**Single Gene Therapies to Prolong the Life of Vein Graft Bypass: a Multiscale Model to Drive Treatment’s Design**

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### Introduction

Vein Graft Bypass (VGB) is the preferred approach to restore the physiological circulation in presence of Peripheral Arterial Occlusive Diseases (PAODs) [1].

VGB adapts to the new operational conditions by undergoing two distinct processes [2]:

- **Intimal Hyperplasia**: thickening of tunica intima caused by cellular migration from media to intima with subsequent cellular proliferation and Extracellular Matrix synthesis.
- **Wall Remodeling**: adaptation of the graft to new pressure conditions resulting in a thickening or thinning of the tunica media.

Their balance dictates the success or failure of the procedure, the latter being unacceptably high with a 12% of re-intervention after 1 month from original operation [2].

**Hypothesis**: an effective therapy aimed to improve the survival of VGBs must be looked for at genetic level, for which a multiscale description of the phenomena cannot be ignored.

**Goals:**

1. To build a multiscale model that reproduces the graft’s adaptation with an integrated system looping together gene, cell, tissue and mechanical forces levels.
3. To challenge the model to systematically test single gene therapies in order to direct the research toward the most suitable genes to be tested for an effective therapy.

### Methods

The multiscale model is based on a Dynamical System that approximates the graft as a mono-compartment thick cylinder where its adaptation is driven by specific cellular events driven by dedicated coefficients. Blood flow is modeled with Poiseuille approximation and the mechanical properties of the wall are derived from our previous work [4].

The connectivity from regulators to mediators is retrieved with a genetic algorithm

- A sensitivity analysis is run in order to individuate the significant regulators.

- Interconnectedness among mediators and from mediators to cellular events is retrieved with a series of genetic algorithms

- A sensitivity analysis individuates the significant mediators

### Preliminary Results

Integrated model validated on normalized graft radius and wall area temporal dynamics with high accuracy.

**Gene Therapy**

A 4-times upregulation of regulator TRIM24 generates a 60% gain in lumen radius with positive outward remodeling.

### Conclusions

- An integrated model of VGB adaptation is proposed encompassing several scales from gene to tissue level.
- The model offers the possibility to perform virtual single gene therapies to prolong the life expectancy of VGBs.
- As future developments:
  - The best therapy administration needs to be found.
  - In silico evidences will be validated on prospective experiments performed ad hoc.

### References


A MULTISCALE MODEL OF ATHEROSCLEROTIC PLAQUE DEVELOPMENT: TOWARD A COUPLING BETWEEN AN AGENT-BASED MODEL AND CFD SIMULATIONS

INTRODUCTION

- Peripheral Arterial Occlusive Diseases (PAODs) hold a high incidence worldwide with more than 200 million people affected annually [1]. Their etiology is mainly attributable to atherosclerosis, a chronic inflammation of the arterial wall that causes the narrowing of the lumen through the build-up of a fatty plaque, mainly localized in areas of disturbed flow [2].
- Perivascular Trans-luminal Angioplasty (PTA), with or without stent, is the preferred endovascular treatment aimed to restore the physiological circulation, however, it suffers of high rates of long-term failure [3].

HYPOTHESIS: the pathology history plays a key role in the intervention outcome - an effective predictive model of surgical outcome must replicate it.

MATERIALS AND METHODS

- Computational models are powerful tools that can provide deeper insights into the multiscale and multifactorial processes governing atherosclerosis and a guidance in the improvement of therapeutic strategies. Among them, Agent-Based Models (ABMs) well suit to replicate pathological physiological processes, in which spatial interaction plays a major role [4].
- Many works simulated the post-surgical follow-up of PTA and stenting by using ABMs but most of them performed their simulations on healthy arteries [5,6].

RESULTS

3 – AGENT-BASED MODEL

The ABM implemented in Matlab® (c. 2016b, MathWorks, Natik, MA, USA) replicates wall remodeling at the cell/tissue scale, by simulating cellular, extracellular, and lipid dynamics. The WSS profile in input in the ABM can promote or maintain the homeostasis of the tissue, or the insurgence of atherosclerosis.

AGENT DYNAMICS

- Agent behavior described by probability laws
- Cellular dynamics
- Lipid dynamics
- Agent death

SENSITIVITY TO WSS

- Three WSS profiles with increasing level of atherogenity (quantified by % of lumen area exposed to low WSS and value of WSSmal):
  - WSS_1: 1.0% of lumen exposed to WSS < 1 Pa; WSSmal = 0.98 Pa
  - WSS_2: 16.5% of lumen exposed to WSS < 1 Pa; WSSmal = 0.69 Pa
  - WSS_3: 52.6% of lumen exposed to WSS < 1 Pa; WSSmal = 0.10 Pa

The ABM predicts a greater lumen area reduction with an increased level of atherogenity of the stimulus.

4 – RETRIEVAL OF THE 3D GEOMETRY

- For each of the ABM output (t=1...85), R_e(t) were computed.
- The deviation δ from the average configuration was evaluated

CONCLUSIONS

- The 2D ABM replicates at the cell/tissue scale the morphological and compositional changes associated with the pathological condition and triggered by an altered hemodynamics.
- The strengths of the model are its multiscale nature and its modularity.
- The model can serve as platform to test in advance the outcome of interventions and pharmacological therapies aimed to restore the physiological circulation on a long-term perspective.