Computational modeling for cardiovascular tissue engineering

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Computational modeling for cardiovascular tissue engineering: the importance of including cell behavior in growth and remodeling algorithms

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Abstract

Understanding cardiovascular growth and remodeling (G&R) is fundamental for designing robust cardiovascular tissue engineering strategies, which enable synthetic or biological scaffolds to transform into healthy living tissues after implantation. Computational modeling, particularly when integrated with experimental research, is key for advancing our understanding, predicting the *in vivo* evolution of engineered tissues, and efficiently optimizing scaffold designs. As cells are ultimately the drivers of G&R and known to change their behavior in response to mechanical cues, increasing efforts are currently undertaken to capture (mechano-mediated) cell behavior in computational models. In this selective review, we highlight some recent examples that are relevant in the context of cardiovascular tissue engineering and discuss the current and future biological and computational challenges for modeling cell-mediated G&R.

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Computational modeling, Growth and remodeling, Tissue engineering, Cytoskeletal remodeling, Cell signaling, Migration.

Introduction

The ultimate goal of (*in situ*) cardiovascular tissue engineering (CVTE) is to regenerate cardiovascular tissues to restore or improve tissue function [1–3]. Current main approaches involve the use of a (synthetic) biodegradable scaffold, which acts as temporary support for infiltrating cells that create their own, ideally native-like extracellular matrix (ECM) environment while the scaffold degrades over time. Such living engineered tissues can potentially overcome the limitations of current cardiovascular replacements, owing to their intrinsic ability to grow (i.e. change in mass and volume) and remodel (i.e. change in material properties) in response to changes in demands. However, current tissue engineering approaches still suffer from some limitations. A mechanistic understanding of the processes mediating functional and pathological growth and remodeling (G&R) is therefore conditional to design novel scaffolds that can guide these processes towards physiological regeneration and preserved long-term functionality.

Mechanical factors are increasingly recognized as important drivers of G&R [4,5]. Computational models capturing the mechanics and mechanobiology of cardiovascular tissues are therefore indispensable to mechanistically understand and predict the complex interplay between mechanics and cardiovascular G&R. In fact, recent studies have clearly demonstrated that integrating computational modeling into the experimental workflow leads to a substantially improved understanding and superior preclinical outcomes of novel tissue engineering approaches [6–9].

Extensive research in the computational biomechanics and mechanobiology field has been devoted to devising constitutive laws describing the biomechanical behavior of cardiovascular ECM (for some recent reviews, see Refs. [10–12]), and to developing algorithms that capture mechanically driven G&R of ECM components (e.g. see Refs. [8,13–16]). These developments are essential for accurately estimating overall tissue functionality and the mechanical cues responsible for tissue G&R. Concurrently, given that cells are key drivers of G&R and a conditional factor discriminating living from nonliving materials, increasing efforts are currently undertaken to model various types of cell behavior as well. This is particularly important for CVTE, as an increased understanding of cellular processes and their downstream effects on ECM G&R may reveal opportunities for steering cell behavior and consequently ECM G&R via rational adaptations in the scaffold design.

In this selective review, we highlight some examples of the current efforts and future challenges in modeling cell behavior that are relevant in the context of CVTE. Particularly, we focus on the aspects of (1) cytoskeletal remodeling, (2) cell turnover and migration, and (3) cell signaling, followed by a more general discussion on the future biological and computational challenges regarding modeling cell-mediated G&R.

Cytoskeletal remodeling

Cellular contractility has evident effects on tissue remodeling, as cellular forces can, for example, lead to tissue compaction (Figure 1A) and reorientation of collagen fibers (Figure 1B) [17,18]. Stress fibers are the main contractile component of the cytoskeleton of nonmuscle cells, such as heart valve interstitial cells [19]. Consequently, the orientation and maturation of these actomyosin bundles, respectively, determine the direction and magnitude of cellular forces (Figure 1B). However, modeling and predicting stress fiber organization is very complex because it remodels in response to several topographical and mechanical stimuli ([20] for a review), respectively provided, for example, by collagen fibers and pulsatile blood flow. For a better understanding, increasing efforts have been drawn toward developing computational models for stress fiber remodeling [21–25].

