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Current Opinion in Biomedical Engineering

Computational systems mechanobiology of growth and remodeling: Integration of tissue mechanics and cell regulatory network dynamics

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Abstract

Growth and remodeling (G&R) of biological tissues is an inherently multiscale and multiphysics process. In the past two decades, computational models of G&R have been developed to improve our fundamental understanding of how tissues adapt to mechanical cues. Models focused on tissue mechanics have successfully captured G&R of tissues but lacking a detailed description of the biological control at the cell level. In contrast, systems biology models of mechanotransduction and cellular processes associated to G&R events have been developed often without coupling to the tissue mechanical behavior at multiple scales. Here, we review novel approaches to fuse the systems biology approach to cell mechanobiology with the continuum mechanics descriptions of G&R.

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Current Opinion in Biomedical Engineering 2020, **15**:75–80

This review comes from a themed issue on **Biomechanics and Mechanobiology: Growth and remodeling in both mechanics and mechanobiology**

Edited by **Ellen Kuhl** and **Jay Humphrey**

For a complete overview see the Issue and the Editorial

https://doi.org/10.1016/j.cobme.2020.01.002

Keywords

Multiscale models, Multiphysics models, Systems biology, Tissue mechanics.

Introduction

Growth and remodeling (G&R) of biological tissues is inherently multiscale and controlled by complex cell-signaling networks. Biological tissues serve specific mechanical functions at the macroscopic scale, on the order of centimeters or millimeters. In response to mechanical cues at this scale, tissues adapt mechanically through G&R [1,2]. This process, although evident at the tissue level, is actually driven by cellular activity at the microscopic scale, on the order of micrometers. Therefore, mechanical cues at the tissue level need to be transmitted to cells in their local extracellular matrix (ECM) and transformed into chemical signals through the process of mechanotransduction [3]. Signaling cascades inside cells and also between cells through direct cell–cell junctions or diffusible cytokines and growth factors coordinate how cells change their local ECM to maintain homeostasis [4]. Eventually, these microscopic G&R events are reflected upscale as mechanical adaptation observed at the tissue level [5,6] (Figure 1).

Toward better understanding of G&R in tissues, theoretical and computational models within a continuum mechanics framework have become extremely popular and useful in the past two decades [7]. Rodriguez et al. [8] introduced the split of the deformation gradient, akin to plasticity, to describe volumetric growth of soft tissues. Humphrey and Rajagopal [9] proposed a model for tissue adaptation based on constrained mixture theory. These two strategies have shed light on tissue-level G&R across many organ systems [10]. Yet, the emphasis of these models, up until recently, has been on the mechanical behavior of tissues but lacking a detailed description of the biological control at the cell level.

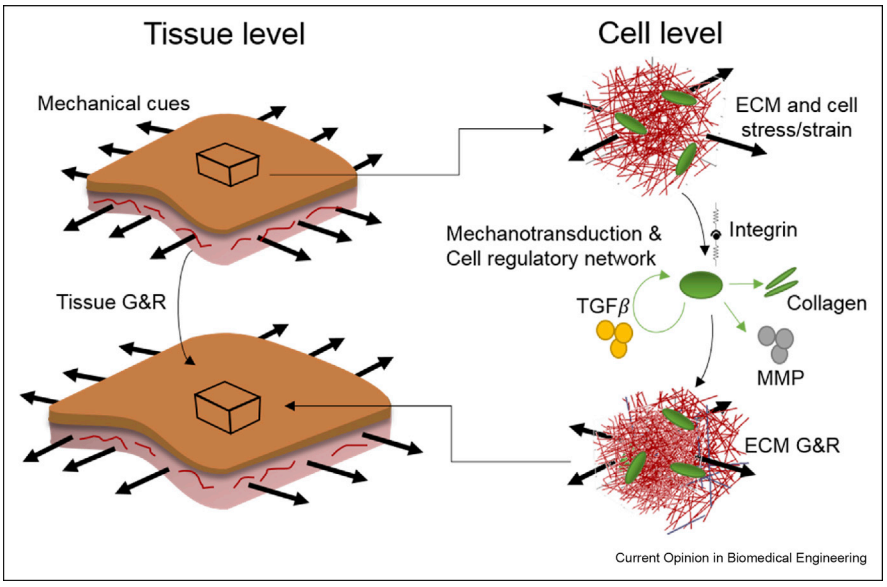
Paralleling the advances in tissue mechanics, in the context of systems biology, models of mechanotransduction and subsequent cellular processes associated to G&R events have been developed [11]. Computationally, cell-level events have been captured with ordinary differential equations, partial differential equations (PDEs), agent-based models (ABMs), or lattice approaches such as cellular Potts models [12–14]. Although these efforts have shed light on the dynamics of cell-signaling networks, they have often lacked a detailed coupling to tissue mechanics.

