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Exploring the link between gene dynamics and intimal hyperplasia– A multi scale model of vascular adaptation

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The most critical issue among vein graft bypass treatments is represented by post-surgical restenosis, which averagely occurs in 12% of cases already within a month from original surgery. It is our hypothesis that an effective post-surgical therapy must be searched for at genetic level and accordingly, we present a multi scale model that can assess the genetic level of restenosis and serve as a platform to test in advance potential gene therapies aimed to prolong the life expectancy of the treatment. Our model is based on two coupled components: (1) a dynamical system that describes the adaptation of the graft to mechanical stresses imposed by environmental conditions variation and (2) a gene network model that replicates the expression of targeted genes and details their impact on the cellular events leading the restenosis. After validation on experimental data from rabbit model, several virtual gene therapies have been performed by modifying the pattern of expression of the gene networks. The analysis of the genes' manipulation showed how by halving the activity of one specific group of genes, it is possible to double the lumen patency on a 30 days follow-up without affecting the wall thickening that is recognized to be a necessary event for the graft's arterialization. The presented in silico model is accurate, robust and predictive. Starting from the current results, a key future step will be to look for a minimal set of genes manipulation leading to significant improvements and to validate its effect on experimental setup.

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