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### Modelling and simulating the dynamics of in-stent restenosis in porcine coronary arteries

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## 7. Summary and Challenges

The results highlighted in this thesis show the importance of iterative model development in parallel with analysis and interpretation of biological data. It is clear that the mathematical models (presented in the previous chapters) used to model the process of in-stent restenosis (ISR) have been able to point to key aspects in the response for which little experimental data exists. Considering the initial response; does ISR initially start due to damage of the intima which activates the medial SMCs to migrate through the IEL into the lumen where they proliferate? Considering the final stage of the response; the appearance of a healthy functional endothelium seems to be the key. Simulations further suggest that the time scales at which a healthy endothelium is established may be significant in determining if ISR appears or not. All these hypotheses require more detailed experimentation within either animal models or controlled *ex vivo* environments. We believe that a close interplay between mathematical modelling and new *in vivo* and *in vitro* techniques is required to significantly improve our understanding of ISR.

The dynamic model of ISR allows computation of the inhibitory effect of drug eluting stents (DES). The use of DES has significantly reduced the risks of ISR. However, the inhibitory effect of drugs coated on the stent struts is associated with a

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*This summary is partially based on the review paper Amartruda CM, Bona-Casas C, Keller B, Tahir H, Dubini G, Hoekstra AG, Hose DR, Lawford PV, Migliavacca F, Narracott AJ, Gunn J. From histology and imaging data to models for in-stent restenosis. International journal of artificial organs (IJA), (Submitted)*

delay in the re-endothelialisation that leads to late stent thrombosis. This is another complication associated with DES, therefore, in the context of this thesis, we mainly focused on bare metal stents (BMS). We demonstrated the capability of the ISR model to simulate the effect of drug on SMC proliferation (chapter 2) which led to a slightly reduced neointimal growth rate (without taking into account the drug effect on other cells like endothelial cells). Additionally, very little quantitative data exists related to inhibition of endothelial regrowth in the presence of DES. We therefore limit the research presented in this thesis to the use of BMS.

The current set of models are the state of the art tools developed on the basis of *in vivo* and experimental data with an aim to understand the dynamics of this complex process. However, the accuracy of descriptions of the physics and biology of restenosis may be improved by further model enhancements. For example, further development of modelling at the cellular level might include representation of inter-cellular processes. However, caution is required in selecting targets for further model development, as increase in complexity of such models across all physical and biological processes is unlikely to aid understanding of the primary determinants of restenosis.

We strongly believe that model improvement should be driven by the availability of experimental or clinical data but also vice-versa. Setting up new experiments should take into account hypotheses that have been suggested and tested in mathematical models. The key role of the stent geometrical properties (strut thickness, shape, type of stent such as bare metal or drug eluting) and re-endothelialisation are good examples. Chapter 2 in this thesis highlights the effects of strut thickness and shape on the neointimal growth. The dynamic simulations of ISR (chapter 3) show that under different scenarios of re-endothelialisation, ISR may or may not develop. The effect of the origin of re-endothelialisation on ISR development is also explored using the ISR2D model (chapter 4) and comparison of the *in silico* results with the *in vivo* data suggest that the regrowth of the endothelium from both sides alone does not seem to match with the histology. Therefore, we propose that experiments need to be designed that observe and study in more detail the appearance of healthy endothelium at the site of the stent and their functionality. This could lead to a better understanding why one specific patient develops ISR, whereas another does not. Chapter 5 presents some preliminary results of SMCs migration in response to the vascular injury caused by the stent. A higher number of initial SMCs migrated from the media into the lumen directly corresponds to a faster neointimal development. Here we

hypothesize that the number of these migrated SMCs might dictate how fast the neointima will develop. Chapter 6 shows the state of the art 3D ISR model and also presents some of the preliminary results. This 3D model includes all the modifications that have already been tested and published using ISR2D model.

The translation of the current set of mathematical models to clinical studies requires model validation in the context of human data obtained for ISR. This requires two major steps. First, the models should demonstrate their validity for diseased arteries, as the porcine model system describes the response to injury in initially healthy arteries. This requires application of both *in vivo* experiments and mathematical modelling to the domain of diseased, stenosed arteries. Next, we need sufficient human datasets to allow calibration and validation of the mathematical models. Only then will we be able to take the next step and apply the mathematical models in clinical settings, as suggested above.

To conclude, this thesis has presented modelling techniques used to describe the physics and biology of ISR. The methods employed to model the process of ISR and the interpretation of model outcomes in the context of porcine histological data have been described. The use of a multi-scale approach to provide a description of both endothelial and smooth muscle cell behaviour during neointimal growth has been described. Comparison between the dynamical response of ISR from simulations and the histological porcine data has been used to propose novel experimental questions to be addressed through further experimentation. Despite of the inherent power of these models to aid our understanding about the dynamics of ISR process as well as to allow hypotheses testing, these models are limited to healthy stented arteries. Translation of such approaches to clinical studies for better device optimization to aid treatment planning at the patient-specific level is still a big challenge that first requires detailed quantitative validation of these models across a range of levels of complexity.