Recently, building on previous models [21,23], our group has developed numerical algorithms to predict stress fiber orientation in response to both topographical and mechanical stimuli [24,26]. By coupling these models with equations describing collagen turnover and prestretch as a result of stress fiber contraction, we could simulate the remodeling of native and tissue-engineered heart valves. Simulations of native heart valves suggested that cellular forces and alignment in response to mechanical stimuli are crucial for the emergence of the physiological collagen alignment at fetal age, whereas cellular alignment in response to topographical stimuli provided by collagen fibers is fundamental to maintain and reinforce the physiological collagen alignment during infancy [27]. Simulations of tissue-engineered heart valves were adopted to elucidate the role of cell contractility in the retraction of tissue-engineered leaflets shortly after implantation and to provide guidelines to avoid this unwanted phenomenon [28]. Further simulations were central to guide and improve the remodeling of tissue-engineered heart valves, such that they can now maintain excellent functionality up to one year after implantation [7]. Overall, these studies highlight the potential of analyzing stress fiber remodeling to achieve an increased understanding of cardiovascular tissue remodeling and eventually improve remodeling outcomes.

The computational models that we have developed to predict stress fiber remodeling [24,26] are mainly based on previous *in vitro* observations and only partly motivated by bio-chemo-mechanical considerations, which might limit their predictive potential in unexpected scenarios. More recently, by modifying a previous thermodynamically motivated framework for stress fiber remodeling [25], Chen et al. [29] proposed a new explanation for the orientation of stress fibers in response to mechanical stimuli. This novel thermodynamic model could be integrated with models for cell-mediated remodeling of cardiovascular tissues to provide a more physically motivated understanding, as already carried out for the investigation of tendon remodeling [30]. Furthermore, future studies could include the remodeling of additional (cytoskeletal) components that interact with stress fibers and contribute to regulate their organization and contractility in response to both topographical and mechanical cues, such as focal adhesions [31], microtubules [32], and vimentin [33]. Analyzing these interactions might inspire new approaches to engineer functional cardiovascular tissues and might elucidate pathologies associated with a dysregulation of these cellular components.

Cellular migration and proliferation

Cellular migration and proliferation can lead to changes in tissue volume, composition, and organization. For example, restenosis of arterial stents and vein grafts is correlated with excessive migration and proliferation of vascular smooth muscle cells in the intima layer [34]. While migrating, cells also secrete matrix metalloproteinases and exert forces, thereby causing ECM remodeling [35,36]. Accounting for migration and proliferation is therefore crucial to understand G&R of tissue-engineered cardiovascular grafts, as cell infiltration and proliferation are the main processes occurring at early stages after implantation (Figure 2).

Cell migration and proliferation can be modeled with continuum or agent-based models, depending on the degree of accuracy and efficiency required. Following a continuum approach, the local cell density can be captured by adopting a single partial differential equation accounting for chemo-attractants (for migration) and the local nutrient concentration (for mitosis/apoptosis) [37,38]. In contrast, agent-based models require a set of rules/equations to describe the movement and proliferation of individually modeled cell agents. The continuum approach is advantageous to investigate relatively large cell populations because it allows for considering the local cell concentration by solving a very limited number of equations. Agent-based models are often adopted when a relatively small population of cells is analyzed and a higher degree of accuracy to describe cell migration and proliferation is desired. For example, given their

importance for restenosis of coronary stents and vein grafts, several agent-based models have been recently proposed to accurately describe these two phenomena in this area [39–44].