In the past few years, the systems biology approach to cell mechanobiology and the continuum mechanics descriptions of G&R started to fuse in computational models. This perspective article is precisely centered on the most recent examples of multiphysics models of G&R that explicitly incorporate chemo–bio–mechanical couplings.

Modeling G&R across organ systems with multiphysics approaches

Wound healing is a quintessential example of G&R that is closely dependent on a complex cell regulatory network. Scar remodeling in the skin, which occurs

Figure 1



Growth and remodeling (G&R) of tissues involves coupling across spatial scales. Mechanical cues at the tissue scale lead to tissue-level G&R. However, the control of this process is driven by cell and ECM interactions at the microscopic level. ECM, extracellular matrix.

toward the end of the healing process, shares many similarities with the repair of other connective tissues, such as tendons or the heart [15,16]. Thus, skin has served as a model system to study the fibrotic response to injury. The commonalities in scar formation across connective tissues stems from a common inflammatory signaling network implicated in tissue remodeling. The computational simulation of dermal wound healing has a rich history [17]. Upon injury, the inflammatory response is characterized by an initial influx of neutrophils, followed by proinflammatory macrophages. These macrophages transform into an alternative macrophage phenotype and create the milieu for infiltration, collagen deposition, and wound contraction by fibroblasts. Therefore, recent wound healing models have improved our understanding of tissue regeneration by accounting for such multiphysics features. In a study by Buganza Tepole et al. [18], the mechanical behavior of skin was described as a hyperelastic material with a microstructure-based strain energy function. G&R of the healing tissue was modeled in two ways. First, kinematically, the multiplicative split of the deformation gradient described permanent volume changes and an evolving vector field described collagen reorientation. Second, changes in collagen mass fraction were considered. The inflammatory cascade and the ensuing fibroblast response were captured with a set of nonlinear reaction–diffusion PDEs. Cell populations obeyed logistic-type equations with nonlinear interaction terms modeled as Hill functions. A two-way coupling between the mechanical and biological fields was considered. The state of stress directly affected inflammation and collagen deposition, and the fibroblast population changed the mechanical environment by controlling collagen turnover and exerting an active stress. The model was discretized with a custom finite element program that solved the coupled system in a monolithic manner. This model was able to capture key mechanical fingerprints of cutaneous wound healing, such as the wound contracture in response to inflammation.

Similar to dermal wounds, healing in the cardiovascular system follows common mechanisms to scar formation in the skin. For example, the work by Rausch and Humphrey was the first to model key chemo–bio–mechanical interactions during venous thrombus maturation [19]. Deep vein thrombosis starts with the formation of a fibrin clot which is slowly degraded at the same time that incoming fibroblasts produce and compact a new collagen matrix. The interplay between fibrin degradation and new ECM formation is key to understand and eventually predict thrombus fate. In a study by Rausch et al. [19], a constrained mixture model was used to describe the evolving mass fraction of fibrin and collagen. The composition of the tissue, in turn, determined its mechanical behavior through a structurally based strain energy function. Cells and chemicals were considered as continuous fields obeying reactive transport PDEs. The constitutive models for fibrin degradation and collagen deposition were explicitly dependent on the concentration of the biological fields, thus coupling the two branches of the model.

A fibrotic response in the heart after infarct is yet another example of healing gone awry. Hence, recent computational models of heart remodeling have also

explored the relationship between tissue-level G&R and the underlying cellular control. Rouillard and Holmes proposed the first multiscale model that coupled a finite element simulation of heart mechanics with an ABM of fibroblast-driven collagen remodeling [20]. Their two-way coupling consisted of: (i) fibroblast migration and collagen turnover in response to both chemical and mechanical cues, (ii) change in tissue mechanical properties based on changes in the collagen mass fraction and orientation by cells. Following this initial article, the same group has continued to refine their modeling approach [21,22]. Notably, the systems biology models of cardiac fibroblast signaling, specifically the hypertrophic response, are among the most detailed and validated [11,23].

Continuing in the context of wound healing, we switch to wounds of epithelial rather than connective tissues. In fetal wound healing, for example, multiphysics modeling is able to reproduce hallmarks of scarless healing [24]. In a study by Roldán et al. [24], the authors multiplicatively split the deformation gradient to describe wound contraction and use an active stress term dependent on nonlinear reaction–diffusion PDEs of actin and calcium dynamics. The work by Sree et al. [25] focused on epidermis necrosis in pressure ulcer formation by coupling a multiscale model of the skin with a set of PDEs describing the underlying inflammation signaling network.

