**Linking Gene Dynamics to Intimal Hyperplasia – A Predictive Model of Vein Graft Adaptation**

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**Abstract**

The long term outcome of Coronary Artery Bypass Graft (CABG) surgery remains unsatisfactory to this day [1]. Despite years of improvements in surgical techniques and therapies administered, a re-occlusion of the graft is re-experienced in 10-12% of the cases within just few months [2].

We suggest that an efficient post-surgical therapy might be found at the genetic level. Accordingly, we propose a multiscale model that is able to replicate the healing of the graft and to detail the level of impact of targeted clusters of genes on the graft’s healing. A key feature of our model is its capability of linking the genetic, cellular and tissue levels with feedback bridges in such a way that every variation from an equilibrium point is reflected on all the other elements, creating in this way a highly organized loop.

Our multiscale model is based on two coupled components: (1) a Dynamical System (DS) that describes the adaptation of the vein bypass graft to mechanical stresses imposed by switching from a venous flow to an arterial one [3], and (2) a Cluster Network (CN) system that replicates the expression of targeted clusters of genes and details their impact on the main cellular events leading the graft’s adaptation.

The model was calibrated at various levels on experimental data from rabbit model. This is a complex process, where a heterogeneous set of data at gene, cellular and anatomy level can be used either for calibration or for further validations. The validation on experimental data showed a high degree of accuracy, with a percentile error less than 1%.

Several gene therapies were simulated by altering the initial expression of the clusters and by maintaining their expression constant for the entire follow-up.

The analysis of the clusters’ manipulation showed that by halving the activity of a specific cluster of genes, a 98% reduction of intimal area respect its value in absence of therapy was recorded. This made the lumen increasing its patency, improving in this way the outcome of the procedure.

Our *in silico* model is accurate, fast to run, easy to use and predictive. Its ability to test in advance the outcome of a broad range of gene therapies can dramatically fasten the research aimed to prolong the life expectancy of aortocoronary vein graft bypasses.

**References**

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