A MULTISCALE MODEL OF IN-STENT RESTENOSIS IN CORONARY ARTERIES INTEGRATING DRUG KINETICS WITH CELL DYNAMICS

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Introduction

In-stent restenosis (ISR) is a major drawback affecting the outcome of percutaneous coronary intervention with drug-eluting stent (DES) implantation. ISR is the result of the impaired arterial healing response to the intervention-induced trauma, leading to excessive intimal growth due to the inflammatory-driven exacerbated vascular cell activities. The complete knowledge of the multiscale, multifactorial mechanobiological processes underlying ISR is still lacking.

Multiscale agent-based modelling frameworks, integrating continuum- and agent-based approaches, have recently emerged as promising tools to capture the mechanobiological events driving ISR at different spatiotemporal scales [1]. However, the integration of drug kinetics within said frameworks has been under-investigated [2]. The present study proposes a novel multiscale agent-based modelling framework of ISR following DES implantation in coronary arteries.

Methods

The multiscale framework (Fig. 1) consists of the bi-directional coupling of two modules, namely (i) the drug transport (DT) module and (ii) the tissue remodelling (TR) module. The framework, applied to a 2D stented coronary artery cross-section, provides as output a 1-month follow-up artery geometry.

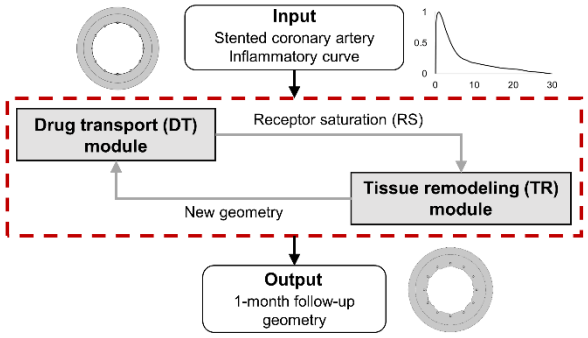

Figure 1: Multiscale framework.

The DT module performs transient simulations of drug transport by coupling Darcy's law with advection-diffusion-reaction equations, in Comsol Multiphysics (Comsol, USA) [2]. The fraction of cell-specific receptor saturation (RS), computed within the DT module, has been considered as a measure of drug efficacy, and thus used to initialize the TR module. The TR module replicates vascular cell dynamics in response to the intervention-induced inflammation and to RS (accounting for the drug effect) through a 2D agent-based model (ABM) implemented in Matlab (MathWorks, USA) [3].

Different scenarios in terms of drug mass (DM), drug release profiles (RP), coupling schemes and idealized *vs.* patient-specific artery geometries were explored.

Results

Changes in the DM, RP and coupling schemes determined a variation in RS over time, in turn affecting the ABM response (Fig. 2, left). Moreover, by applying the framework to a patient-specific stented coronary artery cross-section, with an irregular and asymmetric geometry where the struts were not equally spaced, a heterogeneous RS map was obtained, in turn affecting the growth pattern (Fig. 2, right).

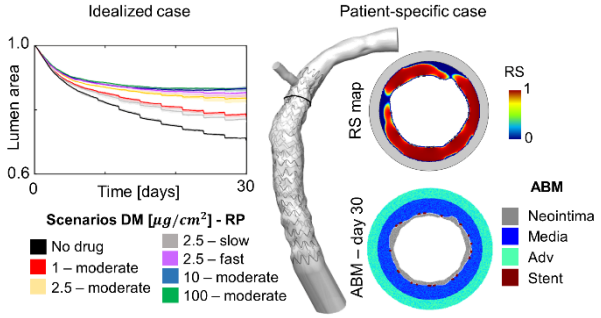

Figure 2: Results of the multiscale framework of ISR.

Conclusions

This work presents a novel multiscale agent-based modelling framework of ISR, integrating drug kinetics with an ABM of arterial wall remodelling. The analyses performed allowed exploring the sensitivity to different settings, coupling modalities and geometries. Moreover, the feasibility to be applied to patient-specific geometries was demonstrated. In future, the effect of different plaque composition on drug release will be assessed.

References

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