Bones also heal after injury. Although there are many differences in the healing of bones compared with connective or epithelial tissues, the combination of G&R at the tissue level with a complex regulatory network at the cell scale is key to improve treatment. Ribeiro et al. [26] proposed a finite element model of bone fractures under loading was coupled with reaction–diffusion PDEs for cellular activity and BMP2 signaling, a protein used clinically to promote bone regeneration. A highlight of their work is the homogenized mechanotransduction model derived from a study Moreo et al. [27]. Other recent models of bone regeneration that explicitly couple a detailed mechanical description of bone tissue with a PDE model of cell signaling include [28,29].

Modeling choices for computational systems mechanobiology

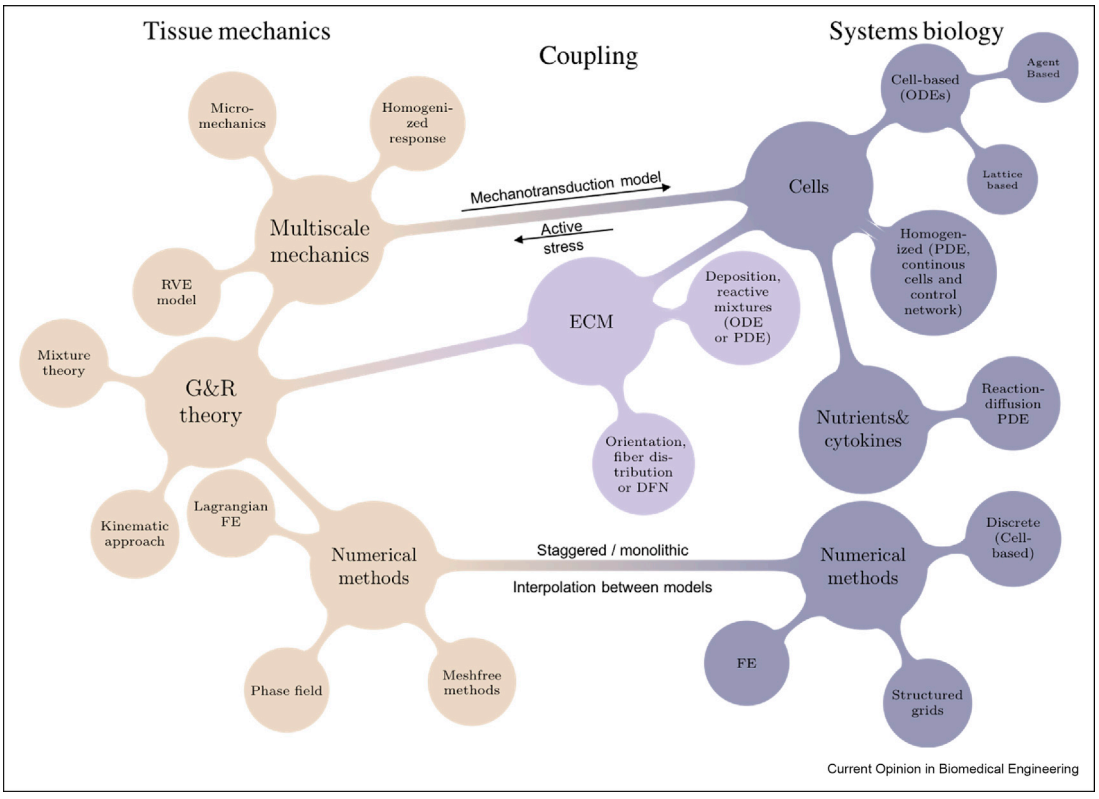
Based on the latest examples of G&R coupled to cell-signaling networks, we review the important choices within the two main components of such models — tissue mechanics and systems biology components — as well as their integration through two-way feedbacks. As discussed in the introduction, one of the current challenges to capture G&R is the multiscale nature of tissues. Although many recent G&R models are developed at the tissue scale, for example [18,30], or at the cell scale, for instance a study by Pastrama et al. [28], coupling across scales remains a challenge. However, multiscale modeling of tissues without G&R is well established [31] for one example. Initial efforts to couple models of G&R at multiple scales is ongoing [22,25]. A popular choice is the creation of models of representative volume elements coupled to a tissue-scale model. Alternatively, homogenized responses or micromechanics approaches are also suitable. Somewhat independently of the multiscale coupling, there are two popular choices for the underlying G&R framework. On the one hand, the kinematic approach relies on the multiplicative split of the deformation gradient into growth and elastic contributions [24], whereas the other common choice is to use constrained mixtures [19,32]. The third crucial decision in the tissue mechanics modeling component is the numerical method. Perhaps, the most common is the development of total Lagrangian finite element formulations [33], but phase-field and mesh-free methods are used within the tissue mechanics community to simulate G&R [34–37].

