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A twofold usage of an agent-based model of vascular adaptation to design clinical experiments

Stefano Casarin[a,*], Scott A. Berceli[b,c], Marc Garbey[a,d,e]

[a] Center for Computational Surgery, Houston Methodist Research Institute, Houston, TX, USA
[b] Department of Surgery, University of Florida, Gainesville, FL, USA
[c] Malcom Randall VAMC, Gainesville, FL, USA
[d] LASIE UMR 7356 CNRS, University of La Rochelle, La Rochelle, France
[e] Department of Surgery, Houston Methodist Hospital, Houston, TX, USA

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ABSTRACT

Several computational models of Vein Graft Bypass (VGB) adaptation have been developed in order to improve the surgical outcome and they all share a common property: their accuracy relies on a winning choice of their driving coefficients which are best to be retrieved from experimental data.

Since experiments are time-consuming and resources-demanding, the golden standard is to know in advance which measures need to be retrieved on the experimental table and out of how many samples. Accordingly, our goal is to build a computational framework able to pre-design an effective experimental structure to optimize the computational models setup.

Our hypothesis is that an Agent-Based Model (ABM) developed by our group is comparable enough to a true set of experiments to be used to generate reliable virtual experimental data.

Thanks to a twofold usage of our ABM, we created a filter to be posed before the real experiment in order to drive its optimal design.

This work is the natural continuation of a previous study from our group [1], where the attention was posed on simple single-cellular events models. With this new version we focused on more complex models with the purpose of verifying that the complexity of the experimental setup grows proportionally with the accuracy of the model itself.

1. Introduction

Peripheral Arterial Diseases (PADs) are the leading cause of morbidity in the Western Society with a 13% people over 50 years old affected [2]. Among the various surgical techniques aimed to restore the physiological circulation, the most performed one consists into bypassing the occlusion by using an autologous saphenous vein graft, a procedure known as Vein Graft Bypass (VGB) [3–5].

Despite years of surgical improvements, the rate of VGBs failure on a medium term follow-up remains unsatisfactorily high, with an 18% of grafts failing within just 2 months from the original operation, a percentage that ramps up to 40% on a longer follow-up [6,7].

The failure of VGBs is mainly identifiable with the re-occlusion of the graft and it is attributable to its adverse adaptation to the new environmental conditions [8–11]. By switching from venous to arterial regime, the graft simultaneously faces two phenomena, which balance determines the success or the failure of the procedure: i) Intimal Hyperplasia (IH) and ii) Wall Remodeling (WR) consisting in the thickening of the innermost and outermost layer of the graft respectively.

Our group of investigators, also along with others [12,13], studied vascular adaptation both on an experimental [11] and on a computational perspective, from deterministic differential equation systems [14] to Multi-Scale Models (MSMs) [15] to Agent-Based Models (ABMs) [16] regulated by cellular automata principles based on Monte Carlo simulations.

Their driving coefficients were retrieved directly from rabbit-based experimental data, a detailed description of which is offered in [9,11,17]. In the process it has been observed that the level of detail carried by the experimental measures drives the resources needed for their retrieval. Simple geometrical measures, e.g. compartments' radii or thicknesses, can be easily evaluated within a

* Corresponding author.
E-mail address: scasarin@houstonmethodist.org (S. Casarin).

