is indeed correctly applied.

4.3. Validation

Data found in the literature [5] show that Sirolimus eluting stents causing a blood concentration peak of 0.57 ng/ml (or $6.23 \cdot 10^{-7}$ [mol/m^3]) cause a significant reduction in restenosis, which is however not complete. This somehow validates our results that suggest a higher drug concentration to totally inhibit cell proliferation and restenosis. Nevetheless, a partial reduction in restenosis may be sufficient to restore a satisfactory blood flow and total inhibition of restenosis may not be absolutely necessary. Unfortunately, we lack clinical data about the precise minimal reduction that is necessary. We know that Sirolimus demonstrates biological activity without displaying toxicity with doses varying from 18 to 1200 µg [5], but we have not found any comparative study with different Sirolimus concentrations on stents and their effect on cell proliferation. As a consequence, our numerical model cannot be fully validated.

4.3. Limitations & Improvements

Our model faces some important limitations, which are partially listed below accompanied with suggestions to overcome these issues

The main limitation concerns probably the drug concentration on the stent and its release. Indeed, our model simulates an unlimited amount of drug that is constantly released. However, in reality, the amount of drug deposited on the stent is limited by the nature of the polymer coating. And drug release also strongly depends on the degradability of the polymer used. Thus, as an improvement, we suggest to limit the drug concentration in time and to model the drug release as a function of the polymer degradation. We think that equations governing this phenomenon could be found in the literature.

Another major limitation concerns the ODE that governs cell proliferation. Indeed, this equation causes an infinite exponential increase of the cell concentration. This is also shown by the analytical solution of the ODE shown in section 4.2. Nevertheless, in reality, cell proliferation is slowed down until it reaches a plateau. This is may be due to limited nutrients and oxygen. Thus, we propose another ODE, inspired by [6], that considers this decrease in proliferation over time:

$$\frac{dN}{dt} = k \cdot drugEffect(c) \cdot N \cdot t \cdot e^{-\alpha \cdot t}$$

N is the cell concentration, k is the restenosis proliferation rate, *drugEffect(c)* is the drug effect function, t is the time and α is a constant parameter.

Moreover, it would be worth to improve the drug effect function, which we approximate as a linear one, while it should be rather a sigmoid.

Other improvements can be done concerning the choice of the parameters, which are taken from in vitro studies. *In vivo* studies could provide parameters that better reflect the reality. The geometry of the coronary artery can also be improved with a curved shape and elastic walls. And the blood pressure can be varied to simulate the high pressure present in patients. Finally, in order to confirm our results, it would be interesting to run our simulation on a longer segment of the stent.

5. Conclusion

The goal of this project was to assess whether the drug concentration on Sirolimus eluting stents given in the literature was sufficient to inhibit restenosis caused by placement of a stent as a treatment for coronary artery stenosis. Our results show that such a drug concentration of $6.23 \cdot 10^{-7}$ [mol/m^3] is not sufficient to prevent immune and smooth muscle cells proliferation and thus to block restenosis. However, the restenosis rate is, all the same, slowed down. Our model predicts a drug concentration of $1.33 \cdot 10^{-4}$ [mol/m^3] to completely stop restenosis. Nevertheless, our model needs to be considerably improved in order to be fully reliable. Indeed, the major defect is the lack of reliability over time since we constantly renew the initial drug concentration placed on the stent.

Once optimized, such a model would be very useful to predict the minimal drug concentration to be deposited on a drug eluting stent in order to prevent restenosis and avoid adverse side effects. The model could be customised, and personalised parameters, such as blood pressure and viscosity for instance, could be entered for each patient. This would be a clear advantage now that the concept of personalised medicine is emerging.

Acknowledgements

This project was realized as part of the course “Numerical Methods in Biomechanics” given by Prof. Alexandre Terrier at EPFL (Ecole Polytechnique Fédérale de Lausanne). We would like to offer thanks to Prof. Terrier and his assistants Adeliya Latypova and Valérie Malfroy Camine for their great help and support during this project.

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