# COMPUTATIONAL MODELING OF IN-STENT RESTENOSIS: PHARMACOKINETIC AND PHARMACODYNAMIC EVALUATION

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## Introduction

Percutaneous coronary intervention (PCI) is a minimally invasive procedure wherein the plaque built up within the coronary arteries, as part of an inflammatory pathosis termed atherosclerosis, is pressed against the arterial walls using balloon angioplasty, and subsequently, a supporting scaffold called a stent is placed to restore normal blood flow within the artery. Endothelial denudation and overstretch injuries caused during the PCI procedure kick start a myriad of signaling cascades within the arterial wall resulting in uncontrolled tissue growth, eventually recreating obstructions to the blood flow. The condition is labeled in-stent restenosis and the mechanism associated is termed neointimal hyperplasia. An attempt is made herein to model restenosis by tracking the pathophysiology's significant contributors including the platelet-derived growth factor (PDGF) and the transforming growth factor (TGF-β), which are released into the arterial wall post platelet aggregation and degranulation. Additionally, the evolutions of the extracellular matrix (ECM), the smooth muscle cells (SMCs) and the endothelial cells (EC) are tracked. A rapamycin based drug (e.g. sirolimus) is considered for evaluation of pharmacokinetics and pharmacodynamics and subsequent influence on the pathology of restenosis. A fully coupled multi-physical finite element system is hence set up that can provide insights with enough fidelity to adapt PCI parameters and alleviate the risks associated with restenosis.

## Methodology

The cellular mediators of in-stent restenosis in the arterial wall (SMCs, ECs) are quantified in terms of cell densities, while the extracellular mediators (PDGF, TGF-β, ECM and the drug) are quantified in terms of their concentrations. The arterial wall is modeled as an open system allowing for transfer of cellular and extracellular species into and out of it. The Eulerian forms of the advection-reaction-diffusion equations that govern the evolution of the aforementioned species are established based on the biochemical interactions involved in the pathophysiology of restenosis. Patient-specific aspects of pathophysiology can be taken into account given the array of parameters defined for the equations setup.

The structural behavior of the arterial wall is assumed to be predominantly influenced by the medial and adventitial layers, and each layer is assumed to be composed of two families of collagen fibres embedded in an isotropic ground matrix. SMCs are considered to be the drivers of the growth process within the isotropic ground matrix, while collagen is assumed to modulate the compliance of the arterial wall.

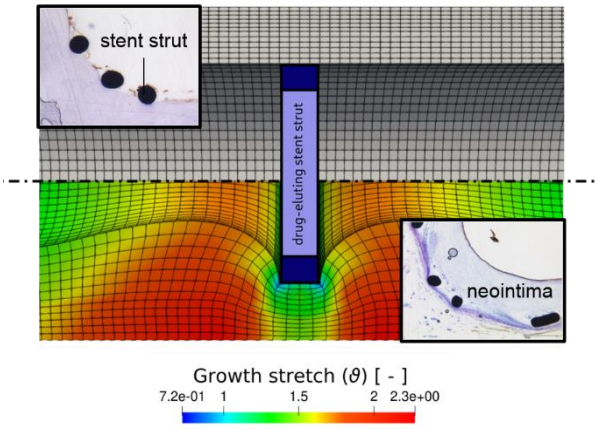


*Figure 1: growth observed around an idealized stent geometry due to endothelial denudation*
*(Inset: explanted stented artery a few days (top left) and a few months (bottom right) after stent implantation [3])*

## References

1. Manjunatha et al., Comput. Biol. Med., 150: 106166, 2022.
2. Reese et al., Proceedings of ECCOMAS Congress 2022, 2022.
3. Internal meeting, DFG project number 395712048, 2021.

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