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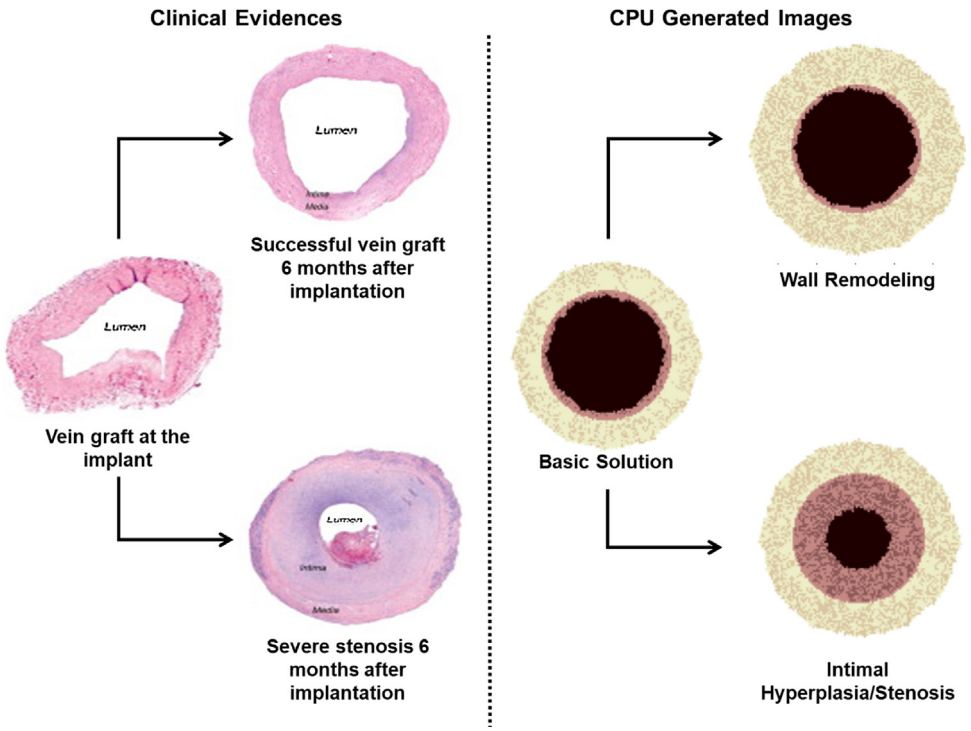

Fig. 1. Agent-Based Model. The ABM (right panel) replicates clinical evidences of a 6 months VGBs follow-up (left panel) [16].

week, while more complex measures like cellular density maps can require a year of work.

As experiments are consuming in terms of time and resources, the golden standard is to know in advance how to design the best experimental setup in order to retrieve the desired coefficients' value. Accordingly, the goal of this paper is to build a computational framework able to pre-identify which are the measurements and which is the size of the specimen suitable enough to explore the experimental observations in a way that allows to effectively setup a computational model of vascular adaptation.

Our hypothesis is that the ABM previously introduced [16] is comparable to a real experiment in a manner that it can be used to generate virtual experimental data. Indeed, on one end the model is relatively accurate in a given coefficients' domain, so much to mimic the fundamental biological functions of the VGB's adaptation with high credibility, an example of which is shown in Fig. 1. On the other end, seen its stochastic nature, the ABM shares the same level of noise of a true experiment.

The rationale of this work stands on the fact that if an experimental setup is not proved to be effective computationally, then there is no point to test it on a real experimental table, because it will certainly result in a failure. This is why the current work wants to be a filter to be placed before the real experiment in order to drive its optimal design.

Accordingly, the computational framework presented is based on a twofold usage of our ABM. The model is used on one end to generate virtual experimental data and on the other end as a true computational model and the two resulting outputs are compared in order to solve the inverse problem established between them. The solution of the latter depends on the winning choice of the measure to be monitored as output of the models, that represent the experimental measure, and on the number of independent simulations, that in turn represents the size of the experimental specimen.

In the previous work from our group of investigators [1], we demonstrated how a simple one-coefficient implementation of the ABM requires an experimental setup relatively easy to prepare and not particularly resources demanding. In addition, the robustness of the experimental setup can be improved by simply using a larger number of samples. However, this has been proved false for multi-coefficients models. The un-verified hypothesis we left behind was that more complex models also require more informative measurements, generally complex and time-demanding to retrieve.

The current work wants to offer a more complete analysis by solidifying the previous evidences and by verifying the cited hypothesis. Accordingly we challenged the presented framework with an increasing degree of complexity of the ABM, by studying first singular cellular events, i.e. intimal/medial mitosis in order to replicate IH and WR respectively, and then by coupling them in order to verify that indeed the complexity of the experimental measurements and/or the size of the specimen grow proportionally with the complexity of the ABM.

Finally, the robustness of our basic assumption relates on an accurate setup of the coefficients driving the ABM and especially on an effective choice of their range of perturbation, as fluctuations of the ABM can lead to large output variations that would be hard to catch with this method. Both the required features are guaranteed by an accurate study of the experimental data [11] preceding the model's implementation and by a thorough validation of the ABM on them in order not to run into unrealistic states potentially given by the model. This is a standard procedure adopted in the development of a computational model and it has been followed in the previous work by our group [16] the basic structure of the ABM is taken from.

2. Methods

Fig. 2 shows the backbone of the computational framework proposed that will be common for all the virtual experiments that will be described. The methodology presented is based on a twofold usage of our ABM [16] that, depending on its implementation, acts both as virtual experimental dataset generator, labeled as ABM1, and as a true computational model, labeled as ABM2.