In the context of tissue engineering, modeling cell migration and proliferation increases our understanding of the processes causing heterogeneity in the distribution of cells and collagen in tissue-engineered constructs, as recently demonstrated by Soares and Sacks [38]. By coupling several partial differential equations, their model considered local and temporal variations in oxygen concentration depending on the tissue-engineered construct porosity, permeability, and deformation; cell chemotaxis toward higher oxygen concentrations; and cell proliferation and ECM deposition dependent on the local oxygen concentration. In agreement with previous experiments, this parsimonious model predicted that mechanical stimulation of tissue-engineered samples increases the oxygen convection, which in turn decreases the transversal heterogeneity of the distribution of oxygen, cells, and ECM observed for statically cultured engineered tissues. However, as pointed out by the same authors in a different study [45], the proposed model cannot explain the recently demonstrated existence of an optimum strain for cell-mediated ECM formation [46]. Although cell-independent phenomena might also play a role, such as the optimum level of strain shielding against degradation observed for collagen [47], this observation invokes additional research. For example, the model of Soares and Sacks [38] could be enriched and adopted to test the hypothesis that the phenomena observed by D'Amore et al. [46] are a consequence of a cell mechanoresponsive behavior in terms of proliferation and apoptosis. Altogether, these studies [38,46] exemplify how a strong interplay between experiments and simulations can lead to new hypotheses and a better understanding of the G&R of engineered tissues, as already demonstrated for other cardiovascular tissues (we refer the reader to a review by Holmes [48] for examples).

Signaling pathways

Cellular phenomena such as cellular forces, migration, and proliferation are regulated not only by local mechanical cues but also by cell–cell signals from neighboring cells (Figure 3). For example, endothelial cells in the arterial intima layer can react to local cues by expressing growth factors (e.g. platelet-derived growth factor (PDGF)) that, while diffusing, influence the behavior of cells in the media [49]. Therefore, including cell–cell signals in computational models is crucial to predict how local cues influence the global G&R of cardiovascular tissues and to guide cells toward a physiological G&R of tissue-engineered arteries (Figure 3A) and heart valves (Figure 3B).

Cell–cell signals can occur at different length scales and are as such classified as endocrine (long distances), paracrine (short distances), and juxtacrine signals (requiring cell–cell contact). In the context of G&R in the vasculature, paracrine and juxtacrine signaling are mostly analyzed (Figure 3C and D). On the one hand, paracrine signals can be modeled via continuum partial differential equations to account for the signal diffusion [50–53]. On the other hand, juxtacrine signals require the adoption of agent-based modeling [54], as this approach enables the consideration of individual cellular positions and thus the identification of the signaling network of contacting cells.

Models accounting for cell–cell signals can be adopted to investigate G&R as a result of communication among different cells. For example, Marino et al. [51,52] have recently proposed a computational framework for cell-mediated ECM remodeling in arteries accounting for the reaction-diffusion of paracrine signals. With this framework, the authors analyzed how the crosstalk between signals coming from macrophages in the adventitia, endothelial cells in the intima, and pharmacological treatments can influence the production of matrix metalloproteases by cells in the media, which in turn affects arterial remodeling. Given the importance of cell–cell signaling for the regulation of cell activity, a similar approach could be adopted to investigate and guide the remodeling of engineered tissues.

