PARAMETER SENSITIVITY AND OPTIMIZATION OF THE MECHANO-IMMUNO-DRIVEN MODEL OF ENDOGENOUS TISSUE RESTORATION

Hadi Shirazi (1), Thibault Vervenne (1), Lauranne Maes (1), Amber Hendrickx (2), Bart Meuris (2), Nele Famaey (1)

1. Department of Mechanical Engineering, KU Leuven, Belgium; 2. Experimental Cardiac Surgery, KU Leuven, Belgium

Introduction

Endogenous Tissue Restoration (ETR) is a promising regenerative biotechnology in which an implanted synthetic scaffold can transform into a fully remodeled and functional tissue. Computational modeling of this process can facilitate the optimization of the scaffold's initial properties and degradation rate for a specific application. We describe a model of neo-tissue deposition and adaptation versus scaffold degradation, both driven by mechanical and inflammatory stimuli. We include a parameter sensitivity analysis and calibration to *in vivo* experimental data.

Methods

A theoretical framework for an ideal thick-walled cylinder was employed to model the growth and remodeling (G&R) of a tissue-engineered conduit graft using the homogenized constrained mixture theory (HCMT). According to the HCMT, the elastic deformation gradient of constituent *j* is

$$\boldsymbol{F}_e^j = \boldsymbol{F}\left(\boldsymbol{F}_g\right)^{-1}\left(\boldsymbol{F}_r^j\right)^{-1} \quad (1)$$

where $\boldsymbol{F}$ is the deformation gradient of the mixture, $\boldsymbol{F_g}$ and $\boldsymbol{F_r}$ are the growth and remodeling deformation gradients, respectively. The densities of every constituent *j* also evolve as [1]

$$\dot{\rho}^j = \dot{\rho}_+^j + \dot{\rho}_-^j \quad (2)$$

Where subscripts + and – represent the production and removal rates. The mass turnover equations, including stress-induced (SI) and immuno-driven mechanisms, were adapted from [2]. The experimental data were collected in a sheep study in the framework of the H2020 SimInSitu project. Using material parameters from baseline scaffold experimental characterization and pressure levels measured during the animal trial, only a subset of 8 parameters - including the fiber material, basal mass turnover parameters, and the duration and shape of the inflammatory response - was selected for optimization. These unknown model parameters were calibrated through an optimization procedure using the animal trial output *i.e.* the inner radius (r_i) over time. Physically sound ranges of parameter values were determined for optimization. A Sobol analysis (SA) was also used to quantify the contribution of the uncertain model input, and their interactions, to the model's output over time [3].

Results

Fig.1 shows the evolution of the vessel radius in time, for 1 case of the animal trial and the optimized model. The optimization process was repeated for 50 initial informed guesses. Out of all converged parameter sets, 10 were retained, for which the normalized root-mean-square error (NRMSE) between the model and experimental output was < 0.05 (see fig. 1).

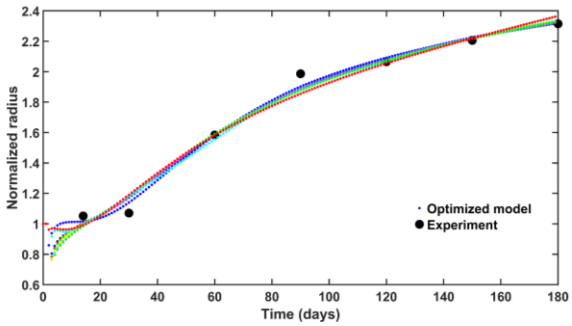

Figure 1. r_i versus time for both optimized model and experimental data.

The SA also indicated that the basal mass production and degradation rates of collagen, as well as the inflammatory response's duration and shape play key roles in the r_i evolution compared to the other parameters. However, the contribution of inflammatory response parameters is dominant mostly in the first days of the process and has only a limited influence on the final neo-vessel geometry.

Discussion

As shown in Fig. 1, the model is nicely capable of reproducing the experimentally measured r_i over time during ETR. For the next phase of the work, we aim to decrease the model uncertainty using more experimental data and to use the model to predict ETR beyond the end point of the animal trials. Next, the model can be used to optimize the scaffold geometry (initial diameter and thickness) and its material properties toward optimal outcomes in terms of desired final radius and mechanical properties of the newly formed vessel.

References

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