For the component of G&R that addresses the cell network dynamics, the first important choice is whether to model cells as discrete entities or as continuum fields. Discrete approaches include ABMs and lattice-based models. An advantage of these types of models is the ability to model intracellular signaling networks and to compare directly the simulation to experimental data [11,20,38]. The challenge is in the restriction to small and often idealized domains, which is an issue that is currently being addressed [22]. The alternative is to consider cells as continuous fields, which facilitates simulation at the tissue scale but loses the resolution of cell-based models [25] (see Figure 2).

Extracellular soluble substances, such as nutrients, growth factors, and other cytokines, are almost exclusively modeled as nonlinear reaction–diffusion PDEs. The modeling challenges in this regard pertain to the constitutive equations, the reaction terms that model the interactions within the signaling network. The choice of numerical method to simulate the systems biology component of G&R models is driven primarily by the choice of discrete cells or continuous cell fields, which in turn tends to depend on the scale of interest. For small scales, structured grids and agents are preferred [20,38], whereas finite element methods are more suitable for the nonlinear reaction PDEs in complex geometries at larger scales [18,24].

Finally, the coupling of the two components of the model is perhaps the most crucial. One of the directions of coupling is from the cell regulatory network to the tissue mechanics. The most natural way to include this coupling is through changes in the ECM composition and structure. At the macroscopic scale, the mechanics of the tissue can be expressed in terms of microstructure

Figure 2



Modeling choices in computational systems mechanobiology. Within tissue mechanics, important considerations include: (i) how to deal with the inherent multiscale nature of tissues, (ii) which theory of G&R to use, (iii) the numerical method to use for simulations. For the systems biology component, important decisions are: (i) whether to consider cells as discrete entities or continuum fields, (ii) which ECM components to consider and whether to model the structure in a continuum or a discrete manner, for example, distribution of fibers or discrete fiber networks (DFN), (iii) which components of the cell-signaling network to include, (iv) the numerical method for simulation. Although models within either tissue mechanics or systems biology have received more attention, how to couple these two approaches requires further developments. G&R, growth and remodeling; ECM, extracellular matrix.

components. At the same time, cellular activity can be directly coupled to changes in ECM microstructure through collagen deposition or reorientation [18,19]. Active stress by cells on their ECM is another coupling from the systems biology component to the tissue mechanics component [18,24]. The opposite coupling is the modeling of mechanotransduction. Constitutive models for mechanotransduction are being developed [11,27,39], yet, this is clearly an area that requires further research, as discussed next.

Future directions

As we have reviewed, there are well established theories for G&R at the tissue scale. Although some multiscale models are emerging [22,25,40], this is an area of research for the near future. Specifically, new theory and numerical schemes are needed to couple G&R models at different scales in a rigorous manner. Similarly, systems biology models are well established for inflammatory signaling, which underlines many G&R events, especially scar formation and fibrosis of connective tissue. However, comprehensive mechanotransduction models are still needed. The excellent methodology by the Zeigler et al. [11] and Frank et al. [41] in this regard, among others, is a good blueprint that should be followed to improve G&R models across organ systems.

There are various modeling choices for computational systems mechanobiology, each with its own advantages and disadvantages. Therefore, modeling choices are very much dependent on the question being investigated with the model and the type of data available for validation. In any case, it is clear that, although components of the model that fall on the tissue mechanics or the systems biology realms are more established, coupling schemes between these two types of models requires further investigation. Finally, owing to the many different strategies available to model G&R coupled with cell regulatory networks, validation is a challenging task, but not less important. Comparison between different models, benchmarks for new models, and developing of open source codes is essential and lacking.

In summary, novel simulations of G&R have been coupled with computational systems biology approaches to better understand the fundamental mechanisms behind tissue adaptation. There are many avenues for future research at this intersection. Eventually, computational systems mechanobiology of G&R could help design better treatments based on modeling and simulation.

Conflict of interest statement

Nothing declared.

Acknowledgements

This article was supported in part by the National Science Foundation Grant # 1916668 to Adrian Buganza Tepole.

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** of outstanding interest

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