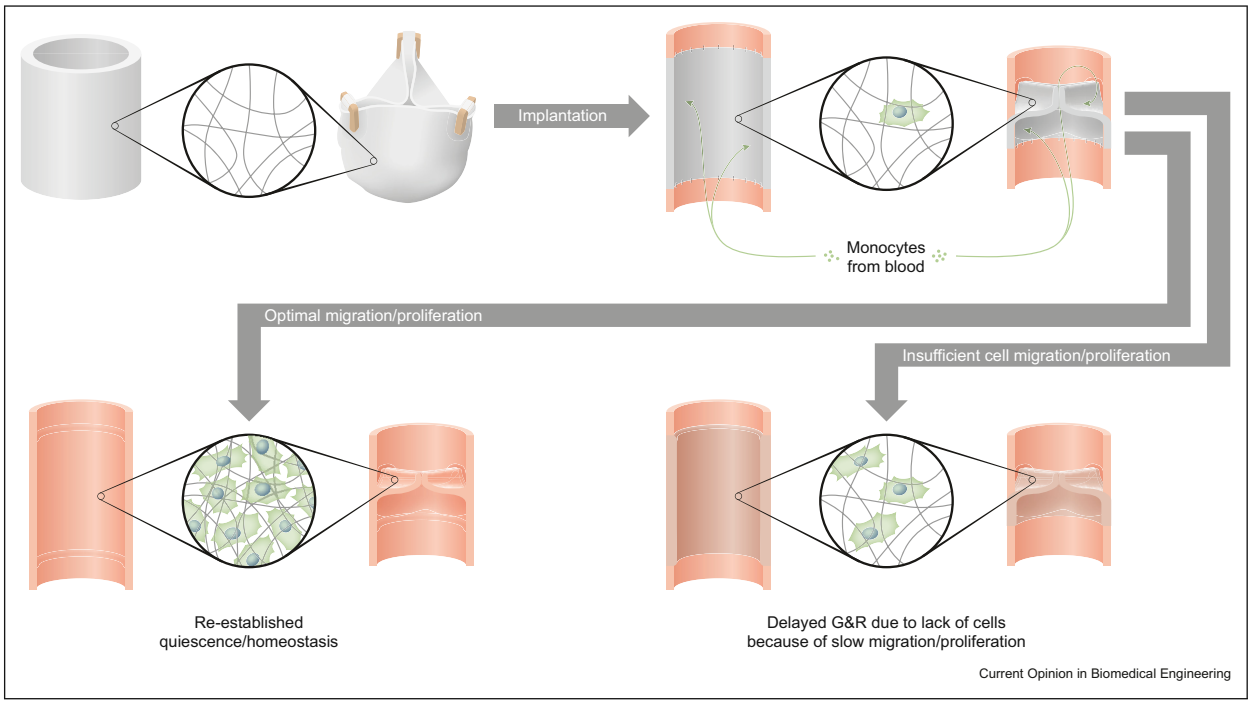
Cell activity is also influenced by juxtacrine signals. For example, transforming growth factor (TGF-β) seems to affect the regulation of the vascular smooth muscle cell phenotype via a crosstalk with Notch [55], a juxtacrine signal influencing several differentiation markers (Figure 3D). *In vitro* experiments have also shown that Notch is affected by cyclic strain [56]. As such, this signaling pathway is most likely crucial for cell-mediated G&R in response to mechanical stimuli. This highlights the importance of developing models for juxtacrine signaling in cardiovascular tissues, such as the model recently proposed by our group [54]. Interestingly, by accounting for the Notch mechanoresponse and the phenotypic modulation of Notch, this model suggested that the communication of arterial cells via Notch induces a collective phenotypic switch of cells from synthetic to contractile (and vice-versa) depending on the arterial wall thickness, which may be essential for the emergence of arterial homeostasis.

As the number of cross-talking signaling pathways that are known to regulate cell behavior will probably only

Figure 1

Effects of cell contractility on the evolution of engineered cardiovascular tissues. **(a)** Cellular contractility strongly influences the remodeling and functionality of tissue-engineered constructs upon implantation. Over time, excessive cellular contractility can cause compaction of tissue-engineered vascular grafts and heart valve leaflets. **(b)** Cellular contractility is strongly regulated by the remodeling of stress fibers: actomyosin bundles in the cellular cytoskeleton determine the direction of collagen fiber deposition and cellular forces, thereby strongly influencing collagen fiber (re)orientation.

Figure 2



Current *in situ* tissue engineering approaches rely on the potential of scaffolds to attract and favor the proliferation of native cells infiltrating from the recipient's circulation. An incorrect rate of migration and proliferation of host cells can lead to an unfavorable delay of the growth and remodeling process of engineered tissues.

increase over time, future efforts should also be directed toward identifying key signaling pathways and how exactly these are affected by mechanics. For example, signaling network models could be developed to identify the main drivers of specific cardiovascular cellular behavior, for example, as demonstrated by Zeigler et al. [57] for myofibroblasts. This will enable the reduction of the model rules and parameters, thereby decreasing the computational costs while increasing the confidence in the model predictions.

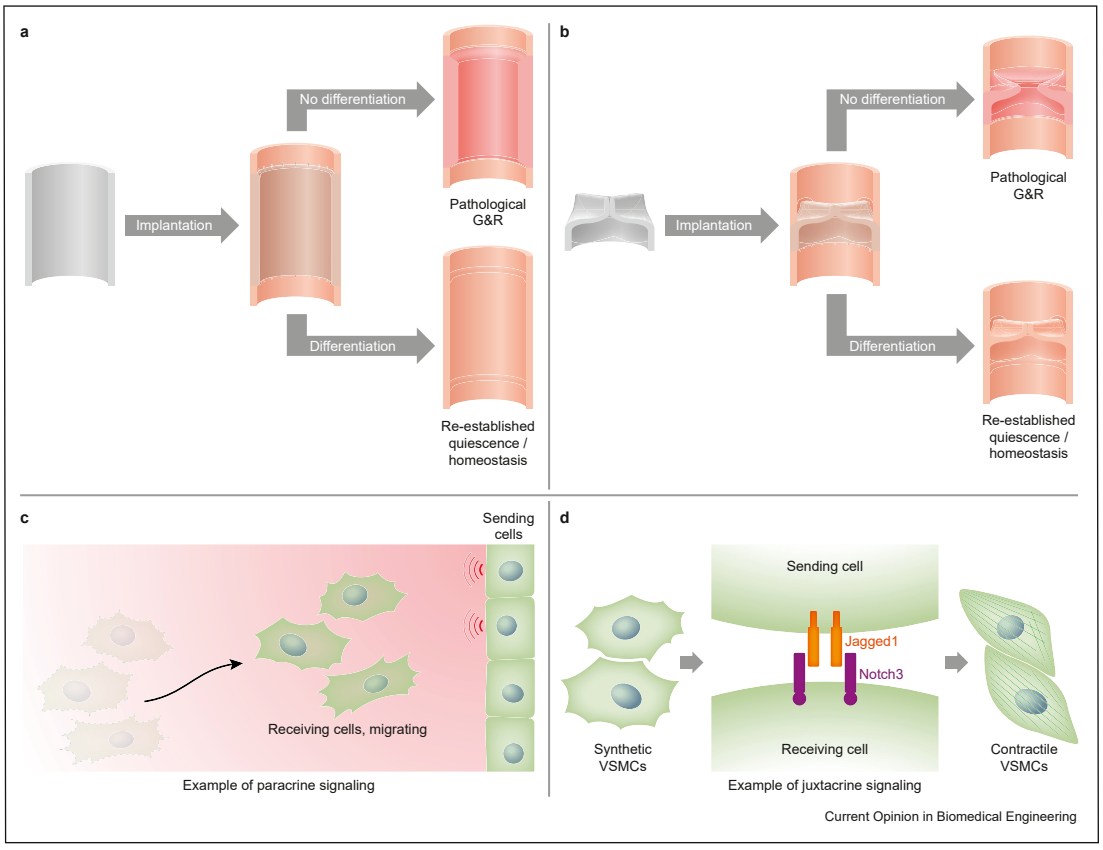
General challenges and future directions

The success of *in situ* CVTE primarily relies on the individual's regenerative capacity, which should enable the (synthetic) scaffold to transform into a living tissue with native-like form and function. Since this intrinsic regenerative capacity varies across individuals owing to subject-specific differences in age, gender, and potential comorbidities, the evolution of engineered grafts can substantially vary across individuals, with consequentially varying degrees of success [58,59]. Therefore, besides focusing on the development of computational models regarding the specific behavior of (healthy) ECM-producing cells, it is also important to model how cell-mediated G&R interacts with other regenerative processes as a function of patient-specific conditions.

The immune system is obviously a key player in regeneration, and *in vitro* [60,61] and *in vivo* [62,63] studies have clearly demonstrated that the inflammatory response during the early phases after scaffold implantation has a key influence on the ultimate G&R of engineered vascular grafts. Over the past years, the Humphrey lab made important progress in modeling the interplay between immuno-driven and mechano-mediated G&R. For example, Miller et al. [13,64] demonstrated that incorporating the transition from inflammatory-mediated tissue formation to mechano-biologically driven G&R is critical for correctly modeling the *in vivo* evolution of engineered vascular grafts. Recently, Szafron et al. [8] investigated the impact of variations in inflammatory response and showed that the moderate inflammatory response to the implanted construct in immuno-compromised mice is more favorable for long-term vessel development compared with the exuberant response exhibited by immuno-competent mice.

In the future, an increased focus on including specific immune cell behavior may lead to novel insights in this area and potentially to tools to direct the immune response toward functional regeneration. Several *in vitro* experiments have demonstrated that macrophages, key players in the foreign body response, are

Figure 3



Regulation and impact of cellular phenotypes. Proper regulation of the phenotype of cells infiltrating scaffolds is a key requirement to avoid excessive thickening of tissue-engineered arteries **(a)** and heart valve leaflets **(b)**. Therefore, after implantation, a quiescent cellular phenotype should be induced when the transformation of the scaffold toward a native-like tissue has been completed. The regulation of cellular phenotype, as well as cellular migration and contractility, is strongly influenced by cell–cell communication. For example, paracrine signaling can influence cell migration **(c)**, whereas juxtacrine signaling (e.g. via Notch) induces differentiation of synthetic vascular smooth muscle cells toward their contractile phenotype **(d)**.

mechanosensitive and can change their phenotype depending on how they are mechanically loaded [65–67]. Including macrophage mechanosensitivity and other relevant cellular phenomena will be important for obtaining a mechanistic understanding of how immune cells, in conjunction with (recruited) tissue cells, drive the cell-mediated *in vivo* evolution of engineered grafts.

On the other hand, the inclusion of increasingly detailed cell behavior in computational models poses several challenges related to computational costs, parameter identification, and model validation. Efforts aimed at more efficiently solving the model equations or approximating their solutions [14,68–70] are essential to ensure that models remain numerically tractable when applied to simulating G&R under complex *in vivo* conditions. The challenges related to parameter identification and model validation can be partially resolved when more, systematic, and quantitative experimental data become available. Still, it is important to minimize the number of mechanisms and model parameters depending on the research question under investigation to balance model complexity and uncertainty, and consequently maximize model credibility [71].

Summary and outlook

Understanding cardiovascular G&R is fundamental for designing successful and robust *in situ* CVTE strategies. Notwithstanding the essential role of experimental research, computational modeling is key for advancing our understanding and particularly our predictive capability of G&R. As cells are the ultimate drivers of G&R, increasing efforts are currently undertaken to model various types of mechano-mediated cell behavior. In this selective review, based on their applicability to the CVTE field, we highlighted some relevant examples of recent developments in modeling cytoskeletal remodeling, cell turnover and migration, and cell signaling and discussed some of the current and future challenges for advancing the computational mechanobiology field.

When combined with algorithms that describe G&R of the ECM, these cell-mediated G&R models will enable further optimization of scaffold properties [72,73], to ideally control cell behavior and optimize downstream matrix formation. Furthermore, these models will be crucial to estimate the sensitivity of CVTE outcomes to variations in patient-specific factors. To facilitate this process, it is important that the computational modeling field joins forces with experts in tissue engineering, cell biology, immunology, medicine, and materials science, as the multidisciplinary nature of tissue engineering [1] naturally calls for multidisciplinary research collaborations to advance the field.

Conflict of interest statement

Nothing declared.

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